Evidence-Based Management of Head and Neck Vascular Anomalies

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We dedicate this book to our parents, families, mentors, practice partners, and colleagues. They have fostered a spirit of inquiry in us and supported us in our professional and personal endeavors. We also dedicate this book to all vascular anomaly patients and their families. We hope the knowledge contained here will provide a foundation from which their lives will be improved.

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1 Evidence-Based Medicine: Key Definitions and Concepts

C. Carrie Liu and Jennifer Shin

Defining Evidence-Based Medicine

During the 1990s, an emerging body of literature called for a shift in the paradigm of medical practice [1, 2]. There was a recognition that the anecdotally informed approach to patient care was insufficient in the face of modern medicine and research. This impetus coincided with key technological advancements, including the creation of online databases that eased accessibility to studies as well as the development and refinement of numerous research methodologies [1]. As part of this paradigm shift, many changes were seen in medical academia. Specifically, journals began to utilize structured abstracts, and practice guidelines became more common; there was also an increasing effort to redesign residency training programs to incorporate competencies surrounding evidence search and appraisal [1]. This movement was eventually termed evidence-based medicine.

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In short, evidence-based medicine describes the systematic search and evaluation of literature to make clinical decisions that are based on the current evidence. The consistent and judicious practice of evidence-based medicine ensures that every clinical decision is based on the best available evidence. In fact, studies have demonstrated that the potential impact is that the quality of delivered care is improved and patient outcomes improve when an evidence-based approach is taken [3–9]. With health economic evaluations becoming more prominent, evidence-based medicine may also lead to a more cost-effective care.

The process of evidence-based medicine encompasses five steps [10]: (1) formation of a specific clinical question, (2) systematic search of the literature for available evidence, (3) appraisal of evidence, (4) interpretation of findings in the context of the individual patient and application to clinical decision-making, and (5) regular evaluation of own performance. It is important to note that the final clinical decision is dependent on individual physician expertise as well as the values and preferences of the patient. Therefore, evidence-based medicine represents the intersection of a systematic examination of literature, clinician experience and expertise, and patient preferences [11]. To become proficient at evidence-based medicine, healthcare providers must be familiar with available resources for evidence, study designs and its implications for the quality of evidence, and, finally, the levels of evidence.

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Accessing Evidence

Journal Articles

There are numerous bibliographical resources that can be used by clinicians to access original studies. The Ovid databases, including Medline and Embase, are among the most prominent databases used in medicine. Medline was established by the US National Library of Medicine (NLM) in 1966. It contains over 5600 journals, with over 22 million references [12]. Embase, which began in 1974, is produced by Elsevier Science. It contains over 8500 journals, with over 30 million references [13]. Both Medline and Embase encompass all areas of biomedicine, while Embase also contains journals on health administration, health economics, and forensic sciences [14]. PubMed is another database produced by NLM. In addition to containing all Medline references, PubMed also contains in-process citations, "ahead of print" citations, and articles from Medline journals that are not within the scope of biomedicine, among many other types of citations. Another database that clinicians should be aware of is CINAHL (Cumulative Index to Nursing and Allied Health Literature). While this database focuses primarily on nursing and allied health journals, there is a wide range of subjects including medicine, education, and health administration [15, 16].

Historically, Medline was felt to be the most comprehensive database, and it is the most commonly used databases in meta-analyses [17, 18]. However, more recent studies have shown that searching additional databases, such as Embase and CINAHL, yields more relevant studies than can be found via Medline alone [15, 18–20]. For more specific inquiries, sources such as the Cochrane Central Register of Controlled Trials [21] and Health Services Research Queries [22] may be helpful. Research librarians are great resources for clinicians in determining the suitability of different databases for specific questions. They are also helpful in devising search strategies that can optimize both yield and efficiency.

Consolidated Evidence

There are ongoing efforts to consolidate data from individual studies to create resources that are practical and accessible to clinicians [23]. First, there has been a growth in the number of evidence-based medicine journals, whereby individual studies are summarized into abstract form, delivering only the most poignant findings from studies that are appraised to be of value. This is an expedited method for clinicians to stay informed of new research. An example of such a journal is *Evidence-Based Medicine*, which spans all medical specialties. Discipline-specific evidence-based journals exist as well. A journal of this concept does not currently exist specific to otolaryngology.

Systematic reviews and meta-analyses represent systematic evaluations of the literature, with syntheses of available evidence to answer specific clinical questions. A systematic review or meta-analysis is helpful for decision-making as it presents all pertinent research surrounding a specific clinical scenario. The Cochrane Library is a good source for quality systematic reviews and meta-analyses. These studies may also be accessed as individual articles from the Medline, Embase, and CINAHL databases.

Evidence-based texts and clinical practice guidelines represent more extensive efforts to systematically review the evidence to make formal recommendations to clinicians. Examples of texts which incorporate a focus on evidence include UpToDate (http://www.uptodate.com), DynaMed (http://www.dynamed.com), and Best Practice (http://bestpractice.bmj.com). Numerous discipline-specific societies and organizations put forth clinical practice guidelines, which are meticulously created over the course of years. In otolaryngology, the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) regularly publishes clinical practice guidelines regarding prominent otolaryngology issues (http://www.entnet.org/content/clinical-practice-guidelines), which are based on data from systematic reviews and high-level clinical trials.

Evidence Appraisal

Critical appraisal of evidence requires sound understanding of study designs, associated biases, and the resulting strength of evidence. Bias is defined as the presence of a systematic error from the design, performance, or analysis of a study [24]. Every study design is prone to its own set of biases. This section presents an overview of commonly encountered study designs in otolaryngology and their associated risks of bias (Table 1.1).

Table 1.1 Study designs and their associated biases

Study design	Bias type	Description of bias
Randomized controlled trial	Selection bias	The presence of systematic differences in the baseline characteristics of the study groups
	Missing data	Bias that results from participant withdrawal or loss to follow-up
	Ascertainment bias	
	Performance bias	Differences in study conditions or in the care provided to study participants based on their group assignment
	Detection bias	Differences in the measurement of outcomes among study participants based on their group assignment
Cohort	Selection bias	
	Non-response bias	The presence of systematic differences among subjects who declined to participate in the study and those who agreed
	Attrition bias	The presence of systematic differences among participants lost to follow-up and those who completed the study
	Information bias	Investigator driven: inconsistencies in exposure or outcome measurement
		Participant driven: inconsistencies in how exposure and outcomes are reported
	Confounding	Without randomization, there may be unknown confounders that are not adjusted for
Case-control	Prevalence-incidence bias	Biased estimate of survival based on prevalent cases (can miss severe disease that leads to rapid demise or mild disease that is subclinical)
	Convenience sampling	The presence of a study population that is unrepresentative of the population they are meant to represent
	Assessor bias	Inconsistent measurement of exposure or outcome secondary to investigator knowledge of the study
	Recall bias	Systematic misreporting of exposure status
	Confounding	Without randomization, there may be unknown confounders that are not adjusted for
Cross sectional	Non-response bias	The presence of systematic differences among those who declined to participate in the study and those who agreed to participate
	Volunteer bias	The presence of systematic differences among those who volunteered to participate in the study and those who did not
	Ascertainment bias	
	Response bias	Intentional misreporting of certain exposures
	Observer bias	The presence of consistent inaccurate recordings of exposure or outcome by the investigator
Studies of diagnostic tests	Lead time bias	Artificial increase in survival estimate caused by a test that leads to a sooner diagnosis of disease
	Length time bias	Artificial increase in survival estimate caused by the preferential detection of slow-growing disease
Case series	Convenience sampling	The presence of a study population that is unrepresentative of the population they are meant to represent
	Confounding	Without randomization, there may be unknown confounders that are not adjusted for

Randomized Controlled Trial

Randomized controlled trials (RCTs) are typically considered the gold standard for evidence [25, 26]. In RCTs, subjects are randomized into two or more groups that are assigned to receive certain interventions [27]. They are then followed for a period of time, and data regarding prespecified endpoints are collected. The advantage of randomization is that it ensures that there is an even distribution of known and unknown baseline confounders [28]. In a well-designed and well-executed RCT, any difference of effects seen between groups likely represents a true treatment effect. There are numerous RCT designs, depending on the clinical question, patient population, disease and treatment characteristics, and outcomes of interest [29].

When reviewing RCTs, clinicians should be mindful of potential biases that are commonly encountered in this type of study design. The first is *selection bias*, whereby there are differences in the baseline characteristics of the study groups [30]. To minimize selection bias, there should be an appropriate randomization sequence by which study subjects are assigned to their groups. Furthermore, the sequence should be concealed such that research staff and subjects cannot predict upcoming assignments [30, 31]. Randomization, however, can only be justified when there is true clinical equipoise [32]. When true uncertainty regarding the superiority of an intervention does not exist, an RCT would not be the appropriate study design.

Performance bias and detection bias are also common biases encountered in RCTs. Together, they lead to ascertainment bias. Both biases stem from a lack of blinding of the study investigators or subjects [31]. *Performance bias* refers to differences in the care or study conditions received or experienced by the study participants based on their group assignment. Similarly, *detection bias* refers to differences in the measurement of outcomes among study participants based on their group assignment. In both scenarios, knowledge of the treatment group may affect the outcome rather than the treatment itself. Sufficient blinding of investigators and participants minimizes the risk of both biases. Standardized methods of subject assessment may also circumvent performance and detection bias [33].

Finally, bias in RCTs can occur when there is missing data. During the course of a study, missing data may arise as a result of participant withdrawal or missed follow-up appointments. When this occurs, baseline characteristics may no longer be equal between the treatment groups, thereby placing the study at risk for bias. To decrease the risk of bias, RCTs commonly utilize an intention to treat analysis [34]. This method ensures that patients are analyzed based on their initial group assignment, even if they did not receive the assigned treatment and/or did not complete the study [35]. Improper handling of missing data may lead to biased estimates of intervention effects. To minimize the amount of missing data, preventative measures can be undertaken during the design and implementation stages of a trial [28]. There are also numerous methods of statistical analysis that can be utilized depending on the nature of the missing data [28]. When reviewing an RCT, the clinician should be critical of the presence of missing data and how this was handled by the investigators.

Observational Analytic Studies

While RCTs are highly regarded on the evidence pyramid [36], it is not suitable for every clinical scenario and question. In surgery, for example, blinding may not always be achievable; it can be impossible to truly blind the treating surgeon to the intervention [37]. In such instances, observational analytical designs are more appropriate and can yield comparable results to RCTs [38, 39].

Cohort Studies

In a cohort study, a group of subjects are identified based on an exposure of interest. A control group without the exposure is identified as well. These groups are then followed for a period of time, and the outcome(s) of interest are identified, recorded, and analyzed [40]. Cohort studies can be prospective or retrospective. In a prospective

design, the exposure groups are identified and followed into the future [41]. The main advantage of this design is that investigators can collect data prospectively, increasing the likelihood of a more complete dataset. However, prospective studies are time-consuming and may be financially burdensome. Alternatively, a retrospective design identifies the groups of interest, and data is collected from a review of established records. It is less time-consuming with lower study costs. The main disadvantage of a retrospective design is the reliance on pre-collected data, which may be incomplete or inaccurate [41].

Cohort studies are susceptible to selection bias, information bias, and confounding [24]. *Selection bias* occurs when the study groups are not representative of the population from which they are drawn, thereby limiting generalizability of the study findings [24]. Selection bias can also compromise the internal validity of the study, such that estimates may not represent the true treatment effect [42]. In cohort studies, specific causes of selection bias are non-response bias and attrition bias [43]. *Non-response bias* occurs when there is a systematic difference among subjects who declined to participate in the study and those who agreed. Similarly, *attrition bias* occurs when there is a systematic difference among subjects lost to follow-up and those who completed the study.

Information bias occurs during data collection. It can come from the investigators, if there are inconsistencies or inaccuracies in exposure or outcome measurement. It may also come from the participants, if there are systematic differences in how exposure or outcomes are reported [24]. Finally, cohort studies are at risk for *confounding*. Due to the lack of randomization, there will likely always be unknown confounders that are not adjusted for [24].

Case-Control Studies

Case-control studies begin with the identification of a group of subjects with an outcome of interest. The control group is then determined, which consists of subjects of similar characteristics but without the outcome of interest. Data on previous exposures and risk factors is then collected retrospectively, and analysis is performed to determine whether there are significant associations between certain exposures and the outcome of interest [44]. Case-control studies are appropriate for outcomes that are either rare or have a long latency period, where a cohort design would be inefficient, time-consuming, and expensive [41].

Similar to cohort studies, case-control studies are susceptible to selection bias. A form of selection bias that is unique to case-control studies is *prevalence-incidence bias*, otherwise known as Neyman's bias [45]. It is based on the tenet that a study that examines prevalent cases may miss either severe disease that led to rapid mortality or mild disease that is subclinical [46]. As a result, survival of the study groups may be biased to be either increased or decreased, leading to inaccurate calculations of mortality [45, 46]. Selection bias can also occur secondary to *convenience sampling*, which is a common way for subject recruitment in case-control studies [47]. Specifically, participants are often recruited from the same institution, and there may be systematic differences in these patients compared to the population that they theoretically represent. This can compromise both internal and external validity.

Case-control studies are also at risk for assessor bias, recall bias, and confounding. *Assessor bias* occurs when knowledge of the study affects the measurement of an exposure or outcome by the investigator [47]. Because case-control studies rely on the retrospective collection of data, often based on participant report, *recall bias* can occur if there is systematic misreporting of exposure status. Lastly, *confounding* can occur for similar reasons as in cohort studies.

Cross-Sectional Study

In a cross-sectional study, data is collected from the study group at one point in time [48]. It is a commonly utilized method for determining the prevalence of a particular condition in the population [49]. The advantages of a cross-sectional study are its brevity, relatively simple methodology, and lower costs. Furthermore, because cross-sectional studies are typically population-based, the sample group is likely to be representative of

the larger population of interest. The main disadvantage of this study design is that it does not allow for hypothesis testing; only associations, rather than causal inferences, can be made. Second, because a cross-sectional study only captures information at one time point, it may not fully capture the truth as there may be variations in conditions overtime [49].

Cross-sectional studies are susceptible to non-response bias, volunteer bias, and ascertainment bias [48]. *Non-response bias*, again, is defined by the presence of systematic differences among those who declined to participate in the study and those who agreed. Alternatively, *volunteer bias* occurs when there are systematic differences among those who volunteered to participate in the study and those who did not. *Ascertainment bias* can occur in cross-sectional studies as a result of either the participants (*response bias*) or investigators (*observer bias*). In the setting of response bias, participants may intentionally misreport certain exposures if, for example, the exposure is viewed to be embarrassing or unacceptable [48]. Observer bias can occur if there are consistent inaccurate recordings of exposure or outcome status. This can occur if data collection requires subjective interpretation by the individual investigator completing the recording.

Studies of Diagnostic Results

A daily challenge encountered by clinicians is determining the utility of specific diagnostic tests and applying this to individual patients. A growing body of literature is aimed at assisting clinicians in performing this important task. Studies of diagnostic tests are observational in nature and examine an investigational modality's key characteristics, such as sensitivity, specificity, and likelihood ratios. A description of these terms is presented in Table 1.2. For a more in-depth review of diagnostic test characteristics, the reader is referred to additional resources [50, 51].

Many diagnostic tests are used for the purposes of screening and surveillance of malignancies. In evaluating studies pertaining to diagnostic tests for these purposes, the clinician should be cognizant of two important concepts and potential biases: lead time bias and length time bias.

Table 1.2 Characteristics of diagnostic tests

Characteristic	Definition	Equation
Sensitivity	Proportion of patients who test positive for a condition given that they truly have the condition	TP/(TP + FN)
Specificity	Proportion of patients who test negative for a condition given that they do not have the condition	TN/(TN + FP)
Predictive value		
Positive	Given a positive test result, the probability that the patient truly has the condition	[(sens)(prev)]
		[(sens)(prev) + (1 – prev)(1 – spec)]
Negative	Given a negative test result, the probability that the patient truly does not have the condition	[(spec)(1 – prev)]
		[(spec)(1 – prev) + (prev)(1 – sens)]
Likelihood ratio		
Positive	The probability of testing positive in patients who have the condition over the probability of testing positive in patients who do not have the condition	sens/(1 – spec)
Negative	The probability of testing negative in patients who have the condition over the probability of testing negative in patients who do not have the condition	(1 – sens)/spec

FN false negative, *FP* false positive, *TN* true negative, *TP* true positive, *Sens* sensitivity, *spec* specificity, *prev* prevalence

Lead time bias refers to a potential artificial increase in survival caused by a test that leads to earlier diagnosis of disease. While rapid identification and timely initiation of treatment in less advanced cases may confer an advantage over

later diagnoses of more advanced disease, it does not change the inherent properties of that disease state; however, earlier detection of disease may shift the estimated overall survival, due to cases detected by screening rather than the occurrence of symptoms [52, 53]. *Length time bias* occurs when there is preferential detection of more indolent and slow-growing tumors. Slow-growing tumors are more likely to be detected by screening given their longer subclinical phase compared to more aggressive tumors. Screening will, therefore, be associated with improved survival outcomes; however, the observed improvement in survival is secondary to the increased detection of more indolent disease rather than a benefit of screening [52].

Observational Nonanalytic Studies

Case Series

In a case series, a group of patients who share a diagnosis or who have undergone the same intervention are followed for a period of time. Outcomes are then measured and recorded. A case series can be performed either retrospectively or prospectively. The main difference between case series and cohort studies is the lack of a control group in the former. As such, case series do not allow for hypothesis testing, and causal relationships cannot be established [54, 55]. Case series are suitable for assessment of disease progression and treatment outcomes. As such, they are often performed as the preliminary step to determine whether a hypothesis may be worthy of further and more rigorous testing.

The main biases that clinicians should be cognizant of in case series are selection bias and confounding. Similar to cohort studies, a case series often employs *convenience sampling*. There are no a priori criteria for who will be included in the study or who will receive a particular intervention. Therefore, participants in a case series may share characteristics that are systematically different from the population that they represent. As a result of convenience sampling and unrepresentative study populations, case series cannot be used to determine the population prevalence or incidence of a particular condition. Second, *confounding* may occur due to the lack of randomization of study participants.

Systematic Reviews and Meta-Analyses

Systematic reviews involve a meticulous and methodological search of the literature to identify all studies pertaining to a clinical question. These studies are then evaluated for bias, and a summary of the findings is provided to answer the clinical question. Meta-analyses are often reported with systematic reviews and represent quantitative syntheses of the literature. Systematic reviews are preferred to traditional narrative reviews, as the latter can be more prone to bias given the lack of standardized methodology [56].

To critically appraise a systematic review or meta-analysis, the clinician should be familiar with the study design. After defining a clinical question, the a priori protocol of the systematic review is typically described. As part of the protocol, data extraction, primary and secondary outcomes, and analysis methods are outlined. The literature search is performed and should include all relevant bibliographical sources and with comprehensive search terms. The review process for the inclusion and exclusion of individual studies should be transparent. The data is then extracted and analyzed, and the overall findings are presented. If a meta-analysis is performed, the method of statistical analysis and the heterogeneity seen in the data are reported. An important feature of systematic reviews and meta-analyses is the assessment of included studies for bias. There should also be an assessment for publication bias. For detailed guides on how to perform and interpret a systematic review and/or meta-analysis, the reader is encouraged to refer to a few suggested resources [57–59].

By knowing what constitutes sound methodology, clinicians can become critical consumers of systematic reviews and meta-analyses. For every element of a study, the clinician should assess adherence to established systematic review and meta-analysis protocols. Checklists have

been established to assist the clinician in their critical assessment of synthesis studies [60, 61]. A study that is conducted with greater rigor is less subject to biases in its search of the literature, the inclusion and exclusion of studies, and its synthesis of the data.

Clinical Practice Guidelines, Clinical Consensus Statements, and Position Statements

With the progression of evidence-based medicine, there has been a rapidly growing body of literature pertaining to all aspects of medicine. It has become increasingly difficult for clinicians to stay current in their fields of practice. For this reason, there has been an effort by numerous professional societies and working groups to distill the vast body of literature into tangible guidelines to assist clinicians in everyday practice. These exist in the form of clinical practice guidelines, clinical consensus statements, and position statements. It is important for clinicians to understand how each category of document is developed and how they should be used.

The Institute of Medicine defines clinical practice guidelines as "statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options" [62]. As the definition suggests, clinical practice guidelines employ a systematic review of the literature at the outset. The working group typically consists of a representative group of medical experts, ancillary healthcare providers, and key stakeholders such as consumer advocates. To minimize the introduction of biases, clinical practice guidelines are developed using rigorous and transparent processes. The guideline presents evidence both on the benefits and harms of the intervention of interest. The evidence should also be graded to give the consuming clinician an estimate of the strength of the evidence. Finally, clinical practice guidelines should be updated in the identical systematic fashion as its initial development. The timing of revisions ultimately occurs at the discretion of the professional society and is influenced by the rate of emerging evidence, as well as external recommendations. The AAO-HNS is continuously developing clinical practice guidelines on clinical entities such as otitis media with effusion [63], adult sinusitis [64], and tinnitus [65], among many others (http://www.entnet.org/content/clinical-practice-guidelines). These guidelines are updated approximately every 5 years. Another prominent guideline initiative that is relevant to otolaryngologists is by the American Thyroid Association and their management guidelines for thyroid nodules [66].

Consensus statements are also developed by a panel of medical experts following an evidence-based review of the literature. They are often borne from structured conferences on certain topics [62]. They are similar to clinical practice guidelines in that there is often a systematic review of the literature, which is then interpreted and presented in the form of recommendations. Consensus statements may focus more on recent evidence rather than examine the entire body of evidence pertaining to a clinical topic [62]. They are also less centered on action statements than clinical practice guidelines, instead focusing on statements on which the panel can agree. The AAO-HNS publishes consensus statements, which are borne out of systematic syntheses of expert opinion (http://www.entnet.org/content/clinical-consensus-statements). Consensus statements may also be developed by interested groups of clinicians who take the initiative to form panels or forums. The methodologies employed may vary. Two examples are a recent consensus statement on the definition and diagnosis of Eustachian tube dysfunction [67] and an extensive and international effort to review and offer recommendations on rhinosinusitis [68].

Position statements represent the least methodologically taxing document. They are often the product of a professional society committee meeting or conference. They exist in a range, and some can be based mainly on the views of a committee or task force whose expert opinions carry weight. Some development groups will begin with a review of the literature, but that is not always mandated. There are also variations in

how the final statements are formulated; they may be vetted only by the internal group or by an umbrella or commissioning organization. Position paper statements present the collective opinions of a group as they pertain to a specific clinical question, but their evidence base may be variable.

Instruments for Quality Assessment

To assist the clinician in assessing the quality of studies, numerous quality rating scales have been developed. In one systematic review of scales developed to assess the quality of RCTs, 21 published scales were identified [69]. Five of these were developed using standardized methodology [70–74]. These scales focus on the key methodological features of an RCT, such as randomization, blinding, outcomes measurement, and management of missing data. The scale developed by Jadad et al. (1996) was found to have the best evidence for validity and reliability [74]. It is also one of the most recognized instruments, with many adaptations since its initial report [69]. The *Cochrane Handbook for Systematic Reviews of Interventions* also provides a set of criteria by which to evaluate biases in randomized controlled trials [30]. This resource is intended for authors in preparation of Cochrane reviews.

In another systematic review of quality assessment of observational studies, 86 tools were identified, 60 of which were proposed for future use [75]. Many of these tools were created for specific study designs. Unfortunately, only half of the studies described the development of the tool or the assessment of its validity and reliability. Ultimately, the authors concluded that there is no single superior tool for the assessment of observational studies at this time.

For systematic reviews, there are numerous critical appraisal tools for quality assessment [76]. Most tools reported in the literature are not validated as of this writing. To date, the most widely accepted and validated instrument is A MeaSurement Tool to Assess systematic Reviews (AMSTAR) [77, 76]. It was designed to assess the methodological rigor of systematic reviews. Another more recently developed instrument, the Risk Of Bias in Systematic reviews (ROBIS), was designed specifically for the assessment of risk of bias in systematic reviews [76]. A quality assessment tool also exists for meta-analyses, pertaining to the evaluation of methodology [78], but currently, there is no risk of bias assessment tool for meta-analyses.

Clinical practice guidelines also vary in quality, secondary to inconsistent adherence to development protocols. This can result in discrepancies in recommendations. The AGREE II (Appraisal of Guidelines and Research Evaluation) instrument was designed to assist clinicians in developing, reporting, and appraising clinical practice guidelines [79]. The Institute of Medicine also provides a detailed prescriptive document for the development of clinical practice guidelines [62].

A caveat to the rating of study quality is that, as alluded to above, numerous quality rating scales exist for each study design. These scales are developed with varying rigor and, subsequently, are of varying validity. They also emphasize different characteristics of a study in judging its quality. Furthermore, different organizations and journals may employ different methods for assessing the quality of the reviewed studies. The same evidence may receive a number of evaluations, depending on the grading system used [80]. This can be confusing to clinicians, who may not know which rating scale is the most reliable in judging the quality of individual studies or which set of guidelines they should apply to practice. The lack of standardization in quality rating scales hinders the broader goal of quality rating, which is to effectively and efficiently communicate the strength of evidence to the medical community. Another consequence of the heterogeneity of rating scales is that depending on the scale used, the classification of a study as high or low quality might differ. As such, depending on the rating scales used, meta-analyses of randomized controlled trials may reach different conclusions even if examining the same studies [81]. Some authors argue against the use of quality scores [81]. Instead, they recommend focusing on the key methodological components of any given trial and assess how the quality of these

components might affect study conclusions by performing sensitivity analyses.

Along with the development of quality assessment instruments for the evaluation of individual studies, there has been a movement toward ensuring the quality of study reporting. In 1999, the QUOROM (Quality of Reporting of Meta-analysis) statement was published [82]. Its contents were updated, and it was renamed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement in the 2009 publication [83]. Analogous statements exist for randomized trials (CONSORT, Consolidated Standards of Reporting Trials) [84], diagnostic test studies (STARD, Standards for Reporting Diagnostic Accuracy Studies) [85], meta-analyses of observational studies (MOOSE, Meta-analysis of Observational Studies in Epidemiology) [86], and observational epidemiological studies (STROBE, Strengthening the Reporting of Observational Studies in Epidemiology) [87]. It is important to note that these consensus statements pertain only to the reporting of studies, not the design and performance of studies. They are intended for the investigators and authors of studies and should not be used by clinicians for evidence appraisal.

Where to Start

There is a recognized hierarchy of evidence, with systematic reviews of randomized controlled trials, with or without accompanying meta-analyses, at the top. This is followed by individual randomized controlled trials, systematic reviews of cohort studies, individual cohort studies, systematic reviews of case-control studies, individual case-control studies, case series, and expert opinion [88]. This hierarchy can help direct the clinician in their literature review, focusing attention first on studies with higher levels of evidence.

Others have proposed an approach to evidence-based medicine that concentrates on pre-appraised literature rather than individually published studies. In 2001, Haynes proposed the "4S" model of information resource hierarchy to direct clinician efforts when seeking evidence [23]. It was subsequently revised to "5S" and, most recently, the "6S" model [89, 90]. The S's of the pyramid represent, in descending hierarchy, systems, summaries, synopses of syntheses, syntheses, synopses of studies, and studies. Systems refers to computerized decision support systems that combine the latest evidence with individual patient information to recommend the most appropriate clinical decision. Summaries refer to clinical practice guidelines and evidence-based texts. Synopses of syntheses refer to summaries of systematic reviews on specific topics. For the sake of efficiency and breadth, the "6S" model suggests that clinicians should start with systems and summaries first, before moving down the pyramid. Based on this model, referring to original studies to answer a clinical question should only be performed when no other sources of evidence exist.

Conclusion

Evidence-based medicine is a multistep process that requires familiarity with literature search methods, the knowledge to critically appraise the evidence, and an ability to interpret and apply the evidence to the specific clinical scenario. Clinicians should also be proactive in reviewing their own performance and seek opportunities for improvement. Proficiency in evidence-based medicine has the potential to improve patient care by ensuring that every clinical decision is made based on the synchrony of best evidence, medical expertise, and patient values.

To assist the reader in gaining familiarity with available evidence, the following rating system has been used to indicate key references for each chapter's content:
***: Critical material. Anyone dealing with this condition should be familiar with this reference.
**: Useful material. Important information that is valuable in in clinical or scientific practice related to this condition.
*: Optional material. For readers with a strong interest in the chapter content or a desire to study it in greater depth.

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Part I

General

2 Challenges and Opportunities for Evidence-Based Practice in Vascular Anomalies

Karthik Balakrishnan and Jonathan A. Perkins

In their very useful introduction to this textbook, C. Carrie Liu and Jennifer Shin describe evidence-based medicine as "the systematic search and evaluation of literature and then applying these findings to clinical decision-making." This succinct description is intuitively appealing to any clinician hoping to improve his or her own clinical decision-making, and the authors expand it into a discussion that will prove a valuable reference for any reader of this book.

This chapter takes the next step from that introduction, discussing several challenges faced by clinicians and scientists hoping to apply principles of evidence-based medicine to the diagnosis and management of patients with head and neck vascular anomalies. We hope that this chapter, and this textbook as a whole, inspires readers to see the opportunities that shine within these challenges, so that future patients may benefit from an ever-expanding pool of high-quality clinical and scientific evidence.

Three general obstacles to the practice of evidence-based medicine are discussed clearly by Mamdani et al. [1]. They are (1) the availability or lack of relevant evidence; (2) the work, time, and knowledge required to interpret evidence; and (3) figuring out how to apply evidence to clinical practice. We will discuss each of these here as it applies to the field of vascular anomalies; we will also present the reader with possible opportunities that stem from these obstacles. To communicate effectively we will rely on the International Society for the Study of Vascular Anomalies (ISSVA) vascular anomaly nomenclature, which is based on careful phenotypic analysis and emerging genetic discovery (Table 2.1). This table is available in more detailed form at http://www.issva.org/classification.

Lack of Relevant Evidence

In developing this textbook, we reviewed several thousand publications covering all major vascular anomaly diagnoses and reaching back over a decade. The results of that review led to two main observations with regard to the current evidence in vascular anomalies. First, very few high-level studies exist in this area. In their introduction, Drs. Liu and Shin mention that random-

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Table 2.1 ISSVA classification of vascular anomalies

Vascular anomalies				
Vascular tumors			Vascular malformations	
Benign	Locally aggressive	Malignant	Simple	Combined
Infantile hemangioma (Chap. 5)	Kaposiform hemangioendothelioma (Chap. 8)	Angiosarcoma (Chap. 12)	Capillary malformation (CM) (Chap. 18)	CVM, CLM
Congenital hemangioma (Chap. 6)	Retiform hemangioendothelioma	Epithelioid hemangioendothelioma	Lymphatic malformation (LM) (Chap. 19)	LVM, CLVM
Pyogenic granuloma (Chap. 7)	PILA/Dabska tumor		Venous malformation (VM) (Chap. 20)	CAVM
Tufted angioma (Chap. 8)	Composite hemangioendothelioma		Arteriovenous malformation (AVM) (Chaps. 21 and 22)	CLAVM
Spindle-cell hemangioma	Kaposi's sarcoma		Arteriovenous fistula	
Epithelioid hemangioma				

ized controlled trials are generally seen as the "gold standard for evidence." If these trials and well-conducted systematic reviews and meta-analyses are considered the highest-quality evidence, we can say confidently that high-level evidence is lacking in our field. The second observation is that where high-level studies do exist, they concentrate on a few diseases particularly infantile hemangioma; most other vascular anomaly diagnoses lack similarly high-quality evidence.

These observations will suggest specific opportunities to the attentive reader. First, this textbook itself is designed in part to promote awareness of the need for better evidence and awareness of the best evidence currently available. Second, vascular anomalies provide wide-open field for researchers to conduct rigorous, collaborative, multicenter, multidisciplinary studies. Several organizations are working to make these studies a reality; groups such as ISSVA (www.issva.org) and the American Society of Pediatric Otolaryngology's Vascular Anomalies Task Force (www.aspo.us) may be useful resources for interested readers. Similarly, many disease-specific groups and organizations provide funding and support for such studies. As a result, new avenues of investigation are steadily becoming available. These avenues include patient registries and tissue banks. In addition, newly validated tools such as the Lymphatic Malformation Function instrument [2] will provide investigators valuable ways to measure disease and outcomes, while standardized terminology [3] and outcome measures [4] will facilitate synthesis of future data.

Work, Time, and Knowledge Required to Interpret Evidence Appropriately

The second hurdle in the application of EBM principles to daily clinical practice is the sheer effort and knowledge needed to interpret and synthesize available evidence. Readers may benefit from close study of the introduction to this book, which provides an excellent overview of various common clinical study types.

Beyond this general foundation, detailed knowledge of, and experience in, the specific field of vascular anomalies is also essential. This piece may be more challenging to acquire. A recent survey of 36 senior otolaryngology residents and pediatric otolaryngology fellows demonstrated that the majority of respondents felt that their exposure to vascular anomalies in residency was not adequate (or nonexistent) and only half felt comfortable diagnosing specific

Table 2.2 Resources for readers to improve their general understanding of medical evidence

JAMA Users' Guides to the Medical Literature. https://jamaevidence.mhmedical.com
Hulley SB, Cummings SR, Browner WS et al. *Designing Clinical Research*, 4th edition. 2013. Lippincott Williams & Wilkins. Philadelphia, PA
www.cochrane.org
Please also see reference list from Chap. 1

anomalies or treating them [5]. In some cases, respondents even had a vascular anomalies clinic at their center but did not participate. Given that every trainee who responded felt that they would benefit from increased exposure to these diseases, the need for improved resident and fellow education in vascular anomalies seems clear.

Again, this apparent problem leads to specific opportunities for improvement. First, we recommend that any interested reader look to develop their own skills in assessing and applying medical evidence. Many resources exist for this purpose, including those detailed in Table 2.2.

Meanwhile, readers who wish to develop deeper knowledge in specific vascular anomaly diagnoses are of course invited to study the rest of this textbook. Beyond this volume, other resources are also available. ISSVA is developing a regularly updated list of key studies in vascular anomalies, while the ASPO Vascular Anomalies Task Force is also developing a list of key publications for use in training programs. Meanwhile, the Accreditation Council for Graduate Medical Education has recently included vascular anomalies in training milestones for plastic surgery residents and pediatric otolaryngology fellows (www.acgme.org). These developments may expand the pool of skilled and motivated researchers developing evidence in this field.

Figuring Out How to Apply Evidence to Clinical Practice

The final, and perhaps most daunting, obstacle facing clinicians is how exactly to apply the vast and diverse body of available evidence to daily clinical practice and to individual patients. Several issues arise here. First, the current literature is rife with heterogeneity, whether in terminology, patient selection, reported outcomes, or how those outcomes are measured. The reader is left to puzzle out how best to synthesize these studies, if such synthesis is even possible. Previous attempts at formal meta-analysis have often been hindered by this problem [6]. However, we expect that ongoing efforts to standardize reporting [4] and to develop multicenter collaborations will eventually mitigate this problem.

Second, apart from infantile hemangioma studies, the vascular anomalies literature generally lacks follow-up studies to confirm or refute previous results or to determine whether long-term outcomes remain consistent with short-term outcomes. As a result, clinical decision-making is often based on single studies or even single case reports rather than a consistently robust body of evidence. This situation presents obvious opportunities for interested researchers, particularly now that information technology has made multicenter collaborations and rare disease studies simpler and more practical.

Third, it is not clear how best to apply the existing evidence to an individual patient. In this area, we direct the reader to the idea of shared decision-making. Previous studies have suggested that treatment priorities vary between clinicians, patients, and parents [7], and recommendations exist for reporting goals of treatment [4, 8]. Other medical fields have addressed these issues by developing specific patient counseling and decision-making tools. Complex diagnoses such as vascular anomalies would certainly benefit from this approach, which integrates evidence-based medicine with careful consideration of the patient's individual priorities and values. As evidence develops in vascular anomalies, a key opportunity will appear to develop decision aids and patient resources to facilitate treatment decisions.

This textbook is intended to present and summarize the best current evidence in the field of vascular anomalies of the head and neck, even when meta-analyses and randomized controlled trials do not exist. We hope, however, that readers will be impressed by the opportunities that still exist throughout the field to improve both the

evidence behind the care we provide and the tools we might use to apply that evidence.

Specific Considerations in Vascular Anomalies Basic Science Research

Most vascular anomalies are rare, sporadically occurring conditions that until recently could only be classified with phenotypic description. Now with the completion of the Human Genome Project and the development of new and powerful automated molecular biologic and genetic investigative tools, these conditions are being characterized at the molecular and cellular level. This new information is allowing types of vascular anomalies to be distinguished from one another using biologic evidence. Recent developments in this ever-changing information will be presented in this book's chapters, as it provides a basis for development of biologically based novel therapies and treatment concepts that are revolutionizing vascular anomaly care. Automation of molecular biologic and genetic classification of vascular anomalies will enable affected individuals and families to have a personalized approach to their condition that was not possible in the past. A "personalized" approach will in turn greatly contribute to creating better evidence-based vascular anomaly treatment.

To assist the reader in gaining familiarity with available evidence, the following rating system has been used to indicate key references for each chapter's content:
***: Critical material. Anyone dealing with this condition should be familiar with this reference.
**: Useful material. Important information that is valuable in in clinical or scientific practice related to this condition.
*: Optional material. For readers with a strong interest in the chapter content or a desire to study it in greater depth.

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3 Molecular Genetics and Vascular Anomalies

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Methods of detecting the sequence of base pairs in DNA and RNA have rapidly changed over the past several decades [1–3]. These techniques are being applied to many human conditions, including vascular anomalies, and are changing our understanding of many human diseases [4–7]. Study of large biopolymers, such as proteins, RNA, and DNA, have centered on determining the sequence of molecules that create these long polymers [8]. DNA sequencing has progressed from smaller DNA molecules in bacteria to the much larger human genome [9–11]. Development of the possibility of sequencing single DNA and RNA molecules in real time (i.e., third-generation sequencing) is possible only through discoveries that have allowed biochemical sequencing (i.e., first-generation sequencing) to become automated (i.e., second-generation or next-generation sequencing). Automation of next-generation DNA sequencing enabled genome assembly in much less time and cost [2, 3]. This same automation has been applied to detect DNA sequence variation, which creates large datasets only analyzable with computational tools developed specifically for sequence data analysis [3, 12]. As our understanding of DNA has evolved, reference genome data has been created through an extensive body of work that can be used to detect genetic variation.

Changing the structure of a gene through alteration of a single base within the gene's sequence is a mutation. One of the molecular genetics goals is detection of change or variation within a given gene. Following the mapping of the human genome during the Human Genome Project, reference human genome data was available for use in the detection of human genetic variation using DNA sequencing [9, 11]. DNA encoded for translation into protein is called "exons," and all exons combined are the "exome." Sequencing of the whole exome (WES), which represents less than 1% of the whole genome, detects genetic variation in exons and has become common since it is reliable and relatively inexpensive. WES has been clini-

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cally used to identify genes causing mendelian disorders [13, 14]. Sequencing of the whole genome (WGS), including chromosomal and mitochondrial DNA, is also possible and is being used for research and the advent of "precision/personalized" medicine [2, 4]. WES and WGS have been used to sequence many individuals DNA, and it is now clear that the ability to sequence whole genomes can be done reliably and inexpensively [3]. The best example of this is non-invasive prenatal testing to detect variation between cell-free fetal and maternal DNA in the mother's blood [15]. What is often unclear is how to best interpret the data from this sequencing so that it has meaning in the clinical arena.

All of the sequencing techniques and computational innovations in molecular genetics have been used to detect genetic causes of rare conditions and de novo mutations. Vascular anomalies are rare conditions, and as a group of conditions, DNA sequencing has been used to identify causal genes for mendelian and nonmendelian anomalies (Table 3.1). One the earliest vascular syndromes of mendelian inheritance that had a genetic discovery in blood-borne cells was the autosomal dominantly inherited, hereditary hemorrhagic telangiectasia (HHT, Chapter) [16]. Since the discovery of endoglin, several other genes have been found to cause HHT, but even analysis of point mutations within these genes has not predicted a HHT patient's natural history [17–20]. WES or DNA microarray technology can be used to detect HHT causing genes in asymptomatic people with a family history of HHT or in symptomatic patients with de novo HHT gene mutation. Future study will hopefully provide evidence to help predict clinical behavior and prevent adverse outcomes [20]. More recently use of highly sensitive automated sequencing technology (i.e., WES, WGS, digital droplet PCR) has enabled the discovery of nonmendelian postzygotic somatic mutations in affected capillary and lymphatic malformation tissue [5, 21]. Current work is being done to understand how these genes are related to malformation phenotype and if biologic medical therapy could change the natural history of these malformations [6]. It is anticipated that better understanding of the biologic consequences of current and future genetic discovery is going to provide a biologic understanding and be the basis for new vascular anomaly treatments.

Table 3.1 Vascular anomaly classification of the international society for the study of vascular anomalies

Capillary malformations (CM)	
Cutaneous and/or mucosal CM (port wine stain)	GNAQ
CM with bone and/or soft tissue hyperplasia	
CM with CNS and/or eye anomalies (Sturge-Weber)	GNAQ
CM of CM-AVM	RASA1
Telangiectasia	
Hereditary hemorrhagic telangiectasia (HHT)	
HHT1	ENG
HHT2	ACVRL1
HHT3	
Others	
Cutis marmorata telangiectatica congenita (CMTC)	
Nevus simplex/salmon patch	
Lymphatic malformations (LM)	
Primary lymphedema	
Nonne-Milroy syndrome	FLT4A/EGRFR3
Primary hereditary lymphedema	VEGFC, GJC2
Lymphedema-distichiasis	FOXC2
Hypotrichosis-lymphedema-telangiectasia	SOX18
Primary lymphedema with mylodysplasia	GATA2
Primary generalized lymphatic anomaly	CCBE1
Microcephaly with/without chorioretinopathy	KIF11
Lymphedema or mental retardation syndrome	
Lymphedema-choanal atresia	PTEN14
Venous malformations (VM)	

Table 3.1 (continued)

Common VM	TIE2 somatic
Familial VM cutaneo-mucosal (VMCM)	TIE2
Blue rubber bleb nevus (Bean) syndrome VM	TIE2
Glomuvenous malformation (VM with glomus cells)	Glomulin
Cerebral cavernous malformation (CCM)	
CCM1	KRIT1
CCM2	Malcavernin
CCM3	PDCD10
Arteriovenous malformations (AVM)	
Sporadic	
in HHT	
HHT1	ENG
HHT2	ACVRL1
JPHT (juvenile polyposis hem. telangiect.)	SMADA4
CM-AVM	RASA1
Arteriovenous fistulas (AVF)	
Vascular malformations associated with other anomalies	
Klippel-Trenaunay syndrome	
Parkes Weber syndrome	RASA1
Servelle-Martorell syndrome	
Sturge-Weber syndrome	GNAQ
Limb CM + congenital non-progressive limb overgrowth	
Maffucci syndrome	
Macrocephaly – CM (M-CM or MCAP)	PIK3CA
Microcephaly – CM (MICCAP)	STAMBP
CLOVES syndrome	PIK3CA
Proteus syndrome	AKT1
Bannayan-Riley-Ruvalcaba syndrome	PTEN
Provisionally unclassified vascular anomalies	
Verrucous hemangioma	
Multifocal lymphangioendotheliomatosis with thrombocytopenia/cutaneovisceral angiomatosis with thrombocytopenia (MLT/CAT)	
Kaposiform lymphangiomatosis (KLA)	
PTEN (type) hamartoma of soft tissue/"angiomatosis" of soft tissue	PTEN

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Developmental Vascular Biology

4

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Introduction

Our understanding of molecular processes governing embryonic vascular development has largely come from in vivo and ex vivo studies using model organisms (laboratory mice, chick, and xenopus embryos) and in vitro studies using human umbilical vein endothelial cells (HUVECs) or human embryonic stem cell lines (hESCs). ESCs have the capability of differentiating into any of the three primary germ layers (endoderm, mesoderm, or ectoderm). These investigations have been foundational to concepts governing our understanding of vascular anomaly development and treatment. At this time it is being determined how much animal and in vitro cellular biology is directly relevant to clinical care of vascular anomalies.

This chapter focuses on findings from these foundational studies and points out how the cellular program varies between species.

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Development of the Circulatory System

Formation of the circulatory system in vertebrates follows two distinct phases: vasculogenesis describes the process by which endothelial cell progenitors develop into terminally differentiated endothelial cells, and angiogenesis is associated with budding and sprouting of preexisting capillaries to form new vascular beds. In humans, it is thought that both of these processes occur during embryogenesis as well as in the adult growth phase [12]. The lymphatic system develops later when cells begin to branch off from existing blood endothelial cells (BECs) after fluid begins circulating through the vessels. This process involves genetic reprogramming of BECs into lymphatic

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endothelial cells (LECs) and is associated with a change in the expression of cell surface markers and transcription factors regulating gene expression [13]. Similar to the process of angiogenesis, lymphangiogenesis directs the formation of new lymphatic vessels from existing ones.

Embryonic Vasculogenesis: Differentiation of Precursors into Endothelial Cells

Endothelial cells arise from mesoderm within the blood islands of the yolk sac and in the developing embryo itself. The mesodermal tissue differentiates into precursors known as angioblasts, and these cells terminally differentiate into endothelial cells [11, 12]. The first endothelial cells can be found in the blood islands within the yolk sacs in mice on embryonic day E7–7.5 and in humans on day 18 postfertilization [11]. The cell signaling governing mesoderm and angioblast formation in mice and humans is also different. Murine embryonic stem cells (mESCs) require BMP4 to differentiate into mesoderm. Further signaling from FGF2/bFGF instructs the mesoderm to differentiate into angioblasts [3]. Human ESCs require FGF2/bFGF for survival and growth in the undifferentiated state, but this growth factor does not appear to commit mesoderm to the endothelial lineage. Instead, signaling from Indian hedgehog (IHH) functions upstream of BMP4 to promote differentiation of mesoderm to endothelial cells [9]. IHH is also expressed by mESC, but its role in determining endothelial fate remains unclear. Murine embryos deficient in IHH still exhibit some degree of endothelial cell differentiation [9]. What is clear, however, is that differentiation of murine mesoderm to endothelial cells requires soluble factors from adjacent endoderm. This signaling enforces VEGFR2/Flt-1/KDR expression on the cell surface of angioblasts where the surrounding endoderm is the source for VEGFA, the ligand for VEGFR2 [4]. Embryos with one null VEGFA allele are not viable and display hugely disorganized vasculature. This phenotype could be rescued by ectopic VEGFA expression. Similarly, VEGFR2 knockout embryos are also not viable and demonstrate arrested vascular development halted at the blood island stage. These findings have been validated in murine, quail, and xenopus models. VEGF signaling also regulates endothelial cell proliferation and migration, processes that are critical for angiogenesis. This soluble factor functions synergistically with FGF2 [4].

Embryonic Angiogenesis: Extension of the Capillary Network

Angiogenesis is governed by endothelial cell migration and proliferation. Endothelial cells bud and branch off from existing vessel beds to extend the capillary network. This process is balanced by increased pro-proliferative signals from VEGF and FGF and decreased anti-proliferative signals mediated by reduced retinoic acid (RA) [7]. RA signaling induces expression of the cell cycle inhibitors p21 and p27, resulting in G1 arrest of endothelial cell proliferation [7].

In addition to molecular signaling by both soluble and transcription factors, mechanical forces exerted within the lumen of capillary beds also regulate angiogenesis. Hemodynamic forces resulting from turbulent blood flow causes shear stress, which promotes endothelial cell survival and proliferation [6]. Shear stress activates mechanoreceptors within the vessel walls. The best characterized mechanosensor is the endothelial cell-specific complex containing VEGFR2 or 3, PECAM1, and VE-cadherin. Mechanoreceptors sensing pulsatile shear stress induce phosphorylation of ERK1/2 in bovine aortic endothelial cells, and this is also associated with increased BrdU incorporation [6]. Laminar shear stress induces Tie2 phosphorylation in primary cultured human vein endothelial cells. Tie2 is a receptor tyrosine kinase that signals through PI3K to eventually produce nitric oxide. Endothelial-derived NO promotes endothelial cell survival [8].

Development of the Lymphatic Network

The lymphatic system develops from the venous system after the onset of circulation [13, 14]. In mice, this happens around embryonic day 9 when LEC progenitors can be seen branching off from the cardinal vein [14]. Initially these cells express the transcription factors SOX18 and COUP-TFII to initiate LEC identity. By day E9.5, these cells express PROX1, the LEC defining transcription factor. PROX1 is required throughout life to maintain LEC identity, and loss of PROX1 expression will result in dedifferentiation of LECs to blood endothelial cells (BECs) [5]. SOX18 and COUP-TFII, on the other hand, are expressed by BECs and LECs [15]. These two transcription factors work together to regulate PROX1 expression spatially and temporally, and the absence of either of these in murine embryos results in a failure of venous endothelial cells to acquire the LEC fate [2, 5]. The development of the lymphatic network is negatively regulated by BMP2 signaling, which inhibits PROX1 expression [9].

The majority of studies in human LECs have been, for obvious reasons, conducted in vitro. Studies on primary dermal LECs have implicated RA and its derivatives in activating proliferation, migration, and tube formation [1]. These findings were corroborated in vitro with mESCs and in vivo where xenopus embryos were exposed to exogenous RA [10].

Conclusion

While murine vascular development shares some similarities with in vitro experiments utilizing hESCs, a clear understanding of normal vascular development in humans can only be realized by using human samples. However, normal vascular development is difficult to study due to the unavailability of starting material to analyze. Systematic collection, storage, and unbiased molecular analysis of human vascular anomaly tissue can begin to address this issue, especially as we begin to appreciate the degree of cellular specialization in the human vascular network. If researchers can identify pathogenic variants in vascular anomaly tissue samples, this may point to critical factors governing vascular development that if altered contribute to vascular anomaly formation.

To assist the reader in gaining familiarity with available evidence, the following rating system has been used to indicate key references for each chapter's content:
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**: Useful material. Important information that is valuable in in clinical or scientific practice related to this condition.
*: Optional material. For readers with a strong interest in the chapter content or a desire to study it in greater depth.

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5 Interventional Radiology Services for Vascular Anomalies: An Update

Giridhar Shivaram, Kevin Koo, and Eric J. Monroe

Overview of Newer Approaches and Techniques

Interventional radiology procedures for the treatment of vascular anomalies have evolved over the last several years. Specifically, newer procedural imaging techniques and embolization materials have expanded the range of options for minimally invasive treatment. For example, preoperative embolization of venous malformations with n-BCA glue to aid in surgical resection has emerged as an effective alternative to traditional percutaneous sclerotherapy [1]. Imaging techniques have also evolved, for example, with the use of cone beam computed tomography (CBCT) adjunctively with angiography. This chapter will discuss these recent advances in interventional radiology for the treatment of vascular anomalies.

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New Diagnostic and Interventional Imaging Techniques for Evaluation of Vascular Malformations

CT and MR Angiography with Volumetric, Shaded Surface, and Time-Resolved Angiographic Displays

Preoperative computed tomography (CT) and magnetic resonance (MR) imaging are a mainstay in embolization and surgical planning for the treatment of vascular anomalies [2]. Characterization of lesion type, flow velocity, and lesion extent can all be accomplished with CT and MR angiography. Three-dimensional and shaded surface displays are often employed to assist in surgical planning (Fig. 5.1).

CT angiography has evolved in recent years from standard acquisition of axial images with coronal and sagittal reformations into more advanced applications of the technique. Multiphase acquisitions can be performed, delineating arterial and venous phases of lesional supply and drainage. With the use of dual energy CT, virtual noncontrast images can also be constructed [3]. Improvements in image post-processing have resulted in the ability to construct volumetric and shaded surface displays which can be invaluable to the interventionalist or surgeon in planning of

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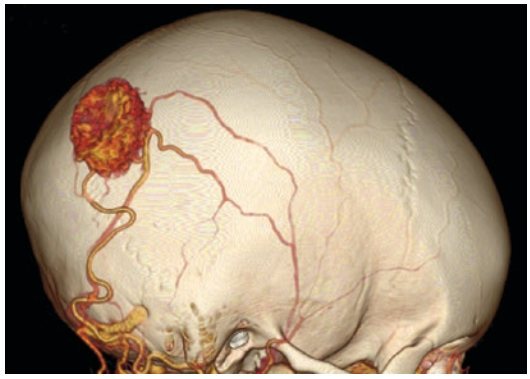

Fig. 5.1 3D shaded surface display of computed tomographic angiogram (CTA) of a 7-year-old female with a symptomatic scalp arteriovenous malformation (AVM). Supply into the AVM nidus is seen from the superficial temporal artery with occipital venous drainage. (Images courtesy of Seattle Children's Radiology, Giridar Shivaram, Eric Monroe and Kevin Koo)

embolization or surgical approaches to lesion removal. These shaded surface displays can be constructed to demonstrate different tissue layers, allowing the surgeon to virtually "peel back" tissue layers in formulating an approach to resection. For the interventionalist, creating accurate multiplanar reconstructions can greatly aid in treatment planning, for example, in calculating sclerosant volume to fill a lymphatic malformation. The angioarchitecture of complex arteriovenous malformations can also be better assessed with these types of reconstructions.

MR angiography has similarly evolved. The specific advantage of MR angiography is the ability to create multiple time-resolved rapid acquisitions, allowing the creation of rich multiplanar display of phases of lesion opacification, such as through the use of the time-resolved angiography with stochastic trajectories (TWIST) algorithm [4]. MR angiography is the workhorse for evaluation of most vascular anomalies, as soft tissue contrast is paramount in differentiating tissue plane involvement (Fig. 5.2). It also has the advantage of avoiding the ionizing radiation required for CT examinations. Some drawbacks of MR studies include long examination times, often requiring the use of general anesthesia in younger patients, and the development and maintenance of complex imaging protocols.

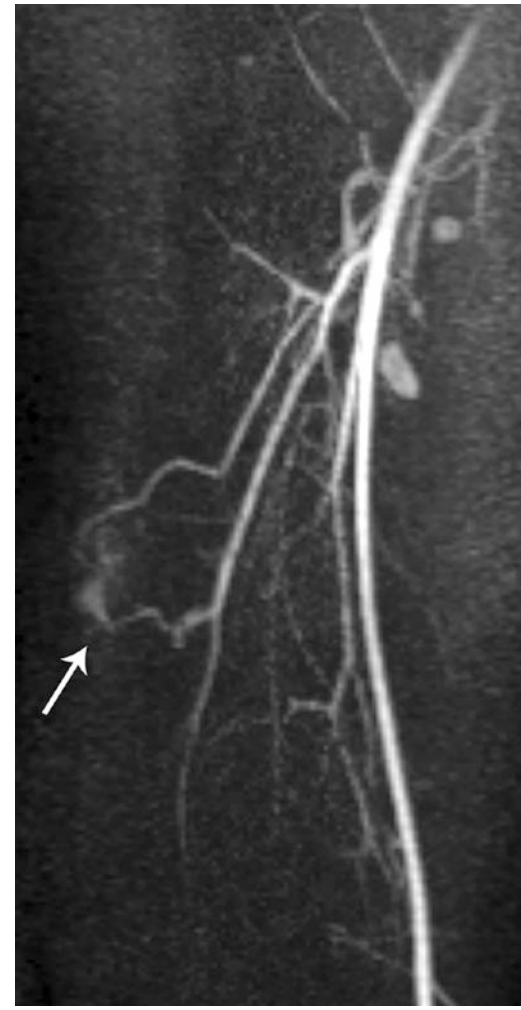

Fig. 5.2 Time-resolved, subtraction maximum intensity projection coronal TWIST image from magnetic resonance angiogram (MRA) in a 17-year-old female with a symptomatic thigh AVM. The small subcutaneous right thigh arterial venous malformation (*arrow*) is seen with a single feeding artery from the descending lateral circumflex artery and a single small draining vein. (Images courtesy of Seattle Children's Radiology, Giridar Shivaram, Eric Monroe and Kevin Koo)

After acquisition, CT and MR angiographic images can be imported into the angiographic workstation and used as overlays during the angiographic procedure for lesion targeting [5]. This process, known as multimodality matching, requires accurate coregistration of anatomic landmarks and must be used with caution when there is significant difference in field of view or patient

orientation during image acquisition. For patients in whom iodinated contrast administration for conventional angiography is limited by patient size or renal injury, overlay of CT or MR angiograms onto 3D CBCT rotational angiograms can provide a virtual roadmap for intervention.

In summary, advanced CT and MR angiographic techniques are essential for treatment planning and even intraprocedural considerations for the management of complex vascular anomalies.

3D Rotational Catheter Angiography

Three-dimensional angiographic images can be acquired using cone beam CT during intravascular contrast injection. When acquired during intravascular contrast injection, these images can be reformatted into volumetric shaded surface vessel map displays as well as conventional multiplanar CT images [6]. As an alternative technique, previously acquired CT or MR angiographic images can be overlaid onto CBCT images, providing a virtual 3D roadmap. This can be useful in the setting of limited contrast volume availability for smaller patients. With both of the techniques described above, roadmap navigation can be performed for tortuous or difficult anatomy, for example, in the embolization of cerebral arteriovenous malformations.

Intraprocedural Cone Beam CT

Using a similar approach as described above,cone beam CT acquisitions can be performed during the interventional procedure [7]. A useful application of this technique is following embolization for delineation of embolic material placement. Shaded surface displays can be created from these images, which can be beneficial when the lesion is immediately resected in the operating room (Fig. 5.3). Cone beam CT has recently been shown to offer potential dose reduction compared to conventional CT [8]. In fact, conventional CT-guided interventional procedures have been almost entirely supplanted in the author's practice by cone beam CT guidance. CBCT has not only the advantage of dose reduction but also allows the interventionalist to remain in the angiography suite for the entire procedure, providing for the use of adjunctive catheter-based techniques. CBCT navigation systems are available on most angiographic systems, allowing for overlay of CBCT images onto orthogonal fluoroscopic projections, providing real-time needle guidance.

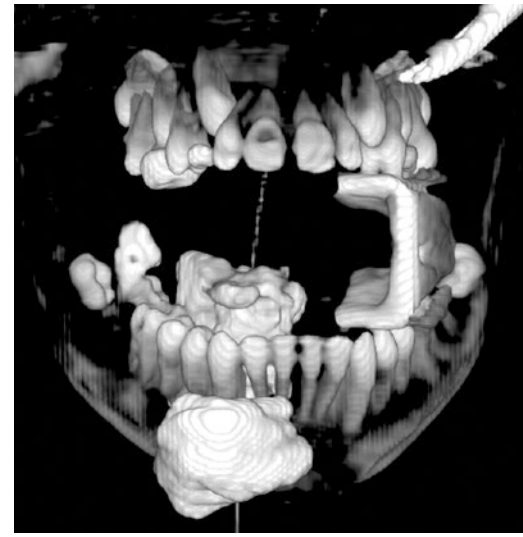

Fig. 5.3 12-year-old male with chin and floor of mouth venous malformation who underwent preoperative n-BCA glue embolization. Post-embolization cone beam CT with 3D shaded surface reconstruction shows deposition of embolic glue material within both locules of the venous malformation. (Images courtesy of Seattle Children's Radiology, Giridar Shivaram, Eric Monroe and Kevin Koo)

Venous Malformations

Sclerotherapy: Newer Agents

A variety of liquid embolization agents are available for percutaneous sclerotherapy of venous malformations. Traditionally, ethanol or sodium tetradecyl sulfate (STS) has been used to induce endothelial damage within the channels of venous malformations [9]. With regard to STS, a detergent sclerosant, a foam preparation is used to provide adequate volume for lesion filling as well as

to ensure adequate dwell time within the lesion. More recently, other sclerosing agents have become available which may have the advantage of diminishing adjacent tissue inflammation. These include polidocanol, a nonionic detergent with local anesthetic properties, and bleomycin, a non-ribosomal chemotherapeutic agent [10]. Other agents are used outside of the USA, including picibanil (OK-432), which is a lyophilized mixture of group A streptococcus pyogenes [11].

Percutaneous Glue Embolization of Venous Malformations Adjunctive for Surgical Resection

As an alternative to percutaneous sclerotherapy, intralesional injection of n-butyl cyanoacrylate glue can be performed for adjunctive surgical resection [1]. This approach can be used as a secondary technique in the setting of failed sclerotherapy or stand-alone resection or can be employed as a primary treatment modality. Potential advantages of this technique include more complete lesion elimination as embolized channels are completely removed from the body and diminished blood loss at the time of surgical resection (Fig. 5.4). As percutaneous sclerotherapy commonly involves multiple procedures, this technique can avoid repeated anesthetics that may be associated with the former approach.

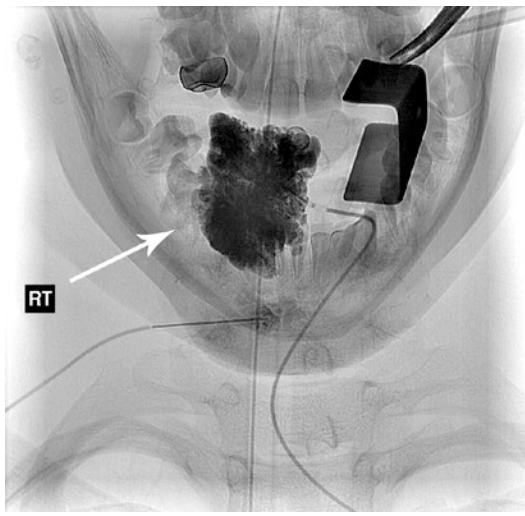

Fig. 5.4 12-year-old male with chin and floor of mouth venous malformation. Post-embolization frontal spot image showing n-BCA glue deposition within the lesion (*arrow*). (Images courtesy of Seattle Children's Radiology, Giridar Shivaram, Eric Monroe and Kevin Koo)

Percutaneous Thermal Ablation

Compared with sclerotherapy, thermal ablation for the treatment of venous malformations is a technique that has been shown renewed interest despite falling out of favor in previous years. Though the data is derived from relatively small numbers and mostly for lesions outside the head and neck, radiofrequency ablation (RFA) and cryoablation (CA) have both shown efficacy in symptom relief particularly in those patients that have failed sclerotherapy with conventional agents, such as bleomycin or STS. In 2015, Garg et al. reported a small case series of five patients with head and neck venous malformations which did not respond to sclerotherapy with bleomycin despite multiple treatments [12]. Intralesional RFA was performed on these patients with reported 80% reduction in lesional volume. Similarly, in 2013 Cornelis et al. reported on the use of CA in a case series of four patients who had symptoms from venous malformations refractory to sclerotherapy. At 6 months post-ablation, all four patients reported complete resolution of symptoms.

While the mechanism is unclear, thermal ablation likely causes localized endothelial injury leading to thrombosis and eventual fibrosis. This in turn leads to decrease in bulk and symptom relief. Further research is likely needed to establish more widespread use of this treatment modality, but early results show that it can be an important adjunct to the current armamentarium for the treatment of venous malformations.

Lymphatic Malformations

Sclerotherapy: Overview of Agents

Sclerotherapy for lymphatic malformations is similar to sclerotherapy for venous malformations in that the goal of sclerosant instillation into the lesion is to cause endothelial injury and eventual fibrosis [1]. While almost all agents that are

used for treatment of venous malformations can be used for lymphatic malformations, the authors' preference is to use a dilute (10 mg/mL) solution of doxycycline, a tetracycline family antibiotic that has an excellent risk profile and is usually very effective in the treatment of lymphatic malformations. Other agents, including ethanol and STS can be employed. For lesions in the head and neck, especially periorbital, bleomycin is often used as it generally results in less soft tissue inflammation [13]. For larger lymphatic malformations, percutaneous access with a drainage catheter is usually used, allowing for sequential treatment for greater therapeutic effect. Usually, lesions with cysts greater than 2 cm in maximal dimension, typically classified as macrocystic lesions, are treated with percutaneous sclerotherapy. Microcystic or more solid-appearing lymphatic malformations are usually not amenable to injection of liquid sclerosant.

Percutaneous Thermal Ablation for Microcystic/Solid Lesions

For more solid or microcystic types of lymphatic malformations, surgical excision is often a first-line approach. However, as was described above for venous malformations, percutaneous thermal ablation has been reported in for treatment of these lesions. Data are emerging for this indication; however, additional investigation is required to determine the feasibility and durability of this approach.

Hemangiomas and Other Vascular Tumors

Transarterial or Percutaneous Embolization Techniques

Infantile hemangiomas (IH) are the most common vascular tumor of infancy. Most IH undergo spontaneous regression or respond to systemic administration of propranolol. However, large hemangiomas, head and neck hemangiomas, or other types of pediatric vascular tumors may require surgical excision [14]. This is usually accomplished as a stand-alone procedure with operative hemostasis achieved with standard techniques. In select cases, however, where the lesion is large or where the arterial supply to the tumor is complex, resection can be facilitated by preoperative transarterial embolization. This can be done the day prior to surgery or immediately before, under the same general anesthetic. Control angiograms are performed to exclude important pathways of nontarget embolization. Following this, occlusion of feeding tumoral vessels can be performed using a variety of particulate, mechanical, or liquid agents. Complete embolization of a lesion can dramatically reduce operative blood loss and make definition of surgical margins easier.

Conclusion

In conclusion, interventional radiology approaches for the management of vascular tumors and malformations have evolved in recent years. More advanced pre- and intraprocedural imaging have allowed for more precise targeting of lesions. A variety of newer embolization materials have increased options for treatment, including preoperative n-BCA glue embolization of venous malformations. Finally, newer interventional therapies are also becoming available, most notably percutaneous thermal ablation for venous and lymphatic malformations.

To assist the reader in gaining familiarity with available evidence, the following rating system has been used to indicate key references for each chapter's content:
***: Critical material. Anyone dealing with this condition should be familiar with this reference.
**: Useful material. Important information that is valuable in in clinical or scientific practice related to this condition.
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Part II

Vascular Tumors

6 Vascular Tumors: Infantile Hemangioma

Graham Strub, Robert Sidbury, and Nancy Bauman

Genetic diagnosis	No
Genetic etiology	Unknown
Level of evidence: treatment	Strong
Evidence	Randomized controlled trials, meta-analyses

Diagnosis

Phenotype and Variations

Infantile hemangioma (IH), also known as hemangioma of infancy, is the most common soft tissue tumor of childhood. IH demonstrate significant clinical heterogeneity in their presentation, ranging from small self-limiting lesions to bulky tumors that impart significant morbidity. IH can present as superficial, deep, or mixed lesions depending on the depth of soft tissue involvement [1, 2]. Most lesions are superficial, presenting as bright red papules or plaques which are typically round and involve the superficial dermis, while deep lesions have a more bluish hue; mixed lesions have characteristics of both. The morphological pattern of IH tends to be localized or segmental [2, 3]. Localized lesions tend to be discrete ovoid or rounded lesions, while segmental lesions, which impart higher risk of complications, tend to involve a broad region and are more geometric in shape.

Most reports identify the head and neck as the most commonly affected anatomical site for IH, although a recent prospective study suggested the trunk was the most common location [4]. Head and neck IH tend to lead to specific complications depending on the particular anatomic subsite involved and the morphologic pattern of the lesion; the majority are focal and appear to form along primitive ectodermal and mesenchymal fusion lines [5]. Focal periorbital IH can cause astigmatism, strabismus, or deprivation amblyopia if left untreated. Focal lesions in the preauricular area may involve the parotid gland; while the facial nerve is spared in these lesions, it is at risk during resection or corticosteroid injection. Focal lesions involving the ears, lips, nasal tip, forehead, and cheek are cosmetically disturbing (Fig. 6.1) and may benefit from intervention in an effort to reduce the social impact of these lesions during preteen years [6]. IH can also occur in the

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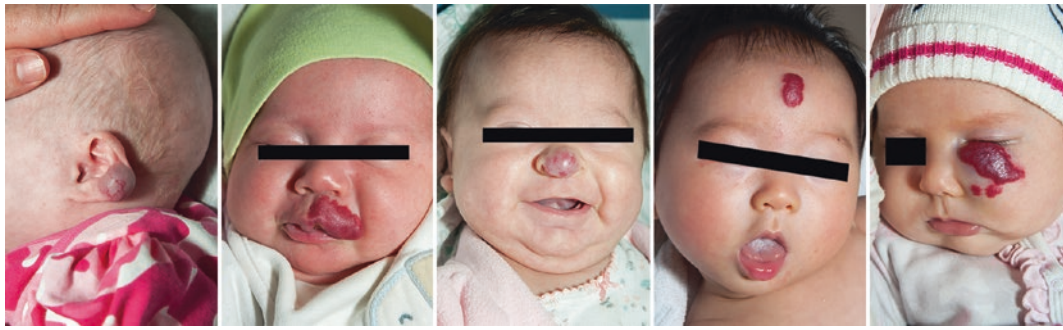

Fig. 6.1 Focal infantile hemangioma of the ear, nose, and forehead and segmental of the upper lip and cheek. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

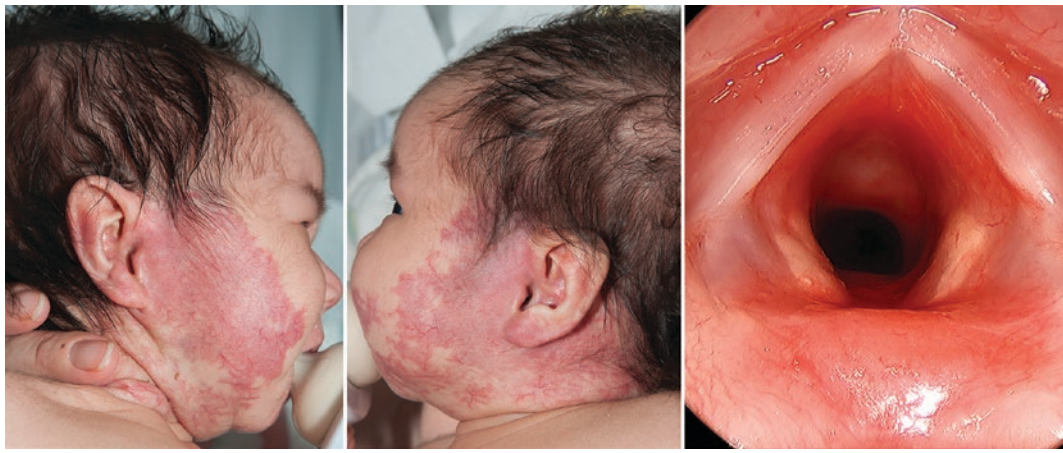

Fig. 6.2 Segmental infantile hemangioma of segment 3 with microlaryngeal view of treated airway infantile hemangioma. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

airway, predominantly in the subglottis, and can lead to symptomatic or life-threatening respiratory compromise.

Segmental IH of the head and neck tend to have a diffuse appearance but do not exactly correlate with a particular dermatome. Segmental head and neck IH are associated with both a higher incidence of ulceration and occult visceral hemangiomas involving the liver and GI tract [7]. Segmental IH found in a "beard" distribution (involving the preauricular area, chin, lower lip, and neck) are associated with an increased incidence of subglottic airway hemangiomas and should prompt the clinician to consider subglottic hemangioma in infants presenting with this pattern, particularly in infants with breathing or feeding concerns (Fig. 6.2) [8, 9]. The presence of a large, plaque-like segmental facial IH is often a component of the neurocutaneous syndrome PHACES (an acronym for *p*osterior fossa malformation, *h*emangioma, *a*rterial anomalies, *c*ardiac defects, *e*ye abnormalities, and *s*ternal malformations). A prospective study of 1096 children with hemangiomas found that 2.3% met criteria for PHACES, representing 20% of children in the study with facial segmental hemangiomas, and that the location of the hemangioma could predict the pattern of associated abnormality. Hemangiomas of the upper half of the face, particularly the temporal area (Fig. 6.3), were associated with brain, cerebrovascular, and ocular anomalies, while hemangiomas of the mandibular region were associated with sternal anomalies [10].

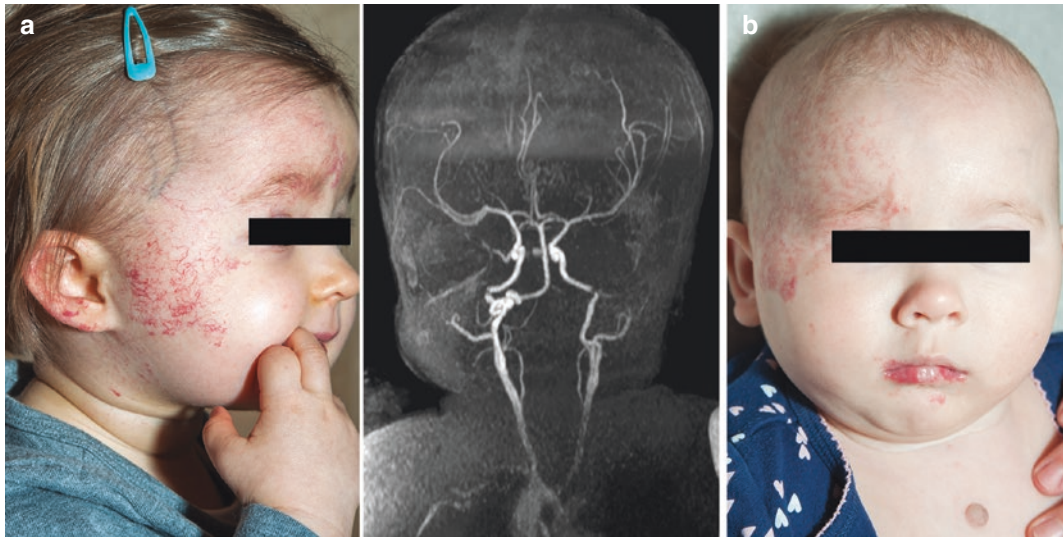

Fig. 6.3 PHACE syndrome associated segmental infantile hemangioma (**a**, **b**) with intracranial arterial abnormalities (patient A). Note the sternal muscular hamartoma (**b**) associated with partial sternal cleft. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer). (Images courtesy of Seattle Children's Radiology, Giridar Shivaram, Eric Monroe and Kevin Koo)

Etiology

The precise etiology of IH remains under investigation, and several mechanisms have been proposed to explain IH pathogenesis including placental origin, hemangioma-derived progenitor cells, hypoxic environment, neural crest/pericyte stem cells, and metastatic niche [11].

A large body of evidence supports the hypothesis that IH form from an endothelial stem cell or progenitor cell. Endothelial cells isolated from IH are clonal [12], and CD133+ hemangioma progenitor cells (Hem-SCs) isolated from IH tissue recapitulate the histological and behavioral characteristics of IH when injected into nude mice [13]. These cells represent ~1% of the IH cell population and are capable of de novo vessel formation, self-renewal, and give rise to several cellular lineages [13–16]. In vitro, Hem-SCs form "tumorspheres" from which differentiated derivatives originate, leading to the hypothesis that IH originates from a dysregulated but not fully transformed multipotent stem cell [17].

There is also evidence to suggest that IH may be of placental origin. The characteristic growth pattern of IH is similar to that of placenta (rapid growth for 9 months, followed by a static period followed by involution), and IH share several specific cell surface markers with placental tissue [18] including the glucose-1-transporter (GLUT-1). Subsequent molecular profiling analysis determined that the transcriptome of IH is more similar to placenta than any other human tissue [19]. Proliferating endothelial cells in IH express human chorionic gonadotropin (HCG) and human placental lactogen (HPL) [20] similar to placental tissue. More recently, the C19MC microRNA cluster was found to be highly expressed in IH endothelial cells and detectable in the circulation of IH patients [21]. C19MC microRNAs are normally expressed in placental trophoblasts and stromal cells and released into fetal and maternal circulation [22, 23]. The detection of C19MC microRNAs in the circulation of IH patients was a distinguishing feature of IH among nine other tested vascular anomalies [21].

While some of the molecular and genetic similarities between IH and placenta may be explained by progenitor cells differentiating toward a placental phenotype, the progenitor cell hypothesis does not account for several other observations. The risk of IH was found to be ten-

fold higher in children of women who underwent chorionic villus sampling, suggesting placental trauma or embolization may play a role in IH development [24]. IH is also significantly associated with maternal placental anomalies including preeclampsia, placenta previa, intrauterine growth restriction, and placental abruption [4]. These observations support a link between hypoxia and the development of IH. IH can initially present as a region of pallor due to vasoconstriction, and IH lesions can exhibit central necrosis which represents a hypoxic environment [25, 26]. Furthermore, IH formation occurs more commonly near facial placode fusion sites, which have an "end artery" vascular supply and are relatively hypoxic when compared to surrounding tissues. Mihm et al. have proposed a "metastatic niche" hypothesis of IH development, whereby the placenta secretes factors into circulation which prime recipient tissues and would presumably favor these "dead-end" locations due to their relatively high concentration of humoral factors and tumor cells [27].

Once formed, IH demonstrate consistent histological findings. Proliferating lesions consist of tiny clusters of endothelial-lined capillaries, supporting pericytes, myeloid cells, mast cells, macrophages, and fibroblasts [28, 29]. Several studies have identified markers shared between IH endothelium and placental endothelium, including GLUT-1, merosin, Lewis Y antigen, F-cγRIIb, type III iodothyronine deiodinase, indoleamine 2,3-deoxygenase, insulin-like growth factor 2 (IGF2), and the C19MC microRNA cluster [18, 21, 30–36]. As IH naturally involute over time, the percentage of GLUT-1 and C19MC expressing endothelial cells decreases [21, 37], and the densely packed regions of endothelial cells are gradually replaced with fibrofatty tissue. This histologic shift results in the typical phenotypic change of enlarging, bright red tumors to paler, scar-like lesions.

Natural History

IH are rarely present at birth, though there may be erythema or blanching in the region of their eventual growth. They tend to occur more frequently in females (2.4:1), fair-skinned infants, premature infants, siblings of infants with IH, and infants of multiple gestations [38, 39]. Advanced maternal age, placenta previa, and preeclampsia are also prenatal factors that associate with a higher incidence of IH [38].

IH typically demonstrate a predictable growth pattern: a proliferative phase, during which the lesion grows rapidly during the 1st year, a stationary or plateau phase, and a gradual involution phase. During the first 3 months of life, IH proliferate rapidly. They continue to grow for a period of approximately 1 year [40], with the majority of growth occurring in the first 5 months. Deeper and segmental lesions tend to have longer proliferative phases than local, superficial lesions [41]. Following the proliferative phase, the majority of IH enter a period of variable time during which their size stabilizes. This is followed by "involution," during which the lesion decreases in size, transitions from firm to soft and compressible, and changes color from bright red to purple/gray. Although parents are often comforted by anticipated involution, the process is rarely complete, and residual loose fibrofatty scar tissue often replaces the original hemangioma.

It is during the proliferative phase that the morbidity associated with pain, bleeding, ulceration, airway compromise, visual, and disturbance is at its highest. The likelihood of complications arising from IH increases with the size of the lesion [42], and specific complications tend to cluster with specific IH locations (Table 6.1) [40, 43].

Treatment

Propranolol

Propranolol is a nonselective β-adrenergic blocker that has been used in children and adolescents for the treatment of hypertension, hypertrophic cardiomyopathy, hyperthyroidism, and migraine since 1964 [45]. In 2008, Leaute-Labreze et al. observed regression of IH lesions in patients who underwent propranolol treatment for obstructive

Table 6.1 Locations at risk for complications from infantile hemangioma

Location	Associated risk
Periorbital and retrobulbar	Visual axis occlusion, astigmatism, amblyopia
Nasal tip, ear, large facial	Cosmetic disfigurement, scarring
Perioral, lip	Ulceration, feeding difficulties, cosmetic disfigurement
Perineal, axilla, neck	Ulceration
Beard distribution, central neck	Airway hemangioma
Liver, large	High-output heart failure
Large facial ("segmental")	PHACE syndrome (see text)
Multiple hemangiomas	Visceral involvement (liver, gastrointestinal tract most common)
Midline lumbosacral	*SACRAL*[44], *s*pinal dysraphism, *a*nogenital, *c*utaneous, *r*enal, and urologic abnormalities associated with *a*ngioma of *l*umbosacral localization)

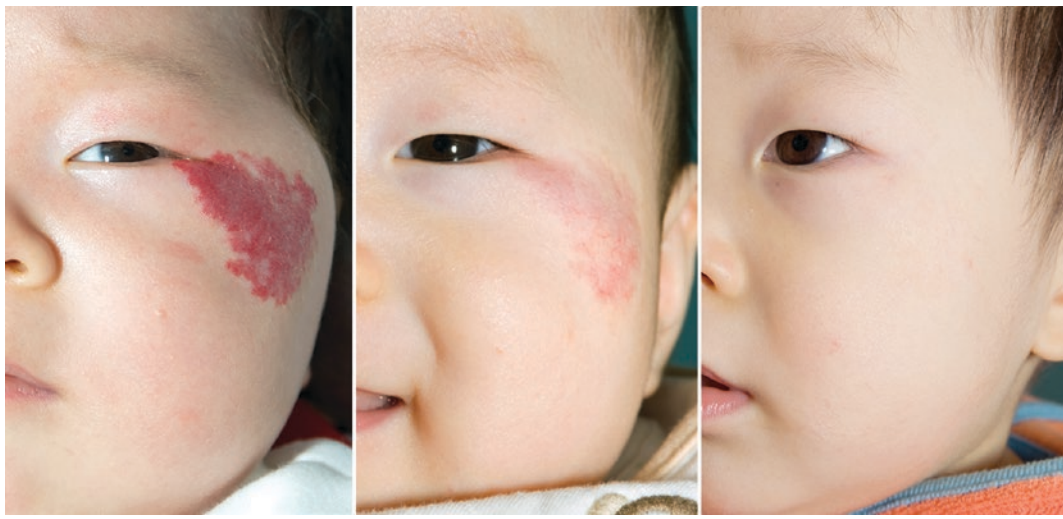

Fig. 6.4 Excellent complete response to propranolol therapy in focal infantile hemangioma on the cheek. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

hypertrophic myocardiopathy [46]. Since that time, propranolol has become first-line treatment for IH, and a multitude of case series [47–49] and placebo-controlled trials [50, 51] have supported the observation that propranolol administration leads to IH regression (Fig. 6.4). A large randomized controlled trial by Leaute-Labreze et al. concluded that 3 mg/kg/day (2 mg/kg/day being the most common dosing) of oral propranolol was safe and effective in treating IH [52]. Several meta-analyses have concluded that propranolol is the most efficacious treatment modality compared to all other treatments for IH [53–57].

The precise mechanism by which propranolol leads to IH regression is still under investigation; hypotheses include stimulation of pericyte-mediated vasoconstriction, inhibition of vasculogenesis, inhibition of catecholamine-induced angiogenesis, induction of apoptosis of IH endothelial cells, prevention of stem cell differentiation, downregulation of proangiotic cytokines, and inhibition of the renin-angiotensin system [58, 59].

Adverse events from appropriately administered propranolol treatment have been relatively minor in studies that have reported side effects during IH treatment. Propranolol decreases heart

rate and blood pressure, although episodes of significant bradycardia and hypotension were infrequent and asymptomatic [60]. Beta-blockers may predispose infants to hypoglycemia, and rarely symptomatic hypoglycemia and hypoglycemic seizures have been reported in infants with IH treated with propranolol. The majority of these incidents occurred during a concomitant illness and/or with poor oral intake. Propranolol directly blocks adrenergic bronchodilation and can lead to bronchospasm. It should be discontinued in the setting of acute viral illness [61] and is relatively contraindicated in the setting of reactive airway disease [62]. Other minor side effects including diarrhea, sleep disturbances, and cold hands/feet have also been reported [52].

Recent consensus statements have emerged regarding indications, contraindications, pretreatment evaluations, dosing, monitoring, and duration of therapy [62, 63]. In summary:

- Propranolol treatment is indicated in patients presenting with ulceration, impairment of a vital function, or risk of permanent disfigurement.
- Relative contraindications include cardiogenic shock, sinus bradycardia, hypotension, greater than first-degree heart block, heart failure, bronchial asthma, history of hypoglycemia, and allergy to propranolol.
- Pretreatment ECG is recommended in patients with bradycardia, a family history of congenital heart condition/arrhythmia, a maternal history of connective tissue disease, or if the patient has a history of arrhythmia or one is detected during physical exam.
- Initiation of propranolol in patients with PHACE and co-existing cardiac and aortic arch abnormalities should be done in consultation with cardiology and neurology practitioners to minimize risk of stroke and should start at the lowest possible dose with slow upward titration in an inpatient setting.
- The target dose should be between 1 and 3 mg/kg/day divided into three doses with a minimum of 6 h between each dose.
- Heart rate and blood pressure should be recorded at 1 and 2 h after the initial dose.
- To prevent hypoglycemia, propranolol should be administered with a feeding shortly after administration and should be held in the setting of acute illness or any circumstances which compromise oral intake.

Corticosteroids

Prior to the discovery of propranolol-induced IH regression, corticosteroids (typically prednisolone 2–5 mg/kg/day) were the mainstay of nonsurgical therapy. The precise mechanism of steroid-induced IH regression remains under investigation but likely involves inhibition of vasculogenesis, downregulation of vascular endothelial growth factor A (VEGF), suppression of nuclear factor κ-light-chain enhancer of activated B cells (NF-κβ activity), and estrogen antagonism (reviewed by Greenberger et al. [59]). The response of IH to corticosteroids is variable, with reported rates between 30% and 60%, primarily characterized as stabilization or incomplete regression rather than resolution [64–66]. Corticosteroid therapy is associated with a variety of adverse effects including cushingoid facies, personality changes, gastric irritation, sleep disturbances, adrenal suppression, immunosuppression, hypertension, bone demineralization, cardiomyopathy, and fungal infection [64, 67–69]. Intralesional and topical steroids have been reported to decrease the size of small and localized IH [70]. Intralesional triamcinolone dosing of 3–5 mg/kg/treatment has been the most effective, although repeated injections are often necessary and should be avoided in periocular IH due to the risk of central retinal artery occlusion. Complications of intralesional steroids include skin atrophy and necrosis.

Pulsed Dye Laser (PDL)

The mechanism of action of PDL is selective thermolysis, targeting vascular structures while minimizing injury to the surrounding dermis

and epidermis [71, 72]. Retrospective and meta-analyses have demonstrated that the most efficacious laser therapy with the lowest side effect profile is the long-pulsed pulse dye laser (LP-PDL) with wavelength 595 nm [73, 74]. The efficacy of PDL is limited by its depth of penetration; it is more useful on relatively flat hemangiomas, residual vascular changes following involution with or without propranolol treatment, and in treating ulcerated IH [75–77]. Newer fractionated CO_2 lasers have shown promise in treating the fibrofatty remains of IH.

Interferon and Vincristine

For lesions unresponsive to other treatment modalities, vincristine and interferon-α have been shown to be effective in several case reports [78–80]. Vincristine, a vinca alkaloid chemotherapeutic agent, inhibits microtubule formation and has anti-angiogenic properties. It is administered through central venous access at 0.05–1.5 mg/kg once per week, every 1–3 weeks, for three to four doses [79]. Side effects include neurotoxicity with a wide range of clinical manifestations, as well as leukopenia and anemia. Interferon-α is a potent anti-angiogenic agent with a severe side effect profile including irreversible spastic diplegia, particularly when administered to infants under 1 year of age [81]. It is therefore no longer recommended in the treatment of IH.

Surgical Excision

Surgical excision is an option for lesions amenable to resection without damaging vital structures and for which scarring would not cause significant morbidity. In addition, lesions which have not responded or partially responded to other treatment modalities are frequently excised. Surgery also remains a primary treatment option for patients whose parents do not wish to undertake the risks associated with systemic therapies.

To assist the reader in gaining familiarity with available evidence, the following rating system has been used to indicate key references for each chapter's content:
***: Critical material. Anyone dealing with this condition should be familiar with this reference.
**: Useful material. Important information that is valuable in in clinical or scientific practice related to this condition.
*: Optional material. For readers with a strong interest in the chapter content or a desire to study it in greater depth.

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Congenital Hemangiomas

7

Megha M. Tollefson

Genetic diagnosis	Partial
Genetic etiology	Somatic activating, GNA 11 and GNAQ
Level of evidence: treatment	Low
Evidence	Case series, case reports

Diagnosis

Phenotype and Variations

Congenital hemangiomas (CHs) are uncommon vascular tumors that are typically present at birth. These are distinct from infantile hemangiomas (IHs), which may be present in precursor form at birth or develop shortly after birth, followed by a period of proliferation and then gradual involution; IHs are the most common tumor of infancy. By contrast, CH does not typically grow postnatally and usually presents as a red-purple vascular tumor with overlying telangiectasias and a surrounding pale halo (Fig. 7.1) [1].

Historically, CH have been divided into two main groups, rapidly involuting congenital hemangioma (RICH) and non-involuting congenital hemangioma (NICH). The distinction between RICH and NICH cannot be made at birth but rather hinges on the natural history of the lesion, as RICH will usually involute by 1 year of age, while NICH does not regress (Fig. 7.2) [2].

Recently it has been increasingly recognized that there are some congenital hemangiomas that involute part of the way, but not all of the way. These have been termed partially involuting congenital hemangiomas [3]. One recent study found about 7% of all congenital hemangiomas to be partially involuting [3].

Congenital hemangiomas present anywhere on the skin but are most common on the head, neck, and limbs [1]. Fully grown at birth, they are usually raised, warm, solitary vascular masses that have overlying telangiectasia and a peripheral rim of pallor, although multiple lesions have been described [4]. Ulceration is rare but may be present, particularly with higher flow lesions [5]. They can vary in size from several centimeters to greater than 20 cm (Fig. 7.3). NICH and RICH usually look very similar at birth, although NICH may be less exophytic than RICH. While congenital hemangiomas are not typically associated with other anomalies, one case of PHACE association has been reported in a baby with a RICH [6].

CH is usually diagnosed clinically. In situations where the diagnosis is unclear, imaging and biopsy may be helpful. For imaging, ultrasonography and magnetic resonance imaging (MRI) are the most helpful. On ultrasound, both

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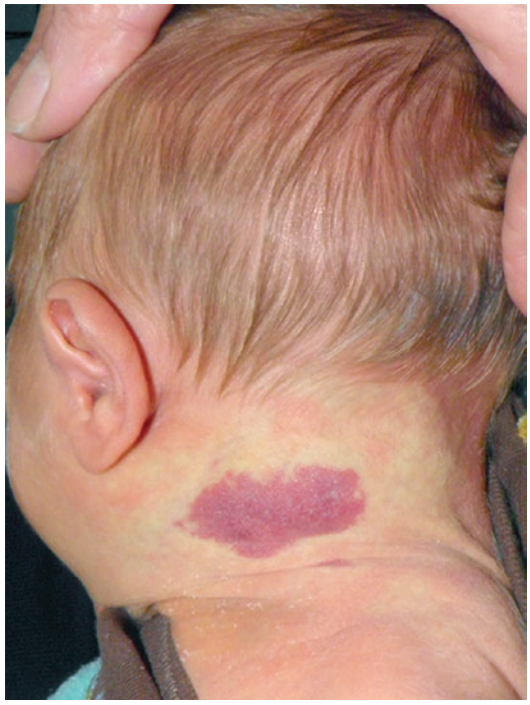

Fig. 7.1 RICH at birth. Note the vascular tumor with a peripheral rim of pallor and overlying telangiectasia. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

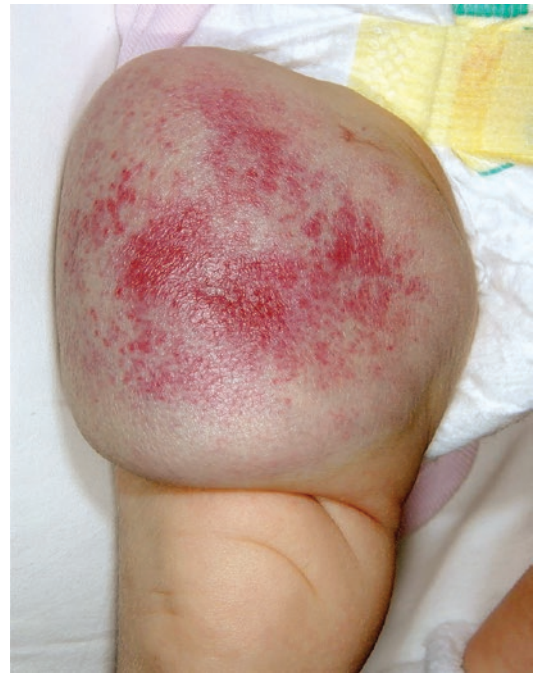

Fig. 7.3 Large RICH on the leg of a neonate

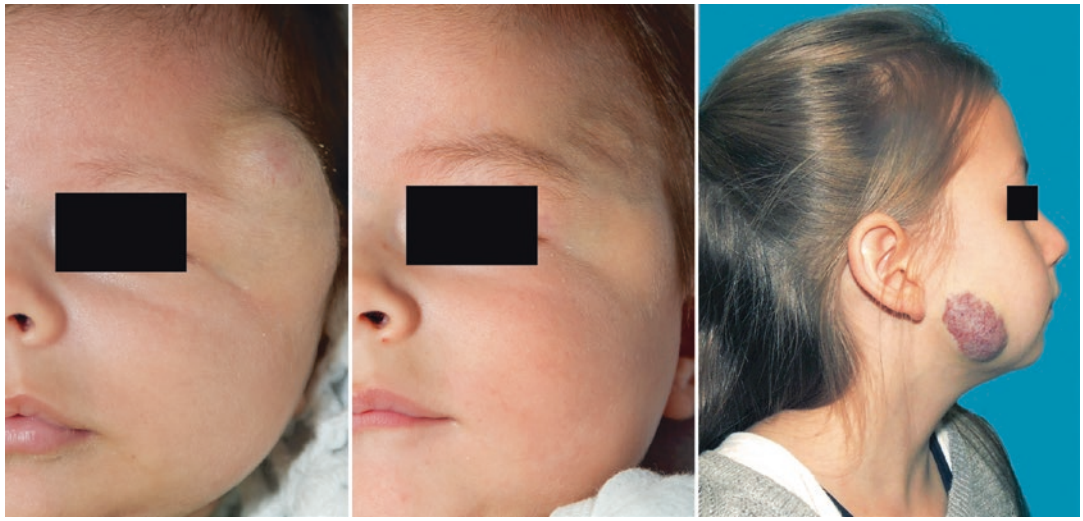

Fig. 7.2 RICH on left pre- and post-involution. On right NICH. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

NICH and RICH are well-circumscribed heterogeneous echogenic masses with visible vessels, calcifications, and high flow [7]. While usually diagnosed at or shortly after birth, occasionally, large CH may be diagnosed in utero on prenatal ultrasound [1, 8]. MRI is often not needed for diagnosis, but when done, features include homogeneous enhancement, fat stranding, and flow voids, although all features may not be seen in all CH [7].

The differential diagnosis for congenital hemangiomas includes other vascular tumors and malformations including infantile hemangiomas, venous malformations, and lymphatic malformations, as well as nonvascular tumors, both benign and malignant. If the diagnosis is still unclear after clinical exam and imaging, lesional biopsy may be helpful.

On histopathology, CH is composed of large lobules of small, thin-walled sometimes tortuous vessels with one or more larger central draining channels [1]. Vessels may have hobnailed endothelial cells and endoplasmic cytoplasmic inclusions with foci of hemosiderin, as well as intraluminal thrombus [1, 9]. Active RICH and NICH have similar histologic features, although the lobules of RICH may be smaller; after regression, there is often scar-like change seen histologically [9]. Special stains may be used to help solidify histologic diagnosis, the most useful of which is the glucose 1 transporter (GLUT-1). CH may be distinguished from infantile hemangiomas (IHs) on the basis of GLUT-1 staining; IH universally stains positive for GLUT-1 while all CHs (RICH, NICH, and partially involuting CH) are GLUT-1 negative [1, 10–12]. Endothelial cell staining is positive for Wilms tumor 1 (WT1) in all vascular tumors, including both IH and CH [10].

Etiology

As recently discovered to be the case with many vascular malformations, somatic mutations have long been theorized as the cause of CH. Until recently, a candidate gene mutation has been elusive; however, somatic activating mutations in GNA11 and GNAQ have recently been found in several CHs, both RICH and NICH, thus suggesting that there are factors other than genetics that influence the natural history in these lesions [4, 13]. Unlike IH, no risk factors have been identified for the development of CH.

Natural History

Congenital hemangiomas may involute or persist. RICH will often start to involute within a few days to weeks after birth [14]. The majority of those that will involute have completed involution by 12–14 months, although fetal involution has been reported [15]. Upon involution, the skin is usually left with an area of anetoderma or skin atrophy but will have normal blood flow (Fig. 7.4) [1]. In contrast, NICH is persistent and does not involute, growing proportionately with the child.

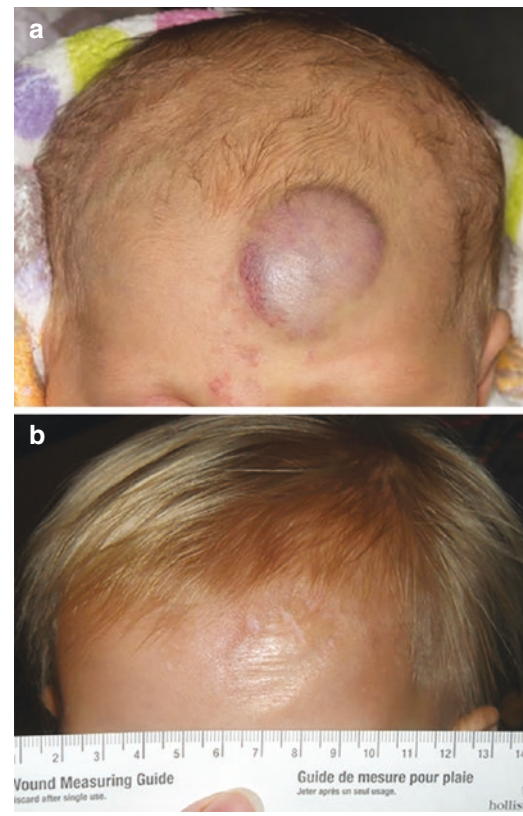

Fig. 7.4 (**a**) Forehead RICH at birth. (**b**) Anetoderma and mild atrophy at location of involuted RICH

In a NICH, blood flow remains high within the lesion, and in some cases, this high flow may lead to changes such as ulceration and scar [11]. In the recently described partially involuting subtype, many will undergo partial involution in the first 18 months of life, followed by stabilization and long-term growth proportionate to the child [3].

Thrombocytopenia and coagulopathy are well-known complications of some vascular tumors, specifically kaposiform hemangioendothelioma and tufted angioma. These are not typical complications in CH; however, transient thrombocytopenia and coagulopathy, as well as resulting problems with bleeding, may occur in RICH; this has never been reported in NICH [16, 17]. The thrombocytopenia and coagulopathy may be profound, rarely even leading to signs of high-output heart failure, similar to that seen in Kasabach-Merritt phenomenon; however it is usually self-limited and improves as the RICH involutes [16, 18]. When described, this phenomenon usually takes place in infants who have large RICH lesions [16, 17].

Treatment

Treatment of CH is usually based upon size and location of the lesion, its natural history, and whether or not complications are present. Uncomplicated RICH generally do not require any treatment other than regular active observation, as they involute spontaneously without complication. They may leave residual telangiectasia, which may be effectively treated with a vascular laser such as the pulsed dye laser if desired by the patient and family. Anetoderma or skin atrophy may also be present after involution; active treatment is generally not required for this, but if desired surgical treatment may be helpful. RICH should be observed for signs and symptoms of ulceration, bleeding, and coagulopathy; in these situations, active treatment may be necessary. In cases of ulceration, diligent topical wound care and pain control should be pursued.

All NICH and partially involuting CH will be persistent unless otherwise treated, but many may not require active treatment, especially if smaller and thinner in size. Smaller and thinner NICH may also be amenable to treatment with a vascular laser.

Surgical excision is a common treatment for CH of all types, particularly those that are larger or thicker and do not involute. Surgical excision is also commonly considered in lesions with persistent ulceration, coagulopathy, bleeding, or hemodynamic instability, even with RICH, as those complications may require urgent treatment [16]. Embolization may be a useful and effective treatment in CH, particularly in those with complications of hemorrhage or cardiac failure, and may also be used adjunctively with surgical removal [5, 16, 18].

Systemic corticosteroids are generally regarded to be ineffective in the treatment of CH. However, steroids have been used in patients with RICH complicated by thrombocytopenia and coagulopathy [16, 17, 19]. While many of these patients did improve while receiving this treatment, involution of the RICH was usually simultaneously seen, thus making it challenging to determine if the improvement in clinical status was spontaneous or due to the medical treatment. Nevertheless, in acute, life-threatening situations of thrombocytopenia and coagulopathy or high-output heart failure, use of systemic corticosteroids should be strongly considered due to the relatively low risk and high potential benefit. Systemic beta-blockers are generally felt to be ineffective in the treatment of CH but may be beneficial if an associated arrhythmia is present [17, 20].

To assist the reader in gaining familiarity with available evidence, the following rating system has been used to indicate key references for each chapter's content:
***: Critical material. Anyone dealing with this condition should be familiar with this reference.
**: Useful material. Important information that is valuable in in clinical or scientific practice related to this condition.
*: Optional material. For readers with a strong interest in the chapter content or a desire to study it in greater depth.

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8 Pyogenic Granuloma (Lobular Capillary Hemangioma)

Kate Khorsand and Deepti Gupta

Genetic diagnosis	No
Genetic etiology	Unknown
Level of evidence: treatment	Medium
Evidence:	Case series, comparative trials

Diagnosis

Clinical Features

Pyogenic granulomas (PG), also known as lobular capillary hemangiomas based on their histopathologic appearance, are commonly acquired, benign vascular tumors arising in both children and adults [23]. Both names are used synonymously in the literature. PG are classified as a benign vascular tumor [36] by the International Society for the Study of Vascular Anomalies (ISSVA). These growths present as rapidly growing, exophytic, pedunculated red papules. PG often have an epidermal collarette of scale present as a marker of its rapid growth. They often bleed easily and profusely, ulcerate, and very rarely spontaneously regress. PG are found in all ages, commonly occurring on the head and neck in children [25, 42]. In adults, the most common location is the trunk, with the exception of pregnant women for whom mucosal pyogenic granulomas are more common [15]. In both children and adults, there is a slight male predominance [15, 42]. PG have rarely been reported in other locations such as intravascularly [4, 32], larynx [9], intraocular [10], subcutaneous [11], and within the spinal cord [1, 16]. Histologically, PG appear as a lobular proliferation of capillaries in the superficial dermis with cytologically bland endothelial cells set in a loose stroma. Immunohistochemical endothelial staining is GLUT-1 negative, distinguishing PG from an infantile hemangioma.

PG are usually solitary, without associated abnormalities [41]. Disseminated PG have rarely been described, in adults and children, with less than 20 reported cases throughout the literature, several of which were congenital [3]. Some authors advocate for distinguishing disseminated and congenital entities given their distinct clinical presentations, despite having similar histopathologic features to PG, and propose the term "PG-like congenital and disseminated angiomatosis" [22]. There are case series of acquired multiple PG that form post trauma, specifically burns. Medications can increase the risk of developing a PG including chemotherapeutic agents, such as capecitabine [27], 5-fluorouracil [5], and

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docetaxel [6]; antiretroviral agents, such as indinavir [2]; retinoids (i.e., isotretinoin) [28]; BRAF inhibitors [29]; EGFR inhibitors [30]; and also rarely levothyroxine and anti-TNF alpha antagonists [17, 26]. Pregnancy is a known risk factor, and lesions are known as pyogenic granuloma of pregnancy or granuloma gravidarum. The gingiva is commonly affected in 2% of women between the 2nd and 5th months of pregnancy [18]. Unlike other PG, these often undergo spontaneous improvement following delivery. PG have also been reported to develop within preexisting vascular anomalies (i.e., capillary and arteriovenous malformations) and near sites of arteriovenous anastomoses [21, 33].

Etiology

The underlying etiology and pathogenesis of the PG is unknown. Angiogenic and hormonal etiologies have been hypothesized. Whole exome sequencing and transcriptional profiling of PG tissue suggest some causal mutations. BRAF (1799 T>A) and NRAS (c.182A>G) mutations were identified in PG tissue which secondarily arose within capillary malformations, with the same BRAF mutation only identified in endothelial cells of 3 of 25 PG which occurred sporadically. It was concluded that BRAF mutations, specifically 1799 T>A, may lead to development of a secondary PG [14]. Identification of heterozygous KRAS and NRAS mutations in PG tissue samples, and subsequent identification of somatic RAS mutations in 10% of archived lesional samples, suggests that PG development is associated with vascular proliferative and angiogenic pathways [19]. Genome-wide transcriptional profiling of PG tissue identified gene signatures possibly linked to the nitric oxide pathway and FLT4 pathways associated with angiogenesis [13].

Natural History

Due to tendency of pyogenic granulomas to bleed easily they are rarely left without treatment.

Fig. 8.1 Ulcerated bleeding lobular hemangioma. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

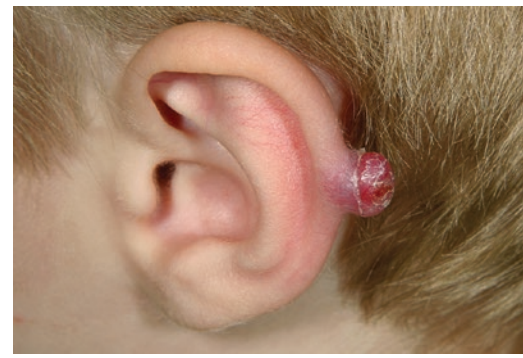

Fig. 8.2 Lobular hemangioma of helical rim. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

Disseminated pyogenic granuloma sometimes spontaneously resolve [3] as has been observed in pregnancy once delivery has occurred. In children with solitary PG, 4.5% spontaneously regressed over a period of 6–18 months [42]. However, given that PG tend to grow, persist, and bleed, treatment is usually pursued by the patient or family (Figs. 8.1 and 8.2).

Treatment

Numerous treatments have been used for PG including excision, curettage, electrodessication, punch excision, cryotherapy, laser therapy, topical beta-blockers, imiquimod, other topical agents such as silver nitrate, and combinations of

the above. The primary treatment risks include PG persistence, patient discomfort, and scar formation. It is important to note that some management options allow histopathologic diagnosis. This is important when the differential diagnosis includes non-benign entities, such as amelanotic melanoma or other cutaneous malignancy.

Surgical Excision

Traditionally, the most definitive PG treatment is elliptical excision of the entire lesion. This is associated with low recurrence rates [7, 31] but requires a more involved procedure, and excision results in a linear scar, which may not be desirable [7]. Excision allows histopathologic confirmation of the diagnosis.

Curettage and Punch Excision

Curettage of the entire PG followed by punch excision of the central vascular stalk is a recently described technique for PG management [7]. It involves curettage of the bulk of the lesion, with specimen preservation for histopathology. Then, a 3 mm punch biopsy tool is used to excise the feeding vascular stalk of the lesion. Comparing this technique with surgical excision, at 2-month follow-up, there was no difference in recurrence between groups. Clinicians blinded to the initial treatment were unable to detect a scar in 72% of the patients who underwent the curettage and punch excision, whereas all patients who underwent traditional surgical excision had visible scar at 2 months after treatment.

Curettage and Electrodessication

Curettage and electrodessication is another PG management technique [38]. Curettage of the entire pyogenic granuloma is followed by electrodessication of the base and central feeding vessel. Curettage and electrodessication has high response rates. Comparing curettage and electrodessication to cryotherapy resulted in PG resolution after one treatment in 97% of patients having curettage and electrodessication [12, 40]. In 69% of the patients, there were no reported scar or pigmentation abnormalities seen after treatment. Diagnostic confirmation by histopathology is possible with this technique.

Shave Excision and Electrodessication

Another treatment modality is PG shave excision and electrodessication of the base and large central feeding vessel [20, 42]. This method also has high response rates with low recurrence rates. In one study, 55% of the patients treated with shave excision and electrodessication reported only subtle scars with minimal pigmentation abnormalities, and none had patient reported recurrence [42]. Histopathologic confirmation of diagnosis is also possible with this technique.

Cryotherapy

Cryotherapy involves the use of one or multiple treatments with liquid nitrogen for PG destruction. Risks of therapy include scar and posttreatment hypo- or hyperpigmentation as cryotherapy affects epidermal melanocytes. In one study of management with cryotherapy, there was complete resolution of the lesion after an average of 1.58 treatments (range 1–4) with 3-month follow-up [24]. Reports of hypopigmentation and/or scar range from 5% to 58% in different studies [12, 24]. There may be variability in the degree of surrounding tissue treated as there can be significant operator dependence for this technique. Cryotherapy does not allow histopathologic diagnosis.

Laser Therapy

A pulsed-dye laser, 595 nm, is a PG treatment option either as a monotherapy or in combination with other topical therapies. This technique can be considered when the PG is in a cosmetically sensitive area. One study found that PG less than 5 mm

required on average 1.8 treatments until resolution, whereas larger PG, 5–10 mm in size, required an average of 2.7 treatments [34]. Recurrence was not assessed in this study, and treatment with laser didn't allow histopathologic diagnosis. There are also a few reports reporting use of the long-pulse Nd:YAG, 1064 nm, and CO2 ablative laser with good efficacy. These lasers, given the deeper penetration, may have higher rates of scarring and procedure-associated pain.

Topical β-Adrenergic Receptor Antagonists

The use of topical beta-blockers, such as timolol, has been explored for PG treatment, particularly in the pediatric population where procedural management options can lead to increased pain and anxiety. A case series of patients treated with topical timolol ophthalmic solution 0.5% showed partial response in all patients at 2 months, with resolution of bleeding in all patients for whom this was a presenting symptom [37]. While topical beta-adrenergic blockade is not as effective as other management options and requires a longer course of treatment than other modalities mentioned above, it could be considered in patients who are averse or unable to tolerate procedural treatments.

Imiquimod

Topical imiquimod has been used to treat PG, particularly in the pediatric population [39]. Imiquimod is an immune modulator through toll-like receptor 7 with subsequent activations of the cutaneous immune system. It is commonly utilized to treat warts in children and superficial basal cell carcinoma or actinic keratoses in adults. One case series of children with facial PG treated with topical imiquimod 5% cream, resulted in complete resolution in three of ten patients and partial resolution with a small hypopigmented or erythematous lesion in five of ten patients [35]. The remaining patients had either a prolonged course of treatment or eventually underwent surgical removal. There were no recurrences at 9.6 month follow-up, and no systemic side effects. An additional case series of five patients treated with topical imiquimod 5% cream resulted in resolution of the lesion with residual erythematous or hypopigmented macules in all patients [8]. Treatment with imiquimod does not allow for histopathologic diagnosis but is a painless treatment in patients who do not wish to undergo procedural management.

To assist the reader in gaining familiarity with available evidence, the following rating system has been used to indicate key references for each chapter's content:
***: Critical material. Anyone dealing with this condition should be familiar with this reference.
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9 Tufted Angioma and Kaposiform Hemangioendothelioma

Deepti Gupta, Amy Geddis, and Robert Chun

Genetic diagnosis	No
Genetic etiology	None known
Level of evidence: treatment	Low
Evidence:	Case series, expert opinion

Diagnosis

Tufted angiomas (TA) and kaposiform hemangioendothelioma (KHE) are classified as benign vascular tumors with locally aggressive potential. They share many similar histologic and clinical features and are believed to be two entities that lie along a spectrum [1, 2]. Within the same tumor, there are focal areas of both KHE and TA histopathologic phenotype, and longitudinal transformation from TA to KHE has been described [3]. A unique feature of these tumors is their potential to develop a severe, life-threatening coagulopathy called Kasabach-Merritt phenomenon (KMP).

TA are slow-growing vascular tumors that develop predominantly during infancy or childhood but can occur at any stage of life [4]. They tend to be smaller in size and more localized to the epidermis and dermis. They have less risk of developing KMP and long-term musculoskeletal sequelae and may spontaneously resolve [5]. KHE can infiltrate deeper structures including bone, muscle, and fascia, extend to adjacent viscera and lymph nodes, and are associated with a higher risk for KMP. Tumors may decrease in size or become dormant over time, but do not completely disappear (Fig. 9.1).

Clinical Features

There are four main presentations for KHE/TA: (1) fulminant KHE with KMP in the neonate/young infant, (2) large cutaneous/noncutaneous KHE/TA with KMP, (3) KHE/TA without KMP, and (4) TA with chronic coagulopathy without thrombocytopenia [2]. KMP is associated with a mortality rate as high as 30%; thus, when findings of coagulopathy are present, they should prompt immediate treatment [6–9].

TA has variable clinical presentations ranging from deep red to purple papules or plaques

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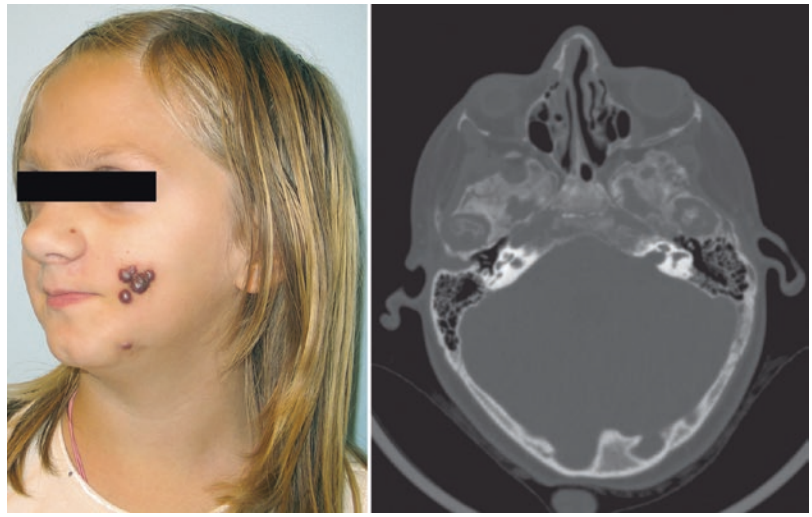

Fig. 9.1 KHE of face and infratemporal fossa with skull base invasion and bone loss causing repeated bouts of meningitis. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer). (Images courtesy of Seattle Children's Radiology, Giridar Shivaram, Eric Monroe and Kevin Koo)

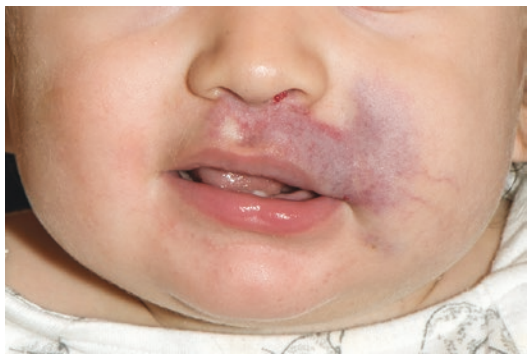

Fig. 9.2 Tufted angioma on the upper lip and cheek of an infant. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

or an indurated vascular stain with ill-defined borders (Fig. 9.2) [10]. There can be associated hypertrichosis with increased lanugo hairs and/or hyperpigmentation present. They enlarge slowly over time and are often warm and tender to touch.

KHE typically presents as a solitary, indurated, ill-defined, red-purple plaque in infancy or early childhood. They can have a nodular appearance, be warm to touch, have associated hypertrichosis or hyperhidrosis, and can have accompanying ecchymoses and telangiectasias. They can rapidly enlarge within weeks and have recurrent episodes of engorgement, swelling, pain, and purpura [11]. Multifocal KHE lesions have been reported, especially within the bone [12], but metastatic disease has not been observed. KHE has a predilection for the extremities but also occurs on the head and neck, trunk, and groin. KHE may also present in noncutaneous locations such as the retroperitoneum, mediastinum, and bone, and there have been reports of extension into adjacent viscera from these locations. The signs and symptoms of this vascular tumor are dependent on the extent of tumor and the tissue layers involved; for example, when KHE infiltrates muscle and fascial layers, there can be reduction in range of motion with risk of contracture development [13]. Visceral organ involvement in KHE is uncommon but portends a more severe clinical course. KHE is typically diagnosed in small children, with >90% of cases being apparent within the first year of life; identification of KHE in adults is being more commonly reported. Tumors in this setting tend to be less invasive and have not been associated with thrombocytopenia or coagulopathy thus far. Even after successful treatment, some amount of mass typically remains, and there is often some residual disease manifesting as skin discoloration, fibrosis, and occasionally lymphedema [14].

Kasabach-Merritt Phenomenon

TA and KHE can potentially develop Kasabach-Merritt phenomenon (KMP) [15, 16]. KMP presents with profound thrombocytopenia thought to result from intralesional platelet trapping typically accompanied by coagulopathy as evidenced by elevation in d-dimer, slight prolongation of PT and aPTT, and reduction in fibrinogen levels. The thrombocytopenia in KMP can be profound, generally with platelet counts less than 50,000/uL. In one large series, the median platelet count reported was 11,500/uL [6].

KMP is distinct from the coagulopathy that can accompany other vascular anomalies (e.g., venous malformation) that more closely resembles disseminated intravascular coagulation with a marked decrease in fibrinogen, prolongation of PT and aPTT, and a comparatively mild reduction in platelet count. KMP can arise in any patient with a lesion within the KHE/TA spectrum but is much more common with earlier onset of the tumors in the neonatal and infant setting and with KHE. Predictors of KMP include age and size and location of lesion. The proportion of infants who develop KMP is much higher than that of older children. KMP has not yet been reported in adult-onset KHE. The size and extent of the lesion has been correlated with increased risk of KMP; lesions >8 cm in greatest diameter and lesions involving muscle, bone, and the thoracic cavity are at increased risk [6, 7]. Although most patients manifest KMP at the time of presentation, 11% developed KMP later, generally within the first year after diagnosis. Changes such as, rapid lesion growth, deepening color, increasing firmness, and pain, should prompt a reevaluation for KMP.

Evaluation

The goal of TA/KHE evaluation is an accurate diagnosis and detection of KMP. This is accomplished with hematologic tests, imaging, and tissue biopsy if needed. Complete blood count will detect anemia and thrombocytopenia and a coagulation panel (PT, PTT, fibrinogen, and D-dimer) to identify a coagulopathy [9]. Imaging is important to evaluate lesion characteristics and extent. Magnetic resonance imaging (MRI) with and without gadolinium is the imaging modality of choice. MRI shows a diffusely enhancing T2 hyperintense infiltrate as well as decreased T1 signal with ill-defined margins (Fig. 9.3a, b) [17]. There may be subcu-

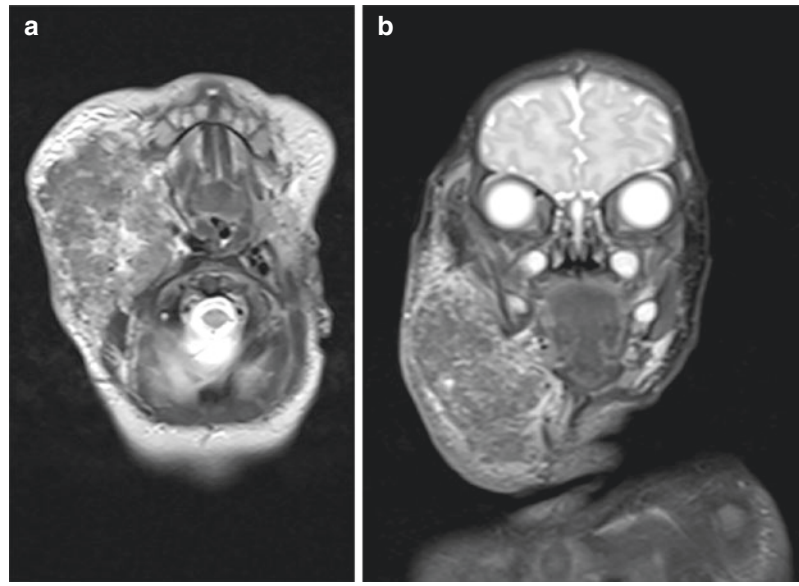

Fig. 9.3 (**a**, **b**) MRI of a cervical KHE demonstrating the diffusely infiltrative nature of KHE, which makes clear margins difficult to obtain

taneous thickening, infiltrative margins into adjacent muscles and structures, and high flow vessels. Gadolinium-enhanced images demonstrate significant enhancement of the lesion. Understanding of the extent of the KHE/TA lesion will help inform treatment decision-making. CT can evaluate and characterize bone involvement, which is important in head and neck lesions, while ultrasound can demonstrate the intralesional flow characteristics (Fig. 9.1). Tissue biopsy is not always required for diagnosis if clinical appearance and imaging are characteristic, especially if KMP is present. Involved tissue, whether deep or superficial, has a characteristic appearance of irregular nodules with infiltrating growth leading to a dense hyaline stromal response [18]. The nodules of KHE/TA frequently coalesce and are formed by tightly packed capillaries focally accompanied by fascicles of moderately plump spindled lymphatic endothelial cells with eosinophilic-to-clear cytoplasm and bland nuclei that form elongated, slit-like lumina containing erythrocytes, reminiscent of Kaposi's sarcoma (Fig. 9.4) [19]. Lumina containing platelet-rich microthrombi are easily found, and the spindled cells often curve around epithelioid nests that are rich in pericytes surrounding the microthrombi [18, 19]. Most tumors are full of thin-walled lymphatic vessels that stain negatively for GLUT-1 [20, 1, 18, 21]. KHE endothelial cells are positive for CD31, CD34, and FLI 1 in spindled areas as well as well canalized areas of KHE [18, 21]. Notably, the spindled endothelial cells of KHE also express lymphatic endothelial markers including podoplanin (recognized by the D240 antibody), LYVE-1, and PROX1, which is useful for histopathologic diagnosis.

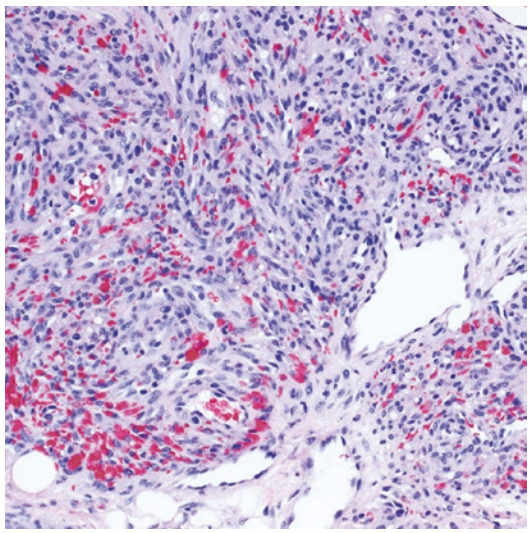

Fig. 9.4 Histopathology of Kaposiform Hemangioendothelioma Courtesy of Dr. Paula North

Treatment

Treatment considers the clinical features of TA/KHE present, extent of involvement, presence of KMP, symptoms, and location to determine the best modality of therapy [22]. Generally accepted indications for initiating treatment include KMP, pain, or functional compromise due to an enlarging tumor. Treatment of lesions involving muscle or crossing joints may be appropriate in the hopes of reducing late complications of atrophy or contracture, although whether or not treatment reduces development of these late complications is an unresolved question.

Surgical Intervention

Complete KHE surgical resection, when possible in localized lesions, is curative. However, complete surgical resection may be impossible, especially when there is KMP and wide infiltration into surrounding structures. In cases of KHE with KMP, severe coagulopathy and associated hemorrhage may worsen with surgical resection [17]. When medical management fails to treat KHE, there may be a role for partial surgical resection or when lesions are imminently life-threatening and medical treatment response is slow [23]. Preoperative embolization may increase success of surgical resection by decreasing blood loss and preservation of normal tissues.

Radiation/Image-Guided Therapy

Intravascular embolization is used as an adjunct to surgical resection, since it does not have lasting benefit as a primary modality [17]. In severe or life-threatening cases prone to hemorrhage, arterial embolization may serve a temporizing role

until medical therapy becomes effective. Radiation therapy has no role in TA/KHE treatment.

Pharmacologic Treatment

There are no prospective studies to guide TA/KHE medical management.

Corticosteroids and Vincristine

If KHE is not accompanied by KMP, then corticosteroids alone (oral prednisolone 2 mg/kg/day or the IV equivalent) are appropriate as starting therapy [9]. Corticosteroid monotherapy is not recommended for KMP [24]. Consensus guidelines recommend corticosteroids combined with vincristine infusion 0.05 mg/kg/week for KMP [25, 26, 9, 27]. Vincristine has been reported to be effective in improving KMP and reducing tumor size [25, 28]. The average time to hematologic response is 7.6 weeks (standard deviation of 5.2 weeks) [28]. Treatment duration is based on individual response, with a goal to wean steroids after 3–4 weeks and stop vincristine after 20–24 weeks. Other combination regimens incorporating vincristine for KHE management include vincristine with aspirin and ticlopidine [29] and vincristine with sirolimus [30]. Combination therapy attempts to reduce corticosteroid side effects. Common side effects associated with vincristine include constipation, peripheral neuropathy, and SIADH.

Sirolimus

Sirolimus has recently gained recognition for its potential efficacy in a wide range of vascular anomalies [31]. A phase 2 study of sirolimus for complicated vascular anomalies enrolled 13 patients with KHE, 10 of who had KMP [32]. Patients received sirolimus as a single drug at a starting dose of 0.8 mg/m^2 q12 h, and dosing was adjusted to maintain a trough of 10–15 ng/ml. Patients could continue treatment for 12 months on study; continued therapy was at the discretion of the treating physician. All patients with KMP had a partial response at 6 months, defined as a greater than 20% reduction in size of the target vascular lesion by imaging, or improvement in target organ dysfunction by at least one grade, or improvement in quality of life instruments; one patient with KHE without KMP had progressive disease. Additional case reports suggest efficacy of sirolimus and other mTOR inhibitors in KHE, including correction of KMP, reduction of tumor size, and improvement of fibrosis [33–35]. Note that infants less than 3 months of age may require lower sirolimus doses to achieve target levels [36, 37]. Sirolimus is currently being compared to standard therapy with vincristine and corticosteroids in a prospective clinical trial (clinical trials.gov NCT00975819), which would be the first study of its kind for patients with vascular anomalies. In practice many specialists use combination therapy with sirolimus, vincristine, and nonsteroidal anti-inflammatory drugs, and lower-dose sirolimus may be effective [30]. Common side effects noted with sirolimus include hematologic toxicities, diarrhea, elevated blood lipids, and infection [32]. Limited data are available regarding long-term effects of this medication.

Propranolol

Propranolol, a beta-blocker, has revolutionized the therapy of infantile hemangiomas, but its role in other vascular anomalies is unclear. Chiu et al. reported a case series of 11 patients with KMP related to KHE/TA who were treated with propranolol; 36% responded, though specific response criteria were not defined [38]. Improvement was relatively slow, and therefore propranolol would not be appropriate for patients with aggressive disease or KMP. Based on a survey of expert opinion, propranolol 2–5 mg/kg/day may be considered for patients without KMP or as adjunctive therapy in patients who do not have a satisfactory response to first-line agents [27].

Interferon-Alpha

Interferon-alpha has demonstrated activity in KHE, but enthusiasm for this treatment has declined due to the risk of spastic diplegia in young infants [39]. Wu et al. reviewed outcomes of 12 children with KHE between the ages of 20 days and 8 months of age who were

treated with interferon-alpha for 3–9 months. Initial dosage was 1 × 10^6 U/m^2/day for the first week then 3 × 10^6 U/M^2/day thereafter. Five patients had KMP and most of the patients had failed prior therapies. All patients with KMP achieved normalization of their platelet counts, and 75% of patients had at regression in the size of their tumors by at least 80%. The time to response to interferon-alpha treatment was 10 days to 5 weeks (mean 3.6 weeks). No severe adverse effects were observed, and no patient developed spastic diplegia [40]. Interferon-alpha remains an option for patients with disease refractory to other treatments, but families should be informed of the warnings associated with its use.

Aspirin

Aspirin is a rational therapy that is postulated to reduce intralesional platelet trapping and inflammation; however, data regarding its efficacy are mixed. Case reports exist in which the use of aspirin, either alone or in combination with ticlopidine, is associated with reduction of painful coagulopathy in tufted angioma [29, 41, 2]. In addition, low-dose aspirin (5 mg/kg/day) was reported to reduce tumor bulk and pain in two patients with tufted angioma who did not have Kasabach-Merritt phenomenon [42, 43]. Aspirin in conjunction with ticlopidine and vincristine is used by some in the treatment of KHE with KMP [29]. The most recent consensus guidelines suggest that aspirin 2–5 mg/kg/day can be considered as adjunctive therapy for KHE without KMP [9].

Supportive Care for Coagulopathy in Kasabach-Merritt Phenomenon

The primary management is directed at tumor treatment. Platelet transfusions should be reserved for clinically important bleeding or surgery, as the half-life of the transfused platelets is short and transfusions are associated with increased platelet trapping within the lesion and resultant pain and tumor growth [16, 9]. Conversely, administration of fresh frozen plasma or cryoprecipitate is recommended for fibrinogen <100 mg/dl and may help reduce bleeding symptoms. Antifibrinolytic agents have been used with variable efficacy [44], though the majority of experts only recommend use of these agents for bleeding not responsive to other therapy [9, 27]. Heparin and antiplatelet agents have not been shown to reduce platelet trapping and are not recommended [27].

To assist the reader in gaining familiarity with available evidence, the following rating system has been used to indicate key references for each chapter's content:
***: Critical material. Anyone dealing with this condition should be familiar with this reference.
**: Useful material. Important information that is valuable in in clinical or scientific practice related to this condition.
*: Optional material. For readers with a strong interest in the chapter content or a desire to study it in greater depth.

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Juvenile Nasopharyngeal Angiofibroma

10

Erin Kirkham, Scott Manning, and Kris S. Moe

Genetic diagnosis	No
Genetic etiology	Unclear; possibly GSTM1 or APC gene
Level of evidence: treatment	Moderate
Evidence	Meta-analyses and systematic reviews of case series

Phenotype and Variations

Juvenile nasopharyngeal angiofibroma (JNA) is a mesenchymal neoplasm of irregular, hyperproliferative vasculature embedded within a fibrous stroma. Histologically, vessels range from slit-like to widely dilated and lack normal smooth musculature, making them delicate and prone to bleeding [1].

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Though histologically benign, JNA can be locally invasive and destructive. Arising from the root of the pterygoid bone, JNA expand as they grow, extending medially into the nasopharynx and causing remodeling of the surrounding sinonasal skeleton. Advanced tumors can extend laterally through the pterygomaxillary fissure into the infratemporal fossa, erode the middle cranial fossa floor, and track along the vidian nerve into the sphenoid sinus.

Phenotypically, JNA vary from well-encapsulated and easily resectable (Fig. 10.1) to aggressive and locally infiltrative [2]. This phenotypic distinction is not fully understood at the genetic level, though the two phenotypes exhibit differences in the expression of over 1000 genes. High-grade lesions express lower levels of the gene encoding the tyrosine kinase SYK, which has been shown to act as a tumor suppressor in some malignancies [2]. In addition, two small studies have independently demonstrated that 40% of JNA patients underexpress the gene encoding cytoprotective glutathione *S*-transferase M1 (*GSTM1*) on chromosome 1 [3, 4]. It is suspected that loss of the cytoprotective activity of this enzyme may predispose to JNA development.

Etiology

Juvenile nasopharyngeal angiofibroma was first described by Hippocrates in the fifth century BC,

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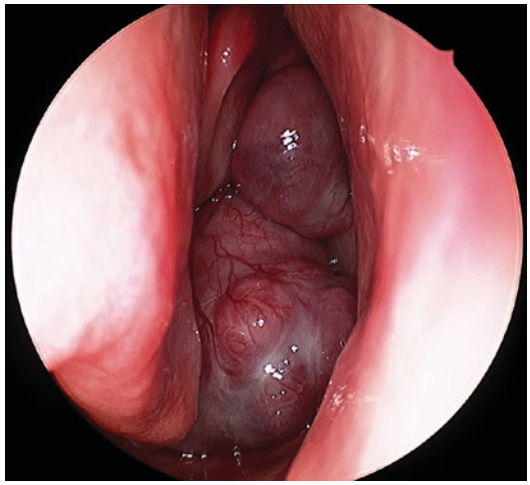

Fig. 10.1 Endoscopic view of the right nasal cavity showing a smooth, vascular mass arising from the root of the pterygoid and region of the sphenopalatine foramen. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

yet its etiology remains an area of active investigation, and controversy exists as to how it should be classified. Though JNA was once thought to be a subtype of vascular anomaly [5], immunostaining techniques have revealed distinct differences with vascular anomalies and key commonalities with vascular tumors [6]. While hemangiomas reliably stain positive for the marker GLUT-1, JNA do not. Zhang et al. demonstrated that unlike nasopharyngeal vascular malformations, JNA exhibit high expression of the markers CD34, VEGF, Flt-1, Flk-1, and PCNA, which are commonly expressed by proliferative vascular tumors [7]. The same authors also found that microvessel density was substantially higher in JNA than in hemangioma. Taken together, evidence suggests that JNA are not developmental anomalies but rather neoplasms resulting from abnormal vessel proliferation.

What drives JNA proliferation is still unknown, and it is unclear whether abnormal growth arises from vascular or stromal progenitors. Most studies suggest that it is the stromal component that drives growth [8], though increased levels of the oncogenic stem cell-related protein c-Kit have been detected in the abnormal vascular component of JNA tissue, and c-Kit expression correlates to increased tumor density [9]. Elevated endoglin (CD105) expression has also been seen in endothelial but not stromal cells. As a transmembrane glycoprotein involved in angiogenesis, CD105 is a reliable marker of neovascularization within many tumor subtypes and has a strong positive correlation with JNA recurrence [10]. Many chromosomal alterations in JNA have been identified, most of those common to both endothelial and stromal components [11].

JNA occurs almost exclusively in pubescent males, and hormonal mediators are thought to play a key role in its development. Tissue array analysis has demonstrated high co-expression of vascular endothelial growth factor (VEGF) and both estrogen and androgen receptors. VEGF is upregulated by estrogen and androgens, suggesting that the pubescent hormonal surge may participate in the regulation of VEGF in JNA tissue [12]. No definitive pathway by which hormones drive JNA development has been elucidated.

Investigation into an infectious etiology for JNA has yielded mixed results. JNA do not stain positive for Epstein-Barr or HHV-8, viruses associated with nasopharyngeal carcinoma and Burkitt lymphoma, respectively [13]. However, investigators using immunofluorescent staining for human papilloma virus (HPV) discovered the virus in all six JNA samples examined and in none of the controls [14], suggesting a possible association between HPV and JNA.

Though JNA does not exhibit strong heredity, the fact that it is commonly seen in males of fair skinned and red-haired phenotype has led investigators to search for genetic alterations that may predispose to JNA formation. Mutations in the APC gene have been linked to a form of syndromic JNA occurring in the setting of familial adenomatous polyposis (FAP). In this syndrome, an inactivating mutation of APC leads to increase in beta-catenin, which is strongly expressed in the nuclei of JNA stromal cells. Beta-catenin is a key regulator of the Wnt signaling pathway, which regulates cell proliferation, differentiation, and function [15]. Outside of this syndromic form, chromosomal imbalances in AURKB, FGF18, and SUPT16H have been detected in both JNA stroma and endothelium [11]. AURKB is a gene essential for mitosis, FGF18 encodes a fibroblastic growth factor, while SUPT16 downregulates genes involved in cell growth and maintenance. In addition, as discussed above,

the GSTM1 null genotype has been linked to the development of JNA [16]. Despite these discoveries, no single unifying mutation has been identified that explains the epidemiologic pattern seen in JNA expression.

Natural History

Comprising less than 0.5% of all head and neck tumors [17, 18], JNA occur almost exclusively in male adolescents from 10 to 25 years old. The incidence is approximately 1:150,000 and is increasing in some populations [17]. The most common presenting symptoms are unilateral nasal obstruction and recurrent epistaxis [19]. More advanced tumors can present with facial swelling, proptosis, diplopia, eustachian tube dysfunction, headache, and pain [20]. Endoscopic examination reveals a smooth, hypervascular soft tissue lesion bulging from the lateral nasal wall at the posterior aspect of the middle turbinate. Biopsy is not recommended, as it can lead to severe epistaxis. Rather, imaging confirms diagnosis, demonstrating a contrast-enhancing lesion centered on the pterygopalatine fossa on CT. JNA are bright on T1-weighted MRI and demonstrate characteristic flow voids due to hypervascularity (Fig. 10.2).

Multiple staging systems have been proposed for JNA. Of those, the Radowski and Fisch staging systems are the most commonly reported in the literature [18]. All staging systems were developed prior to the advent of endoscopic resection techniques and are based on tumor size and extent. As the surgical treatment paradigm for JNA has transitioned from open to endoscopic approaches, there has been a call for an updated staging system that incorporates the boundaries of endoscopic resection [18]. These boundaries are continually expanding, however, as multiportal endoscopic techniques gain traction [21, 22]; transnasal, transmaxillary, and transorbital approaches are now used in various combinations to optimize access to, and non-obstructed visualization of, these tumors. The addition of preoperative embolization procedures has also impacted resectability, leading to the recent proposal of a modified Fisch staging system based on major feeding vessels to the tumor [23].

Surgery is the mainstay of treatment, though recurrence rates are high, ranging from 6% to 31% [18–20, 24]. The majority of recurrences appear within the first 2 years of treatment. In one study, 50% recurred within 8 months, and 95% recurred within 2 years of transpalatal resection

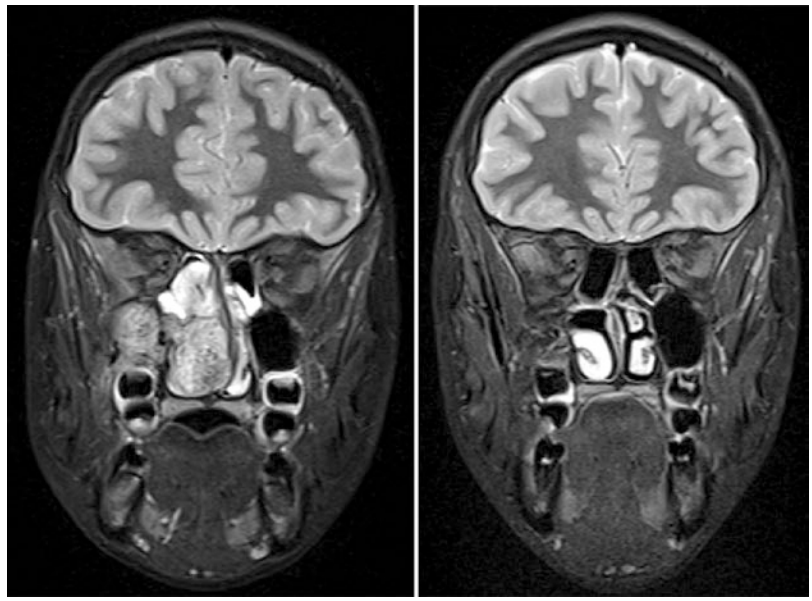

Fig. 10.2 Contrast-enhanced coronal MRI showing brightly enhancing tumor pre and post endoscopic resection. (Images courtesy of Seattle Children's Radiology, Giridar Shivaram, Eric Monroe and Kevin Koo)

[24]. Though postpubertal spontaneous regression has been reported [15, 25], the majority of lesions must be treated to avoid complications of the disease.

Treatment

Contemporary treatment of JNA consists of preoperative angiographic embolization followed by surgical resection via an open, endoscopic, or combined approach. Large-volume intraoperative blood loss is one of the most common and serious complications of JNA resection, and greater blood loss is associated with higher rates of postsurgical complications [26]. Though preoperative embolization carries a 5% risk of complications including neurologic deficits and blindness [27], multiple studies have demonstrated its effectiveness in reducing intraoperative blood loss [20, 28, 29] (Fig. 10.3). Despite its widespread use, embolization may not be required for all patients; small- and intermediate-sized tumors can be successfully and safely resected without embolization [30].

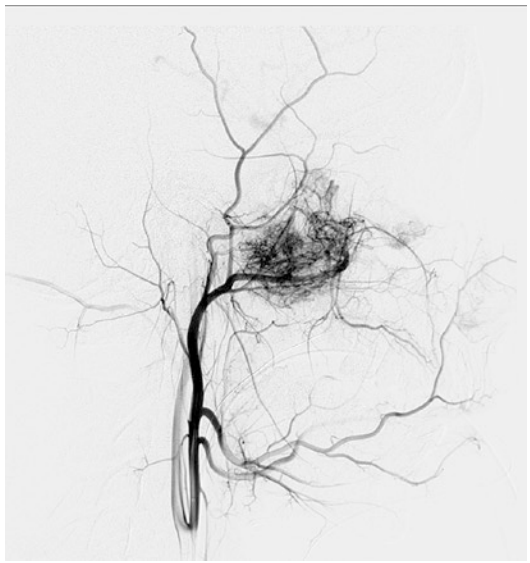

Fig. 10.3 Preoperative angiogram prior to embolization, showing dense vascularity of tumor. (Images courtesy of Seattle Children's Radiology, Giridar Shivaram, Eric Monroe and Kevin Koo)

In addition to embolization, intraoperative neuromonitoring has been used as an adjunct to surgical resection in order to reduce postoperative complications. Elangovan et al. presented a retrospective series of 129 patients between 1999 and 2013 who underwent endoscopic surgical resection of skull base tumors with intraoperative neuromonitoring. Of those, 22 (17%) had a diagnosis of JNA. The authors reported that only six (0.05%) subjects sustained postoperative cranial nerve deficits, one transient and five permanent. The authors conclude that the use of free-run EMG and triggered EMG are effective methods for detecting nerve involvement during endoscopic skull base resection.

Another technological advance that the authors have found to be highly effective is the use of ultrasonic devices that allow synchronous coagulation and transection of tissue. Originally used in laparoscopic procedures, these instruments significantly decrease the amount of intraoperative blood loss, complementing the use of preoperative embolization. Advanced instrument designs now allow the use of these devices for the resection of skull base JNA through transnasal, transmaxillary, and transorbital portals.

Given its rarity, the majority of surgical outcomes published on JNA are drawn from retrospective case series. Pooling data from these studies has allowed comparison of surgical techniques and more accurate predictions of complication and recurrence rates. A systematic review of published studies from 1990 to 2012 pooled data from 1047 cases of JNA of all stages. Individual data was pooled from 345 cases resected via endoscopic (158), endoscopic-assisted (15), or open (172) approaches [20]. The overall recurrence rate was 14.2% over a mean follow-up of 33 months. Out of 345 cases, two deaths were reported with the open approach and none with the endoscopic approach. Among tumors of the same stage, there was no difference in recurrence rates between the endoscopic and open approaches. However, the endoscopic-assisted group had a significantly higher rate of recurrence than the other two. While preoperative embolization resulted in significantly less intraoperative blood loss in the endoscopic group, the

reverse was true for those resected with open approaches. The authors also pooled aggregate data from 702 cases for which individual data was unavailable; 150 of these were endoscopic, 24 endoscopically-assisted and 518 open. In this cohort, overall recurrence was 18.7%. There was a significantly lower recurrence rate in the endoscopic than in the endoscopic-assisted and open approaches.

Leong et al. performed a systematic review pooling 72 patients from 15 studies of surgical management of advanced JNA with intracranial extension from 1990 to 2012 [29]. Ten percent underwent endoscopic treatment, and the remainder required craniofacial approaches, including open craniotomy, infratemporal fossa, lateral rhinotomy, facial translocation, midface degloving, Le Fort I, transpalatal, or a combination. In this review, preoperative embolization resulted in significantly less blood loss (an average of 1500 vs. 4000 milliliters). The most common complications included facial paresthesias (16%), ophthalmoplegia (12%), and intranasal crusting (12%). The recurrence rate was 18% overall.

Khoueir et al. conducted a systematic review of 821 patients who underwent an endoscopic-only approach from 1995 to 2012 [18]. The majority (68%) underwent preoperative embolization. The overall complication rate was 9%, and most were minor. Residual tumor was left in 8%, and the overall recurrence rate was 10%. Huang et al. also analyzed a series of 162 subjects resected via open (96) and endoscopic (55) approaches and found lower blood loss and fewer complications in the endoscopic group [31]. Taken together, these reviews of pooled data suggest that a purely endoscopic approach may be safer and more effective than an open approach. However, tumor extent and staging must be considered when interpreting outcomes, and these reviews highlight the need for an updated and unified staging system for JNA in order to standardize reporting of outcomes allowing for informed treatment recommendations.

Nonsurgical treatment is typically reserved for persistent or recurrent disease. Low-dose radiation (30–36 Gy) and intensity-modulated radiotherapy are options for advanced or recurrent lesions not amenable to surgical resection. Radiation can provide local control in up to 90% of patients, but late complications (including malignant transformation) are seen in 15–32% of patients [32]. Systemic cytotoxic therapies have been effective in individual case reports but remain experimental. Flutamide, an androgen receptor blocker, has been used as a neoadjuvant treatment prior to surgical resection. Mean volume reduction has ranged from 7% to 29% in three studies of 32 total patients. Lastly, therapies targeted at inhibiting VEGF have shown potential for treatment but are as yet unproven.

To assist the reader in gaining familiarity with available evidence, the following rating system has been used to indicate key references for each chapter's content:
***: Critical material. Anyone dealing with this condition should be familiar with this reference.
**: Useful material. Important information that is valuable in in clinical or scientific practice related to this condition.
*: Optional material. For readers with a strong interest in the chapter content or a desire to study it in greater depth.

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Temporal Bone Paraganglioma

11

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Genetic diagnosis	Yes
Genetic etiology	Multiple identified
Level of evidence: treatment	Strong
Evidence	Large series and meta-analyses

Introduction

Temporal bone paragangliomas (TBPs) are slow-growing, highly vascular primary neoplasms of the middle ear and lateral skull base that are composed of paraganglion cells derived from the neural crest. Paraganglioma can be found throughout the body, though in the temporal bone, two forms predominate: tympanic paraganglioma (TP) that originate in the middle ear cleft along the tympanic plexus associated with Jacobson's (IX) and Arnold's (X) nerves and jugular paraganglioma (JP) derived from chief cells located in the adventitia of the jugular bulb [1–5]. Most TBP are solitary, non-biochemically secreting and benign, while less than 5% are associated with catecholamine release or malignant character; up to 17% of patients display multiple paragangliomas [6]. TBP exhibit a female predominance and most commonly manifest during the fourth to fifth decades of life with symptoms of unilateral pulsatile tinnitus, conductive hearing loss, and less commonly lower cranial neuropathy. Owing to the rare prevalence and typical insidious growth, many patients endorse a long duration of symptoms at diagnosis [1, 2].

Following refinements in surgical approaches and greater access to advanced imaging modalities, most patients with TBP treated in the 1980s and 1990s received upfront microsurgery with the goal of complete tumor resection [6–9]. While surgical removal of TP and limited JP was often uncomplicated, many patients with moderate-to-large JP were left with conductive hearing loss, transient or permanent facial nerve paralysis, and worsening lower cranial neuropathy even when surgery was performed by an experienced skull base team [7, 10–12]. These outcomes led several

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innovative groups to offer alternative treatments including subtotal tumor removal, stereotactic radiation (SRS), and observation; however, it was not until years later that these strategies gained more widespread acceptance [13].

Historically, radiation was generally reserved for patients with recurrent disease and advanced medical comorbidities [12]. Part of this strategy was motivated by early clinical studies suggesting that radiation had little direct effect on tumor cells and also from concerns over using non-conformal external beam radiation in the treatment of a benign disease [14–16]. Beginning in the 1990s, evidence emerged that SRS provided a viable treatment alternative to surgery for JP [17]. With time, the treatment paradigm for JP has evolved, and today many centers consider SRS first line. Paralleling the escalation in radiation use, some centers have advocated for subtotal tumor removal with or without adjuvant SRS [3, 18–21]. Together, these recent trends demonstrate that preservation of function has taken precedence over "surgical cure" via radical resection.

Since the primary objectives of SRS are to halt tumor growth and ease worsening cranial neuropathy rather than to eradicate disease, it is important to compare the results of SRS with the natural course of untreated disease in order to delineate benefit. Quoted rates of tumor control and cranial nerve outcomes following SRS are difficult to interpret without knowledge regarding the natural history of untreated JP [22, 23]. Furthermore, such information is especially valuable toward counseling patients with minimal symptoms as well as those of advanced age and poor surgical candidacy. Unfortunately, studies detailing the clinical course of untreated JP are sparse [2, 23, 24].

The current chapter focuses on the evaluation and management of TBP, including JP and TP. Notably, vagal paraganglioma may involve the jugular foramen and lateral skull base; however this diagnosis is discussed in a separate chapter within the context of cervical paraganglioma and will not be reviewed here. Additionally, facial paraganglioma or so-called glomus faciale may involve the temporal bone, though these tumors are exceptionally rare and are beyond the scope of this chapter.

Diagnosis

Phenotype and Variations

The presenting clinical signs and symptoms of TBP are largely determined by extent of disease. As TBP rarely metastasize, symptoms are related to compression, displacement, and invasion of contiguous structures. The most commonly reported symptoms of both JP and TP are ipsilateral conductive hearing loss and pulsatile tinnitus, present in approximately 75% of cases. Less commonly, involvement of cranial nerves VII and IX–XII may result in facial paralysis, dysphagia, dysarthria, and hoarseness. Overall, cranial nerve deficits are seen in approximately 40% of patients with JP at presentation, with vagal paresis being most common [15–18]. Involvement of the facial nerve, most commonly in the mastoid segment, may result in sudden or progressive facial paralysis occurring in up to 25% of cases [2, 19, 20]. Much less commonly, a primary paraganglioma may arise from the facial nerve and will often present with facial paralysis; however, imaging will typically reveal an epicenter at the fallopian canal and less/no involvement of the jugular foramen. Overall, cranial nerve paralysis with TP is exceptionally rare and should raise suspicion for JP or an alternative diagnosis. Up to 15% of TBP are asymptomatic and incidentally discovered during routine otoscopy or head and neck imaging [1]. Though the probability of encountering a catecholamine-secreting TBP is low, specific symptoms including episodic hypertension, palpitations, headaches, flushing, or diarrhea should heighten suspicion.

A pulsatile red or purple hypotympanic or mesotympanic mass is characteristic of TBP (Figs. 11.1 and 11.2). When the entire tumor can be seen on otoscopy, the diagnosis of TP can be made. However, it is impossible to distinguish TP and JP on physical examination alone when the inferior aspect of the tumor extends below the tympanic ring into the hypotympanum. In such

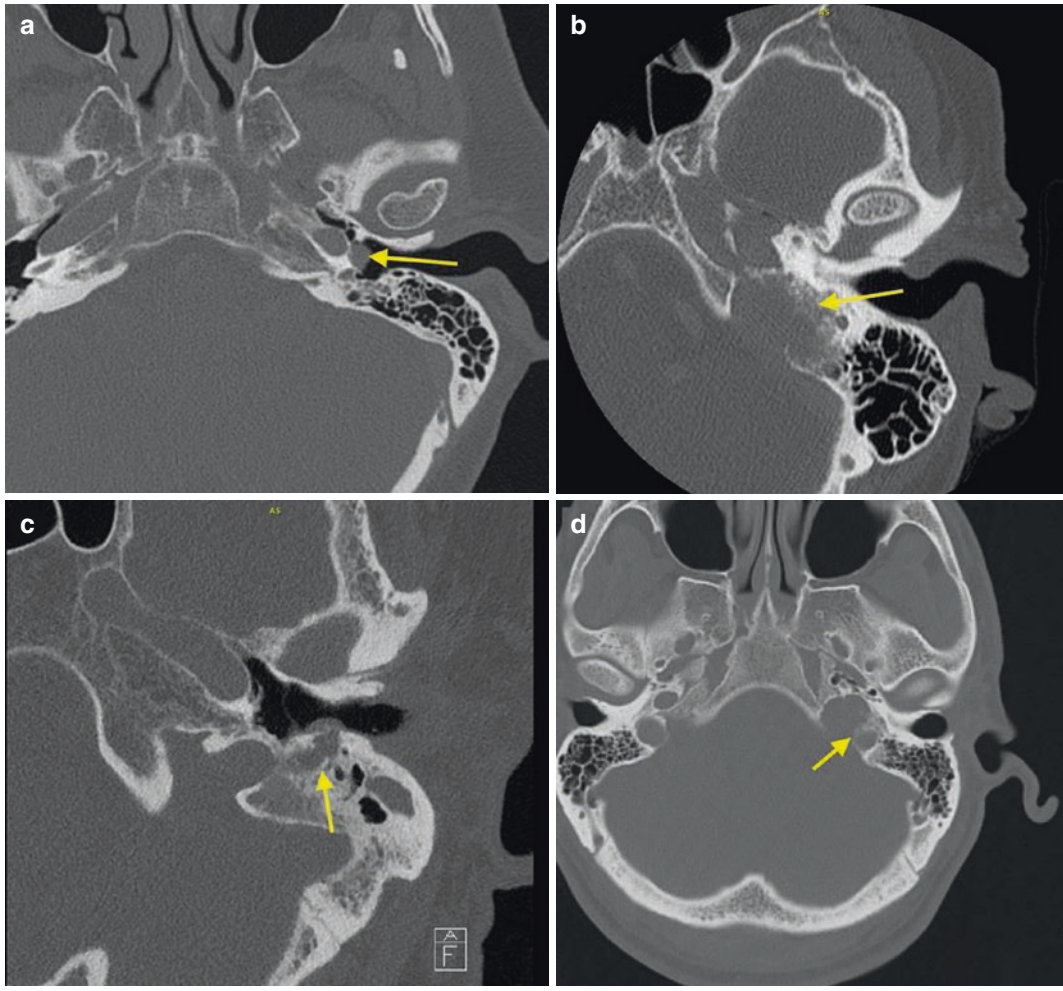

Fig. 11.1 (**a**) Axial CT demonstrating an isolated retrotympanic mass located in the hypotympanum and over the promontory surface indicative of a tympanic paraganglioma. (**b**) Axial temporal bone CT demonstrating an extensive left-sided jugular paraganglioma with erosion of the jugulotympanic spine and infralabyrinthine-retrofacial air cell system. (**c**) Axial CT demonstrating a rare case of a facial paraganglioma, with mottled bone centered over the fallopian canal and erosion into the ear canal. (**d**) Axial CT demonstrating a left-sided vagal paraganglioma with involvement of the jugular foramen. Not shown here, is the absence of a middle ear component, which is commonly seen with a skull base vagal paraganglioma

cases, imaging is required to ascertain the extent of the tumor.

To fully assess the extent of disease and the structures affected by tumor growth, diagnostic imaging is tremendously important.

High-resolution temporal bone CT is the best imaging technique for demonstrating the characteristic bony destructive changes seen with TBP. Tumors confined to the middle ear and mastoid without erosion of the bone overlying the jugular bulb are TP, whereas tumors involving the jugular foramen with erosion of the jugulocarotid spine are JP. In addition to narrowing the differential diagnosis, temporal bone CT characterizes extent of disease, which is critical for counseling and surgical planning. CT angiography can further augment radiological assessment and often adequately substitutes for invasive diagnostic catheter angiography. Evaluation of jugular vein compression, occlusion, or tumor infiltration on CT angiography can influence surgical planning. Finally, if intraoperative image-guidance is

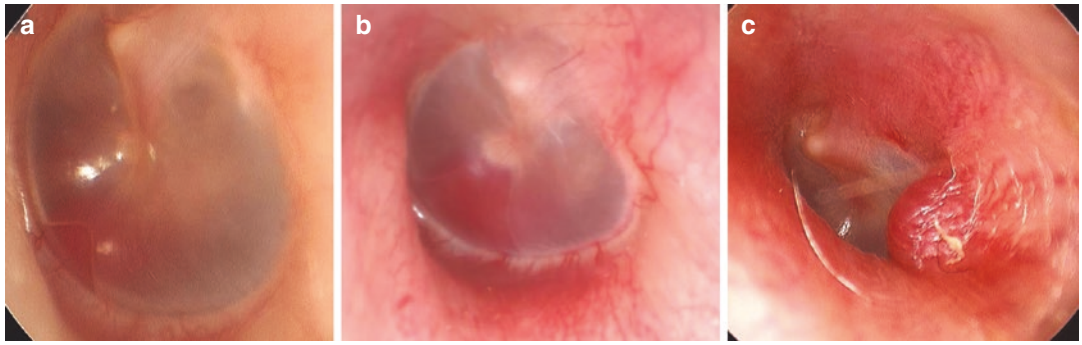

Fig. 11.2 (**a**) Isolated red middle ear mass with limited extension in to the hypotympanum, indicative of tympanic paraganglioma. (**b**) Pulsatile red middle ear mass with extension into the hypotympanum and modest vascularization of the medial ear canal seen with jugular paraglioma. (**c**) Erosive lesion involving the medial ear canal with sparing of the middle ear space in a patient with complete facial nerve paralysis, seen with a mastoid segment facial nerve paraganglioma

desired, high-resolution, thin-slice CT is needed for optimal registration and navigation.

MRI supplements information gathered from CT, investigating intracranial extension or neurovascular invasion. Characteristic MRI features of TBPs include low signal on T1-weighted images, intermediate to high signal on T2-weighted sequences, and avid enhancement with gadolinium administration. The presence of tumor flow voids on spin-echo sequences, commonly referred to as the "salt and pepper" appearance, is typical of paraganglioma but not specific to the disease.

For most TBP, additional imaging below the clavicles is not indicated. However, in cases where excess catecholamine secretion is detected or in patients with predisposing germline mutations (e.g., SDH, vHL, NF1), supplementary imaging should be obtained to evaluate for coexisting paraganglioma and pheochromocytoma. Additionally, functional total body imaging should be considered in patients with catecholamine-secreting paragangliomas, including 123I-labeled metaiodobenzylguanidine (MIBG), somatostatin-based gallium 68 (68-Ga) 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)-octreotate (DOTATATE), and PET scanning with 18F-fluorodeoxyglucose (FDG).

One of the final steps in TBP evaluation is tumor staging. Many different classification systems have been proposed, though two have historically predominated: Fisch-Mattox [25] and Glasscock-Jackson [26]. The two systems are notably different with regard to their handling of tumor origin and extent. When using the Fisch-Mattox scale, tympanic and jugular paraganglioma are on one disease spectrum, while the Glasscock-Jackson system has separate staging tools for either tumor.

Etiology

As with many tumors of the head and neck, the genetic basis of TBP development and behavior is an active area of research. Some of the initial work in this realm identified so-called paraganglioma loci (PGL) on chromosomes 1 and 11, which were associated with co-occurrence of paraganglioma and pheochromocytomas [27–30]. Presently, it is thought that a familial predisposition to tumor development accounts for at least 10% of paraganglioma cases, and at least 12 syndromes have been identified that carry a propensity for paraganglioma development including multiple endocrine neoplasia types 2A and 2B, neurofibromatosis type 1, and von Hippel-Lindau disease [31, 32]. Factors that indicate a potential underlying germ-line mutation include male sex, younger age, family history of paraganglioma development, and multicentric disease. Recent work on succinate dehydrogenase (SDH) in tumor pathogenesis has identified a variety of aberrations in this enzyme [33, 34]. Certain mutations, such as those arising at SDH-B, may influence the likelihood of rapid growth as well as metastasis [35, 36].

Special Considerations: Malignancy and Catecholamine Secretion

TBPs are considered malignant in approximately 5% of cases. There is no clear consensus on criteria to distinguish benign versus malignant disease [37–39]. Many tumors are locally aggressive, making bone and soft tissue destruction common. Generally, such behavior, an increased mitotic index, radiographic evidence of tumor necrosis, and invasion into surrounding vascular and neural structures indicate more aggressive disease. Yet, these features do not define malignancy in the case of paragangliomas. In fact, inverse relationships have been described between clinical behavior and cellular atypia in pheochromocytomas, which have a similar origin to TBP [40]. At present, malignancy in paragangliomas requires the presence of metastasis, regardless of primary tumor histopathologic findings [40, 41].

Clinically significant catecholamine secretion from TBP is uncommon, which distinguishes head and neck paragangliomas from similar tumors elsewhere in the body. Indeed, elevated catecholamine markers should raise suspicion for a coexistent abdominal or thoracic pheochromocytoma. When a secreting tumor is found in the head and neck, norepinephrine is generally produced due to the lack of the enzyme phenylethanolamine-N-methyltransferase in extramedullary paragangliomas [40, 42–44].

Though secreting tumors are rare, the potentially fatal consequences of unexpected, excessive catecholamine release during tumor manipulation warrant vigilance. Historically, preoperative venous sampling was encouraged prior to surgical management, though this strategy has fallen out of favor [37, 41, 42]. At present, diagnosing a secreting tumor involves laboratory testing of blood and urine to identify excess catecholamines or catecholamine byproducts. Blood testing should include fractionated metanephrines (metanephrine and normetanephrine) and fractionated catecholamines (dopamine, norepinephrine, and epinephrine). Furthermore, 24-h urine metanephrine and catecholamine measurement is believed to have a sensitivity and specificity greater than 95% for detecting secreting paragangliomas.

Treatment

Natural History and Conservative Management

To the best of the authors' knowledge, only four major studies to date have evaluated the clinical behavior and growth pattern of JP [2, 13, 23, 24]. These studies represent a small selected subpopulation of patients, which introduces selection bias. Furthermore, these studies did not utilize true three-dimensional volumetric analysis, which is an important consideration given the irregular and often ill-defined tumor margin within the temporal bone. Despite limitations, these case series provide the best information to date on the natural history of JP.

The Otology Group of Vanderbilt, Nashville Tennessee

In 2015, Carlson et al. reviewed a 20-year experience at Vanderbilt University [2]. During this time period, there were 16 JP in 15 patients that were observed with serial imaging after initial diagnosis and had a minimum of 2 years of clinical follow-up. This cohort of patients represented less than 10% of all JP at the author's center between 1995 and 2015. The most common reasons for conservative management were advanced age and patient preference, though five patients refused intervention despite receiving recommendations for treatment. Two patients had bilateral skull base paragangliomas.

Overall the median age at diagnosis was 70 years (38–80 years) and 12 of 15 patients were women. Hearing loss (75%) and pulsatile tinnitus (69%) were the most common symptoms, while vagal (38%), accessory (19%) and hypoglossal (12%) paralyses were less common at diagnosis. The median duration between symptom onset and diagnosis was 31 months (range 0–144 months).

Six (38%) JP demonstrated medial intracranial extension at the time of diagnosis. There was no statistically significant correlation between age and tumor size at diagnosis. Over a median imaging follow-up of 58 months, 7 (58%) tumors were stable while 5 (42%) enlarged with a median growth rate of 0.8 mm/year (range 0.6–1.6 mm/year) or

0.44 cm^3/year (0.14–0.87 cm^3/year). No significant age difference was seen between the cohort of patients with growing versus stable tumors. However, it is noteworthy that patients with growing JP had a longer duration of follow-up.

At a median clinical follow-up of 86 months (24–158 months), 6 (38%) patients experienced progressive hearing loss, 2 (12.5%) developed bloody otorrhea, pulsatile tinnitus remained stable in all patients, 8 (50%) maintained normal vagal function, and 11 (69%) maintained normal accessory and hypoglossal function. New or progressive lower cranial nerve paralysis developed in less than a third of cases, and only 1 (6%) experienced partial facial paresis. Four (25%) patients underwent type 1 thyroplasty with arytenoid adduction, and one (6%) received injection laryngoplasty. No patients required feeding tube, tracheostomy, or ventriculoperitoneal shunt placement. At last follow-up, none of the 15 patients experienced death from disease.

Gruppo Otologico, Piacenza Italy

In 2014, Prasad et al. reviewed 47 patients with JP (Fisch type C and D) who were managed conservatively and analyzed tumor growth and cranial nerve status on follow-up [23]. Of these patients, 32 (68.1%) were older than 65 years. Tumor volume was measured using diameter in two perpendicular planes, though specific values were not reported. Tumor growth was determined by the increase in the maximum linear dimension on follow-up and stratified into two groups: slow-growing (<3 mm/year) and fast-growing (>3 mm/year) tumors.

In 24 patients, duration of follow-up was less than 3 years, and the authors found that tumor size remained stable in 22 patients (92%). In the remaining 23 patients with follow-up of longer than 3 years (median, 61 months), tumor size remained stable in 12 (52%), regressed in 3 (13%), and progressed in 8 (35%) patients. This decrease in tumor control after 3 years emphasizes the indolent growth pattern of many JPs and the need for long-term follow-up. Of the eight (35%) patients with progressive tumors, seven were slow-growing and were still managed with observation, while one fast-growing tumor was treated with radiotherapy. Only seven (30%) patients developed a new lower cranial nerve deficit. Two subjects had facial paresis at time of diagnosis, and no patient experienced new onset or progression of facial weakness during the course of observation.

The authors propose a treatment algorithm whereby surgery is the treatment of choice for patients younger than 65 years with Class C and D JPs. For patients older than 65 years, an initial wait-and-scan approach is taken to identify the growth rate of the tumor. Slow-growing tumors can be observed with little risk given the low incidence of new cranial nerve deficits and the ability for the contralateral nerves to simultaneously compensate for any loss of function. Fast-growing tumors, on the other hand, may necessitate radiotherapy or subtotal resection.

Leiden University, Leiden Netherlands

In a seminal paper published in 1992, van Der Mey and colleagues reported on 108 patients with head and neck paragangliomas evaluated over a 32-year period [13]. Within this cohort were 52 jugulotympanic paragangliomas, of which 13 were untreated (observed), 16 underwent gross total resection, and 23 underwent subtotal resection. Although tumor growth rates and quantitative comparison of cranial nerve morbidity between groups were not described, the authors argued that for many patients with JP, radical surgery does not improve survival and results in greater cranial neuropathy. Because surgical intervention did not seem to prolong life expectancy in their series, the authors believe that the goal of treatment should be to reduce morbidity in patients with JP, rather than eradicate disease. This study was limited by the era of imaging and lack of modern stereotactic radiation therapy in their treatment algorithm.

In a later series from 2000 by the same center, 11 jugulotympanic tumors were conservatively observed [24]. Tumor volume was analyzed using three perpendicular axes using the ellipsoid volume calculation, and the average volume was 0.8 cm^3 (equating to a ~1.1 cm diameter). After a mean follow-up of 3.8 years, 55% of tumors

demonstrated radiologic progression with a median growth rate of 0.79 mm/year and a median tumor doubling time of 13.8 years. In an analysis of all head and neck paragangliomas including jugulotympanic, carotid body and vagal paragangliomas, the authors observed a biphasic growth pattern, whereby growing tumors were more likely to be intermediate in size compared to very small or large tumors. Jugulotympanic paragangliomas, however, tended to be smaller and exhibit a more indolent growth pattern compared to these other head and neck paragangliomas. However, in this study it is not clear how many of the observed tumors were TP rather than JP.

Given overlapping similarities and the potential for multifocal disease with TBP, it is pertinent to also review the literature regarding the natural history of other head and neck paragangliomas. In particular, two studies in the modern era provide valuable information regarding the behavior of untreated carotid body tumors and vagal paraganglioma. In 2000 Jansen et al. examined 20 carotid body tumors and 17 vagal paragangliomas [24]. After an average follow-up for 4.5 years, 60% of carotid body tumors demonstrated growth, the median linear growth rate was 0.83 mm/year, and median doubling time was 7.13 years. Of the 17 vagal paragangliomas, the mean follow-up period was 4.6 years, 65% exhibited growth, the median growth rate was 1.0 mm/year, and the median doubling time was 8.9 years. Within these cases, the authors observed no significant difference in growth rates between sporadic and hereditary cases. Finally, in approximately 80% of cases, symptoms did not change over the course of follow-up even with growth.

In 2012, Langerman and colleagues characterized growth patterns of untreated asymptomatic cervical paragangliomas, including 28 carotid body tumors and 19 vagal paragangliomas [4]. The mean age at diagnosis was 56 years, and the mean follow-up was 5 years. Within this cohort, reasons for observation included patient preference (35%), advanced age (28%), and pre-existing contralateral cranial nerve deficits (26%). Given limitations in available imaging, volumetric analysis was not performed. Overall 42% of tumors remained stable in size, 38% grew, and 20% shrunk in size. Of the tumors that exhibited growth, the average growth rate was only 0.2 cm/year. In this review, the authors stressed the importance of close follow-up and consideration for intervention should concerning symptoms such as pain, rapid growth, or adenopathy develop. Collectively, these two studies further validate an initial trial of observation for head and neck paraganglioma in select patients.

Surgery, Tympanic Paraganglioma

When discussing treatment options for TBP, TP and JP are generally discussed separately given that the risks of surgery, surgical approaches, and anticipated outcomes differ. As discussed above, TP are generally confined to the middle ear and mastoid, without involvement of the jugular bulb. Very rarely do TP cause facial paralysis, engulf the petrous carotid, invade the inner ear, or extend intracranially. Surgery remains the gold standard for the management of TP, and to date, there are no large studies evaluating conservative observation or radiation therapy for this subset of TBP. In most cases, complete tumor excision and symptom relief are achievable. However, before proceeding to the operating room, preoperative surgical planning is necessary. Given the vascular nature of these tumors, surgery can be particularly bloody. Preoperative angiography with embolization is most commonly discussed in the context of JP; however, embolization of advanced TP may also be considered. While intraoperative bleeding during TP excision rarely can cause hemodynamic instability, the anesthesia team should be aware of the potential for blood loss beyond what is generally seen with chronic ear surgery. Furthermore, as with any otologic case, aggressive management of intraoperative hypertension and tachycardia may help to lessen the degree of bleeding. Facial nerve monitoring should be considered in every TP surgery, due to the probability that tumor bleeding could obscure visualization within the middle ear.

The most appropriate surgical approach to TP depends mostly on the extent of the tumor. When

using the Glasscock-Jackson staging system, transcanal excision can generally address stage I disease. Atticotomy and hypotympanotomy can also be used for disease that extends superiorly into the attic or inferiorly into the hypotympanum, respectively [45]. With stage II–IV disease, a postauricular incision is preferred. With exposure to the mastoid cortex, a mastoidectomy and a posterior tympanotomy can provide additional visualization of tumor margins. In some cases, an extended facial recess is necessary when tumors grow far into the hypotympanum [46]. For class IV disease, a modified radical mastoidectomy can be used. When profound sensorineural hearing loss exists preoperatively, a subtotal petrosectomy with canal closure is worth considering [47].

With contemporary microsurgical techniques, total resection can generally be expected, and tumor control rates approach 100%. Additionally, the use of a laser or micro bipolar cautery often helps with hemostasis [48–50]. Once the tumor has successfully been mobilized from critical structures, the location of the tumor's vascular pedicle can be determined, and this vessel, frequently a derivative of the ascending pharyngeal artery, can be managed with cautery, laser, or bone wax [51]. The tumor is then removed from the middle ear cavity. Subsequently, reconstruction of the tympanic membrane, ear canal, and/or ossicles may be necessary. If tumors cannot be readily separated from important structures in the middle ear or mastoid, such as the facial nerve or petrous carotid, subtotal resection is recommended. In these cases, leaving a small adherent tumor remnant may avoid significant and unnecessary morbidity. In such a case, clinical and radiographic observation can monitor tumor growth [47]. In rare cases, alternatives to surgical management must be pursued due to patient comorbidities. Not every patient with a TP is a good candidate for general anesthesia. In this setting, clinical and radiographic observation should be considered, and patients are counseled as to the potential for disease progression as well as the associated symptoms – notably, tumor bleeding in the ear canal as well as acquired dysfunction of the facial nerve and inner ear.

Surgery, Jugular Paraganglioma

In contrast to TP where treatment has largely remained surgical, the management of JP has evolved considerably over the last 30 years. In the late 1970s and early 1980s, improvements in diagnostic imaging and refinements in surgical approaches to the infratemporal fossa established gross total resection as the preferred treatment of JP, regardless of tumor size. The infratemporal fossa approach type A, first described by Fisch, remains the most common surgical approach utilized for resection of extensive JP when gross total or aggressive subtotal resection is pursued. In the classic description, the jugular foramen is accessed via anterior rerouting of the facial nerve, and the middle ear and petrous carotid are optimally exposed via subtotal petrosectomy with blind-sac external auditory canal closure. With this approach, the patient is left with a maximal conductive hearing loss and at least a transient facial nerve paresis. Modifications include preservation of the external auditory canal, use of a fallopian bridge without facial nerve rerouting, or limited rerouting of the inferior mastoid segment. With each modification, a potential improvement in functional outcome is gained at the expense of surgical exposure. Other approaches have been commonly described for JP resection, including the far lateral approach; however the infratemporal fossa approach is the only one that provides simultaneous access to the upper neck, temporal bone, and intracranial space.

While gross total resection affords low recurrence rates, complete radical tumor removal is often accomplished at the expense of cranial nerve function [12, 20, 52, 53]. This trade-off is especially true for larger tumors with medial extension to involve the pars nervosa and posterior fossa. Bacciu et al. reviewed 122 patients with Fisch class C and D JP and found that 54% of patients developed one or more new cranial nerve deficits after surgery, achieving gross total resection in 86% of cases [54]. Similarly, the Vanderbilt Otology Group's review of 202 patients with JP found a 60% rate of new cranial nerve injuries after performing gross total resection in 90% of cases [55].

The impact of cranial nerve sacrifice should be a major consideration in the treatment algorithm of JP. The nerves at highest risk are cranial nerves IX, X, and XI, due to their course relative to the jugular foramen; however, cranial nerves VII and XII can also be involved in advanced tumors. With unilateral paralysis of any one of these nerves, patients can struggle significantly with speech and swallowing function. Even those with pre-existing vagal dysfunction manifesting as vocal fold paralysis, for example, may experience worsened dysphagia following surgery due to loss of pharyngeal or palatal innervation or vocal fold muscle tone. While certain deficits can be rehabilitated, this often requires additional surgical procedures with focused rehabilitation, and overall function frequently never reaches a near-normal state, especially when multiple cranial nerves are injured or in patients of advanced age [56].

As more is discovered about the natural history of these benign tumors and as data regarding tumor control and functional outcomes with SRS develop, most treatment paradigms have shifted toward more conservative approaches in certain patient populations to avoid the morbidity associated with cranial nerve injuries. Despite such developments, there remain several scenarios where primary surgery should be strongly considered: small resectable tumors in young patients, tumors with aggressive behavior concerning for malignancy, secreting tumors where the benefits of radiotherapy are not well elucidated, and tumors with large intracranial extension and brain stem compression.

Overall, three strategies of subtotal resection for JP have been described in the literature, each defined by a particular objective: limited resection of only the middle ear portion of the tumor for audiological symptom improvement, resection the intracranial portion of the tumor to relieve brain stem compression, and aggressive resection of all tumor except the portion intimately involved with the carotid artery or functional cranial nerves in an effort to potentially provide long-term cure while minimizing morbidity. These three strategies are outlined in greater detail below.

1. *Resection of the middle ear tumor alone:* Many JP are quiescent or slow-growing and can be observed for several years without risk of rapid growth. With this in mind, some authors have considered limited surgery with the primary goal of symptom relief [18, 19]. Cosetti et al. treated three patients over the age of 70 with limited resection that primarily addressed the middle ear component of tumors [18]. All three patients had immediate relief of their pulsatile tinnitus after surgery, improved hearing, and no new cranial nerve deficits. One of these patients had radiologic progression 6 years after surgery and was treated with radiotherapy. Willen et al. described similar outcomes for five patients over the age of 60 with Fisch class C3 tumors or greater; however, all patients in their series also underwent postoperative radiosurgery to the residual tumor [19]. All patients had relief of their pulsatile tinnitus and stable or improved hearing. They reported no new lower cranial nerve deficits as a result of their treatment, and no tumors had grown after a mean 19-month follow-up period.
2. *Posterior fossa tumor resection for brain stem decompression:* Rarely, patients may present with symptomatic brain stem compression or hydrocephalus from aggressive disease. In these cases, primary radiation treatment is not advisable due to concerns for posttreatment swelling leading to greater brain stem compression. While gross total resection is still preferred in young, relatively healthy patients, this can be an extremely challenging endeavor and may cause unnecessary morbidity in patients of advanced age or limited life expectancy. In this scenario, performing a subtotal resection with the primary goal of brain stem decompression can be considered. Carlson et al. described four cases of advanced (Fisch grade D_2) jugular paragangliomas presenting with significant brain stem compression [57]. Subtotal resections were performed in three cases via combined transtemporal and transcervical approaches. All three patients received postoperative radiation treatment to

their residual tumor. Successful decompression as well as long-term tumor control was achieved in all three patients with 6–9 years of follow-up.

3. *Aggressive subtotal resection for tumor control and enhanced cranial nerve outcomes:* Wanna et al. described subtotal resection in 12 patients with Glasscock-Jackson grade 3 or 4 tumors and an average age of 46 years [3]. Patients with preoperative evidence of cranial nerve injury were excluded from the study. In 8 (66.7%) cases, no subsequent growth was observed after surgery with a mean follow-up of 3.7 years. The remaining four tumors grew at an average of 2 years after surgery. It was noted that the latter cases had significantly higher residual tumor following subtotal resection compared to those that showed no growth (59.2% vs. 11.9%). Moreover, no cases achieving greater than 80% of tumor resection when comparing pre- and postoperative imaging showed postoperative growth. There were no new permanent cranial nerve deficits following surgery, and no patient experienced carotid artery injury. Wanna et al. advocate for a more aggressive resection in most cases, usually via an infratemporal fossa approach with external ear canal overclosure and limited mobilization of the mastoid segment facial nerve [3]. Generally, with this approach, the medial surface of the jugular bulb is left undisturbed so that the pars nervosa of the jugular foramen is not threatened.

Stereotactic Radiosurgery for Primary Jugular Paraganglioma

Advances in SRS in the past two decades have led to decreased complications and promising tumor control rates in patients with JP. A 2011 meta-analysis examining 869 patients with JP found pooled estimates of tumor control after SRS were 95% versus 86% for gross total resection [20]. They also found lower rates of lower cranial nerve injury in patients who underwent primary SRS versus gross total resection. Indeed, the majority of patients with JP are candidates for SRS or hypofractionated stereotactic radiotherapy (SRT). However, those with impending or already present intracranial sequelae should be treated with upfront subtotal resection with adjuvant SRS. Furthermore, dose planning for very large JP may place nearby structures at greater risk than would be estimated for surgical resection. Some radiosurgical delivery devices have limitations regarding cervical tumor extent; for example, the Gamma Knife system cannot reliably treat lesions below roughly the C2 vertebra.

Consensus regarding SRS treatment parameters for JP has been reached over the past two decades. Published series report marginal dose ranging from 13.6 to 20 Gy and maximum dose from 30 to 36 Gy. Single fraction therapy has not been found to be significantly different than multiple fraction therapy that may be employed with linear accelerator devices (assuming similar total dose) in terms of tumor control or acute toxicity [58]. Two meta-analyses published in 2011 provide pooled estimates of tumor control rates with SRS or hypofractionated SRT. The overall tumor control rates reported by each study group were 95% [59] and 97% [20] for 335 and 339 patients, respectively.

Publications by Foote et al. and Pollock summarize available data on tumor control and functional outcomes after SRS for JP at the Mayo Clinic [17, 60, 61]. The overall tumor control rate was 98%, with actuarial progression-free survival of 100% at 7 years. One tumor exhibited growth during follow-up, likely due to inadequate initial treatment dose (marginal tumor dose 12 Gy). Retreatment was performed 8 years later with a marginal tumor dose of 14 Gy, and over the ensuing 5 years, the tumor demonstrated a decrease in size. This patient developed an ipsilateral true vocal fold paralysis after salvage radiosurgery; no other new CN X paralyses were noted in these series. Pollock reported an actuarial rate of hearing preservation of 81% at 4 years post-SRS. Given the natural history of late radiation effects, these patients are followed closely to determine if delayed cranial nerve deficits are present.

Stereotactic Radiosurgery for Recurrent Jugular Paraganglioma

Recurrent JP presents a difficult challenge. Defined as residual disease exhibiting growth, these JP often represent more aggressive tumor variants and may exhibit greater variability in response to treatment [62]. Merely determining true tumor boundaries on MR imaging is challenging; even high-resolution modern techniques often cannot resolve differences between post-treatment change and viable tumor. As discussed earlier, large, rapidly growing, or unusually infiltrative JPs do not necessarily exhibit cytologic evidence of aggressiveness like other neoplasms [57]. Therefore, it is difficult to predict both the growth potential of residual disease and its response to radiotherapy. That said, the risk of surgical morbidity in the salvage setting is unquestionably higher than in the primary treatment setting, and radiosurgery has shown excellent promise in halting the growth of tumor residua. In general, there are two separate clinical scenarios for use of SRS following prior microsurgery: the first is in adjuvant form, where a subtotal resection of recurrent tumor is performed with planned postoperative radiosurgery; the second is the treatment of tumor recurrence typically discovered months to years after initial surgical resection. The majority of available series do not differentiate between these clinical situations due to the relative rarity of each, but on the whole, salvage SRS offers excellent long-term tumor control in a number of published series.

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To assist the reader in gaining familiarity with available evidence, the following rating system has been used to indicate key references for each chapter's content:
***: Critical material. Anyone dealing with this condition should be familiar with this reference.
**: Useful material. Important information that is valuable in in clinical or scientific practice related to this condition.
*: Optional material. For readers with a strong interest in the chapter content or a desire to study it in greater depth.

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Cervical Paraganglioma

12

Alexander P. Marston and Eric Moore

Genetic diagnosis	Yes
Genetic etiology	Multiple identified; succinate dehydrogenase subunits and mitochondrial complex II most common, VHL, RET, NF1
Level of evidence: treatment	High
Evidence	Meta-analyses, large series

Introduction

Paragangliomas are rare tumors that arise from neural crest cells occurring at an incidence of between 1 in 30,000 and 1 in 100,000 [1]. Ninety percent of these tumors occur in the adrenal paraganglia and are termed pheochromocytoma [2]. Among the paragangliomas that occur outside of the adrenal gland, 85% are located in the abdomen, 12% in the thorax, and 3% in the head and neck [2]. The carotid bifurcation is the most common paraganglioma tumor subsite within the head and neck, accounting for 60–78% of head and neck paragangliomas [3]. Paragangliomas of the head and neck can also arise from other sites, including the jugulotympanic region, vagus nerve, sympathetic trunk, laryngeal paraganglia, ciliary ganglion, nasal cavity, and paranasal sinuses [4, 5]. Head and neck paragangliomas are typically parasympathetic in origin and non-secreting (non-chromaffin paragangliomas); only 3–5% hypersecrete catecholamines [6]. Paragangliomas can either be hereditary or sporadic. When hereditary, gene mutations are usually found in the succinate dehydrogenase or mitochondrial complex II genes [4]. Most sporadic paragangliomas present as a single tumor, with only 10–20% demonstrating multifocality. However, familial paragangliomas are multifocal in up to 80% of cases [7]. This chapter will focus on head and neck paraganglioma of the lateral cervical region, specifically carotid body and vagal paragangliomas.

Phenotype and Variations

Paragangliomas are typically painless, slow-growing lateral neck masses, often incidentally detected. When symptomatic, patients can describe difficulty with tongue movement, throat fullness, cough, voice change, and trouble swallowing. Rarely, head and neck paragangliomas secrete catecholamines leading to potential complaints of excessive sweating, headache, flushing, palpitations, and chest or abdominal pain. Thorough personal and family medical histories

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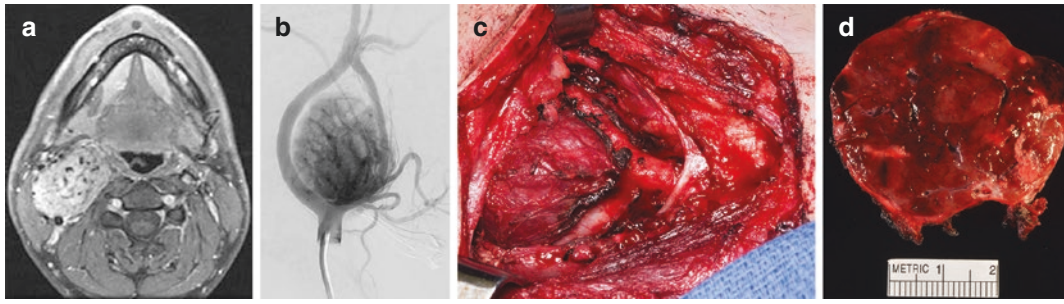

Fig. 12.1 (**a**) T1, post-gadolinium magnetic resonance imaging study demonstrating a hypervascular mass with multiple flow voids at the level of the carotid bifurcation consistent with a carotid body paraganglioma. The internal and external carotid arteries are splayed as a result of the tumor. (**b**) Common carotid artery cervical angiogram demonstrates a large hypervascular carotid body paraganglioma. (**c**) Gross pathologic carotid body paraganglioma sectioning shows a red-pink, smooth cut surface, with focal embolization changes. The tumor cells were found to be positive for chromogranin and negative for AE1/AE3. (**d**) Intraoperative image demonstrating a large paraganglioma at the bifurcation of the common and external carotid arteries

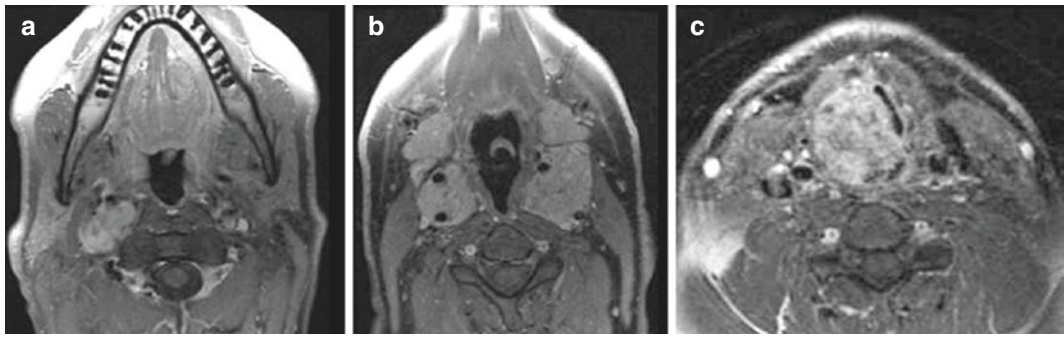

Fig. 12.2 (**a**) Patient with multiple cervical paragangliomas. Magnetic resonance T1, post-gadolinium imaging demonstrates multiple enhancing masses with internal flow voids. This image depicts a right neck vagal paraganglioma. (**b**) Bilateral carotid artery paraganglioma with splay of the internal and external carotid artery. (**c**) Right supraglottic paraganglioma with narrowing of the glottic airway. Removed via transoral CO2 laser-assisted approach

can provide information as to the possibility of a spontaneous versus hereditary paraganglioma disease pattern. Exam findings may demonstrate a lateral neck mass that is mobile in an anterior-posterior plane but immobile in a cranio-caudal plane. Cranial neuropathy involving cranial nerves X through XII and Horner's syndrome can be associated with cervical paragangliomas.

Head and neck magnetic resonance imaging with contrast is recommended for mass characterization and to rule out multiple or bilateral lesions (Fig. 12.2b, c). Magnetic resonance imaging findings show hyperintensity on T2-weighted images and a distinct pattern on T1-weighted contrast-enhanced imaging with evidence of flow voids [8]. Radiographically, these flow voids produce a "salt and pepper" appearance on post-contrast images. Carotid body paraganglioma can splay the internal and external carotid artery producing an imaging finding termed the "lyre sign" (Fig. 12.1a–c). Vagal paraganglioma typically displaces the great vessels medially (Fig. 12.2a), while tumors of the sympathetic trunk displace the vessels anterolaterally [5, 9]. If a genetic predisposition is suspected or confirmed, [18F]-DOPA positron emission tomography (PET) is the preferred diagnostic imaging modality to detect potential multiple paraganglioma tumor sites with high levels of both sensitivity and specificity [10, 11]. In a retrospective

study published by El-Rabadi et al. in 2016, 28 consecutive patients were retrospectively investigated after undergoing computed tomography (CT) and combined [18F]-DOPA-PET/CT imaging. All patients were clinically suspected to have a paraganglioma prior to imaging, and the final diagnosis was confirmed by histologic analysis or clinical follow-up. These 28 patients were found to have a total of 45 paraganglioma lesions. On a per-patient basis, the sensitivity and specificity for CT versus [18F]-DOPA-PET/CT were 86.7% and 84.6% versus 100% and 100%, respectively. If a secreting paraganglioma is suspected, urinary or plasma fractionated metanephrines are obtained. Fractionated metanephrines are more sensitive and preferred over catecholamine concentration measurements [12].

Etiology

The paraganglia serve a similar functional purpose throughout the body, acting as neuroepithelial structures that can respond to both reduced PaO2 and inspired O2 concentration [13]. When stimulated, the paraganglia release neurotransmitters that result in increased ventilation, heart rate, and blood pressure [14, 15]. The carotid body is the largest [16] and most important oxygen sensing paraganglion within the head and neck. It is derived from the mesoderm of the third branchial arch and neural crest tissue of ectodermal origin [13]. The carotid body is located within the periadventitial tissue [17] at the medial aspect of the carotid bifurcation and innervated by the glossopharyngeal nerve. The average dimension of the carotid body in adults is 1.7 × 2.2 × 3.3 mm [18]. The carotid body is made up of two primary cell types: chief cells and sustentacular cells [16]. The chief cells serve a chemoreceptive function and are classically arranged in small nest-like arrangements called *zellballen*. The sustentacular cells play a supportive role and encase the chief cells with characteristics similar to Schwann cells [13]. Other paraganglionic tissue throughout the body is arranged in a similar histological configuration as the carotid body [16]. Likewise, pheochromocytoma and paraganglioma from both sympathetic and parasympathetic origins are histologically similar [19]. Immunohistochemical markers of paraganglia cells show positivity for neuroendocrine markers such as CD56, chromogranin, neuron-specific enolase, and synaptophysin (Fig. 12.1d) [20, 21]. Paraganglioma can be associated with both heritable and nonheritable etiologies. Numerous genes have been identified in relation to heritable paraganglioma, and this will be discussed in a subsequent section. Most nonheritable paragangliomas are sporadic in nature; however, carotid body paraganglioma can arise in the setting of chronic hypoxemia. The original study to detect a possible role of low atmospheric oxygen levels and carotid body tumor development was published in 1976 and reported that Peruvians living at higher altitudes had larger carotid bodies [22]. The exact etiology of carotid body tumor development in the setting of high altitude environments is incompletely understood. It is postulated that a chronic hypoxic state can lead to chief cell hypertrophy, followed by diffuse hyperplasia and then possible neoplastic development [16]. Individuals living at an altitude above 2000 m demonstrate an increased risk of carotid body tumors, and the incidence increases in direct relation to altitude [22–24]. Vagal paragangliomas are significantly less common than those originating from the carotid body and jugular foramen. These tumors generally arise from one of three vagal ganglia within the neck, most commonly the nodose ganglion [2].

Genetics

Current recommendations state that a genetic etiology is more likely for patients who have a positive family history, are male in sex, are less than 40 years of age, and have a history of multiple or malignant head and neck paraganglioma or a history of phenochromocytoma [1]. Familial disease represents approximately 10–15% of all paraganglioma cases [25]. The most common genes involved code for the subunits of the succinate dehydrogenase (SDH) or mitochondrial II complex. These genes include SDHD, SDHB, SDHC,

and SDHAF2 [4]. Failure of developmental apoptosis and pseudohypoxic drive are potential mechanistic processes that lead to paraganglioma development in the setting of SDH mutations [26]. Heritable head and neck paraganglioma can also result from non-SDH mutations, such as in patients with von Hippel-Lindau disease (VHL gene), multiple endocrine neoplasia type 2 (RET gene), and neurofibromatosis type 1 (NF1 gene) [27]. Gene inheritance from a parent or de novo mutations can both lead to an individual with a hereditary paraganglioma syndrome. The incidence of de novo mutations is not known. SDHD mutations are the most frequent genetic cause of head and neck paraganglioma [4]. The SDHD gene codes for a subunit of the mitochondrial complex II, an important element of the Krebs cycle electron transport chain [26]. SDHD inheritance patterns also demonstrate imprinting, with the phenotype presenting in individuals who inherited the pathogenic gene from the father. When the SDHD gene is inherited from the mother, the phenotype is not observed [25]. This phenomenon occurs by way of DNA methylation and subsequent silencing of the SDHD allele [1]. Paraganglioma in the setting of SDHD mutations is associated with primarily head and neck lesions, while SDHB mutations predominately are related to abdominal paraganglioma and pheochromocytoma [1]. Multiple paraganglioma tumors have been reported to occur in 10–20% of sporadic paraganglioma; however, multifocal occurrence is observed in up to 80% of familial cases [7].

In a 2012 study, 175 patients with 224 head and neck paragangliomas were reviewed from a single German institution in a retrospective, nonrandomized fashion [1]. Of the 224 total tumors, 68 were within the carotid body and 26 were found on the vagus nerve. Additionally, 87 tumors were jugular, 32 were tympanic, and 11 tumors were reported at other head and neck sites. Thirty-four of 86 (39.5%) genetically tested individuals were found to have a SDH gene mutation, and 1 (1.2%) individual had a von Hippel-Lindau gene mutation. Among the patients with SDH mutations, 22 were SDHD mutation carriers, 7 were SDHC mutation carriers, and 5 were SDHB mutation carriers. Twenty-two of 34 (64.7%) patients with SDH mutations had multiple paraganglioma tumors. Specifically, 18 of 22 (81.8%) SDHD gene mutation carriers, 3 of 7 (42.9%) SDHC, and 1 of 5 (20%) were found to have multiple tumor locations. In the entire patient cohort, 11 (6.3%) had a malignant paraganglioma with 7 patients demonstrating a SDH gene mutation, 3 without a genetic alteration, and 1 patient without genetic analysis. Importantly, this study found that the occurrence of catecholamine-secreting paraganglioma tumors of the head and neck is extraordinarily rare with only 1 of 175 being a hormonally active tumor. Piccini et al. performed genetic analysis on 79 consecutive patients with 114 head and neck paragangliomas [4]. The mean age at tumor presentation was found to be significantly lower in the 36 patients with genetic mutations versus the 43 patients in the wild-type category (39.7 ± 14.9 years versus 50.8 ± 16.8 years, $p < 0.01$). Including all patients, 45.6% (36 of 79) were found to have a germline mutation. In patients initially categorized with a single sporadic head and neck paraganglioma in the absence of a positive family history, genetic testing revealed a germline mutation in 18.8% (10 of 53) of individuals. This result is similar to other current reports published on French, Italian, and Spanish populations between 2007 and 2009 where between 14.3% and 22.2% of sporadic paraganglioma patients were ultimately found to have genetic mutations [28–30]. Mutations in the SDHD gene were the most common accounting for 80.5% (29 of 36) of the genetic alternations observed.

Natural History

The natural history of paragangliomas was investigated by Langerman et al. in 43 patients with 47 cervical paragangliomas, either carotid body or vagal tumors, retrospectively reviewed over a mean follow-up period of 5 years [31]. The patients in this group did not have a history of rapid neck mass growth, pain, or lymphadenopathy; the authors chose this treatment course based on either patient preference, advanced age, or the presence of a contralateral cranial nerve deficit.

Computed tomography or magnetic resonance imaging was used to follow tumor growth. Nineteen (42%) tumors remained stable, 17 (38%) grew, and 9 (20%) regressed in size. Interestingly, mean growth rate was 2.0 mm/year among the 17 growing paraganglioma, indicating that many cervical paragangliomas do not rapidly change in size.

In contrast, Jansen et al. examined 26 patients with a total of 48 paragangliomas (20 carotid body, 17 vagal and 11 jugulotympanic) and found that a volume increase of 20% was observed in 60% of lesions over a follow-up period of 4.2 years [32]. However, 40% of paraganglioma tumors did not demonstrate any growth, and the median growth rate was only 1.0 mm/year.

Treatment

Treatment options for head and neck paraganglioma include observation, radiotherapy, and surgical excision. Patient age and comorbidity status, tumor location and growth rate, catecholamine secretion, tumor multicentricity, cranial nerve deficits, and sporadic versus hereditary tumors are key factors to consider when determining an optimal treatment strategy. As a result of tumor vascularity and association with nearby neurovascular structures, surgical excision can portend a high risk of blood loss, stroke, phonation and deglutition dysfunction, and even death. Potential high levels of surgical morbidity and recent published evidence [5, 32] that cervical paragangliomas demonstrate slow or even absent growth have led to increased utilization of a "wait and scan" observation approach [2]. Nevertheless, surgery remains the best treatment option in a number of circumstances for cervical paragangliomas, and treatment algorithms will herein be discussed.

Carotid Body Paraganglioma

Surgery is the gold standard of treatment for resectable carotid body paraganglioma due to the risk of adjacent neurovascular compression with progressive tumor growth and a small, but non-zero, risk of malignancy [3]. However, surgery can carry a high risk of perioperative morbidity, and patients must be carefully selected to avoid a catastrophic surgical complication. In order to best select surgical candidates, an angiographic study should be obtained to confirm the diagnosis, evaluate the contralateral carotid system, assess the collateral intracerebral vasculature, and embolize the tumor, if indicated. For patients who are poor surgical candidates and those with extensive tumor involvement around the carotid artery or multiple tumor sites, observation and radiotherapy are viable treatment alternatives.

Successful surgical outcome is defined as absence of tumor recurrence after complete resection. In young, healthy patients undergoing complete resection of carotid body tumors, local control rates are most recently reported to be between 94% and 100% [33–35]. Predicting operative morbidity and mortality can be challenging due to patient and tumor heterogeneity. The most established classification system to determine operative complexity and risk is the Shamblin grade, which separates carotid body tumors into three groups [36]. Group 1 tumors do not encase the internal or external carotid arteries, group 2 tumors partially encase the carotid arteries, and group 3 tumors completely encase the carotid arteries. A particular limitation of the Shamblin classification is that tumor infiltration, rather than just the degree of carotid encasement, can only be determined intraoperatively and is an important factor in predicting the risk of surgical resection [3]. This is demonstrated by numerous published studies that have reported on the variable utility of Shamblin tumor classification. In one series of 27 tumor resections, 33% of patients experienced a cranial nerve injury; multivariate analysis showed that only tumor size, not Shamblin grade, predicted cranial nerve injury ($p = 0.045$) [37]. However, in a 2012 retrospective study by Power et al., 131 patients underwent resection of 144 carotid body tumors, and the Shamblin classification was found to correspond with a higher risk of neurovascular complications [38]. These conflicting results underscore the need for future larger studies to better understand

the predictive value of the Shamblin grading system and tumor size on surgical risk profile.

For patients who elect to undergo surgical excision, preoperative tumor embolization may be considered. Abu-Ghanem et al. published a meta-analysis in 2015 on 15 retrospective studies including a total of 470 patients with carotid body paraganglioma. The analysis found no significant difference with regard to blood loss, vascular injury, operative time, cerebrovascular accident, cranial neuropathy risk, or duration of hospital stay between the embolization and non-embolization treatment groups [3]. Possible complications of embolization include pain, post-embolization fever, transient ischemia attack, and cerebrovascular accident [39]. Taking into account the benefits and potential risks of embolization, the authors concluded that tumors larger than 3 cm and Shamblin class II or III lesions should be considered for preoperative embolization but that no clear evidence or guideline indicates when embolization is most appropriate.

Radiotherapy of carotid body tumors is generally reserved for tumors determined to portend an unacceptable risk of severe perioperative complications; however, some institutions cite a similar rate of tumor control as compared with surgical resection and a potentially lower complication risk [40]. In a 2008 study, 23 of 24 carotid body tumors were successfully treated with radiotherapy [41]. The mean follow-up period was 10.6 years among the entire head and neck paraganglioma cohort examined. Twenty-two patients had not previously been treated, one patient had prior surgery, and one patient had prior surgery and radiation treatment. The patient who had undergone prior surgery and radiation was the single patient to fail radiotherapy in this report.

Vagal Paraganglioma

Historically, surgery was the gold standard treatment for vagal paragangliomas due to their relatively accessible location within the lateral neck. However, recent evidence has demonstrated that many lesions are slow growing and can safely be observed or treated with radiotherapy, while avoiding potential operative neurovascular complications. A 2013 meta-analysis included 226 vagal paraganglioma treated surgically from 15 studies [6]. Mean duration of follow-up was 86.7 months. Disease control with surgery was achieved in 93% of patients. However, there was a significant increase in postoperative cranial neuropathy; 147 cranial nerves were damaged preoperatively, and this increased to 445 damaged cranial nerves postoperatively. Importantly, a functional vagus nerve was only preserved in 11 of 226 (4.9%) surgically resected vagal paragangliomas. Additional perioperative morbidity also included aspiration/pneumonia (10.2%), CSF leak (2.6%), wound infection (2.2%), and stroke (2.2%). As this study demonstrates, complete resection of a vagal paraganglioma requires removal of the involved vagus nerve resulting in velopharyngeal insufficiency, pharyngeal numbness, and vocal fold paralysis. This potential surgical morbidity has driven the shift in treatment strategy to favor observation and radiotherapy protocols. Nevertheless, surgery may be indicated when there is compression of nearby critical neurovascular structures, concern for malignant vagal paraganglioma, or a catecholamine-secreting tumor.

The efficacy and safety of radiotherapy treatment for vagal paragangliomas are highlighted in a 2014 study by Gilbo et al. In this series, 156 benign carotid body, vagal, and jugular bulb paragangliomas were reviewed retrospectively at a single institution [42]. All tumors were treated with 45 Gy in 25 fractions. Overall local control rates (defined as no increase in tumor size) at 5 and 10 years were 99% and 96%, respectively. Five of 156 patients recurred (4 jugular bulb paraganglioma and 1 carotid body tumor). No patient experienced a radiotherapy complication. Presently, intensity-modulated radiotherapy has become more common than conventional radiotherapy to limit radiation exposure to surrounding structures by way of conformal techniques. Stereotactic radiosurgery is an alternative for patients with skull base paraganglioma less than 3 cm and in individuals who are unable to complete a fractionated radiotherapy protocol [42].

Observation of vagal paragangliomas can also be an appropriate strategy for selected patients without worrisome clinical features. A 2005 retrospective study by Bradshaw et al. reported a low rate of progressive cranial nerve dysfunction in this treatment group [43], with only 3 of 40 (8%) patients with vagal paragangliomas developing cranial nerve palsy when a "wait and scan" protocol was used over a mean follow-up 8.5 years. No validated imaging algorithms are currently available; however, repeat magnetic resonance imaging every 12 months is recommended [2].

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To assist the reader in gaining familiarity with available evidence, the following rating system has been used to indicate key references for each chapter's content:
***: Critical material. Anyone dealing with this condition should be familiar with this reference.
**: Useful material. Important information that is valuable in in clinical or scientific practice related to this condition.
*: Optional material. For readers with a strong interest in the chapter content or a desire to study it in greater depth.

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Angiosarcoma

13

Katherine A. Lees, Christoph M. Prummer, and Jeffrey R. Janus

Genetic diagnosis	No
Genetic etiology	Unknown
Level of evidence: treatment	Low
Evidence	Case series; single meta-analysis for prognostic factors

Introduction

Angiosarcoma (AS) is a rare but aggressive mesenchymal tumor arising from vascular or lymphatic endothelial cells. It accounts for <2% of all soft tissue sarcomas and approximately 10% of sarcomas occurring in the head and neck [1, 2]. Primary cutaneous angiosarcomas that arise sporadically represent the majority of these tumors, but they can also occur in the setting of previous radiation, chronic lymphedema, or in the deep soft tissues or parenchymal organs. The incidence has been gradually increasing since the 1970s, which is likely due in part to the greater use of radiation treatment for breast and other cancers. It carries a poor prognosis due to delays in diagnosis, extensive treatment modalities, and a high rate of locoregional recurrence and distant metastasis.

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Because of its rarity and poor prognosis, most of the available literature is composed of single-institution case series and small clinical trials. The focus of this chapter will be on diagnosis and treatment of head and neck angiosarcomas.

Phenotype and Variations

Primary cutaneous angiosarcomas represent over half of all angiosarcomas, and nearly 60% of these arise in the head and neck [1]. The prototypical patient is an elderly, white male, with almost 90% of tumors occurring in the Caucasian population with a 2:1 male predilection [3]. Tumors often present with insidious onset of an ill-defined red, purple, or blue lesion on the scalp or face (Fig. 13.1). Many lesions initially have a bruise-like appearance but as they progress may become nodular, ulcerated, or painful (Fig. 13.2) [4]. Clinically, they may be mistaken for benign hemangioma, atypical vascular lesions (particularly in a previously irradiated area), epithelioid hemangioendothelioma, or Kaposi sarcoma. Due to their indolent onset and similar appearance to other vascular lesions, diagnosis can be delayed up to 1 year or more [4].

On gross inspection, cutaneous angiosarcomas are dark red with a soft, sponge-like consistency and diffuse hemorrhagic appearance (Fig. 13.3). The dermis is most extensively involved by tumor, but invasion into subcutaneous tissue, fascia, and

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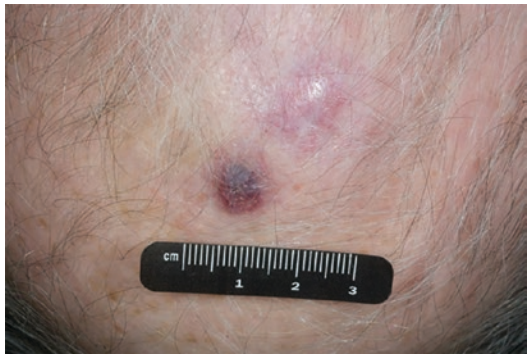

Fig. 13.1 Scalp angiosarcoma. These tumors often present insidiously as a purplish, bruise-like lesion that are often mistaken for benign processes

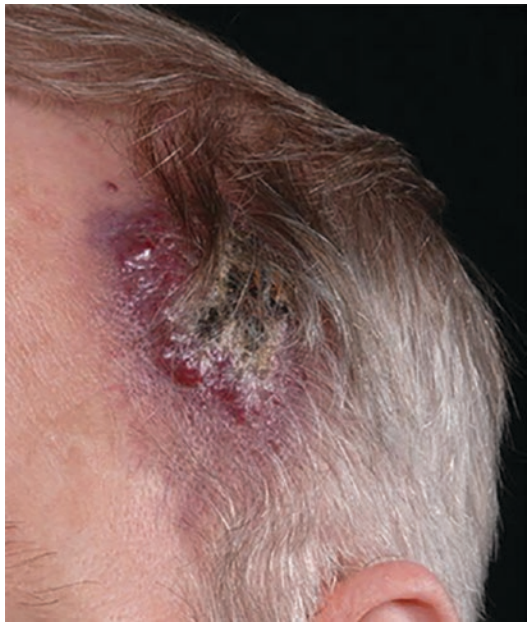

Fig. 13.2 As angiosarcomas progress, they can become raised and ulcerated. This tumor also demonstrates ill-defined borders

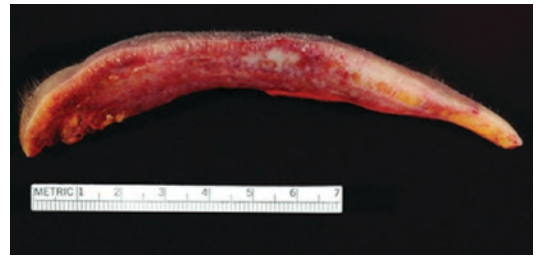

Fig. 13.3 Angiosarcoma with extensive infiltration of the dermis and subcutaneous tissues

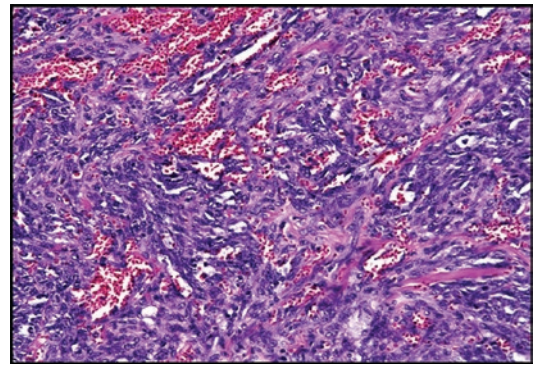

Fig. 13.4 Angiosarcoma (H&E). Microscopic examination reveals a haphazard distribution of atypical vascular channels. Tumor cells are characterized by marked pleomorphism, hyperchromatism, and elevated mitotic activity

other deep structures can occur. Histologically, tumors can vary significantly based on the extent of differentiation. Well-differentiated tumors display haphazard networks of vascular channels with a single layer of abnormal, pleomorphic endothelial cells (Fig. 13.4). These endothelial cells may exhibit an epithelioid appearance, posing a diagnostic challenge for surgical pathologists. As tumors become less well-differentiated, they may develop multilayered endothelial linings and intraluminal papillary projections. Poorly differentiated tumors often lack distinct vascular structures or framework, making them difficult to distinguish from other sarcomas or carcinomas. In these particularly challenging cases, immunohistochemistry for endothelial markers is an important tool to confirm the diagnosis or rule out other pathologies. CD31 is the most sensitive marker for angiosarcoma, which also stains positive for CD34, von Willebrand factor, and VEGF. More recently, Fli-1 and ERG have been adopted as sensitive and specific markers of endothelial differentiation to distinguish vascular tumors, especially those with epithelioid components, from other malignancies (Fig. 13.5) [5, 6].

Postradiation angiosarcoma is most commonly described after radiotherapy for breast cancer, although it can occur at any site in the body. These secondary angiosarcomas typically

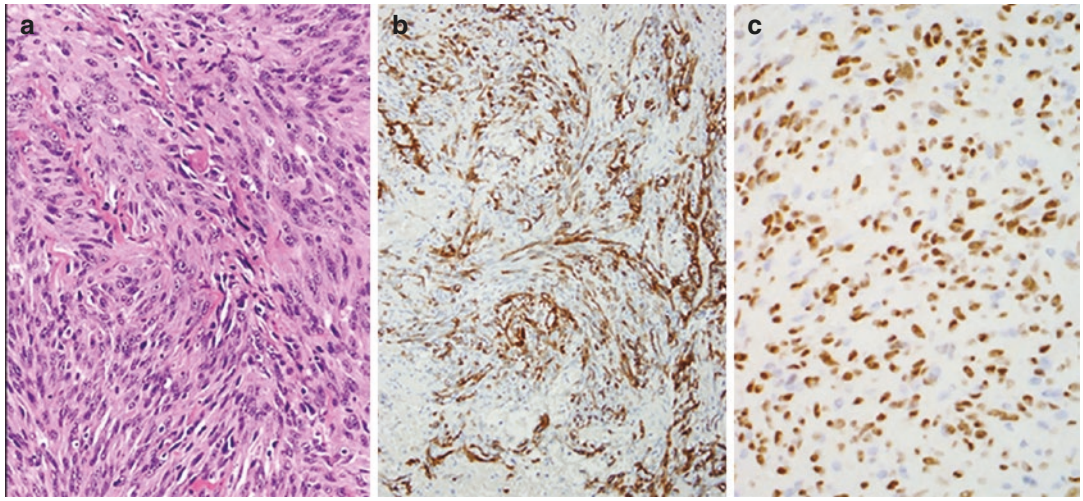

Fig. 13.5 Angiosarcoma (H&E, CD34, FLI-1). Immunohistochemical stains are often required to confirm endothelial origin of vascular neoplasms. Immunohistochemical stains for CD34 and FLI-1 show cytoplasmic and nuclear staining, respectively, in angiosarcoma

arise 5–10 years after completion of radiation treatment, and studies of breast cancer patients have shown a 5- to 16-fold increase in the risk of angiosarcoma after radiotherapy [7, 8]. In a review of laryngeal angiosarcomas, 6 out of 16 patients (37.5%) had a history of head and neck radiation [9].

Chronic lymphedema is another risk factor for the development of angiosarcoma, an association known as Stewart-Treves syndrome. Initially described in patients with lymphedema following mastectomy, this association has also been found in other disease processes causing long-standing lymphedema, such as filarial parasitic infection, Milroy's disease, and Klippel-Trenaunay syndrome.

Deep soft tissue angiosarcomas, which represent about 10% of all tumors, occur equally in all age groups and are the most common subtype occurring in the pediatric population [10–12]. They frequently develop in patients with underlying genetic conditions such as Maffucci syndrome, neurofibromatosis, and Aicardi syndrome. These tumors more often display epithelioid pathology, which can make histologic diagnosis challenging. Hepatic angiosarcoma, which is the most common parenchymal angiosarcoma, is associated with environmental exposures such as vinyl chloride and thorium dioxide (Thoratrast) [13].

Although the skin is the most common subsite for angiosarcomas in the head and neck, other areas including the thyroid, sinonasal tract, oral cavity, and salivary glands have been described in small case series in the literature. Thyroid angiosarcoma is found most commonly in people living in the mountainous Alps of Italy, Switzerland, and Slovenia and is thought to be related to the prevalence of iodine-deficient goiter in these regions [14]. A series of sinonasal angiosarcoma found that they were diagnosed at a younger age and portended a better overall prognosis [15].

Etiology

Angiosarcomas arise from the malignant transformation of endothelial cells, almost exclusively within small blood vessels or lymphatic channels; it is extremely uncommon to have malignancies of large vascular structures. Although the majority of these tumors occur sporadically, known independent risk factors include radiation, chronic lymphedema, and chemical exposure. Although rare, there are several reports of angiosarcoma arising within benign vascular lesions

such as hemangiomas or vascular malformations [16]. Sarcomatous malignant change within benign nerve tumors such as schwannomas and neurofibromas, such as those seen in neurofibromatosis, can produce angiosarcoma [17].

Angiosarcomas are a heterogeneous group of tumors with regard to the genetic and molecular abnormalities they harbor. Unlike other sarcomas such as Ewing sarcoma, there are no unique chromosomal translocations associated with their development. There are also no specific genetic mutations universal among angiosarcomas, and many of the abnormalities found are also common in other sarcomas and carcinomas.

Because angiosarcoma is thought to derive from the malignant proliferation of endothelial cells, the focus of much research has been on alterations in angiogenesis. Vascular endothelial growth factor A (VEGF-A) has been most widely investigated due to its prominent role in promoting angiogenesis and vascular permeability. In several studies, VEGF-A has been found to be overexpressed in angiosarcoma compared to benign vascular tumors [18, 19]. When VEGF-A binds to its main receptor, VEGFR-2, it leads to pro-angiogenic signaling; interestingly, decreased expression of VEGFR-2 has been found to be associated with worse prognosis in one study [18].

Mutations involving the p53 gene (*TP53*), a tumor suppressor protein involved in regulating the cell cycle, are the most common abnormalities in human cancers, including angiosarcoma. Several studies have demonstrated increased expression of abnormal p53 protein in angiosarcoma compared to benign controls [20–22]. In an interesting study by Farhang et al. [23], the authors found that p53-deficient mice had a high incidence of hemangiosarcoma. However, when they also deleted one or both of the VEGF alleles in these mice, the incidence of hemangiosarcoma significantly decreased from 61.9% to 8.7%, suggesting that abnormalities in both the p53 pathway and VEGF expression are implicated in the development of angiosarcoma.

Alterations in the MAPK and AKT-mTOR pathways, which are both involved in endothelial cell signaling and angiogenesis, have also been found in many angiosarcomas. Greater than 50% of tumors demonstrated an alteration in the MAPK pathway, and tumors showed upregulation of the AKT-mTOR pathway with increased expression of downstream components compared to normal controls [10, 20, 24]. Staining for c-Kit, which is a receptor tyrosine kinase, has shown overexpression in 58% of angiosarcomas compared to no staining in normal endothelial cells, suggesting a possible application for agents targeting c-Kit as part of the treatment regimen [10]. MYC amplification is a common finding in radiation-induced and lymphedema-associated angiosarcoma but is not commonly seen in sporadic tumors. Although these alterations do not indicate a single mutation or abnormality leading to development of these tumors, they provide useful information regarding potential treatment targets for agents such as mTOR or MAPK inhibitors as part of the treatment regimen.

Natural History

Angiosarcoma is a notoriously aggressive malignancy with a high propensity for recurrence and distant metastasis and overall poor prognosis. Because tumors often involve both vascular and lymphatic channels, nodal and distant metastasis rates are similar at the time of diagnosis, around 10–15% for nodal disease and 10% for distant metastasis, usually to the lungs. There is a high rate of satellite lesions or multifocal primary tumors at the time of diagnosis, around 40% from several series in the literature [4, 25–28]. Additionally, one study found that greater than 50% of patients that were clinically stage T1 were found to have T2 tumors on pathology, suggesting that the clinical diagnosis may underestimate the true extent of tumor invasion [4].

In a recent meta-analysis by Shin et al. [29], the overall 5-year survival rate was estimated at 35% for head and neck angiosarcomas. The authors identified several factors associated with worse prognosis, including age >70 years, tumor

size >5 cm, location on the scalp, and positive margins after surgical excision. Around 45% of patients develop locoregional recurrence after treatment, and about 35% go on to develop distant metastatic disease. The most common site of distant metastasis is the lung, followed by the liver and bone. Lung metastases are often described as thin-walled cysts or nodules located in the subpleural area; these lesions can lead to pneumothorax and other severe respiratory complications in these patients [30].

Treatment

Angiosarcoma is complex to treat and requires multimodality therapy. Surgery, radiation, and chemotherapy all have significant roles, though no prospective studies have been implemented thus far to provide stringent treatment guidelines. Treatment strategies are somewhat established for primary cutaneous angiosarcoma, as it is most frequently encountered.

Surgery

When possible, negative margin resection with postoperative radiation therapy is considered standard of care treatment for cutaneous angiosarcoma [31, 32]. Given the rather insidious nature of the disease, margins can be difficult to clear. This is due in part to the pathophysiology of the disease with involvement of the lymph channels and due in part to diagnostic difficulties on frozen section pathology analysis. With this in mind, the recommended margins for resection of cutaneous angiosarcoma are 3–5 cm [33]. Pawlik et al. note that the average defect size for surgical patients upon resection of scalp angiosarcoma was 14.3×11.3 cm, making primary closure of most of these wounds impossible [4]. Thus, availability of a reconstructive surgeon and a progressive algorithm based on defect size is imperative. Timing of reconstruction is also a bit of a conundrum, as histopathologic challenges and pushing boundaries may lead to frequent delayed positive margins, with rates in some studies as high as 50–78% [4, 34]. Obviously, these instances necessitate further resection if possible and have the potential to disrupt attempts at primary reconstruction. If feasible, delayed reconstruction may be contemplated, particularly in instances of narrow margins. Another strategy is the use of mapping biopsies, either preoperatively or intraoperatively, to determine the extent of disease and conceptualize reconstruction.

Radiation Therapy

Postoperative adjuvant radiation therapy is another critical component of treatment in cutaneous angiosarcoma. In a review of angiosarcoma of the scalp and face, the Mayo Clinic found that multimodality therapy that included radiation therapy significantly improved overall survival, recurrence-free survival, and locoregional control in a cohort of 55 patients [35]. This has been corroborated by multiple other institutional reports [36, 37]. Acknowledging the lack of clinical trials to support concrete guidelines, general established trends for radiation administration are 4000–7000 cGy in 10–35 fractions, with the median dose being around 6000 cGy. The precise dose and number of fractions vary based on whether radiation therapy is primary treatment or adjuvant and margin status if resection has been performed [35, 37] (Table 13.1). With many cutaneous angiosarcomas occurring on the face and neck, radiation dosing and fields can be limited by critical structures such as the eye and brain. Other avenues of radiation administration, such as proton beam therapy, have yet to be explored.

Table 13.1 Radiation dosages by treatment plan

Clinical setting	Radiation dose (cGy)	Fractions
Adjuvant radiation, negative surgical margins	4500–6000	25–30
Adjuvant radiation, positive surgical margins	6000–6600	30–33
Definitive radiation	6600–7000	33–35

Chemotherapy

The role of chemotherapy in the treatment for cutaneous angiosarcoma is still under investigation. Chemotherapy using a doxorubicin-based regimen had long been regarded as the preferred option for unresectable or metastatic disease. However, the management of these difficult tumors changed considerably when Fata et al. and Nagano et al. showed that taxanes were effective for the treatment of cutaneous angiosarcoma, with an 89% response rate for paclitaxel and 67% for docetaxel [38]. In a follow-up study by Fujisawa et al., patients treated initially with a combination of taxane chemotherapy and radiation therapy showed a 94% response rate, with multiple patients achieving either complete or partial remission [39]. This treatment regimen proved more effective than primary surgery and radiation therapy for a matched cohort, which is in line with other studies showing high response rates to taxane chemotherapy [40]. Of note, that cohort consisted mostly of patients with large (>5 cm) primary tumors, which historically have had a dismal prognosis. Building on this study, several authors have also shown an advantage to maintenance taxane chemotherapy beyond the period of radiation therapy, citing better control of distant metastasis and longer overall survival [39, 41–43]. Unfortunately, for patients that develop distant metastasis following chemoradiation, there are currently no salvage regimens with proven efficacy [39].

Given the poor overall prognosis of patients with this disease, as well as the challenging side effect profile associated with available chemotherapeutic agents, multiple researchers are investigating novel therapies. Since angiosarcomas have been shown to overexpress multiple vasoactive epithelial growth factor (VEGF) receptors, several studies evaluating antiangiogenic agents including the VEGF monoclonal antibody bevacizumab have been undertaken. Though early clinical trials showed considerable promise, a recent randomized phase II clinical trial performed by Ray-Coquard et al. did not demonstrate any statistically significant advantage in using bevacizumab in conjunction with paclitaxel vs. paclitaxel alone with regard to overall and progression-free survival. Also, the combination arm experienced considerably more serious side effects [44]. Thus, the recommendation for the routine use of bevacizumab cannot currently be made. However, this lack of effect is thought to be due to gene mutations in vascular growth factor tyrosine kinases, and further investigation is being pursued. Such investigations may incorporate the use of genome sequencing and gene therapy, allowing more effective and accurately targeted treatments.

Summary

Angiosarcoma is a complex neoplastic process that has a high propensity for metastasis and a challenging prognosis. In most locations, particularly in the most common cutaneous presentation, it requires multimodality therapy in the form of surgery, radiation, and in certain circumstances, chemotherapy. Despite low overall long-term survival, many patients have survived the disease with early and aggressive therapy.

To assist the reader in gaining familiarity with available evidence, the following rating system has been used to indicate key references for each chapter's content:
***: Critical material. Anyone dealing with this condition should be familiar with this reference.
**: Useful material. Important information that is valuable in in clinical or scientific practice related to this condition.
*: Optional material. For readers with a strong interest in the chapter content or a desire to study it in greater depth.

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Part III

Vascular Tumors: Site-Specific Considerations

14 Periocular Vascular Tumors: Infantile Hemangioma

Erin Herlihy and Marcelo Hochman

Level of evidence: treatment	Moderate
Evidence	Medical therapy: randomized controlled trials, systematic reviews Other treatments: case series

Diagnosis

Diagnostic Testing

Periocular infantile hemangiomas are typically diagnosed clinically, though additional testing may occasionally be required. Differential diagnosis includes rhabdomyosarcoma, neuroblastoma, lymphatic malformation, cellulitis, and orbital cysts (Fig. 14.1).

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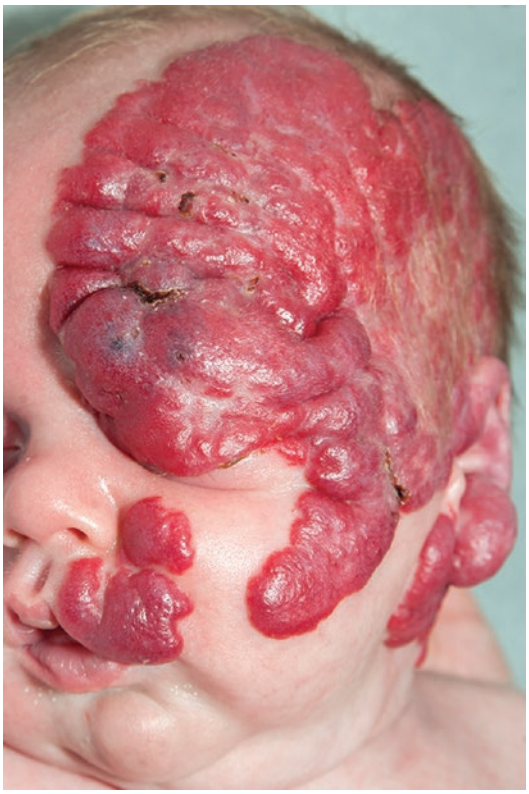

Fig. 14.1 Proliferating segmental infantile hemangioma causing visual axis obstruction. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

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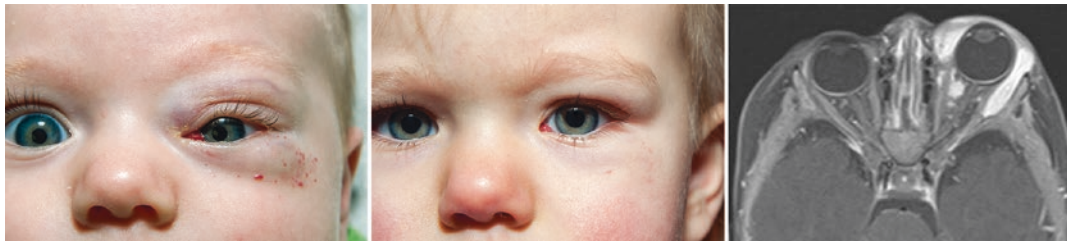

Fig. 14.2 Infantile hemangioma involving orbit, eyelids and conjunctiva, pre- and post-propranolol therapy. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer). (Images courtesy of Seattle Children's Radiology, Giridar Shivaram, Eric Monroe and Kevin Koo)

Infantile hemangiomas are not clearly identified on plain radiographs. Soft tissue enlargement may be seen, along with orbital enlargement if an orbital lesion grows rapidly during infancy (Fig. 14.2). However, these findings are not specific or diagnostic. Ultrasonography demonstrates an irregular mass with variable reflectivity and may be helpful to monitor the extent of orbital involvement and tumor size. A-scan ultrasonography may demonstrate areas of low internal reflectivity representing solid, hypercellular endothelial cell proliferation, moderate reflectivity of vascular channels, and high reflectivity of fibrous septae separating tumor lobules [1].

Computed tomography (CT) can be used to monitor tumor growth and to evaluate the relationship of the mass to other orbital structures. Infantile hemangiomas often appear as homogeneous soft tissue masses without destruction of orbital bone. They may be well-defined or irregular with infiltration of surrounding tissue and may occur in the anterior orbit or in the extraconal space with posterior extension. Infantile hemangiomas enhance after contrast administration, and contrast can be helpful in defining tumor borders and identifying feeder vessels. Infantile hemangiomas typically appear as well-circumscribed, lobulated tumors on magnetic resonance imaging (MRI) studies. They are of intermediate intensity on T1-weighted studies and are moderately hyperintense on T2 MRIs. The tumor may enhance following gadolinium injection, and fat suppression can help with tumor visualization.

Angiography is rarely used diagnostically for infantile hemangiomas but may be useful in planning surgical intervention for lesions unresponsive to medical therapies. Likewise, tissue biopsy is rarely required. However, tissue sampling may be imperative for certain orbital lesions to aid differentiation from lymphangioma, rhabdomyosarcoma, or metastatic neuroblastoma.

Ophthalmologic Evaluation

A thorough ophthalmologic examination and frequent ophthalmologic follow-up are important. Age-appropriate visual acuity assessment is the first step in determining whether a periocular lesion is visually significant. Visual behavior, fixation and tracking, and response to monocular occlusion can be subjectively assessed, and babies as young as several months of age can undergo preferential looking tests with Teller acuity cards. Toddlers can be tested with Lea or Allen pictures and older children with letter optotypes. Pupillary responses can give information regarding optic nerve function. The ophthalmologist will assess for strabismus, motility deficits, or obstruction of the visual axis by periocular lesions or induced ptosis. Cycloplegic refraction detects anisometropic refractive error that can lead to amblyopia. Finally, a dilated exam allows assessment of the optic nerve and retina. Photographs can be useful in monitoring natural history or response to treatment.

Management

Accurate diagnosis is essential for favorable treatment outcomes, because treatment approaches differ for different vascular lesions. IHs that require treatment are often managed with a combination of serial observation and interventions

including systemic therapy, laser treatment, and surgical excision for various phases of IH growth. The treating clinician should be familiar with all treatment options and demonstrate flexibility in combining therapies to achieve the best possible end result. Treatment success is facilitated by family education throughout the process and a multidisciplinary, collaborative approach.

Medical Treatment

Although infantile hemangiomas typically regress spontaneously in early childhood, ptosis and induced anisometropic astigmatism are risk factors for amblyopia (Fig. 14.1). Additional adverse effects of periocular lesions include strabismus, proptosis with lagophthalmos and exposure keratopathy, eyelid skin distortion and ulceration, and optic nerve compression. When periocular lesions threaten visual development or the overall health of the eye, treatment is indicated to reduce tumor volume and preserve vision. Any medical or surgical treatment must be combined with amblyopia therapy to maximize visual recovery.

Vision-threatening hemangiomas have long been successfully treated with topical, intralesional, or systemic corticosteroids [2, 3]. Topical steroids can be effective, especially for superficial lesions, but may be associated with local cutaneous atrophy. Systemic prednisolone, usually dosed 2–3 mg/kg/day, was long the mainstay of treatment, despite serious adverse effects including behavior changes, hypertension, gastrointestinal upset, and adrenal suppression with risks of growth delays and vulnerability to infections. Intralesional corticosteroid injection is also effective in slowing tumor growth and inciting lesion regression, reducing mean induced astigmatism. In one study, a single intralesional injection of 0.3–1.0 mL of a 50:50 mixture of triamcinolone and dexamethasone led to a 63% reduction in mean astigmatism [4]. As with systemic corticosteroid administration, however, intralesional steroid injection has been associated with adrenal suppression [5], as well as eyelid hypopigmentation, periocular calcification, retrobulbar hemorrhage, and ocular penetration. Blindness due to central retinal artery occlusion is a rare and dreaded risk of injected corticosteroid [6]. Figure 14.2 demonstrates the complex extra- and intracranial vascular relationships that may be present.

The fortuitous discovery of the effectiveness of oral beta-blocker therapy in suppressing the growth of and inducing the regression of infantile hemangiomas [9] has changed the treatment paradigm in recent years. Oral beta-blocker therapy has largely supplanted systemic or intralesional corticosteroid administration for vision-threatening lesions (Fig. 14.2). Extensive literature documenting the reduction of tumor growth with minimal side effects has justified this switch [10–14]. A recent randomized controlled trial of 456 children confirmed the effectiveness of oral propranolol 3 mg/kg/day for 6 months [15]. A 2011 review described results in 100 patients from 19 studies treated with oral propranolol for orbital periocular lesions [13]. The youngest child treated was 1 week of age, and the oldest was 18 months (mean 4.8 months). The most common propranolol dose was 2 mg/kg/day, and treatment duration varied between 2 weeks and 1 year, with mean duration of 6.9 months. It was generally recommended that treatment be continued until the proliferative phase was ended (6–12 months of age) or until refraction had stabilized if the lesion had induced astigmatism. Adverse effects were documented in 26 of the 100 cases but were serious enough to require discontinuation of propranolol in only 5 cases. Although there was no standard method of defining successful treatment in the reviewed studies, improvement or resolution of the lesion was observed in 96 of the 100 documented cases. Recurrence of the hemangioma (mild recoloring or rebound growth) occurred in 15% cases after propranolol withdrawal, regardless of the duration of treatment or age of the patient.

An additional study published in 2016 compared the efficacy and time course for treatment of anisometropic astigmatism in a cohort of children treated with systemic propranolol 2 mg/kg/day in three divided doses to a similar cohort treated with intralesional corticosteroid injection. The oral beta-blocker was well-tolerated, and treatment effects were comparable to the steroid

treated group [16]. There have been no randomized controlled studies of propranolol versus corticosteroid therapy, though a 2014 systematic review including 31 studies and 425 patients compared the efficacy and safety of propranolol versus injected corticosteroid for the treatment of periorbital lesions [7]. In most studies, the initial oral propranolol dose was 0.1–1 mg/kg/day and was increased incrementally to 2–3 mg/kg/day. The most common injected steroid treatment was a combination of triamcinolone (40 mg) and betamethasone/dexamethasone (46 mg). The mean response rate was 94.0% for propranolol and 82.3% for corticosteroid, with a nonsignificant difference in rebound growth rate between the two treatments. Astigmatism was reduced in both propranolol and steroid studies, and a total of 31.1% of patients treated with corticosteroids developed amblyopia, compared to 16.7% of propranolol-treated patients. Propranolol seemed to induce more temporary adverse events than intralesional corticosteroids, but most propranolol side effects were considered minimal and benign.

Additional systemic medications, including interferon alpha, vincristine, and cyclophosphamide, have been used successfully to treat large disfiguring periocular hemangiomas, but frequent severe side effects limit their use [8].

Topical timolol maleate 0.25% or 0.5% solution or gel applied to the lesion once or twice daily has also proven effective for treatment of infantile hemangiomas [17]. Topical beta-blocker was initially thought to be most effective for small, superficial, or localized lesions, though recent studies have reported benefit in mixed and even deep lesions [18, 19]. Danarti and colleagues recently demonstrated that timolol maleate 0.5% solution and gel were significantly superior to topical ultrapotent corticosteroids in reducing the size of superficial infantile hemangiomas [20].

Interventional Radiology and Sclerotherapy

In very rare cases, interventional radiology serves as an adjunct to surgery to reduce the volume of periorbital IH lesions requiring resection. Bleomycin has been described as a sclerosing agent in IH, with complete resolution in as many as 50–75% of children and total response rates >90% [21–23]. Complications are similar to those seen in intralesional steroid injection, including changes in pigmentation, scarring, and local ulceration. In addition, flulike symptoms and hair loss are possible [21, 22]. However, experience with the use of bleomycin in the periocular region is very limited [24, 25], and this approach is generally not recommended [26].

Arterial embolization of IH is rarely performed preoperatively in order to decrease the required extent of surgical resection [27–29]. Again, there is paucity of literature on the use of embolization specifically in the periocular region, and its use should be reserved to physicians with extensive experience in this area. It should also be noted that in young children, persistence of the anastomosis between the internal and external carotid systems frequently exists, necessitating precise review of the angiogram and cautious deployment of the occlusive agent.

Laser

Selective photothermolysis forms the foundation of the treatment strategy for the superficial component of IH, including those in the periocular region. Pulsed dye laser (PDL) is the most commonly used laser for vascular lesions, as its 585–595 nm wavelength is specifically absorbed by oxyhemoglobin and avoids unsightly skin scarring. Historically, the shallow penetration (<2 mm) of PDL reduced its usefulness in larger, deeper lesions of the type that would typically threaten vision in the periocular region. However, refinements of laser technology such as the use of the 595 nm wavelength allow for deeper penetration which may broaden the indications for laser therapy in this area. Though not specific to periocular lesions, a clinical report from the American Academy of Pediatrics recently suggested four indications for the use of PDL in IH: (1) early superficial IH, (2) superficial component of compound IH in which the overlying skin must be preserved, (3) refractory ulceration, and (4) in the

context of significant residual telangiectasia after involution [30]. PDL is quite beneficial for ulcerated IH, specifically lesions that have failed medical management [31]. Children's skin is susceptible to the complications (atrophic scarring, pigmentation changes) of laser therapy [32], the consequences of which are amplified in the periocular region. Additionally, the need for corneal protection and general anesthesia adds additional risk in young children that needs to be weighed when devising a management scheme. Moreover, if the child is deemed safe for general anesthesia, surgical treatment (either definitive or debulking) may seem the more appropriate choice.

Alternatives to PDL such as interstitial use of longer-wavelength lasers have been reported, though their use has not gained widespread acceptance given the propensity for scarring and unpredictable benefit. Neodymium:yttrium aluminum garnet (Nd:YAG) lasers are able to penetrate deeper to reach larger lesions but are also nonselective and can result in significant post-treatment edema and blistering that may further obscure the visual axis in periocular IH. When Nd:YAG is coupled to potassium titanyl phosphate crystal (KTP), the wavelength is halved, and thus the penetration is significantly weakened, and hemoglobin is targeted more specifically. However, melanin is also targeted at this wavelength, and thus KTP use is limited by the substantial risk of pigmentation disturbances, especially in darker-skinned patients [33]. Despite the effects demonstrated by both Nd:YAG and KTP, PDL consistently outperforms these lasers in both effect size and lack of complications.

Surgery

In some ways, the decision whether or not to operate on periocular IH is more straightforward than that for IH in general. Of course, cosmetic and age-related psychosocial factors must be taken into account. However, in the case of periocular IH, the development of functional deficits (see above) may hasten surgery. Regarding timing, Frank et al. describe a risk assessment system that incorporates the child's age (>1 year old) and indicators of high-risk lesions (rapid growth, anisometropia, astigmatism, or existing visual deficiencies) that should prompt urgent surgical referral [34]. Earlier excision of eyelid lesions threatening vision, even before the age of 8 months, may be appropriate [35].

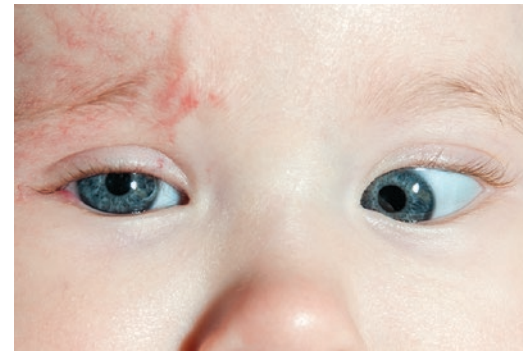

Fig. 14.3 Strabismus in PHACE patient. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

When indicated, surgical excision of lesions can lead to rapid improvement of amblyopia and allow for conservation of the eyelid, extraocular muscles, and orbit (Fig. 14.3) [36–38]. The excision technique is straightforward, with the perceived risk of bleeding being historically exaggerated, likely due to misdiagnosis of periocular IH as other vascular lesions (Fig. 14.4). There are relatively few feeding vessels that can be easily cauterized as the dissection is carried out. The mass itself expands the tissue locally, allowing for simple primary closure in the majority of cases. Occasionally, skin excision due to cutaneous involvement of the lesion or excess skin from expansion is required. Incisions are made along the natural eyelid crease and relaxed skin tension lines to improve cosmesis.

The risk-benefit discussion between the surgeon and the child's parent is unique for periocular IH compared to other IH of the head and neck. In this region, a vital functional outcome is threatened, and the cosmetic risks, while still a main focus of the operation, are less likely to deter a decision for surgery. Nevertheless, every attempt must be made to thoughtfully place incisions in inconspicuous locations. Given the tissue expan-

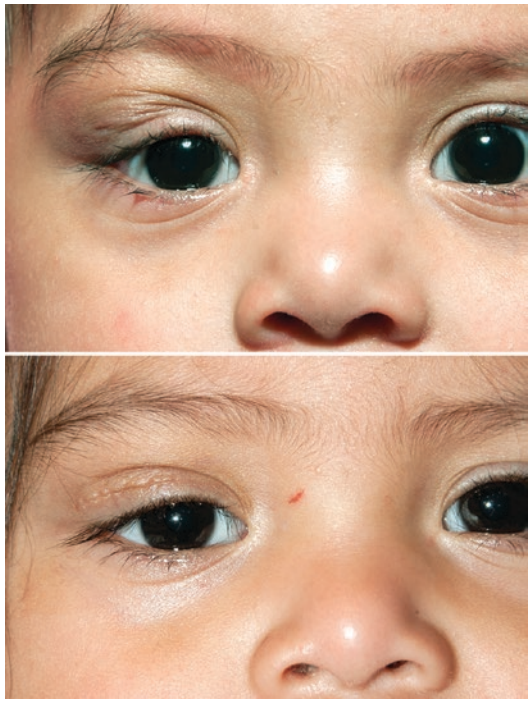

Fig. 14.4 Pre- and postoperative appearance of small upper eyelid infantile hemangioma. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

sion and occasional need for skin excision, ptosis and lagophthalmos are unwanted complications potentially requiring reoperation. Bleeding is rarely reported; in three contemporary retrospective studies of early surgical intervention for periocular IH totaling 59 operations, no significant intraoperative bleeding occurred [36, 38]. To prevent untoward bleeding, correct differentiation of IH from other vascular lesions is imperative, which may require preoperative imaging. Imaging can also rule out intraconal extension if suspected [39]. It should be noted that imaging is rarely needed for surgical planning as this can typically be accomplished with thorough physical examination and knowledge of the natural history and anatomical characteristics of these lesions.

Perhaps most importantly, a team approach incorporating ophthalmology, facial plastic surgery, dermatology, and pediatrics with effective and efficient communication is essential to prevent vision loss associated with periocular infantile hemangioma.

To assist the reader in gaining familiarity with available evidence, the following rating system has been used to indicate key references for each chapter's content:
***: Critical material. Anyone dealing with this condition should be familiar with this reference.
**: Useful material. Important information that is valuable in in clinical or scientific practice related to this condition.
*: Optional material. For readers with a strong interest in the chapter content or a desire to study it in greater depth.

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15 Site-Specific Considerations: Vascular Tumors and Vascular Malformations of the Ear

Josephine A. Czechowicz

Phenotype and Presentation

Vascular tumors and malformations can involve all parts of the ear from the auricle to the internal auditory canal. The clinical approach to each lesion varies greatly depending upon which anatomic unit of the ear is involved. For the purpose of this discussion, we will divide the ear anatomically into the auricle, the external auditory canal and tympanic membrane, the middle ear, and the inner ear and internal auditory canal. These lesions are not common, and the current literature is limited to case reports and series.

Auricle

Both vascular malformations and vascular tumors can present on the auricle. The most extensively described vascular lesions of the auricle are arteriovenous malformations (Fig. 15.1). The auricle is the second most common site for extracranial head and neck AVMs (after the cheek, please see "Extracranial AVM" chapter). The largest series describes 41 patients with auricular AVMs [22]. This study classifies the lesion's grade at presentation using the Schobinger staging system (Table 15.1) [10]. The lesions typically progressed in size and stage – some starting in early childhood (7/41), more in puberty (14/41) and pregnancy (10/41), and still others after trauma to the ear (5/41) [22]. Yoshida et al. describe a patient with an aural AVM presenting only with macrotia (Yoshida 2005) [23].

The pathophysiology of AVMs of the auricle may be related to its embryology. The auricle develops from six hillocks of His. The tragus, root, and body of the helix are products of the first pharyngeal arch and supplied by the superficial temporal artery (STA), and the antihelix, antitragus, and lobule arise from the second pharyngeal arch and are supplied by the posterior auricular artery (PAA) [22]. Houseman et al. have proposed the "angiosome concept" – that AVMs occur at "choke territories" between adjacent angiosomes. In their series of 49 AVMs, Wu and colleagues presented observations that both supported and refuted this hypothesis [7]. The angiograms of pinna AVMs did show that the lesions were supplied by two or more named vessels, typically the STA and the PAA. However, the telltale arterial blush and venous drainage were not always present in the watershed between the two ambiosomes. Furthermore, many of the lesions had substantial extra-auricular components.

Both infantile and congenital hemangiomas sometimes present on the pinna. As in other locations, infantile hemangiomas of the auricle undergo a proliferative phase followed by involu-

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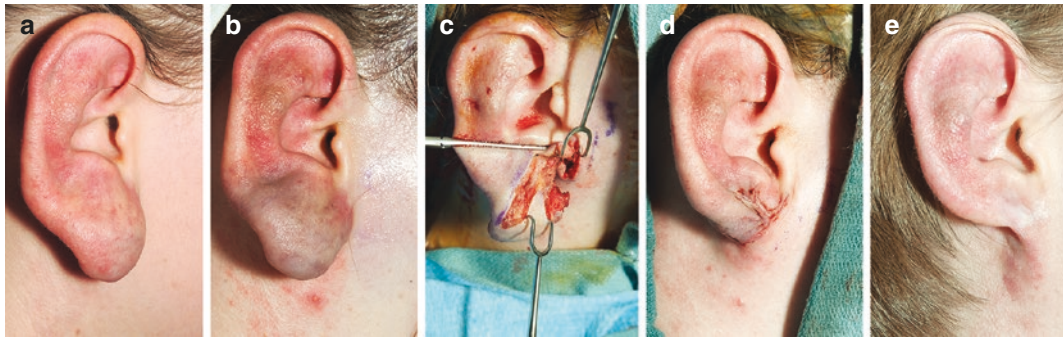

Fig. 15.1 Localized AVM (Schobinger Stage 2) of auricle. (**a**) Pretreatment, (**b**) immediately post-endovascular embolization, (**c**) intraoperative appearance and nidus resection, (**d**) immediate postoperative appearance, and (**e**) 2-year postoperative appearance. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

Table 15.1 Schobinger AVM classification

Schobinger classification	
Stage I	Warm and mildly erythematous skin
Stage II	Expanding lesion with bruit
Stage III	Expanding lesion with bruit and bleeding, pain, or ulceration
Stage IV	High output causing cardiovascular overload

tion. Daramola et al. describe ten young patients with symptomatic auricular hemangiomas who failed medical treatment and underwent surgical excision. Most (8/10) involved the post-auricular skin and helix. Auricular hemangiomas occur in adults as well. Kim et al. describe a 22-year-old patient who presented with a gradually enlarging, non-tender, well-circumscribed non-subcutaneous mass of the lobule; on pathology, the lesion was found to be a hemangioma with arteriovenous histology [9].

External Auditory Canal/Tympanic Membrane

Vascular tumors involving the EAC (specifically infantile hemangiomas) are more commonly reported than vascular malformations (Fig. 15.2). In 2010, Rutherford and Leonard summarized the reports to date of EAC hemangiomas, discussing 17 cases in the English language literature. All patients were adults, ranging in age from 26 to 78 years of age. Conductive hearing loss was the most common presenting symptom, along with bloody otorrhea, aural fullness, pulsatile tinnitus, and otalgia. Four of 17 patients were asymptomatic [19]. The lesions appear purple in color and are

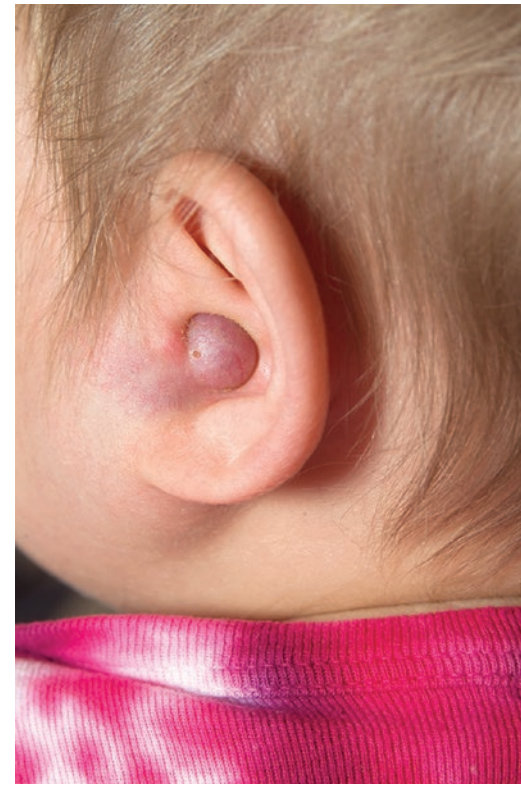

Fig. 15.2 Focal infantile hemangioma in external auditory canal. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

soft and typically exophytic. Erosion of the temporal bone is rare. A broad differential diagnosis of an EAC lesion must be considered, including inflammatory entities such as granulation tissue or an aural polyp, neoplastic processes such as glomus tumors, hemangioendothelioma or carcinoma, as well as cholesteatoma. An audiogram and imaging (CT or MRI) are important in the workup to evaluate for hearing loss and to understand the extent of the lesion prior to excision. In cases where watchful waiting is the chosen course, a biopsy is important to rule out malignancy.

Middle Ear

Vascular anomalies isolated to the middle ear cleft are uncommon but should be included on a broad differential diagnosis of retrotympanic masses appreciated on otoscopy. The differential should include vascular lesions (arteriovenous malformation, high jugular bulb, intratympanic internal carotid artery), neoplastic lesions (hemangioma, glomus tumor, meningioma, rhabdomyosarcoma, histiocytosis X, lymphoma, pyogenic granuloma), and inflammatory lesions (cholesterol granuloma, oral polyp, granulation tissue) [5]. Salamat and colleagues compiled 22 cases of middle ear capillary hemangiomas described in the English language literature [20]. Patients (ages 4 months to 80 years) presented with fluctuating hearing loss, bloody otorrhea, otalgia, and vertigo. Pavamani presents one patient with an expansile middle ear hemangioma involving the TM, EAC, Eustachian tube, and mastoid cavity. Odat et al. describe another patient with extensive vascular malformation of the middle ear, TM, and EAC which was found on pathology to be a cavernous hemangioma [15].

Inner Ear/Internal Auditory Canal

Vascular anomalies also can involve the medial portion of the temporal bone. The symptoms of anomalies involving this portion of the lateral skull base are more likely to include sensorineural hearing loss, hemifacial spasm or palsy, vertigo, and tinnitus. Excitatory symptoms related to neurovascular contact are more common.

The most commonly reported lesions are so-called cavernous hemangiomas, which are now more properly categorized as venous malformations. Zhu et al. present a series of six patients with these venous malformations of the internal auditory canal [25]. All six patients had moderate to severe sensorineural hearing loss. Four of six had facial nerve paralysis, weakness, or spasm. Five of six underwent surgical resection with resultant deterioration in facial nerve function. Yue et al. describe a separate series of 17 patients with what are thought to be facial nerve hemangiomas involving the geniculate ganglion and the internal auditory canal [24]. Similarly, patients with this pathology presented with facial nerve symptoms. Arteriovenous malformations of the IAC are especially rare. Mahran et al. present a single case of a patient with an AVM involving the IAC [13]. The patient presented with headache, sensorineural hearing loss, facial spasm, tinnitus, and vertigo.

Etiology, Histology, and Natural History

Vascular Tumors

The International Society for the Study of Vascular Anomalies classifies vascular tumors as benign, locally aggressive, and malignant [21]. There are case reports of most subtypes of vascular tumors in the ear (discussed above), and their behavior in this anatomic location does not differ substantially from other anatomic locations. The terminology used to describe vascular anomalies has evolved over time, so any retrospective review of previously published cases requires some translation.

The most common vascular tumor of any site, including the ear, is the infantile hemangioma. These cutaneous neoplasms are found on 4–10% of neonates with a female predominance. They are not present at birth but appear in the 1st year of life, growing rapidly in a proliferative phase and then subsequently undergoing involution. Histologically, infantile hemangiomas are composed of endothelial

cells and pericytes. These cells typically express several unique immunohistochemical markers including glucose transporter 1 (GLUT-1), Lewis Y antigen, FC-gamma II receptor, and merosin. In prior studies, these hemangiomas were referred to as capillary hemangiomas because of a capillary predominant appearance on histology.

Congenital hemangiomas, those that are present at birth, are also found in the ear. The 2014 ISSVA schema distinguishes between rapidly involuting congenital hemangiomas (RICH), non-involuting congenital hemangiomas (NICH), and partially involuting congenital hemangiomas (PICH), based on their behavior. These lesions share similar histology and were likely grouped in with infantile hemangiomas as "capillary hemangiomas," but congenital hemangiomas are GLUT-1 negative. In addition to a predominance of capillary lobules, CH typically have extralobular veins and lymphatics.

Some reports and case series of vascular tumors found in the ear refer to "capillary hemangiomas." From the histology descriptions in these reports, these seem to have much in common with IH and CH. However, their behavior – appearing as late as the seventh decade of life – does not make them congenital or infantile. In this report, we use the general term "hemangioma" when it is unclear from the histologic description exactly what class of benign vascular tumor is being discussed.

Another benign vascular tumor reported in the ear is the tufted angioma. This lesion appears as red or brown macules on the skin and histologically is made up of small capillary tufts in a fibrous dermis. Kaposiform hemangioendotheliomas are also described in both the internal auditory canal and the external auditory canal. These locally aggressive vascular lesions have similar histology to tufted angiomas but are more grossly infiltrative. Both lesions express podoplanin and prox-1 (both lymphatic markers) and can be associated with consumptive coagulopathy, the Kasabach-Merritt phenomenon, although this has not been described in an ear lesion. Both tufted angiomas and kaposiform hemangioendotheliomas typically appear before 10 years of age.

Vascular Malformations

The classification system for vascular malformations was also revised at the 2014 meeting of ISSVA, dividing the lesions into simple, combined, anomalies of major named vessels, and those associated with other anomalies. The simple lesions are further subdivided into capillary,

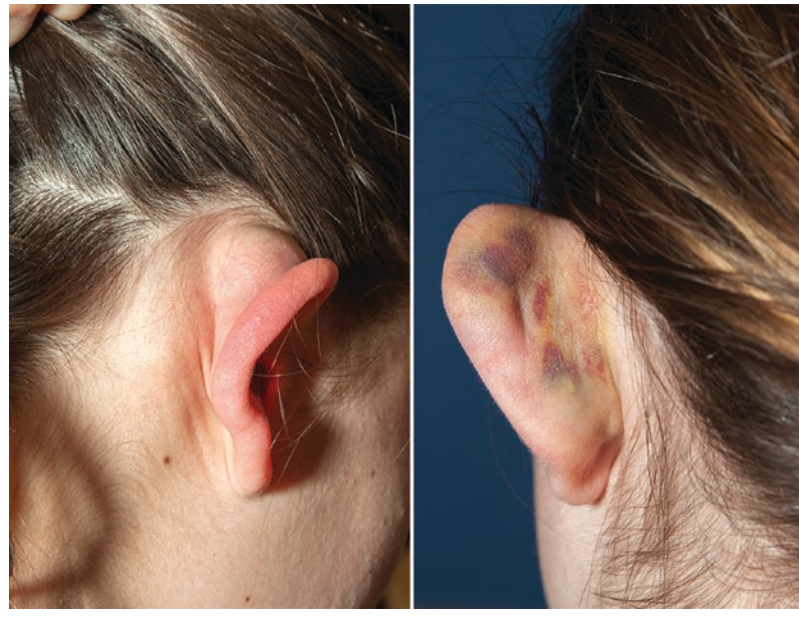

Fig. 15.3 Unusual auricular involvement with lymphatic malformation. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

lymphatic, venous, and arteriovenous malformations and arteriovenous fistulas (Fig. 15.3).

There are a few reports of isolated vascular malformations isolated to the ear, but the most commonly reported lesions are the capillary lesions associated with segmental port wine stains and AVMs of the auricle.

Port wine stains are composed of ectatic capillary vessels in the superficial dermal vascular plexus. These are present at birth as flat macules, but as time progresses, they are associated with underlying soft tissue hypertrophy and nodularity and even bony changes. In some cases of Sturge-Weber, the auricle is extensively involved; this can lead to cosmetic deformity and canal obstruction.

AVMs are the most comprehensively described vascular malformations of the ear. AVMs are congenital vascular lesions with hypertrophic arterial inflow shunted into a tortuous, dilated venous system with an absent intervening capillary bed. The auricle is the second most common extracranial site in the head and neck for AVMs. They can be sporadic or related to hereditary hemorrhagic telangiectasia or RAS p21 protein activator-related disease.

Entities previously referred to as "cavernous hemangiomas" are now thought be venous malformations. In relation to the ear, they are well described in the internal auditory canal, thought to originate from the vascular plexus of the epineurium around Scarpa's ganglion. The symptoms of sensorineural hearing loss and facial nerve weakness often progress more quickly in patients with cavernous hemangiomas than with vestibular schwannomas.

Treatment

The clinical management of vascular anomalies depends on multiple factors. It is crucial to understand which anatomic subunits of the ear are involved, as each has distinct functional concerns. Additionally, one must consider is the severity of the lesion – some presenting purely aesthetic challenges, others with varying degrees of functional impairment, and still others life threatening. Finally, one must balance the risks of any intervention with its potential benefits.

Auricle

The most common vascular tumor of the auricle is the infantile hemangioma. The management of auricular infantile hemangiomas is very similar to managing any cutaneous hemangioma. The decision whether or not to treat these lesions depends largely on the morbidity they cause. Many resolve with no treatment whatsoever. Traditionally, surgical excision was reserved for cases that were expected to result in deformities or for other complications. In a series of ten young children with auricular hemangiomas who underwent surgical removal, six of ten were removed for deformity alone. The other four had recurrent

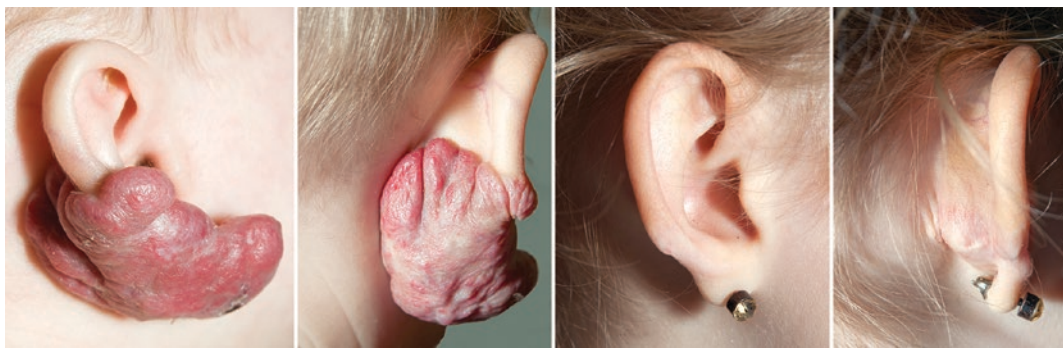

Fig. 15.4 Ulcerated focal infantile hemangioma minimally responsive to propranolol, treated with single surgical resection with immediate reconstruction. Figure demonstrates ulcerated appearance, immediate preoperative status, and late postoperative result that was satisfactory to the patient family. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

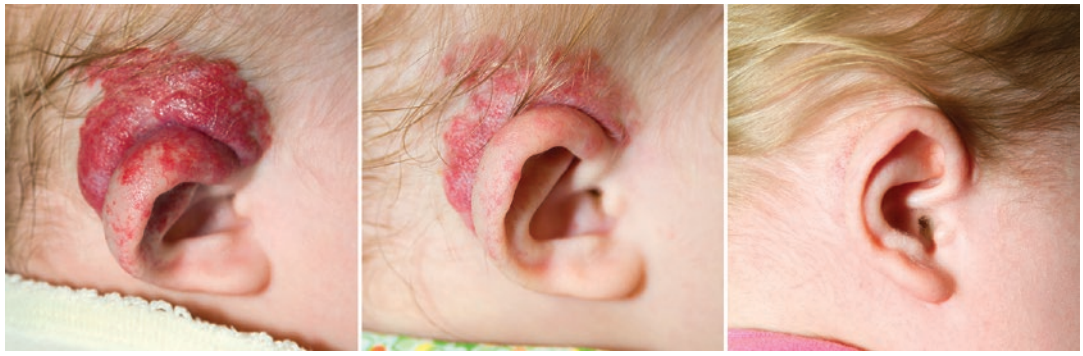

Fig. 15.5 Segmental infantile hemangioma treated successfully with propranolol alone, note cartilage overgrowth. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

bleeding (3/10), pain (2/10), ulceration (1/10), and hypertrophic scar (1/10). All six operated on for deformity were in the involuting or involuted histological phase [4] (Fig. 15.4).

The use of propranolol to treat infantile hemangiomas has been well described and noted to be safe and effective [11, 12] . In spite of relatively uncommon (symptomatic bradycardia, hypotension, hypoglycemia), many centers have substantial experience with the safe initiation of oral propranolol up to 2 mg/kg divided into three doses per day, on an outpatient basis [16]. Indications for propranolol treatment for auricular hemangiomas include obstruction of the external auditory canal, rapid growth with expected cosmetic deformity, and ulceration/wound complications (Fig. 15.5).

Prior to 2008, corticosteroid treatment was first line for management of complex hemangiomas. A multicenter retrospective analysis comparing systemic propranolol versus systematic corticosteroids demonstrated that propranolol was more clinically effective and cost-effective, with fewer side effects than corticosteroids [18]. Local intralesional corticosteroid injection has efficacy in lesions with 67% of lesions displaying some regression and 37% with stabilization of grown [2], although often injection requires a general anesthesia. Finally, even after full involution, many hemangiomas leave characteristic telangiectatic vessels on the overlying skin. Multiple groups have reported success with pulse-dye laser in addressing these residual vessels [1].

Treatment of auricular AVMs can be challenging. In terms of surgical approach, they have high recurrence rates with subtotal resection, but complete resection often involves a disfiguring total auriculectomy. The Schobinger staging system has clinical utility, with more conservative interventions taken for Schobiner Class 1 and 2 lesions, and more definitive treatments once lesions progress to class 3 and 4. Selective embolization with ethanol was reported to reduce symptoms and complications with auricular AVMs over the short term (<1 year) [8]. However, they typically progress and require sometimes radical approaches for resection and reconstruction.

EAC/TM/Middle Ear

Hemangiomas of the external auditory canal, tympanic membrane, and middle ear share histological similarities with those of the auricle. While the aesthetic concerns are less of an issue, they can have a more profound functional impact, namely, hearing loss. Additionally, there are numerous reports of canal lesions being the tip of the iceberg and attempts to partially resect via a limited canal approach results in recurrence. Therefore, contrast-enhanced imaging is advisable to ascertain the extent of the lesion.

The most common treatment is surgical. A transcanal approach is favored for small lesions limited to the external canal and tympanic

membrane. However, transcanal-transmastoid approaches have been reported in cases of disease involving the middle ear [20]. Gradual involution in a 4-month-old with an EAC/TM hemangioma (biopsy proven) was reported [6] and thus would not be an unreasonable course of management in a young child. There is one published report of a 26-year-old female patient with hemangioma of the ear canal, traversing the TM and involving the middle ear and Eustachian tube. The lesion was reported to have intermittent, profuse bleeding. She was treated with radiotherapy and was free of disease after 5 years of follow-up [17].

Inner Ear/Internal Auditory Canal

Approach to treatment of vascular anomalies involving the internal auditory canal depends upon the suspected pathology and the degree of symptoms. Surgical outcomes are not without complications – almost all result in hearing loss and transient and sometimes permanent deterioration of facial nerve function. If surgical resection is deemed appropriate, the standard approaches to the internal auditory canal – middle fossa, translabyrinthine, and retrosigmoid – all have utility, depending upon the size of the lesion, as well as the degree of hearing loss and facial nerve function. A comprehensive review of cases of IAC cavernous hemangiomas discussed 65 cases and presented evidence that near-total resection was often adequate to preserve facial nerve function without recurrence [14]. For facial nerve hemangiomas involving the temporal bone, a transmastoid approach was found to provide excellent hearing outcomes and the possibility of facial nerve preservation in all cases [3].

In summary, vascular anomalies of the ear are rare and vary in presentation and pathology. Proper treatment requires consideration of functional and sometimes aesthetic issues. It is useful to divide the ear into distinct anatomic regions – auricle, external auditory canal, tympanic membrane, middle ear, and inner ear/IAC when devising a differential diagnosis, as well as when choosing the proper treatment.

To assist the reader in gaining familiarity with available evidence, the following rating system has been used to indicate key references for each chapter's content:
***: Critical material. Anyone dealing with this condition should be familiar with this reference.
**: Useful material. Important information that is valuable in in clinical or scientific practice related to this condition.
*: Optional material. For readers with a strong interest in the chapter content or a desire to study it in greater depth.

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Nasal and Lip Infantile Hemangiomas 16

Milton Waner and Teresa M. O

Level of evidence: treatment	Moderate
Evidence	Case series, systematic review, meta-analysis

Nasal Infantile Hemangiomas

Infantile hemangiomas (IH, hemangiomas) of the nose comprise 15% of head and neck hemangiomas [1, 2]. Nasal hemangiomas are important because of their prominent location on the face and because of the possibility of severe disfigurement that can result from distortion of the normal shape of the nose. These hemangiomas may be focal or segmental, and their behavior is typical for these types of lesions.

Focal Hemangiomas

Focal nasal hemangiomas may involve one or more of the nasal subunits and may be superficial, deep, or compound (Fig. 16.1). The nasal tip is a common site for these lesions. However, nasal hemangiomas can run the full gamut from a small superficial hemangioma to a massive compound lesion involving several subunits. Their life cycle is similar to hemangiomas elsewhere in the body, with the exception of nasal tip lesions which tend to leave a residuum of fibrofatty tissue at the end of involution (Fig. 16.2). This results in a widened, bulbous nasal tip, also known as Cyrano nasal tip deformity [3].

Segmental Hemangiomas

Segmental nasal involvement occurs in frontonasal lesions. Once again, segmental hemangiomas may be superficial, deep, or compound. These lesions can be more aggressive and have a higher propensity to ulcerate [2]. Ulceration of the columella can be catastrophic and destroy the entire nasal columella including part or all of the nasal septum with resultant collapse of the nasal tip (Fig. 16.3). Segmental hemangiomas appear to have a longer growth cycle, and their proliferative period sometimes extends far beyond that seen with focal hemangiomas. This will impact the length of medical treatment necessary to prevent rebound growth.

Nasal tip hemangiomas appear to originate along the intercartilaginous ligament between the lower lateral cartilages of the nose. As these

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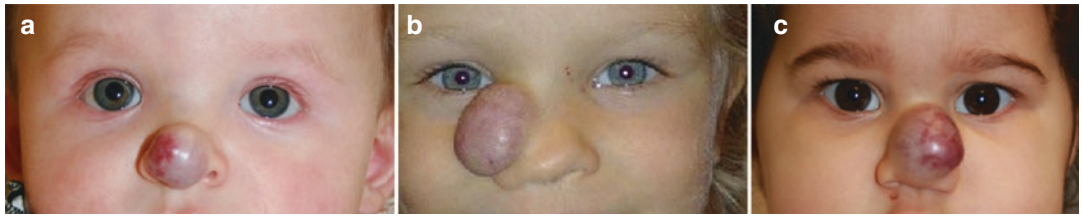

Fig. 16.1 Three children with nasal infantile hemangiomas involving different subunits of the nose. (**a**) This is a classic nasal tip hemangioma with some cutaneous involvement. (**b**) A typical paranasal hemangioma extending onto the lateral nasal wall. (**c**) This is a compound lesion involving the lateral nasal wall

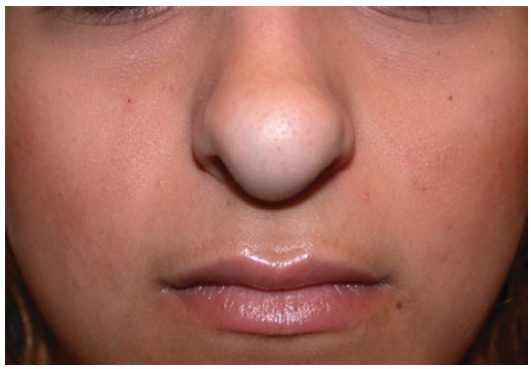

Fig. 16.2 An involuted nasal tip hemangioma in a 20-year old. Note the excessive fibrofatty tissue forming a wide, bulbous nasal tip

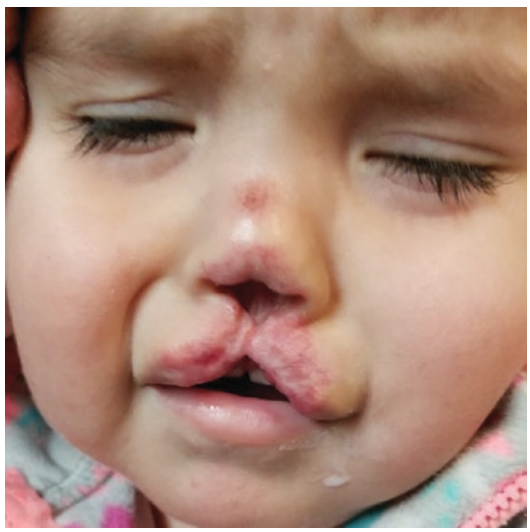

Fig. 16.3 A child with an aggressive frontonasal segmental hemangioma. Note severe ulceration with loss of the philtrum of the upper lip and the nasal columella and septum

lesions grow, they tend to displace the lower lateral cartilages laterally from the midline as well as rotate them outward in an open-book fashion (Fig. 16.4) [4]. Compounding this is the tendency of nasal hemangiomas to involute with excessive fibrofatty tissue, resulting in ongoing disfigurement. This will give rise to a very wide nasal tip, which is likely to be permanent [3–5]. Hamou et al. observed this outcome in 29 out of 39 nasal hemangiomas [5]. Most nasal tip hemangiomas are midline, but their growth may be asymmetric; this leads to an asymmetric displacement of the lower lateral cartilages. Unfortunately, there is no evidence that this will autocorrect during involution. Instead, the combination of fibrofatty tissue and displaced cartilages gives rise to the typical nasal deformity (Fig. 16.3).

Indications for Treatment

Since it is impossible to predict how large a hemangioma will grow, all children with proliferating nasal hemangiomas should be followed closely. Any lesion that appears to be proliferating rapidly and causing disfigurement should be treated. Obviously, this threshold will differ from center to center, and there are no hard and fast rules. The objective of treatment is to restore a normal nasal appearance and function.

Treatment Modalities

Most of the published literature predates the widespread use of propranolol and is therefore

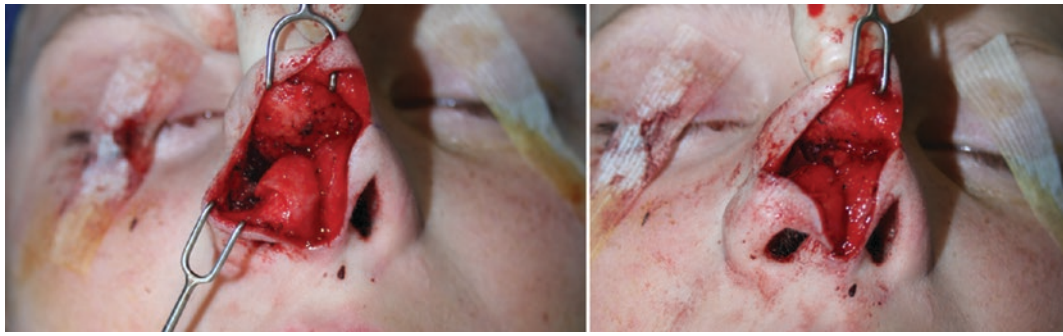

Fig. 16.4 An older child with a persistent mainly right-sided nasal tip hemangioma during excision. Note the rotation and displacement of the right lower lateral cartilage (left photo) before and (right photo) after correction with dome-binding sutures

of limited relevance [4–6]. Ben-Amitai et al. studied the effect of propranolol on nasal hemangiomas [7]. Although their data was limited to ten patients, they were able to determine that propranolol was effective in treating nasal tip hemangiomas and likely reducing the number of patients requiring surgical correction. Early treatment appeared to prevent or limit proliferation of nasal hemangiomas, and these patients appeared to benefit the most. In established lesions, there was also improvement including lightening of the skin involvement, softening of the deeper component, and reduction in lesion diameter. It is not clear whether or not this latter group of patients required surgical correction. Perkins et al. were also able to show that patients treated with propranolol were less likely to need invasive procedures such as laser treatment and/or surgery [8]. These data suggest that propranolol should be the first line of treatment for nasal hemangiomas.

Although there is no systematic study looking at the effect of topical timolol on nasal hemangiomas, Rashmi et al. reported on a single patient with a superficial nasal hemangioma who responded well to topical timolol [9]. This is not surprising given the wealth of success timolol has enjoyed in treating very superficial hemangiomas.

Several studies have looked at surgical techniques for nasal hemangiomas [3, 4, 6, 10, 11]. All of these studies are retrospective and propose one or another technique as being the best. Many of the earlier studies described are retrospective reviews of a small number of patients. Waner et al. described a modified subunit approach to nasal lesions in 44 patients. This approach allowed resection of excess skin but left visible scars at the junction of the alar and nasal tip subunits. They recommended surgery between 1 and 2 years of age to minimize scarring. Arneja et al. preferred a transcolumellar rim incision [6]. Excess skin was excised external to the rim. They documented 15 patients who underwent surgery, 11 of whom were operated in the postinvolutional phase and 4 during the proliferation plateau phase. The advantage of this approach was a rim scar. They cautioned against alar stenosis and recommended the use of intranasal stents. Hamou et al. suggested that the surgical approach be dictated by the severity of the lesion [5]. A total of 39 cases were described. A rim incision was used for mild cases with no lower lateral cartilaginous realignment, a Rethi incision for larger lesions with cartilaginous realignment, and a midline incision for severe cases. Most authors, however, prefer to avoid a midline incision.

In consideration of all of these data, a rim incision or a modified subunit incision is the preferred surgical approach to a nasal hemangioma.

Focal Hemangioma: Treatment

Proliferating Hemangiomas

The mainstay of treatment during this phase is β-blocker therapy. Many studies suggest that early treatment with a β-blocker will diminish the need for surgery and laser treatment [7, 8]. Perkins et al. suggest that β-blockers inhibit further growth of

the infantile hemangioma and shrink existing lesions [8]. The type of β-blocker used will depend on the depth and extent of the lesion.

- For very superficial small lesions less than 2 cm in diameter, we recommend topical timolol (one to two drops applied two to three times daily).
- For larger lesions, superficial, compound, and/or deep, propranolol is recommended (2–3 mg/kg/day given TID).

The duration of treatment is important. Early cessation of treatment is associated with a higher rebound rate. Price et al. noted a rebound rate of 3% with a mean treatment duration of 7.9 months [12]. We believe that segmental hemangiomas have a longer proliferation cycle and therefore require a longer duration of treatment. If rebound is experienced after cessation of propranolol, restarting treatment will usually take care of this.

- Surgery is usually not recommended for proliferating nasal hemangiomas due to the risk of recurrence, which may necessitate a second surgery.

Involuting Hemangiomas

Nasal tip involvement or obvious disfigurement should favor surgical and/or laser treatment. In general, pulsed dye laser (PDL) treatment is used for any superficial residuum, while surgical resection is used for deeper disease. Serial pulsed dye laser treatments may be necessary for a satisfactory result. Atrophic skin changes can be improved with fractional CO2 laser treatment. Once again, several treatments may be necessary. Laser treatment of the superficial component of a hemangioma has been extensively researched and is effective, especially during involution [13].

Involvement of the nasal tip or extensive residual deep hemangioma should be addressed surgically. Nasal tip hemangiomas tend to displace the lower lateral nasal cartilages, thereby deforming the nasal tip. This can only be corrected operatively. The surgical approach will depend on the preference of the surgeon. Two surgical approaches have been popularized [4, 6]. Both of these have their advantages and disadvantages. The modified subunit approach, first reported by Waner et al. and subsequently endorsed by Hochman et al., provides direct access to the hemangioma and the ability to resect any excess skin from the tissue expansion caused by the hemangioma [4, 10]. The distraction and displacement of the lower lateral cartilages can be corrected. The major disadvantage of this approach is the possibility of a visible scar. For this reason, early surgery performed between 1 and 2 years of life is advocated [4]. Burgos et al. also felt that early surgical intervention was necessary to improve the quality of life of their patients [14]. The rim approach has the advantage of hiding the scar along the nasal rim. The main disadvantage is a loss of distinction of the nasal alar groove. Excess skin from tissue expansion can be excised, and the lower lateral cartilages can be medialized with dome-binding sutures.

Surgical complications include recurrence, necrosis of a portion of the overlying skin flap, damage/loss of the lower lateral nasal cartilages, and asymmetry of the nose. Recurrence can be prevented by delaying surgery until after the end of the proliferative phase. The patient should have stopped propranolol or any other β-blocker at least 2 months prior to surgery, as this may mask ongoing proliferation. Necrosis of the skin flap will result from compromise of the blood supply to the flap and/or venous congestion of the flap, which can occur when there is significant skin involvement by the hemangioma. In these cases, several laser treatments of the overlying skin prior to surgery minimize this risk. Necrosis appears to be due to venous congestion and stasis. Therefore, reducing the cutaneous load of hemangioma and replacing it with fibrosis will be helpful.

Segmental Hemangiomas

Proliferating Hemangiomas

As with focal lesions, the first line of treatment during the proliferative phase is β-blockers; topical timolol for superficial lesions and systemic propranolol or nadolol for deeper lesions. One of the most important distinctions between proliferating

focal and segmental hemangiomas is the length of the proliferative phase. Segmental hemangiomas may proliferate for a longer period. In extreme cases, this may last up to 48 months. The duration of treatment is therefore longer, and recognition of this distinction will prevent undertreatment.

Involuting Hemangiomas

Surgical correction should not be considered until after the end of proliferation. The patient should be off β-blockers for at least 2 months to ensure that there is no rebound growth. Any involvement of the overlying skin should be pretreated with a pulsed dye laser several times to prevent postoperative venous congestion of the skin flap.

Since segmental hemangiomas tend to be more diffuse and involve more than one nasal subunit, the surgical approach should permit access to a wider field of involvement. The modified subunit approach offers more versatility and the ability to extend the incision beyond the nasal tip to the paranasal area [4]. The surgeon should also be prepared to improvise if it becomes necessary to remove the lesion. Using the modified nasal subunit approach, incisions between subunits will allow hemangioma resection, excess skin redraping and excision [4].

Timing of Surgery

Most authors agree that surgery should be delayed until after the proliferative phase has ended [4, 11, 14]. For focal lesions, this means around the end of the 1st year of life. For segmental hemangiomas, this could be anywhere from 18 to 42 months or even later in rare cases. As mentioned previously, the child should be off propranolol for at least 2 months to ensure that proliferation is over and that there is no rebound.

Delaying surgery until 5 or 6 years of age serves no purpose. Partial involution might reduce the volume of hemangioma, but exposing the child to the additional psychosocial trauma will not be helpful [15].

Lip Hemangiomas

Lip hemangiomas are common (20% of all hemangiomas) and are very noticeable due to their prominent central location [16]. Furthermore, given the dimensions of the lip, what would in another anatomic location be considered small and inconsequential can appear prominent and distort the lip anatomy (Fig. 16.5). For this reason, most "prominent" lesions should be treated. The definition of "prominent" is variable, and the indications to treat will vary from center to center. Clearly, our objective should be to prevent a poor outcome, defined as an anatomic deformity, scarring, or a functional impairment (feeding and speech). Yanes et al. determined that they were able to prognosticate the likely outcome based on the size and location of the lesion [16]. These data are helpful in determining which lesions to treat. Lesions larger than 3.09 cm or greater were associated with a poor

Fig. 16.5 Two children with upper lip infantile hemangiomas. While the hemangiomas are small, their appearance and the amount of distortion are prominent

outcome, whereas those which were 0.72 cm or less were associated with a good outcome. Lesions that involved the vermiliocutaneous junction were most likely to have a poor prognosis. Lesions of the upper lip, especially the lateral portion, had a poorer prognosis than lower lip lesions. Segmental hemangiomas of the lip, especially lower lip lesions, had a higher incidence of ulceration and functional impairment [2]. Yanes et al. also determined that even with treatment, larger lesions (>2.84 cm) were associated with a poorer outcome. They were able to show that there were fewer poor outcomes in the treated group than in the untreated group (18% vs 42%). They did not differentiate between early and late treatments. Therefore, given the success of early propranolol treatment and the data showing a statistically significant advantage of treatment, physicians should consider treating any lip lesion early. Early treatment may not only prevent a poor outcome, it may well alter the course of the nascent hemangioma.

Waner et al. noted that hemangiomas occurred in sites of predilection which were related to the embryological development of the face [2]. They also noted that hemangiomas could be differentiated into focal and segmental lesions. O et al. described the sites of predilection of both focal and segmental lip hemangiomas [17]. This work was corroborated by Yanes et al. who refined the hypothesis and added two more sites of predilection. Based on these anatomical sites of predilection, the pattern of growth of any lip hemangioma can be predicted. A large upper lip lesion is likely to result in an increase in the horizontal and vertical dimensions of the lip, creating an obvious deformity (Fig. 16.6). This will not correct with natural involution, thereby causing permanent disfigurement. Lesions that cross the vermiliocutaneous junction will disrupt it and result in a moth-eaten lip line (Fig. 16.7). Lesions that involve the vermillion

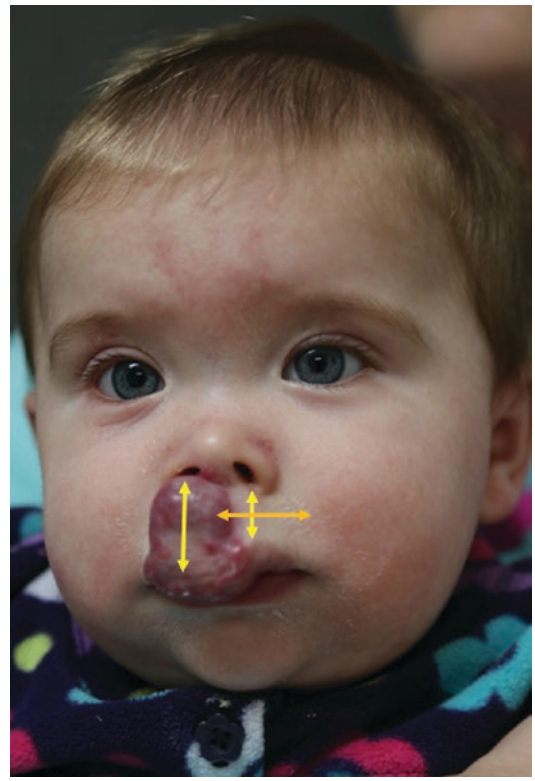

Fig. 16.6 A child with an extensive upper lip hemangioma. The hemangioma has lengthened the horizontal (*orange arrow*) and the vertical (*yellow arrows*) dimensions of the upper lip

Fig. 16.7 An involuted V3 segmental hemangioma. The lesion had involved the lower lip and left a moth-eaten appearance of the vermiliocutaneous junction. Excessive fibrofatty tissue of the lower lip is also noted

can similarly distort the anatomy and cause disfigurement. Since the tissue that makes up the vermillion is unique and very difficult to reconstruct, every effort should be made to preserve it [18]. Large lower lip lesions have a tendency to enlarge and lengthen the lower lip. This may lead to oral incompetence, drooling, and speech difficulties. Thirty-three percent of segmental hemangiomas will ulcerate, especially V3 segmental lesions [2]. It is also worth noting that 65% of these lesions also involved the airway [19].

Focal Lip Hemangiomas

Proliferation

Any lesion 1 cm or greater or any lesion that crosses the vermiliocutaneous junction should be treated. Superficial lesions can be treated with timolol, but when and if it becomes obvious that they have a deeper component, propranolol is warranted. Propranolol (b-blocker) is a first-line medical treatment, and guidelines on the initiation and ongoing treatment have been established [20]. The usual dose is 2–3 mg/kg/day, divided twice or three times daily. In order to minimize rebound growth after cessation of treatment, treatment should continue until the child's first birthday for a focal lesion and longer for a segmental hemangioma.

Couto and Greene et al. still advocate for the use of intralesional steroid injections for lesions 3 cm or less in diameter [21]. They used triamcinolone (40 mg/ml). The mean age at treatment was 11 weeks, and an average of 1.8 injections per patient were administered. The timing between injections was about 6 weeks. On this regimen, 63% regressed and 37% stabilized. The only side effect they reported was a 2% incidence of atrophy at the injection site.

As with nasal hemangiomas, there are very few indications for surgery during the proliferative phase. Severe ulceration that does not respond to conservative measures and that interferes with feeding may warrant early operative intervention [22].

Involution

The timing of surgical correction varies. Given the prominent location of lip hemangiomas and their visibility, most authors suggest early correction. When planning surgery, one should always be cognizant of the fact of ongoing involution after early correction and make allowances for this. Chang et al. caution against overcorrection during the phase of involution and advocate a staged approach with minimal perioral scarring and preservation of the normal anatomical structures of the lip [18]. They also caution against correction of several vectors during the same surgery. Li et al., on the other hand, prefer a one-stage correction and draw on the experience of 200 cases [23]. Despite this, most authors recognize the dynamics of lip correction with special reference to reestablishment of the normal dimensions. They all describe techniques aimed at correcting these dimensions. The techniques described by O et al. and Li et al. are similar [17, 23]. Chang, on the other hand, accomplishes the same but with minimal perioral scarring [18]. However, their series is very small (11 cases) when compared with Li et al. (214 cases) and O et al. (342 cases). It would be very interesting to see a more extensive series by the same authors.

Laser treatment is useful for treating residual telangiectasias and atrophic/hypertrophic scarring. Pulsed dye lasers and diode lasers will treat any residual redness and telangiectasias, and CO2 lasers with fractional delivery systems are useful for scarring [13, 24].

Segmental Lip Hemangiomas

Proliferation

Segmental hemangiomas run the gamut from very mild to very severe. It is these very severe cases that are particularly destructive and can be extremely disfiguring. Ulceration is not infrequent and can be particularly destructive. For example, in a very short period, a frontonasal segmental hemangioma can progress from mild ulceration to profound tissue loss with

complete destruction of the philtrum, nasal columella, and cartilaginous nasal septum. Since it is impossible to predict the final outcome, and since a seemingly innocuous lesion can progress with such rapidity, all early segmental hemangiomas should be investigated and treated. The association with other abnormalities (PHACES syndrome) should be investigated, and treatment with propranolol should be initiated. The diagnosis of PHACES syndrome is not a contraindication to propranolol treatment [20].

In cases where propranolol is contraindicated, systemic steroids should be considered. Greene et al. reported a series of children with problematic hemangiomas who were treated with a 1-month regimen at 3.0 mg/kg, followed by a long slow taper, and continued until the child reached 10 months of age. Eighty-eight percent of patients showed regression of their lesions, and in a further 12%, the growth stabilized [25]. Although these results are at least as good as those of propranolol, the risk of long-term side effects is high [26, 27].

Laser treatment is contraindicated during the proliferative stage since it has been shown to increase the risk of ulceration [28].

Involution

Once involution is underway, corrective surgery should be planned and executed. Surgical debulking, dimensional correction, and laser treatment of residual telangiectasia and scarring should be undertaken. All of these procedures are the same as those described in the section for focal hemangiomas [17, 18, 23].

To assist the reader in gaining familiarity with available evidence, the following rating system has been used to indicate key references for each chapter's content:
***: Critical material. Anyone dealing with this condition should be familiar with this reference.
**: Useful material. Important information that is valuable in in clinical or scientific practice related to this condition.
*: Optional material. For readers with a strong interest in the chapter content or a desire to study it in greater depth.

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Vascular Tumors of the Airway

17

Ravindhra G. Elluru

Level of evidence: treatment	Moderate
Evidence	Case series, meta-analysis, multi-institutional retrospective studies

Introduction

The most common vascular anomaly of the airway, defined as the airway between the glottis and carina, is the infantile airway hemangioma. This chapter will focus exclusively on the airway infantile hemangioma, and less commonly occurring vascular anomalies of the airway will be discussed in other chapters. Infantile hemangiomas (IH) are proliferative vascular tumors, composed of endothelial cells, which can be located on the skin or within the subglottis, trachea, and/or mediastinum. At birth hemangiomas are either absent or minimally evident. However, they grow quickly in the first months of life, following predictable stages of rapid proliferation, prolonged involution, and finally end-stage degeneration to fibrofatty residuum. In the case of airway infantile hemangiomas (AIH), rapid growth during the proliferative stage leads to life-threatening airway obstruction and requires emergent treatment.

The goal of treatment is to reduce AIH size and to maintain an adequate airway until the lesion spontaneously regresses. Until recently, corticosteroids were the first line of therapy, though the mechanism of action is not fully understood. Other medical treatments, though seldom utilized, have included vincristine, interferon, and other chemotherapy agents. A wide variety of surgical/interventional treatment methods have been employed including intralesional steroids, embolization, laser therapy, tracheostomy with observation, and surgical excision.

Overview of Specific Diagnostic Criteria for Airway Vascular Tumors

AIH can occur anywhere within the tracheobronchial tree, though they are most commonly seen in the subglottis (Fig. 17.1). The predominant presenting symptoms are stridor and respiratory distress [1, 2]. Other presenting symptoms can include cough, poor feeding, retractions, wheezing, cyanosis/mottling, hoarseness, and croup. The age at presentation is typically around 2–4 months of age (Table 17.1). Definitive diagnosis and assessment of the extent of the lesion require rigid endoscopy and occasionally MRI imaging to assess for extra-tracheal involve-

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ment. Surveillance evaluations after initiation of therapy are typically made by a bedside nasopharyngoscopy.

There is a close association of IH in a cutaneous beard distribution with the presence of AIH. It has been reported that 50% of infants with airway hemangiomas also have cutaneous IH. Patients with IH in the mandibular or the distribution of a beard are known to be at especially high risk. In the published reports presented in this paper, 18–76% of the patients with a known AIH had also a cutaneous IH in the beard distribution. Large facial IH in the beard distribution can also be associated with a neurocutaneous disorder termed PHACE syndrome. PHACE syndrome is defined as involving a facial hemangioma and one or more of the following abnormalities: structural brain anomalies, arterial cerebrovascular anomalies, coarctation of the aorta or cardiac anomalies, ocular anomalies, and/or ventral developmental defects. The incidence of PHACE syndrome in patients with large facial cutaneous IH was recently estimated to be 31%. In the studies reported in this chapter, the incidence of PHACE syndrome in patients with a diagnosed AIH ranged from 2% to 47%.

AIH can occur anywhere in the tracheobronchial tree, though the most common site of occurrence leading to airway symptoms is the subglottis. AIH of the subglottis can occupy a por-

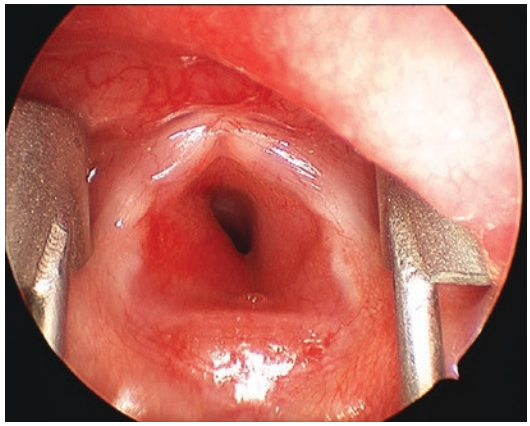

Fig. 17.1 Endoscopic pictures unilateral AIH. Note the AIH often is covered with flesh colored mucosa and therefore does not always appear bright red in color and Lindholm laryngeal spreaders increase lesion visualization and operative field. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

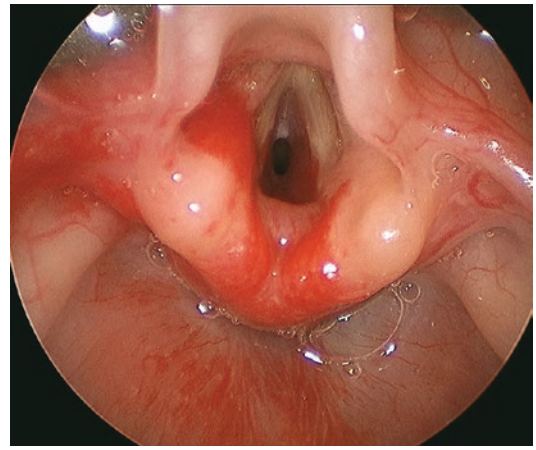

Fig. 17.2 Endoscopic appearance of circumferential AIH in PHACE patient with transglottic extension. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

Table 17.1 Demographics and characteristics of patients with airway hemangioma

Study	*n*	Average age at presentation (months)	Description of airway hemangioma	Facial cutaneous involvement
Elluru et al. 2015 [3]	27	2.3	Focal: 26%	Zone 3: 52%
			Circumferential: 74%	PHACES: 2%
Haggstrom et al. 2011 [2]	17	1.7	Focal: 42%	Zone 3: 76%
			Circumferential: 58%	PHACES: 47%
Javia et al. 2011 [4]	30	3	Median obstruction: 90%	PHACES: 17%
Rahbar et al. 2004 [5]	117	4.7	Mean obstruction: 65%	Data not available
Vijayasekaran et al. 2006 [1]	22	5	Data not available	Data not available
Vlastarakos et al. 2012 [6]	61	2.4	Mean obstruction: 72%	Zone 3: 18%
				PHACES: 3%

tion of the subglottis (focal) or involve the entire circumference of the subglottis (circumferential) (Fig. 17.2). Furthermore, the size of the AIH can vary, and therefore the amount of obstruction of the airway lumen can also vary. The location of the hemangioma, along with the extent of involvement and luminal obstruction, determines the severity of airway symptoms at presentation.

Overview of Treatment for Symptomatic Airway Hemangiomas

Though small asymptomatic airway hemangiomas can be managed by close observation only, symptomatic hemangiomas will likely need either medical or surgical intervention. The primary goal in the treatment of airway hemangiomas is to reduce the size of the obstructing lesion, to maintain an adequate airway, and allow the residual lesion to regress on its own. The mainstay of medical management for AIH is propranolol, both because of its efficaciousness and safety profile. Other medical treatment options however include intralesional steroid injection, systemic steroids, and vincristine. The use of a surgical modality for the treatment of AIH has decreased in popularity with the introduction of propranolol, though surgical treatment options are appropriate when medical modalities fail to alleviate respiratory symptoms expeditiously or when emergent or imminent severe airway compromise is present. Surgical modalities include laser ablation, open excision with airway reconstruction, and tracheostomy.

Evidence regarding the efficacy of treatment modalities for AIH is modest and is limited to mostly retrospective studies with small cohorts. Furthermore, the difficulty in objectively quantifying the size of an AIH and the severity of associated symptoms leads to cohort variability both within and between studies. Finally, there are no studies directly comparing one treatment modality to another, and reported outcome measures vary between studies making comparisons of different studies difficult. A few of the global outcome measures that can be used to evaluate the literature include number of treatment failures as a proxy for the efficacy of the treatment modality and complications associated with treatment.

Propranolol Treatment

Among the medical treatment modalities for AIH, propranolol is currently considered the first-line choice (Fig. 17.3). Propranolol has been used extensively in children to treat atrial

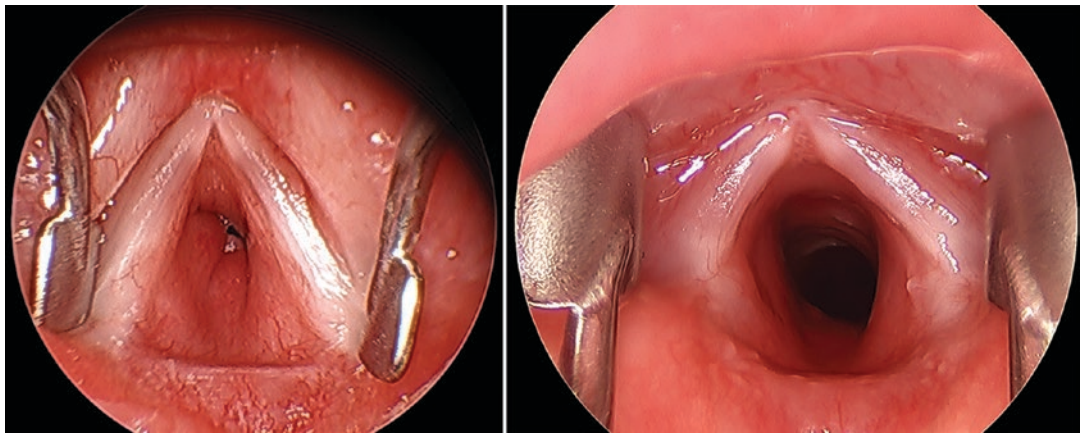

Fig. 17.3 Endoscopic appearance of AIH pre- and post-propranolol therapy. Note that Lindholm laryngeal spreaders increase lesion visualization and operative field and the AIH is not more red than the surrounding mucosa, since it is a deep lesion. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

arrhythmias, and its safety profile has been verified in many studies. It has been shown to be effective and safe at a dose range of 1–4 mg/kg/day. The introduction of the use of propranolol for the treatment of cutaneous IH in 2008 revolutionized treatment and has become the first-line treatment of this category of IH. The exact method of action by which propranolol inhibits IH growth remains unknown, though β2-adrenergic receptors have been shown to be expressed in IH endothelial cells. Adverse effects reported with the use of propranolol in the treatment of AIH listed from likely to least likely include bradycardia, hypotension, sleep disturbance, decreased appetite, constipation/diarrhea, and hypoglycemia. Serious side effects such as symptomatic bradycardia, hypotension, and heart failure have been reported but are rare occurrences.

Vlastarkakos et al. [6] performed a meta-analysis of 18 studies published between 2009 and 2011, evaluating the efficacy of propranolol in a total of 61 patients. The mean follow-up interval in this meta-analysis was 8.4 months. The vast majority of patients (n = 43) received propranolol at a dose of 2 mg/kg/day divided into two or three doses per day. Ten children received propranolol at a dose of 3 mg/kg/day, and in four children the dose was not reported. Fourteen children had been treated only with propranolol. Thirty-three children were treated with propranolol after failing steroid therapy, ten children after failing laser therapy, and three children after failing vincristine therapy. Of the 61 patients in this meta-analysis, 4 (6.5%) were reported to be non-responders, and seven additional children (11.5%) relapsed after stopping propranolol treatment. Four children experienced adverse effects in this meta-analysis, including two patients with asthmatic attacks, one patient with pallor without loss of consciousness, and one patient who developed an oral ulcer.

Elluru et al. [3] performed a retrospective multi-institutional study of 27 patients treated with propranolol. All patients were treated with a dose of 2 mg/kg/day divided into two or three doses per days, with a median duration of treatment of 15 months. Eleven patients had an intralesional steroid injection at the time of propranolol initiation, and five patients had both laser ablation and steroid injection at the time of steroid injection. Most patients had a resolution of respiratory symptoms within 24 h of the initiation of propranolol. Six of the 27 patients had an additional intralesional steroid injection. Five of the 27 patients required additional systemic steroids or laser ablation after the initiation of propranolol. One of the patients (4%) was thought to be a non-responder and was treated successfully with open excision. No adverse effects of propranolol treatment were identified in this cohort.

Luv et al. [4] performed a retrospective review of patients with AIH treated with different modalities. Twelve patients were treated with propranolol, with the majority being treated concurrently with systemic steroids. Four patients (33%) were thought to be non-responders. Two of the patients experienced decreased appetite, constipation, and diarrhea.

Steroid Treatment

Prior to the popularization of propranolol for the treatment of IH, steroids were considered first-line treatment. Steroids can be used intralesionally or systemically. However, only the role of systemic steroids in AIH treatment has been studied in detail. In their meta-analysis, Vlastarakos et al. [6] found only 2 out of 35 patients who responded to systemic prednisolone at doses ranging from 0.1 to 3 mg/kg/day. In the prospective multicenter trial by Haggstrom et al. [2], only 2 of 14 patients with symptomatic AIH treated with systemic prednisolone alone were treated successfully. Tracheostomy was required in 3 of 14 patients treated with steroids. The mean duration of steroid treatment was 8 months. The other nine patients required additional systemic and/or surgical

treatment. Finally, in the retrospective multicenter trial by [5], systemic steroid treatment alone was only successful in 11 of 47 patients treated. Prednisolone at a dosing of 2–3 mg/kg/day was used for a mean duration of 86 days. The other 36 patients required additional treatment modalities.

Surgical Ablation or Removal

Several methods have been reported for surgical treatment of AIH including laser ablation, microdebrider excision, and open excision. Laser and microdebrider treatment are generally used in conjunction with other treatment modalities, and therefore there is no data for the efficacy of these treatments as a "stand-alone." Though tracheostomy is a surgical option which is uniformly successful in alleviating symptoms of respiratory insufficiency, it will not be covered here because this treatment option does not directly treat the underlying AIH.

Vijayasekaran et al. [1] presented a retrospective review of 26 patients with AIH who underwent open surgical resection. Twenty-one patients were treated as single-stage procedures, and one patient was treated as a staged procedure with decannulation 2 months after the procedure. Cartilage graft augmentation was required in 15 patients. Three patients required additional endoscopic treatment of granulation tissue, one patient developed an anterior glottis web, and one patient required additional systemic steroid treatment. Rahbar et al. [5] presented 25 patients treated with open excision, 21 of whom who had failed medical and/or surgical treatment. Twenty-one patients had cartilage augmentation. One patient failed treatment and required a tracheostomy, and four patients required endoscopic removal of granulation tissue.

Conclusion

The treatment of AIH has evolved over the years and will continue to change over the next several years as both medical and surgical treatment modalities are developed and refined. In evaluating various treatment modalities, not only does efficacy and safety of treatment have to be considered, but value should also be considered. In the category of medical treatment options, steroids and propranolol are the main treatment options. Treatment of AIH with vincristine or interferon though reported, has never been popularized secondary to their side effect profiles. Systemic steroids have shown a modest efficacy with fairly significant side effects including Cushing's disease, infection susceptibility, and growth retardation. Propranolol treatment on the other hand has shown to be more efficacious and have less side effects and is therefore currently considered first-line treatment (Fig. 17.4). However, treatment failures do occur and should be recognized early in the treatment course. Patients who fail propranolol treatment can be treated with steroids and/or surgical ablation or excision. Surgical options in general are not considered first-line treatments given their inherent invasiveness and potential association complications.

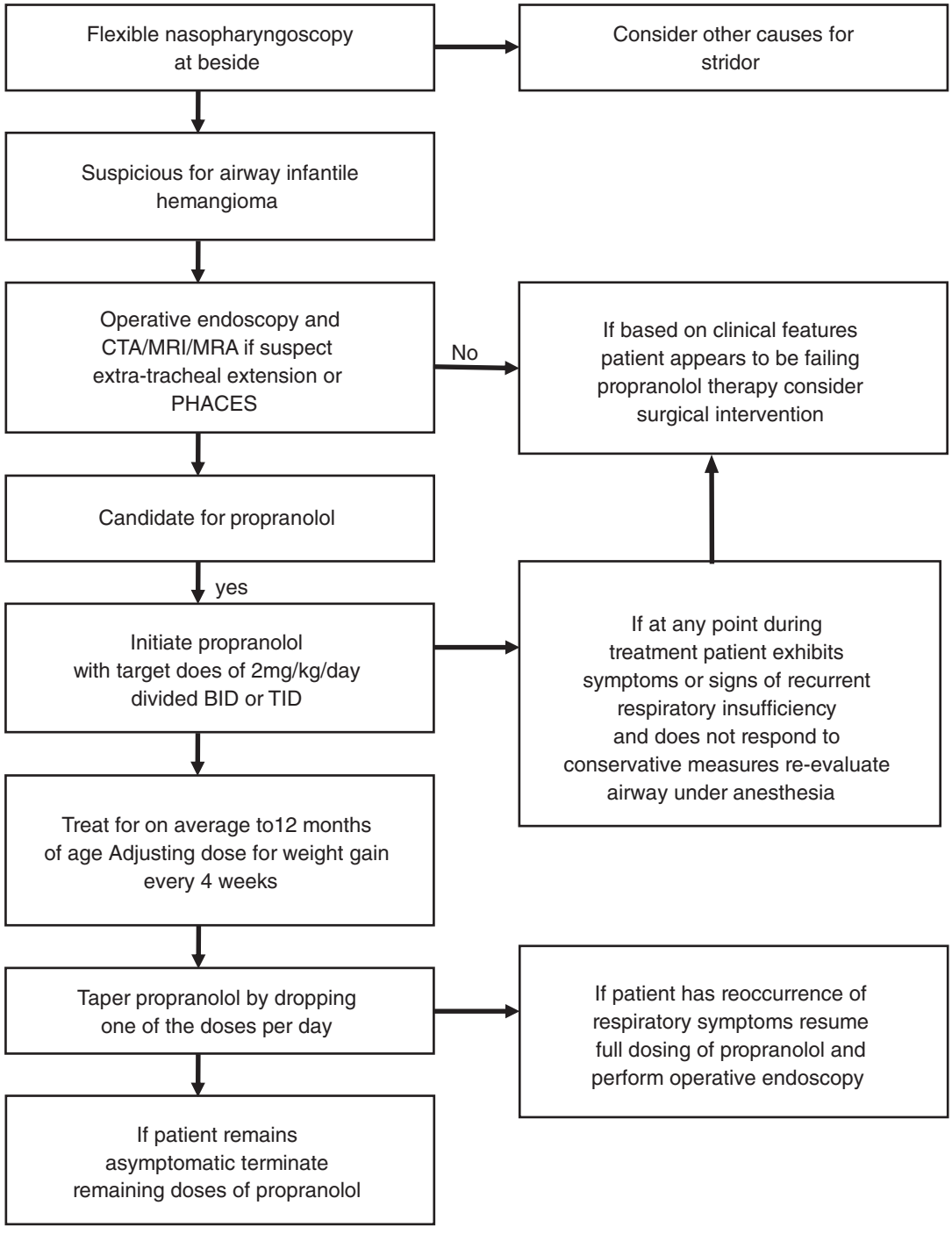

Fig. 17.4 Algorithm for treatment with propranolol

To assist the reader in gaining familiarity with available evidence, the following rating system has been used to indicate key references for each chapter's content:
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**: Useful material. Important information that is valuable in in clinical or scientific practice related to this condition.
*: Optional material. For readers with a strong interest in the chapter content or a desire to study it in greater depth.

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18 Parotid and Deep Vascular Tumors

Craig Miller and Randall A. Bly

Level of evidence: treatment	Low
Evidence	Case series

Diagnostic Considerations

Vascular anomalies frequently involve the face and lateral face, making them difficult to treat, as all treatments can cause facial disfigurement and motor nerve dysfunction. This chapter highlights the unique treatment challenges these lesions pose.

Hemangioma

Parotid infantile hemangiomas (IH) are benign growths of endothelial cells that arise in any tissue of the face after normal neurovascular development has occurred. In the pediatric population, IH is the most common parotid mass [1]. For further details on the natural history and etiology of these benign neoplasms, please see Chap. 6. Typically asymptomatic, their predictable course often permits a conservative management approach. However, some parotid IH can grow rapidly or respond poorly to medical therapy, leading to facial distortion (Fig. 18.1), as well as obstruction of surrounding structures, such as the external auditory canal (EAC) and the airway [2]. Parotid region IH may be associated with PHACE syndrome [3, 4]. A patient such as this may have up to 50% risk of a concomitant airway hemangioma [3].

Vascular Malformations

In contrast to IH, vascular malformations are usually present at birth and grow commensurately with associated structures during development but can present in adulthood. Malformations are collections of abnormal vessels thought to occur during and through abnormal vascular development precipitated by de novo genetic alteration [5–9]. The type of vessel that is predominate in the malformation dictates treatment strategy. Capillary, venous, and lymphatic "low-flow" lesions are treated differently than arterial or arteriovenous "high-flow" lesions.

Lymphatic malformations (LM) are most commonly found in the head and neck region and are the most common vascular malformation to involve the lateral face. Rarely are LM isolated to the parotid gland most involve and lateral

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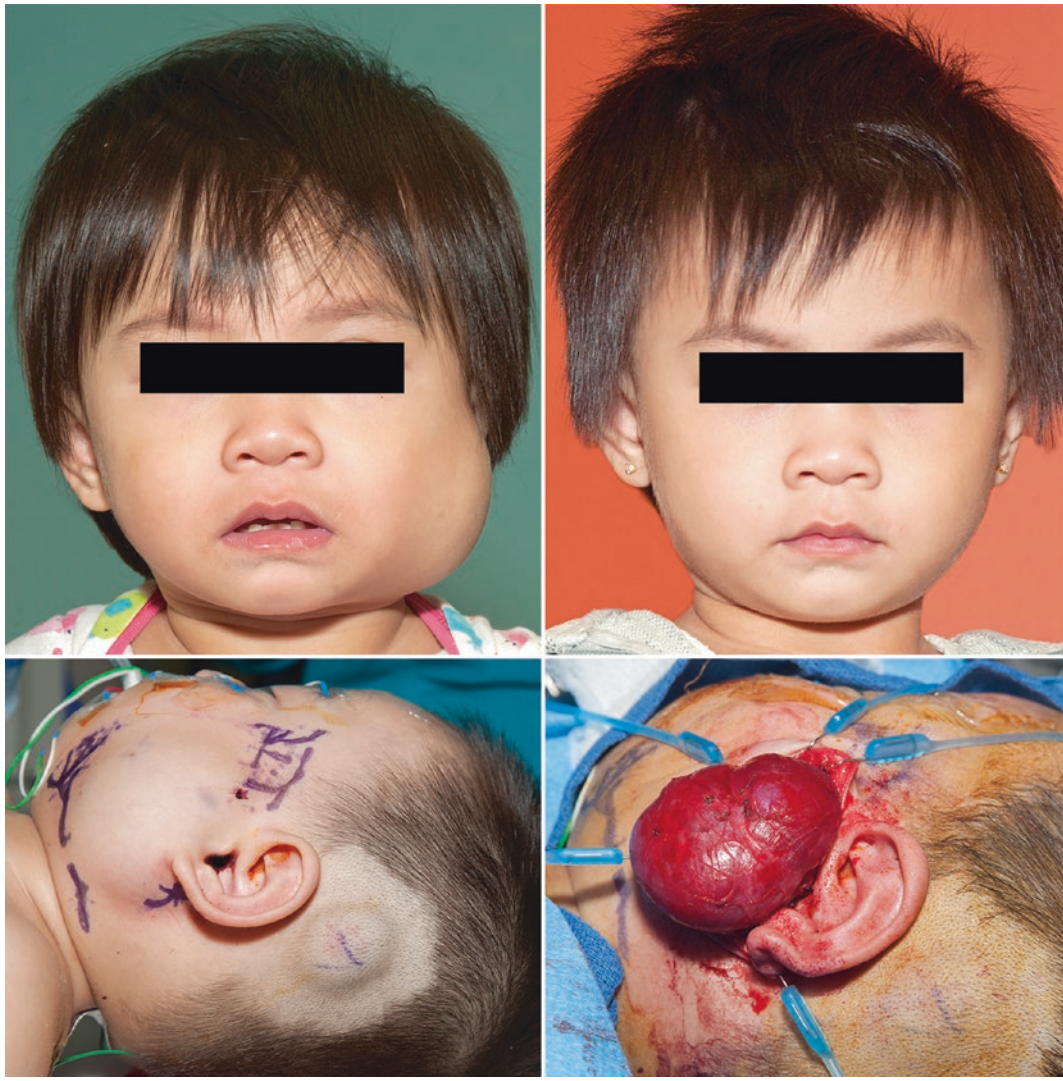

Fig. 18.1 Deep infantile hemangioma of the left parotid gland, minimally responsive to propranolol removed with the assistance on preoperative embolization and nerve mapping. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

face and parotid secondarily [10]. Presentation typically involves a painless, soft, fluctuant mass. Imaging is essential for accurate presurgical planning and intraoperative approach. MRI is most useful to evaluate the expansion and invasion of deep structures, as well as the delineation of soft tissue planes. Due to their cystic nature, lymphatic malformations have low attenuation of T1-weighted images, with hyperattenuation on T2-weighted films. CT imaging may be useful for bony detail, particularly if there is adjacent bony overgrowth of the mandible.

Treatment Considerations

Evidence-based treatment approaches to vascular anomalies of the parotid region and lateral face are lacking. Treatment plans must be individualized to the patient and the extent of disease. Conservative management and observation are appropriate in asymptomatic patients. The low risk of acute lesion enlargement from inflammation or intralesional hemorrhage should be considered when choosing treatment. Conservative management should be pursued in patients

without functional compromise or significant disfigurement, or if patients and their families are not interested in surgery. In these cases, complete resection or sclerotherapy may result in functional deficits. Typical follow-up for these patients is done on a twice-yearly basis.

Infantile Hemangioma

Some evidence has suggested that propranolol may not be as effective in treating parotid IH as those in other parts of the body and head and neck [11]. Other studies have demonstrated good response of oral propranolol treatment for infantile hemangiomas of the parotid. Further research is needed to clarify this issue, but the low risk of propranolol therapy makes it worth trying in otherwise stable patients. Treatment is indicated in certain situations, including aesthetic concern, psychosocial trauma, bleeding, ulceration, pain, and functional compromise. Functional compromise may occur due to either the location of the hemangioma, its size, or both. In lesions that involve the parotid and lateral face that are not satisfactorily responsive to propranolol, superficial IH can be treated with pulsed dye laser therapy or resected with deeper portions of the IH (Fig. 18.1). If surgery is contemplated in large well-vascularized IH, then adjunctive preoperative embolization is usually considered.

Vascular Malformation

Vascular malformations of the parotid region and lateral face can be treated with sclerotherapy or surgery [12, 13]. This is best demonstrated by treatment experience with LM, as they are the most common malformation in the area. Localized low-stage LM are amenable to both treatments, and the frequency of intervention is the same for sclerotherapy and surgery [14]. As the understanding of how molecular genetics affect specific cells and cause LM and other vascular malformations emerges, treatment concepts for these lesions are changing (please see other lesion-specific chapters for in-depth discussion). For example, there are reports of using agents that suppress a portion of the PIK3CA pathway being used to treat LM [15]. It is too early to determine how effective this will be in the lateral face.

Experience with invasive therapy in the lateral face is best described with LM. Any invasive therapy for lesions in this area can damage the facial nerve, a structure that is essential to preserve normal facial appearance and function. Sclerotherapy can be successful in obliterating LM macrocysts but may require multiple sessions and ultimately require surgery due to lesion persistence. OK-432 in particular has been shown to be safe and beneficial through immunological upregulation it induces [16]. The low fibrogenic nature of OK-432 allows for surgical resection after sclerotherapy as well. However, this drug is not FDA approved for sclerotherapy in the Unites States. Other sclerosants are used for lesions in this area, but all have more potential for neurotoxicity and have not been systematically evaluated [13].

The extent of LM surgical management is based on the extent of the malformation as determined with imaging. The radiographic appearance does not matter if LM surgery is done prior to or in lieu of sclerotherapy. Those confined to the parotid gland can be completely resected with facial nerve preservation. Larger lesions that extend into the neck and parapharyngeal regions require total parotidectomy with facial nerve preservation (Fig. 18.2). Facial nerve preservation is of utmost importance; intraoperative facial nerve monitoring should be a standard procedure to reduce the risk of facial nerve injury and resultant dysfunction. Complete resection is essential to remove as many genetically altered cells and tissue as possible. Success is largely based on complete resection and preservation of normal structures. Since overgrowth occurs in all vascular malformations, including LM, malformation removal may not result in perfect facial symmetry (Please see Chap. 33). Studies have demonstrated increased rates of persistence when lesions were located in both the parotid and neck regions [17, 18]. Additionally, these lesions require more operations or sclerotherapy sessions and have higher complication rates and higher rates of persistence of disease. Surgical complications associated with resection of LM include facial nerve damage, infection,

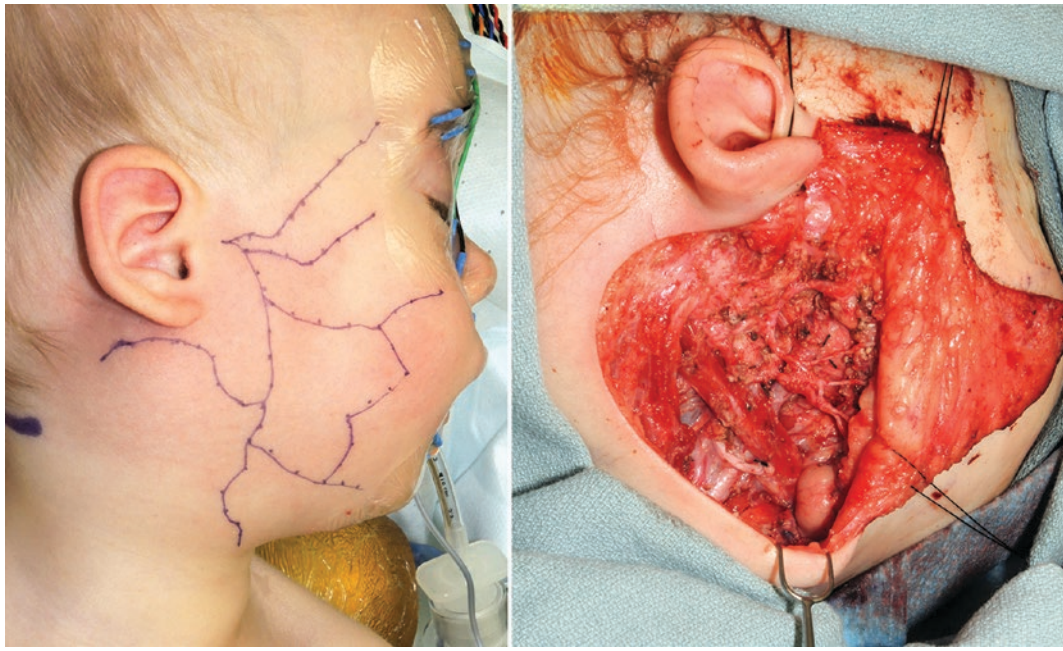

Fig. 18.2 Stage III lymphatic malformation removed with total parotidectomy and facial nerve dissection/preservation of elongated nerve after nerve mapping. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

scarring, contour defect, bleeding, and hematoma. No operation in this region should be done without adequate postoperative drainage, usually lasting several days to a week.

In patients with vascular malformations (please see lesion-specific chapters) where surgical resection is unlikely to be successful, either due to inability to resect the entire lesion or risk of complications associated with resection, alternative treatment methods may be used or surgery delayed (Figs. 18.3 and 18.4).

Facial Nerve Mapping

Vascular malformations of the face and parotid region are associated with the facial nerve. The infiltrative nature of these lesions and their intimate involvement with the nerve, as well as the tendency for distortion of surrounding normal tissues including the parotid gland and facial nerve, increase the likelihood of facial nerve damage during surgery [19, 20]. Due to variable facial nerve displacement and involvement, incidences of facial nerve injury during resection of parotid vascular anomalies are higher than typical rates for standard parotid surgery [19]. Vascular anomalies in this region can involve soft tissue, can completely surround the facial nerve, and can elongate the facial nerve, thus displacing branches of the nerve from their typical and expected anatomic locations. In an effort to reduce the risk of facial nerve injury and dysfunction after resection of parotid vascular anomalies, detailed nerve monitoring and mapping has been described [21]. Using this technique, the main trunk and all facial nerve branches are transcutaneously identified and marked out by a neurophysiologist and continuously monitored during the operation. Motor nerve identification and functional status are determined by the neurophysiologist in direct communication with the operating surgeon, allowing the surgeon to completely focus on removal of the lesion. Studies have demonstrated a low incidence of facial nerve injury using the preoperative nerve mapping technique, decreased operative time, and greater flexibility in facial nerve dissection preserving normal structures [22].

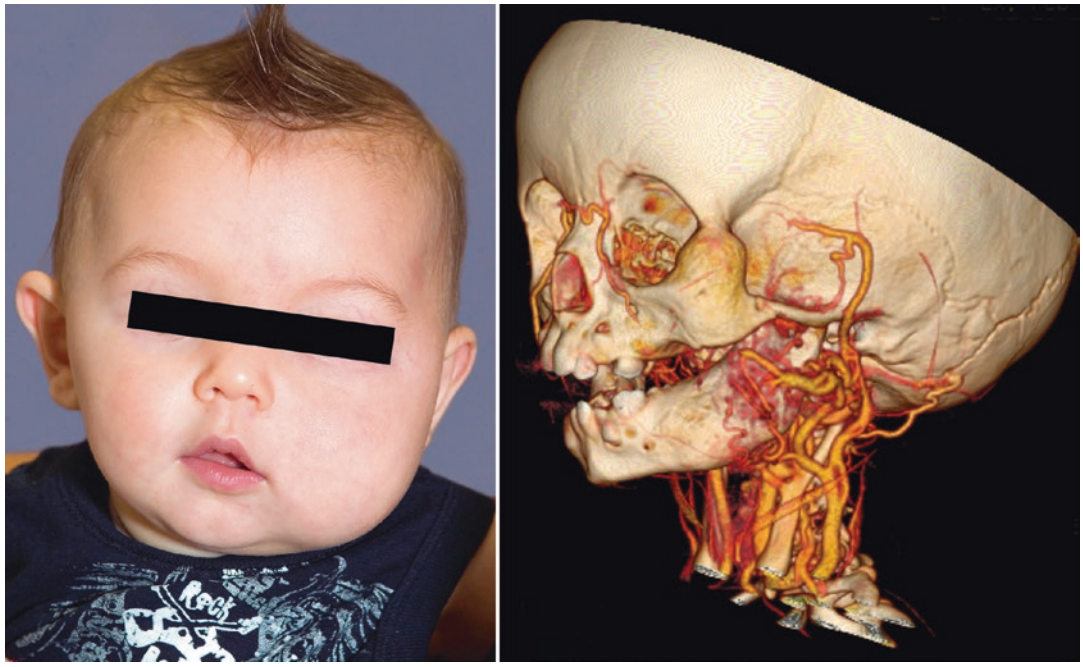

Fig. 18.3 Extensive parotid region and lateral facial AVM in young patient. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer). (Images courtesy of Seattle Children's Radiology, Giridar Shivaram, Eric Monroe and Kevin Koo)

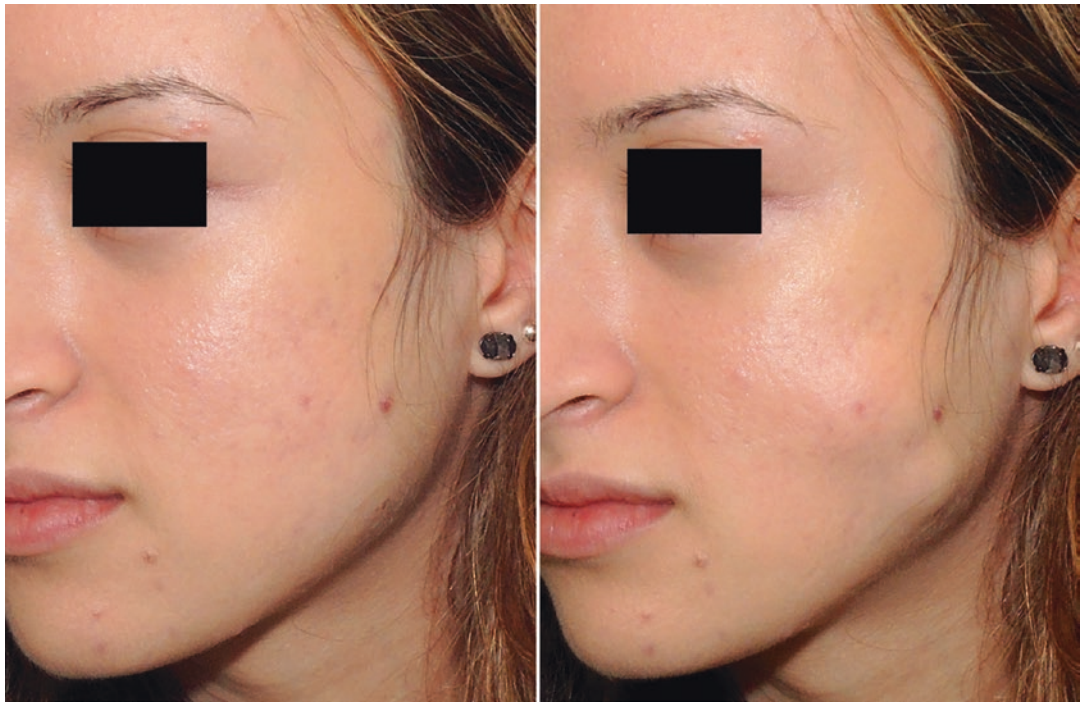

Fig. 18.4 Typical intramasseteric/parotid venous malformation with patient at rest and with teeth clenched, enlarging the malformation. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

Table 18.1 Vascular anomaly and associated genetic etiology

Type	Causal gene
Common venous malformation	TEK/TIE2 somatic, RASA1, PIK3CA
Familial venous malformation cutaneo-mucosal (VMCM)	TIE2
Blue rubber bleb nevus (Bean) syndrome venous malformation	TEK/TIE2
Glomuvenous malformation (GVM)	Glomulin, GLMN
Cerebral cavernous malformation (CCM)	
CCM1	KRIT1
CCM2	Malcavemin
CCM3	PDCD10

Conclusion

Vascular anomalies of the parotid region require multidisciplinary care and management both in diagnosis and treatment. Treatment options are aimed at reducing morbidity. In cases of surgical resection, preoperative facial nerve mapping and monitoring can provide an efficient and safe method for preserving facial nerve function (Table 18.1).

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**: Useful material. Important information that is valuable in in clinical or scientific practice related to this condition.
*: Optional material. For readers with a strong interest in the chapter content or a desire to study it in greater depth.

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Part IV

Vascular Malformations

Capillary Malformation

19

Deepti Gupta and Marcelo Hochman

Genetic diagnosis	Yes
Genetic etiology: capillary malformation	Postzygotic somatic mosaic, GNAQ
Level of evidence: treatment	Medium
Evidence:	Randomized crossover case series, expert opinion

Phenotype and Variations

Capillary malformation (CM) is an overarching term that includes various different vascular stains with different morphologies, associations, natural courses, and prognoses. Some are isolated findings, while others are associated with an underlying syndrome. The following discussion outlines the prevailing classification schemes for CM [1].The descriptive and historic terminology used in the headings should be used as a complement the International Society for the Study of Vascular Anomalies classification (www.ISSVA.org) updated in 2018.

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Nevus Simplex

Nevus simplex (aka salmon patch) is the most common capillary malformation seen in infancy with reported prevalence of up to 82% and is seen more commonly in Caucasian infants [2]. It has been known by many other colloquial terms such as "angel's kiss" when located on the glabella and middle of the forehead and "stork bite" for the lesions located on the nape of the neck. They consist of ectatic capillaries located in the dermis with an overlying normal epidermis. Clinically, they occur as partially blanching erythematous macules or patches with feathery and indistinct borders most often over the eyelids, glabella, posterior occiput, and nape of the neck and less commonly occur on the nose, perinasal skin, upper lip, lumbosacral area, and infrequently upper and mid-back. Those involving the glabella and forehead often have a characteristic V shape. When nevus simplex is more extensively and involving sites that are less commonly seen, then the term nevus simplex complex has been used [3]. Most lesions of nevus simplex resolve over a few months to years, but nuchal lesions and to a smaller extent glabellar lesions may persist. Most individuals with nevus simplex are otherwise normal, but there are a few genetic syndromes that have other characteristic findings to help with their diagnosis that have been associated with nevus

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simplex including Beckwith-Wiedemann syndrome, Nova syndrome, macrocephaly-capillary malformation syndrome, and Roberts-SC syndrome.

Port Wine Stain (Nevus Flammeus)

PWS are persistent CM that grow in proportion to a child's somatic growth. They present with well-demarcated pink to dark red patches that can occur anywhere on the body. They can be distinguished from nevus simplex in that they are often more well-demarcated, persist and can darken and thicken with age, and often have a more lateral location. PWS location is helpful in predicting risk of associated anomalies, syndromes, and clinical courses. PWS on the limbs and truck tend to be stable in color and thickness and some may lighten with time. Facial PWS tend to become a darker crimson or deep purple, thicken, and develop focal pyogenic like blebs or other epithelial or mesenchymal hamartomas [4]. There is often associated soft tissue and bony hypertrophy, as well as gingival hypertrophy and dental anomalies. PWS may appear to lighten between 3 and 6 months of age, but this is not a sign of overall lightening or resolution, but rather corresponds to a physiologic lightening due to a decrease in blood hemoglobin concentration as there is a change in fetal to adult hemoglobin type [5]. PWS can be associated with pigmentary abnormalities such as dermal melanocytosis, nevus spilus, and other cutaneous nevi such as epidermal nevi and nevus anemicus and is termed phakomatosis pigmentovascularis (PPV). PPV is classified into four types based on clinical findings and can be associated with extracutaneous manifestations. Facial PWS often occur as an isolated finding, but approximately 10% have been associated with Sturge-Weber syndrome (SWS) [6–8]. Please see SWS chapter.

Telangiectasia

Telangiectasias are characterized by small-dilated capillary vessels that appear as punctate red macules with a stellate or spiderlike shape. A pale vasoconstrictive halo may surround the telangiectasias. They can be distributed as isolated or multiple discrete macules or in a segmental, unilateral, or diffuse pattern. Common findings in toddlers and young children are spider angiomas that present as solitary or multiple discrete telangiectasias with a central papule with radiating fine spiderlike telangiectasias. They often present in sun-exposed areas and are more predominant in fair skin individuals and areas of minor skin injury. They may spontaneously resolve over time or can persist. Children presenting with diffuse and multiple telangiectasias should be evaluated for three main clinical entities: unilateral nevoid telangiectasia, hereditary benign telangiectasia, and hereditary hemorrhagic telangiectasia (HHT, please see HHT chapter). Unilateral nevoid telangiectasia is a sporadic disorder that presents with multiple telangiectasias with a fine spiderlike quality that occur in a segmental and unilateral distribution often occurring over the neck and upper extremities. Hereditary benign telangiectasia is an autosomal dominant condition with multiple diffuse fine telangiectasias that may have varying shape and size. They may present first on the face and then become more widespread throughout childhood and adolescence [9]. Both unilateral nevoid telangiectasia and hereditary benign telangiectasia do not have any other sequelae or associated abnormalities, and further workup is not needed.

Cutis Marmorata Telangiectatica Congenita (CMTC)

CMTC is a congenital vascular malformation, which has a distinctive pattern of reticulated erythema with a livedo reticularis-like appearance [10, 11]. Most cases occur sporadically. There is a well-defined dark blue to purple coarse reticulated vascular stain that can be admixed with telangiectasias. It can present in a small-localized area or more diffuse but is often unilateral. Within affected areas there can be focal atrophy or ulceration. Ulcerations occur most often over joints and can happen from

birth into childhood. The atrophy, coarse nature of reticulated erythema, and persistence with warming distinguish it from the normal finding of physiologic cutis marmorata. They most commonly occur on the lower extremities, followed by the trunk, upper extremities, and then the face. The natural course for CMTC is partial involution but the cutaneous atrophy, if present, persists throught life. CMTC has been associated with a variety of abnormalities, but the most widely accepted of these as true associations are glaucoma, capillary malformations, and body asymmetry [12]. The asymmetry that is often seen is differences of limb girth with affected limbs being thinner in appearance due to decreased fat, muscle, and bone.

Reticulated Capillary Malformations

CM can also have a reticulate morphology and in the past were likely misdiagnosed as CMTC. Reticulated CM have a pink to light red coloration, are "blotchy," and tend to be more poorly defined [13]. They can be quite extensive but lack the coarse, dark color, and atrophy or ulceration than can be seen with CMTC. Clinically, reticulated capillary malformation can be an isolated phenomenon or can be seen in macrocephaly-capillary malformation syndrome (M-CM) or diffuse capillary malformation and overgrowth syndrome (DCMO).

Macrocephaly-Capillary Malformation (M-CM) Syndrome

Individuals with M-CM present with an extensive reticulated capillary malformation, prominent nevus simplex often with involvement of the philtrum and glabella, macrocephaly, or megalencephaly. They can present with neonatal hypotonia. They also have coarse facial features, polydactyly or syndactyly, and can have asymmetric overgrowth that presents early on in life. They can be at risk for Wilms' tumor as well as multiple potential intracranial complications such as Chiari 1 malformation, cerebellar herniation ventriculomegaly, cerebral asymmetry, and polymicrogyria.

Diffuse Capillary Malformation and Overgrowth Syndrome (DCMO)

DCMO describes a condition with an extensive reticulated CM with proportional and nonprogressive overgrowth. The overgrowth is secondary to hypertrophy of soft tissues and bones and can occur ipsilateral or contralateral to the affected area of stain [14]. DCMO can have prominent subcutaneous veins and varicosities but lacks the lymphatic component, which distinguishes it from Klippel-Trenaunay syndrome (KTS). In KTS, the overgrowth also tends to be progressive.

Geographic Capillary Malformations

Geographic CM tend to be well-demarcated, irregularly shaped, deep red and purple in color, and localized in nature in comparison to reticulated capillary malformations and can develop hemorrhagic papules and vesicles. They often accompany venous anomalies, overgrowth that can be progressive and not proportional, and lymphatic malformations. The geographic stain has been seen in Klippel-Trenaunay syndrome (KTS), congenital lipomatosis, overgrowth, vascular malformations, epidermal nevi and spinal and skeletal abnormalities (CLOVES) [15] and CM of the lower lip, lymphatic malformation of the face and limbs, and partial or generalized overgrowth (CLAPO) [16]. All of these conditions have been found to be due to PIK3CA mutations [17]. They are risk for significant pain, thrombosis from coagulopathy as well, and progressive overgrowth causing significant limb differences.

Capillary Malformation-Arteriovenous Malformation (CM-AVM)

CM-AVM is an autosomal dominant vascular disorder that presents with multiple, round to oval, pink-red brown vascular stains, many of which

will have a vasoconstrictive halo surrounding them [18, 19]. Some describe them as having a "thumbprint"-like quality. They can present anywhere on the body, but rarely the palms, soles, and mucosa. Approximately one third of patients can present with an arteriovenous malformation that can occur in the brain, spine, bone, skin, or soft tissue. CM-AVM is due to mutations in RASA-1.

Etiology

Emerging DNA sequencing technologies have allowed detection of genetic variation that causes CM and/or syndromes associated with CM (Table 19.1). Currently the clinical implications of these genetic discoveries are evolving. Genetic testing may be helpful in determining course and role for targeted therapy.

Natural History

The natural history of CM is dependent on their morphology and clinical pattern and if it is part of an underlying syndrome. Some CM, such as a majority of nevus simplex, resolve, while other facial PWS get darker and thicker. The natural history of the various CM phenotypes is summarized above.

Table 19.1 Genetic mutations associated with CM

Type of capillary malformation or syndrome	Mutation
Nevus simplex	Unknown
Port wine stain, nonsyndromic	GNAQ
Sturge-Weber syndrome (see Sturge-Weber syndrome chapter)	GNAQ
Hereditary hemorrhagic telangiectasia (HHT) (see HHT chapter)	
HHT1	ENG
HHT2	ACVRL1
HHT3	SMAD4
PIK3CA overgrowth-related spectrum (PROS) (see PROS chapter)	
Macrocephaly-capillary malformation	PIK3CA, AKT1
Klippel-Trenaunay	PIK3CA
CLOVES	PIK3CA

History and Physical Exam

A complete full body examination in CM patients is essential to look closely at lesion morphology, extent, locations of involvement, and any other associated clinical findings such as overgrowth, limb abnormalities, digit abnormalities, scoliosis, macrocephaly, and other dysmorphic features.

Imaging for Capillary Malformation Evaluation

Neuroimaging in patients with facial CM has been the subject of research and discussion for more than 30 years [6]. Neurological malformations associated with SWS (leptomeningeal vascular anomalies, calcifications, choroid plexus enlargement, cortical atrophy, venous malformations) should be identified early; however, the clinician should be judicious with imaging so as not to unnecessarily subject children to radiation or anesthesia (please see Sturge-Weber syndrome chapter). Consistently, involvement of the V1 dermatome portends a potential diagnosis of SWS which should be evaluated with neuroimaging, with either CT or MRI. A recent retrospective study on 259 patients with facial CM supported this approach: all 15 patients in this cohort who eventually were diagnosed with SWS had V1 region involvement [20, 21].

Optimal age at which to image the brain is unclear. False-negative brain imaging can occur when imaging is performed before 9 months of age [22, 23]. As such, neuroimaging in an infant with V1 CM involvement should likely be delayed until or repeated after 9–12 months of age [24]. Imaging is necessary to diagnose the intracerebral manifestations of SWS, and it plays no role in treatment planning for the cutaneous CM itself.

Capillary Malformation Treatment

By far the most important factor for favorable treatment outcomes in facial CM is accurate diagnosis (discussed above), as treatment

approaches differ for different vascular lesions. Once a diagnosis is made, parents should be counseled on the natural history of the lesion, the expected outcomes of therapy, and the variability of these outcomes. Early intervention is the strategy of choice given the inevitable phenotypic [25] (increasing darkness and nodularity) and psychosocial [26–28] sequelae of the condition. Treating at an early age while minimizing the risks from anesthesia (typically beginning at 6 months) allows for more favorable cosmetic outcomes of treatment because the lesion and its vascular components are dimensionally smaller and more superficial. The optical qualities of infant skin allow for less scatter and reflectance of incident laser light than in later years.

Therapeutic modalities for facial CM have evolved alongside our understanding of the disease process and with technological medical innovation. Treatments no longer in use due to unfavorable outcomes include sclerotherapy, dermabrasion, cryotherapy, X-ray treatment, and even cosmetic camouflage with tattooing. Years of research have borne out therapeutic efficacy and safety with laser therapy most consistently, and thus, lasers form the mainstay of facial CM treatment.

As discussed below, pulse-dye laser (PDL) is the first-line treatment for CM. However, a subset of lesions are PDL-resistant, and decisions must be made regarding alternate therapies including addition of anti-angiogenic drugs to PDL, lasers of differing wavelengths, intense pulsed light, and photodynamic therapy. Discussion of a tiered approach to treatment in the context of the best available literature follows.

Laser Treatment

Proper laser safety should always be a top priority; eye protection for patient and staff should be mandated at all times. Laser treatments can be done safely in the office, but cooperation is often difficult in the toddler years. In these cases, the procedure can be done in the operating room with simple mask general anesthesia.

The entire lesion should be treated. It is a typical practice to begin by treating the border of the lesion and working inward, careful not to overtreat any particular area. Applied laser energy degrades in a Gaussian manner as the edge of the pulse, so a 10% pulse-pass overlap is necessary for uniformity. Appropriate fluence will be obvious when tissue response is purpuric white; white-gray discoloration is concerning for overtreatment.

Petroleum ointment can be applied to the treatment area for 5–7 days after treatment, and analgesia is generally achieved with over-the-counter medications. The effect of treatment can continue to progress for 3–4 weeks. Serial treatments at 6-week intervals are typical until resolution of the lesion or diminishing treatment return.

Pulse-Dye Laser

CM are thought to represent proliferation of postcapillary venules; optimal laser therapy would selectively target these small, red blood cell-containing (and thus hemoglobin-containing) vessels while sparing the mostly water-containing surrounding skin and tissue. At a wavelength of 585–595 nm, PDL corresponds closely to the second of two absorption peaks of hemoglobin (540 nm and 575 nm) [29] and induces selective photothermolysis of this molecule. Moreover, at pulse widths of 450 microseconds, PDL pulses do not span the relaxation time of skin (700–900 ms) resulting in only a negligible amount of thermal injury and scarring.

Much of the pioneering research demonstrating efficacy and safety of PDL for facial CM was performed in the 1990s, which places it out of the scope of this chapter. Though this data is now a bit dated, it forms the basis for the choice of PDL as first-line therapy and from which more recent setting-optimization studies were performed; exemplary studies from this period are not discussed but cited below [30–33]. A contemporary systematic review of randomized controlled trials of lasers and light sources for treatment of facial CM concluded that the evidence supports the use of PDL for this purpose, while there is a paucity of randomized data for the other treatment modalities [34].

Upon review of 49 cases, a clearance rate of 88.6% at 1 year was found for facial CM treated

with 595 nm PDL before 6 months of age [35]. Surface area, location (V1 distribution), treatment number, and higher fluence were all associated with increased clearance in this study. A smaller study demonstrated a trend toward increased clearance with higher fluence, but did not reach significance [36]. In a prospective randomized trial of PDL at 585 nm vs 595 nm wavelength in 15 patients, 585 nm yielded a significantly greater clearance rate (using a blinded but non-validated clearance rating scale) but was also associated with more purpura, pain, and crusting [37].

Single-pass treatment is not inferior to double-pass treatment when assessed by spectrophotometry [36, 38] and across most studies; the addition of cryogen cooling improves the cosmetic and analgesic result of PDL treatment [36, 39]. Traditionally, treatment interval is approximately 6 weeks, though there are no studies specifically validating this choice. Moreover, a randomized trial in 15 patients demonstrated that a 2-week interval resulted in statistically significant increase in clearance compared to a 6-week interval [40] and allows for decreased overall treatment length. This has not, however, been incorporated into routine practice.

Despite the success of PDL therapy, patients may experience clinically apparent darkening of the lesion up to 10 years after completing treatment, though not back to pretreatment levels [41].

Pharmacologic Additives to PDL Therapy

Recently, promising data has emerged from studies investigating the addition of various topical medications to a PDL treatment strategy. The most notable of these additives is rapamycin, an immunosuppressive mTOR (mammalian target of rapamycin) inhibitor thought to have anti-angiogenic properties. A phase II, randomized, double-blind, intraindividual placebo-controlled trial from 2015 demonstrated that topical rapamycin + PDL therapy was superior to all other arms (placebo alone, PDL + placebo, and rapamycin alone) in terms of photographic scoring and histological analysis [42]. This result is supported by a histological study in hamsters demonstrating decreased reperfusion rates in vessels treated with PDL + rapamycin compared to PDL alone [43]. Since the advent of PDL treatments, the use of adjuvant rapamycin is the most significant recent addition to the armamentarium. It is used topically as a 10% preparation in a liposomal base two times per day for months.

Imiquimod is another immunosuppressive molecule that reduces angiogenesis via a variety of mechanisms [44] which has demonstrated improved clearance when combined with PDL therapy [7, 45]. Conversely, a multicenter trial investigating similar use of the nonselective beta-blocker timolol failed to demonstrate improved clearance relative to PDL alone [46].

Laser Alternatives for PDL-Resistant Lesions

Initial management of PDL-resistant lesions should first center around troubleshooting and adjusting PDL settings [47], including longer pulse durations [48] and varying fluence. If the lesion persists, intense pulsed light has demonstrated the greatest second-line clinical efficacy (see below). Failing all this, alternative laser therapy can be used for certain lesions, though typically with inferior results to PDL.

Long-pulse alexandrite is a 755 nm laser with demonstrated success in lesions that showed inadequate response to PDL [49–51]. However, judicious use is warranted as the deep penetration of this wavelength can induce significant dermal injury and unsightly scarring. Similarly, Nd:YAG (1064 nm) [51–53] and KTP (532 nm) [51, 54] lasers have been used for PDL-resistant lesions but also can lead to increased scarring.

Intense Pulsed Light

Intense pulsed light (IPL) is emerging as a promising alternative to PDL for facial CM. This technology involves administering intense, visible spectrum light (400–1200 nm) via a computer-controlled flashgun. Filters can be applied to select wavelength ranges being applied in order to allow for a certain degree of specificity. Fluence and pulse duration can also be varied in a similar manner to that in PDL.

In a randomized side-by-side study in 20 patients with CM, PDL outperformed IPL in terms of blinded clinical evaluation as well as skin reflectance values [55]. However, this study was not limited to CM of the face. Conversely, when IPL was compared head-to-head to both short and long (0.45 ms and 1.5 ms) PDL in an intraindividual study of 25 patients with facial CM [56], IPL performed better than short PDL but equivalently to long PDL. This was true for both untreated and previously treated lesions and all lesions were on the face. In a more dated series of 15 patients, PDL-resistant facial CMs were stratified into two groups: those that responded to IPL and those that did not [57]. Of the "responders" (n = 7/15), 85.7% demonstrated 75–100% reduction of the lesion, while the remainder experienced less than 25% reduction.

Photodynamic Therapy

Photodynamic therapy (PDT) involves visible light treatment of a lesion that has been photosensitized with a drug (often porphyrin derivatives) leading to a photochemical reaction producing cytotoxic activated oxygen species. This therapeutic modality is especially popular in Asian patient populations and appears to be most effective in purple flat lesions [58, 59]. In a Chinese cohort of 642 Fitzpatrick skin type V patients or those with nodular lesions, PDT was associated with 5% complete clearance rate, and 70% of patients exhibited at least 25% clearing [60]. However, 10% of patients experienced complications (blistering, hypopigmentation, hyperpigmentation, scabbing, eczema dermatitis, and photo allergy). Moreover, in another study of PDT using PDL as the energy source, PDT was not superior to PDL alone, though adverse events were similar in the two groups [61]. Limitations to PDT that have thus far precluded its more widespread application include high cost (physician time, drug cost, and equipment), inefficient transcutaneous absorption of chromophores, and prolonged systemic visible light sensitivity with intravenous porphyrins [62].

Surgical Management

Surgery plays a very limited role in the treatment of facial CM, a role typically limited to debulking of tissue hypertrophy commonly seen in the lips and nodularity of progressing CMs. In some lesions there can be an underlying venous malformation, which would elicit imaging and further workup and treatment (www.ISSVA.org) (Fig. 19.1).

Key Study Summaries

- **Rozas-Munoz E, Froeden IJ, Roe E, Puig L, Baselga E. Vascular stains: Proposal for a clinical classification to improve diagnosis and management. *Pediatric dermatology.* 2016; 33(6):57–584.
- In this review they highlight the various morphologies and clinical characteristics of the various capillary malformations and aid to improve clinical diagnosis. They go through systematically various syndromes and conditions related to capillary malformation and help place them into categories.
- **Dutkiewicz AS, Ezzedine K, Mazereeuw-Hautier J et al. A prospective study of the risk for Sturge-Weber syndrome in children with upper facial port wine stain. *J Am Aacd Dermatol* 2015;72:473–480.
- Previous studies had suggested that facial port wine stains are secondary genetics mosaicism and secondary to embryogenesis of the vascular placodes rather than trigeminal nerve distribution. This study sought to refine the cutaneous distribution of upper facial PWS and risk of SWS. They discovered that specific patterns were associated with an increased risk of SWS. Risk of SWS syndrome is related to forehead involvement and increased risk with central forehead or more extensive facial involvement of the PWS.
- ***Faurschou A, Olesen AB, Leonardi-Bee J, Haedersdal M. Lasers or light sources for treating port wine stains. *The Cochrane Database of Systematic Reviews.* Nov 09 2011 (11):CD007152.
- In this systematic review from 2011, the major literature databases were queried from their

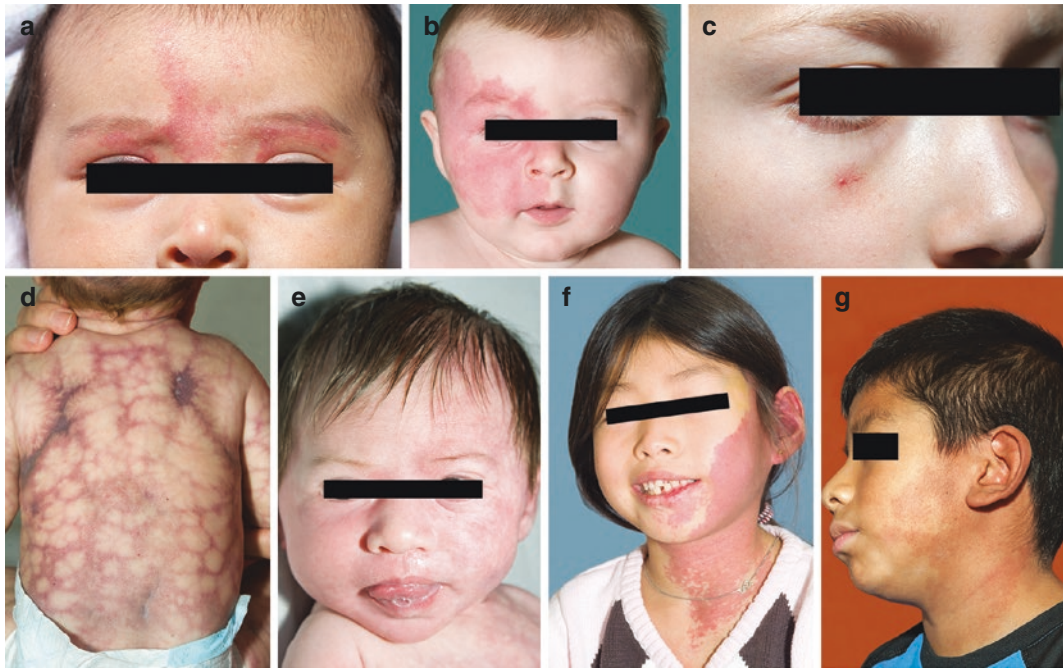

Fig. 19.1 (**a**) Nevus simplex, (**b**) capillary malformation in V1 and V2, (**c**) telangiectasia, (**d**) cutis marmorata telangiectasia congenita, (**e**) reticulated capillary malformation, (**f**) diffuse capillary malformation and overgrowth syndrome (lip, mandible, maxilla), (**g**) CM-AVM or auricle. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

inception through 2010 for randomized controlled trials (RCT) studying the use of lasers or light sources for the treatment of facial capillary malformations. Five RCTs summing to 103 subjects were included in the review; heterogeneity of endpoints precluded meta-analysis. The authors conclude that PDL leads to clinically relevant reduction in redness, whereas IPL and Nd:YAG had insufficient data but appeared to be inferior to PDL. However, the quality of the included studies was questioned given the short follow-up and lack of consistent and appropriate outcomes.

- ***Marques L, Nunez-Cordoba JM, Aguado L, et al. Topical rapamycin combined with pulsed dye laser in the treatment of capillary vascular malformations in Sturge-Weber syndrome: phase II, randomized, double-blind, intraindividual placebo-controlled clinical trial. *Journal of the American Academy of Dermatology.* Jan 2015;72 (1):151–158 e151.

  This phase II, intraindividual RCT sought to determine the efficacy of the addition of topical rapamycin to a PDL treatment regimen. Patients with Sturge-Weber syndrome identified at multiple participating institutions were included, and the study randomized lesion quadrants to be treated by one of four strategies: (1) placebo, (2) PDL + placebo, (3) rapamycin, and (4) PDL + rapamycin. A scoring system incorporating blinded, independent clinical assessment with spectrophotometric, histologic, and immunohistochemical analysis was used to compare results. PDL + topical rapamycin was superior to all other intervention arms and was well tolerated by participants. Though confirmatory studies are still needed, this study could signal a paradigm shift in the treatment of capillary malformation. Similar (though less powered) results are being seen with topical imiquimod as well.

To assist the reader in gaining familiarity with available evidence, the following rating system has been used to indicate key references for each chapter's content:
***: Critical material. Anyone dealing with this condition should be familiar with this reference.
**: Useful material. Important information that is valuable in in clinical or scientific practice related to this condition.
*: Optional material. For readers with a strong interest in the chapter content or a desire to study it in greater depth.

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20 Head and Neck Lymphatic Malformation Diagnosis and Treatment

Jonathan A. Perkins, Eric J. Monroe, Randall A. Bly, and Gridhar Shivaram

Genetic diagnosis	Yes
Genetic etiology	Postzygotic somatic mosaic, PIK3CA
Level of evidence: treatment	Medium
Evidence:	Case series, expert opinion

Diagnosis

Diagnosis of head and neck lymphatic malformation (HNLM) has changed over time from pure description to detection of their molecular cause [1, 2]. Nomenclature used to describe HNLM has broadened from "cystic hygroma" and "lymphangioma" to malformation, as evidence for continued use of these terms is not apparent [2]. This is most apparent in HNLM prenatal diagnosis where in utero ultrasound imaging detects HNLM [3] (Fig. 20.1). In the perinatal literature, soft-tissue lucency and thickening in the posterior/dorsal neck are still called "cystic hygroma" and are associated with increased risk for abnormal fetal karyotype [4]. Now the widely available highly sensitive and specific noninvasive prenatal testing (NIPT) can detect abnormal karyotypes and specific genetically determined syndromes (i.e., Noonan) from fetal DNA in maternal blood, without invasive testing [5]. This shift in our understanding on maternal-fetal physiology and our ability to detect differences between circulating fetal and maternal DNA has also changed our understanding of in utero ultrasound detected large fluid-filled spaces in the head and neck, so we know that they are a result of molecular changes in DNA and not just "watery tumors" or "lymph tumors." As investigation into the cause and nature of HNLM has occurred, it is felt that "malformation" is a more accurate way of categorizing these lesions.

Prenatal detection of HNLM occurs in at least 50% or pregnancies [2]. Posterior cervical malformations that are associated with karyotype or syndromic conditions can regress by birth [3]. Malformations that we are discussing in this chapter are ventral and not associated with these genetic alterations but instead are thought to result for a gain-of-function postzygotic somatic mutation in PIK3CA [1, 6]. When detected, these lesions can be further functionally assessed with in utero

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magnetic resonance (MRI) and three dimensional duplex imaging of the upper aerodigestive tract. Polyhydramnios associated with HNLM is usually due to malformation induced swallow dysfunction and should be considered as an indicator for high-risk delivery planning (i.e., planned cesarean section or other procedures) and anticipated postnatal invasive airway management [7, 8].

Postnatal HNLM diagnosis is either anticipated or made with clinical examination and radiographic characterization, infancy or later in life [2]. In older children HNLM can arise suddenly in conjunction with upper respiratory inflammation or trauma [9]. In both situations the malformation presents as a non-pulsatile mass or, if localized to skin or mucosa, an area of fluid-filled blebs (figure). Usually the HNLM is nontender. Radiographic characterization can be done with high-resolution computerized tomography (CT) or MRI when HNLM is often categorized as microcystic or macrocystic, based on the size of fluid-filled spaces.

Moving past the clinical diagnosis of HNLM, there is a wide range of clinical manifestations that until recently have been under recognized and unexplained. Evaluation of HNLM occurrence, natural history, and treatment efficacy, in both situations, has been aided by staging or grading [10] (Fig. 20.2). In a large two institution prospectively

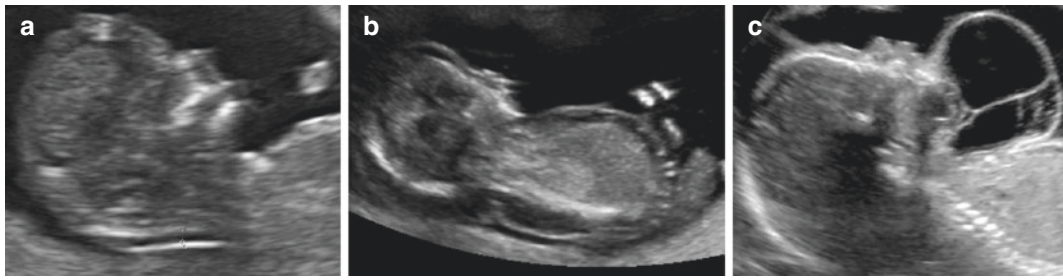

Fig. 20.1 Ultrasound images demonstrating (**a**) nuchal thickening, (**b**) dorsal lymphatic malformation, and (**c**) ventral lymphatic malformation

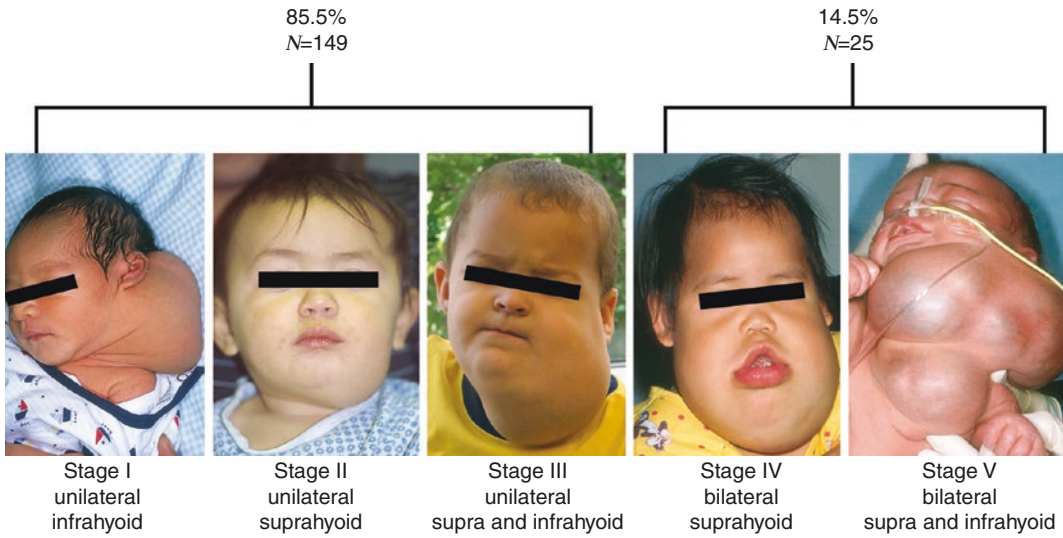

Fig. 20.2 The de Serres head and neck lymphatic malformation staging system used to improve treatment outcome measurement and allow for quantitative data analysis. In a series of 174 head and neck lymphatic malformations, 85.5% were stages 1–3, and 14.5% were stage 4 or 5 and that in lower-stage lesions, surgery and sclerotherapy had the same efficacy [7, 12]. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer). (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Scott Manning)

collected series, unilateral lower stage (1–3) HNLM represented over 80% of all HNLM [11] (Fig. 20.2). This is also important in understanding the natural history of some HNLM, as stage 1 and 2 lesions do not cause functional compromise (i.e., airway obstruction, dysphagia), have been reported to shrink without invasive therapy in up to 30% of cases, and also respond to consistently treatment (Fig. 20.3). In contrast, higher stage 4 and 5 lesions cause functional compromise and are bilateral prone to persist and be recalcitrant to standard therapies [11]. High-stage HNLM also is predominately microcystic and is associated with lymphocytopenia and recurrent pain, inflammation, and tissue overgrowth. In analysis of HNLM in specific sites, such as the tongue and larynx, lesion staging has been applied to analyze natural history and treatment. Smaller, lower stage localized tongue lesions persist without treatment but with treatment can be cured, whereas transmural malformations involving the tongue mucosa, muscle, and multiple anatomic spaces in and adjacent to the tongue are not completely responsive to treatment [12] (Fig. 20.4).

If after clinical and radiologic evaluation the diagnosis is still in question, histologic assessment of HNLM will enable identification of malformation lymphatic endothelium with podoplanin (D2-40) immunostaining. Of note, the radiographic distinction of macrocystic and microcystic HNLM is not apparent histologically [13].

Etiology

Development of massively parallel DNA sequencing technology has enabled detection of molecular genetic causes of rare conditions, including HNLM [1, 6]. In 2015, researchers discovered that the majority of "anterior or ventral" HNLM are caused by a gain-of-function postzygotic somatic gene

Fig. 20.3 Stage 1 HNLM demonstrating regression without therapy. From left to right top row, age 2.5 months and 3 months. From left to right bottom row, age 6 months and 17 months. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

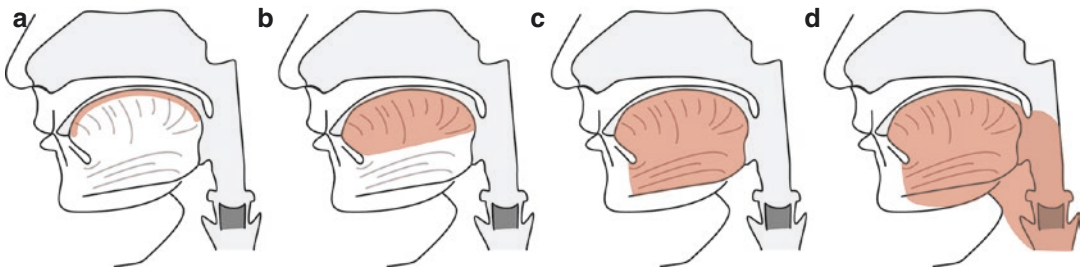

Fig. 20.4 Tongue lymphatic malformation staging used to describe treatment outcomes and strategies in malformations involving the tongue (shaded area is involved with lymphatic malformation [13]). Malformations ranged from superficial to transmural. The more extensive the malformation, the poorer the treatment outcome and malformation persistence. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

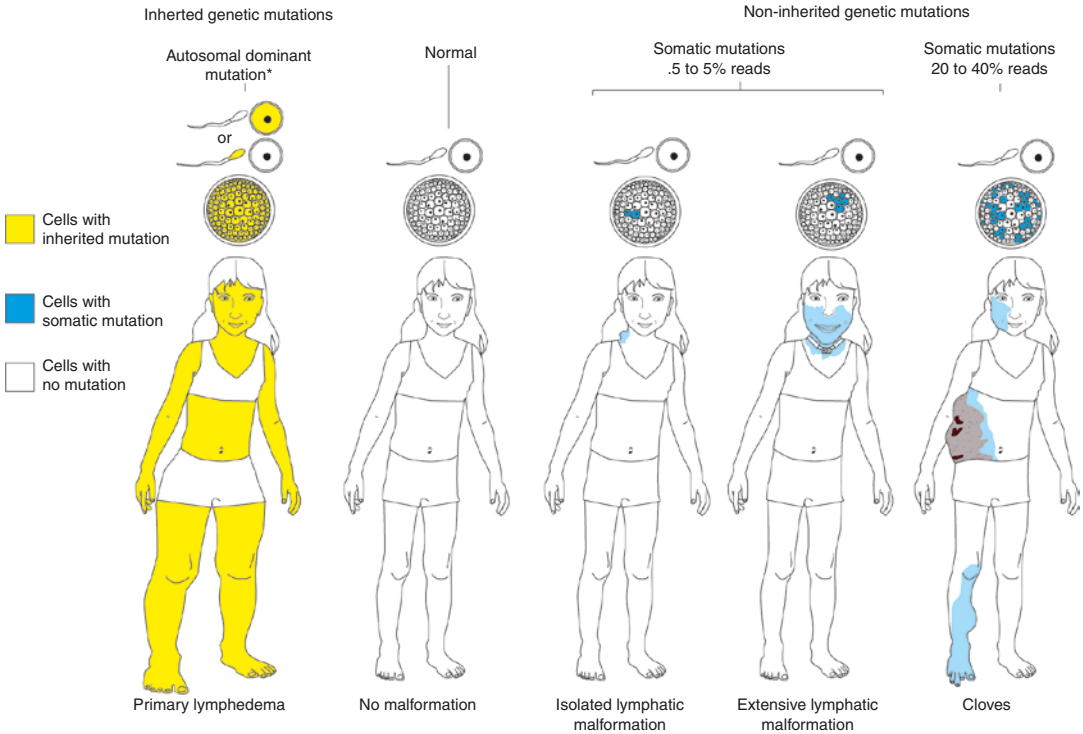

Fig. 20.5 Schematic diagram of current theory of molecular genetics applied to germline and postzygotic somatic gene mutations and creation of phenotype. On the left a person without malformations has a normal genome in all cells. In autosomal dominant germline inheritance, all cells in the body have a mutation, shown as yellow. Somatic mutations occur after conception (i.e., zygote formation) and affect a variable number of cells in the blastomere, shown as blue. Cells with somatic mutations, by unknown mechanisms, affect one portion of the body as seen in blue. When 5–10% of cells, assuming "reads" are a surrogate measure for affected cells, are affected, the involved area is small. The involved area becomes larger and more dysfunctional when more cells have that mutation. *At this time there are no known autosmal recessive vascular anomalies. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

mutation (phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (PIK3CA)), present in HNLM tissue [1]. Mutations in this gene have been detected in other types of tissue overgrowth and are changing our concept of HNLM. Somatic mutations differ from germline mutations, as the mutation is isolated to the affected malformation area and thought to be present in a specific cell type or types (Fig. 20.5). This gives rise to genetic mosaicism at the cellular level and means

that pathogenic mutations are not present in unaffected tissue (i.e., blood). One study sequenced DNA from lymphatic endothelial cells extracted from lymphatic malformation tissue. In three different LM, one being HNLM, the *PIK3CA* somatic mutation was detected in the lymphatic endothelium [14, 15]. It is unknown if this is the only affected cell type in HNLM. Another concept, "cell nonautonomous behavior," that may be important is that cells containing somatic mutations may influence abnormal histologic phenotype and function in adjacent cells with normal genomes [16, 17] (Fig. 20.6). It is unclear how genetic mosaicism in a single cell induces cell nonautonomous

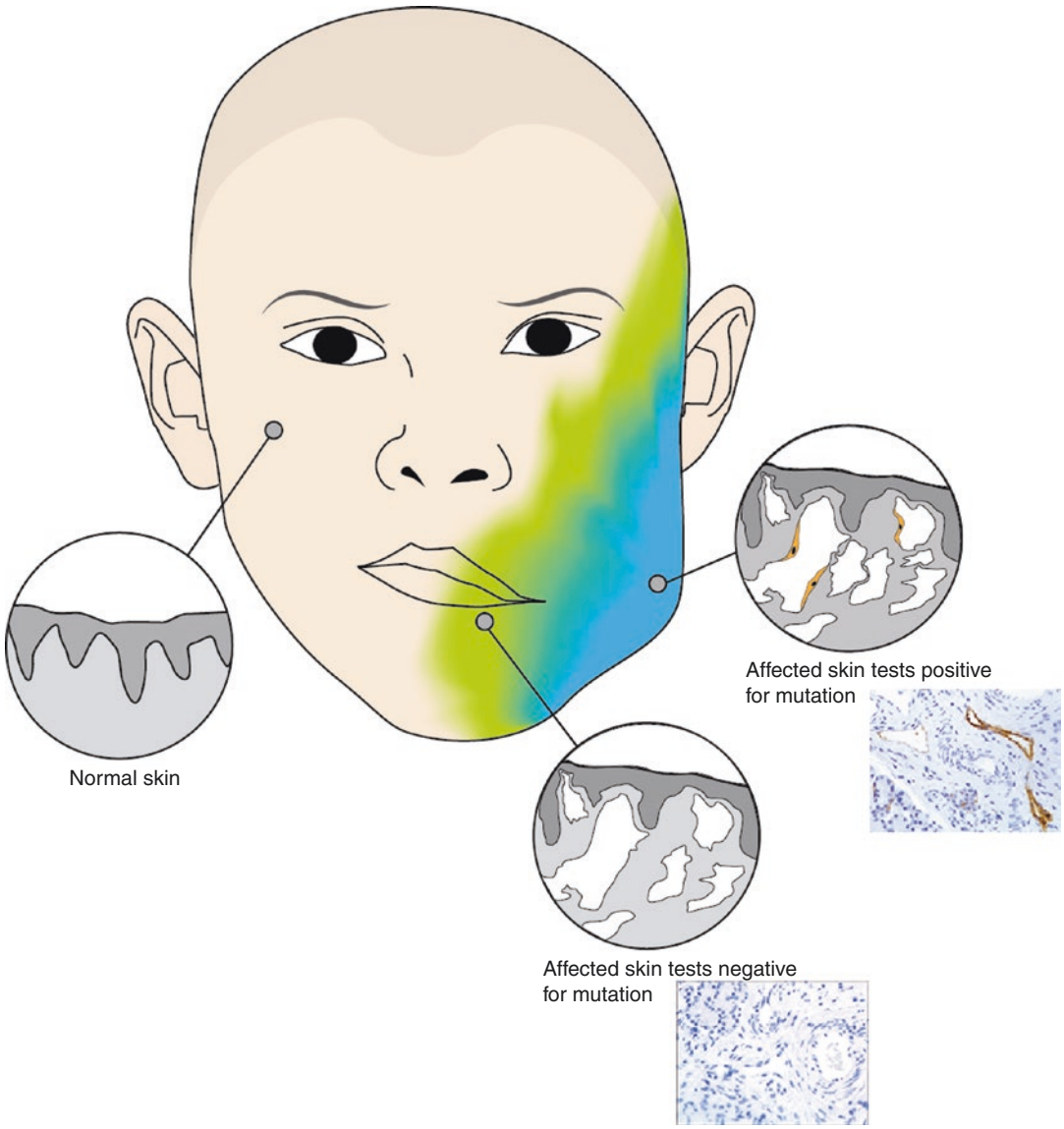

Fig. 20.6 Adjacent cells interact, through mobile genomic sequences (i.e., transposable elements) and programmed cell death (i.e., apoptosis), creating an environment in which cells with somatic mutations cause neighboring genetically normal cells to exhibit mutant histologic phenotype. This may explain the occurrence and persistence of large areas of histologically abnormal lymphatic malformation tissue, schematically depicted and mirrored with HNLM tissue sections (top image with D2-40 immunostained lymphatic endothelium (brown)), while not all cells in the region have detectable mutations. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

behavior and occurs in complex tissues or if this is the reason that multiple cell types actually produce abnormal histologic appearance in HNLM. Gain-of-function *PIK3CA* gene mutations cause with larger cell size and tissue overgrowth, things that are present in most HNLM (Fig. 20.7). The molecular mechanism that induces tissue overgrowth in HNLM is unknown. Medical suppression of the mTOR ("molecular target of rapamycin"), an enzyme in the overactive PI3K pathway, using rapamycin (Sirolimus), has been described as a novel primary or adjunctive therapy for HNLM (Fig. 20.8). Rapamycin (sirolimus), which suppresses the mTOR enzyme, a component of the PIK3CA cellular signaling pathway, has been used with varied success for severe lymphatic conditions, including some HNLM [18]. This may be the beginning of biologically based medical therapy for HNLM.

Management

Evidence-based HNLM management and treatment are in its infancy [2, 11, 19, 20]. Developing evidence in rare conditions is difficult even when the condition is one of the most common vascular malformations. Management decisions can begin when HNLM is detected with prenatal imaging. This chapter is describing approached to ventral HNLM since they persist at birth, but any prenatally diagnosed HNLM requires an evaluation/counseling by knowledgeable geneticists and vascular anomaly specialists. This gives families accurate understanding of the fetus' condition, and it can be determined if the HNLM is causing functional compromise (i.e., poor swallow or airway compromise) potentially necessitating a careful delivery plan [7, 8].

Treatment of HNLM has centered on reduction of lesion size while preventing functional compromise. This has been done with sclerotherapy and surgery, but more recently it has become possible to consider biological medical therapy. Work has been done to determine which treatment is more effective. A thorough systematic literature review assessing differences in invasive HNLM therapy (i.e., surgery, sclerotherapy) demonstrated that these differences could not be determined using existing medical literature [21]. Current medical literature lacks consistent reporting of pretreatment LM find-

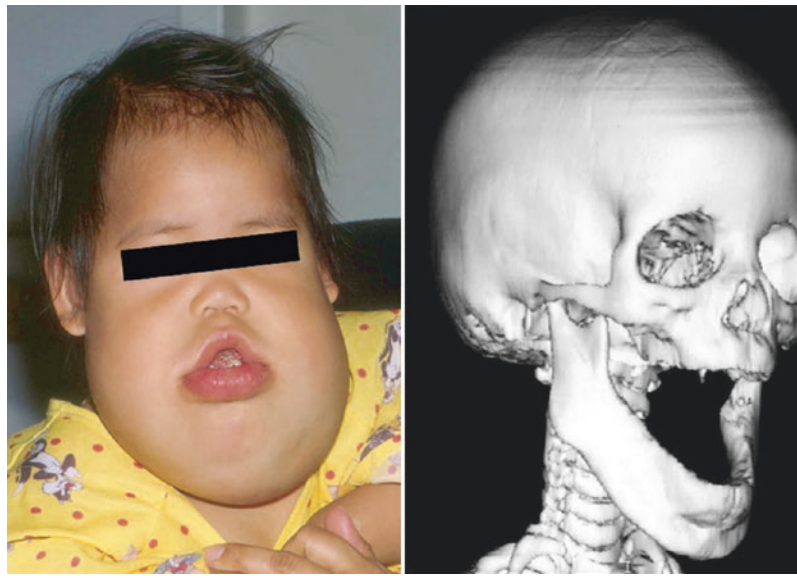

Fig. 20.7 The gain-of-function postzygotic somatic mutation in PIK3CA causes the persistent soft tissue and boney tissue overgrowth in this LM patient. Interestingly the one of the other known functions of the PIK3CA gene pathway is T-cell or lymphocyte differentiation by the mTOR enzyme. This patient also has persistent lymphocytopenia which is probably related to disordered PIK3CA function. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

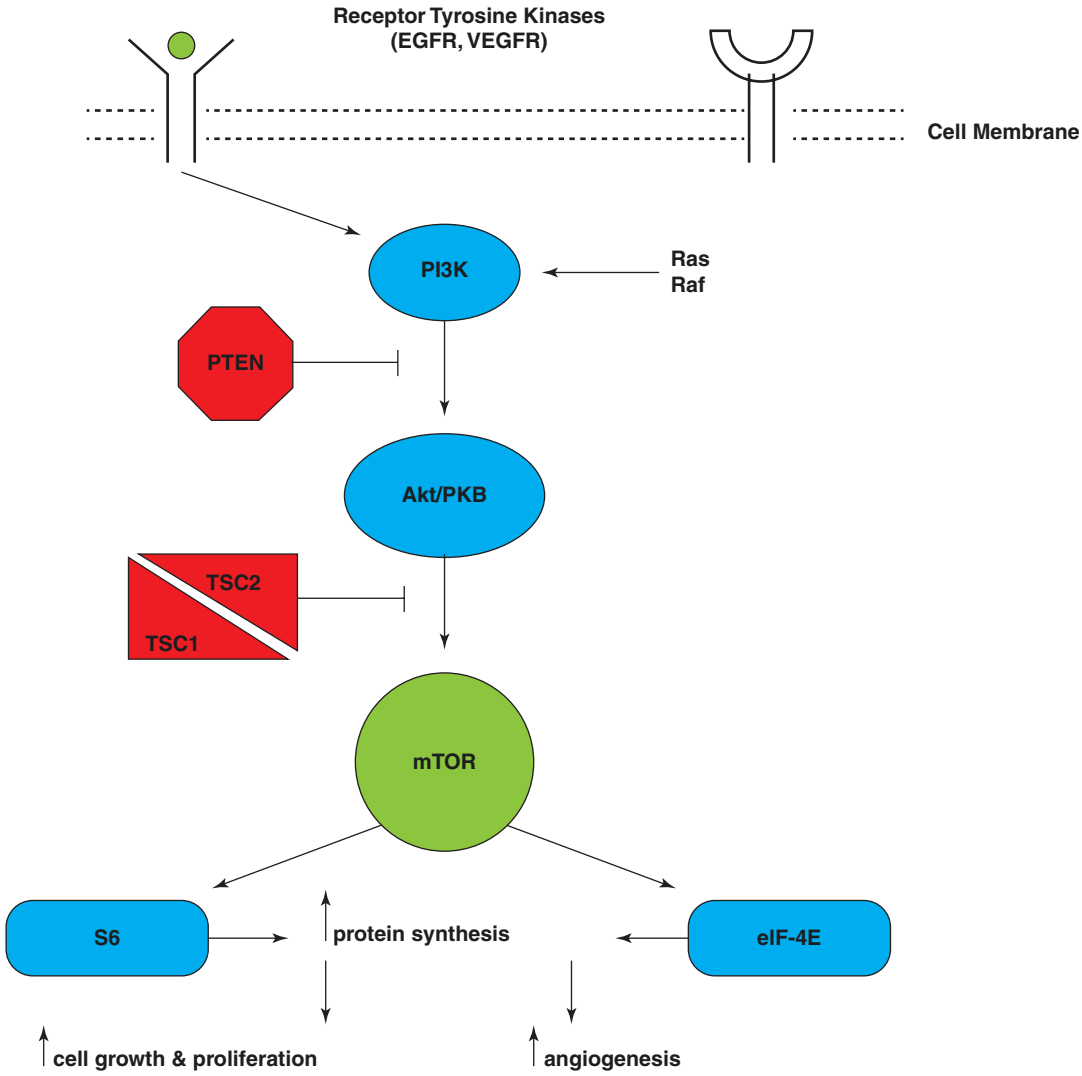

Fig. 20.8 Schematic representation of PIK3CA cellular signaling pathway. Note, one of the principle functions of the mTOR enzyme is T-cell differentiation or programming. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

ings, defined treatment endpoints, comparative treatment trials, and consistency in reporting treatment outcomes and/or safety. This is largely a result of differences in treatment philosophies and goals among differing medical, radiologic, and surgical specialties. Following finding in this literature review, a multidisciplinary group representing differing treatment philosophies began a work to establish HNLM treatment reporting guidelines for future reports, in an effort to create higher levels of evidence for HNLM treatment decisions [22]. One of the areas of HNLM investigation has been to associate pretreatment HNLM stages with treatment frequency and outcomes. This has demonstrated that in a large multisite series, stages 1–3 HNLM represent over 80% of these lesions and that treatment efficacy for sclerotherapy and surgery was the same for low-stage HNLM [11]. Conversely high-stage HNLM (4 and 5) requires multiple interventions, and consideration of medical therapy and/or strategies to reduce pro-

cedure frequency is important [23]. Now that it is known that HNLM is caused by a gain-of-function somatic gene mutation in specific cells, this knowledge and further study may provide a basis for understanding how some malformations regress without treatment, why some lesions respond to medical therapy, and why removal of abnormal cells, when possible, may be an optimal malformation treatment [9].

Medical therapy for HNLM has been symptomatic with antibiotics and corticosteroids until recently when suppression of the mTOR enzyme has been tried as primary and adjunctive therapy [2]. Chronic inflammation in HNLM can cause periodic swelling of intraoral portions of the malformation resulting in tongue swelling and pain. Please see Chaps. 26 and 27 for examples of this problem. High-stage HNLM that is superior to the hyoid bone is particularly prone to this inflammation, and in some patients lymphocytopenia and chronic inflammation contribute to these inflammatory episodes [24–27]. When evaluating HNLM oral cavity and tongue treatments, it is important to determine the extent of the malformation as this is associated treatment outcome. Experience with mTOR inhibitors for HNLM is small, but it seems that sirolimus on unselected HNLM improved malformation-induced lesion pain, and mucosal and skin changes, but inconsistently reduced HNLM size and had no effect on locoregional tissue hypertrophy [28]. Sildenafil has also been tried in HNLM treatment, but the risk of off-label use of this medication and biologic basis for its use are unclear [19, 29]. Future efforts are ongoing to improve these outcomes and develop disease-specific tools to measure treatment outcomes [30, 31].

Sclerotherapy for HNLM is primarily used for macrocystic HNLM, although intralesional bleomycin injection into microcystic HNLM has been described [32–35]. For macrocystic lesions various sclerosants have been used successfully to reduce macrocyst size in smaller low-stage HNLM [34, 35]. This often requires multiple sclerosing sessions, and success is added by intraprocedural cyst drainage [36]. In these series the treatment goal has been macrocyst obliteration. No comparison between sclerosants has been done, but in children use of EtOH as a sclerosant is debated, due the risk of cardiac arrest [32]. Doxycycline is also effective but the possibility of dental staining has not been studied [37]. The use of bleomycin is also debated because of concern with development of interstitial fibrosis. Despite these concerns it is being used in tongue and oral cavity malformation [38–40]. In these reports sclerotherapy indications and complications and treatment outcomes are not explained. Sclerotherapy can be used secondarily as an adjunct to surgery or in a staged manner [32]. Future work is necessary to refine sclerotherapy use for HNLM treatment.

Surgery for HNLM is usually done to reduce lesion size and reduce lesion side effects, such as oral bleeding and upper airway obstruction. Surgical outcomes are fairly predictable for low-stage HNLM, as the malformation can often be completely excised. Some HNLM become significantly smaller or disappear without treatment, so watchful observation is essential in reducing risks associated with HNLM treatment [9]. There has never been a treatment trial in young untreated HNLM patients using a mTOR inhibitor, but these are being used in an attempt to reduce treatment morbidity, such as avoid tracheotomy and/or gastrostomy tube placement, and improve outcomes. In theory this type of medical therapy may offer significant advantages. High-stage HNLM will frequently induce functional compromise and require airway support with tracheotomy and nutritional support with gastrostomy tube feeding [23]. Evidence is lacking in understanding how to reduce these risks. Certainly careful surgical planning and preservation of normal cervical structures are necessary to reduce surgical morbidity. One technique that has been described that does this is facial nerve mapping and monitoring. Lateral facial and parotid region HNLM are common, and the facial nerve is intertwined with the malformation as lymph vessels and nerves share developmental pathways [41, 42]. The use of facial nerve mapping and intraoperative nerve monitoring has reduced the risk of facial nerve

injury [43]. Please see Chap. 19 for further details.

In summary knowledge of HNLM etiology is impacting treatment concepts and possibilities for these lesions. Since we now have the possibility of effective biologically based medical therapy for HNLM, with continued study, evidence on which to base HNLM treatment could become a reality.

To assist the reader in gaining familiarity with available evidence, the following rating system has been used to indicate key references for each chapter's content:
***: Critical material. Anyone dealing with this condition should be familiar with this reference.
**: Useful material. Important information that is valuable in in clinical or scientific practice related to this condition.
*: Optional material. For readers with a strong interest in the chapter content or a desire to study it in greater depth.

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Venous Malformations

21

Randall A. Bly, Giri Shivaram, and Eric J. Monroe

Genetic diagnosis	Yes
Genetic etiology: venous malformation	Postzygotic somatic mosaic, TEK/TEK1, PIK3CA
	Germ line
	RASA1
Glomuvenous malformation	Germ line
	Glomulin
Level of evidence: treatment	Low
Evidence:	Case series, expert opinion

Introduction

Venous malformations account for 40% of congenital vascular anomalies and are most commonly located in the head and neck. Abnormal vein development, coupled with dysplastic connections to the normal venous system, creates a mass-like cluster of perfusing channels. The venous malformations can fluctuate in size with gravity, blood pressure, and local trauma. The dysplastic channels frequently form phleboliths comprised of lamellated thrombus and varying levels of mineralization. The clinical presentation, diagnosis, and treatments are presented below.

Diagnosis, Epidemiology, Phenotype, and Locations

Although rare, venous malformations (VM) are the most common subset of vascular anomalies and are present in an estimated 1–4% of the population, occurring equally in males and females. As many are asymptomatic or otherwise subclinical, the true prevalence is likely underestimated. Venous malformations are classified under slow-flow, simple vascular malformations, distinctly separate from arteriovenous, lymphatic, and capillary malformations [1]. They have a cervicofacial predilection, especially within muscles of the face such as the masseter muscle and within mucosal membrane surfaces [2]. The upper and lower extremities are the second most common location. All true vascular malformations, including the venous variety, are present at birth. They have a tendency to grow proportionally with the child and may not be noticed until teenage years when symptoms of pain, swelling, and discomfort develop [3].

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On examination, there are multiple phenotypes. The first is a diffuse, submucosal lesion, frequently occurring in the oral cavity (Fig. 21.1). The second phenotype is a mass-like cluster of dysplastic channels in the deep, frequently intramuscular, tissue that typically causes symptoms with activity (Fig. 21.2). Other prominent phenotypes include sub- and intracutaneous varieties, creating obvious contour distortion and skin color change (Fig. 21.3).

Clinical relevance of VM is largely limited to discomfort. Spontaneous hemorrhage is rare. Localized intravascular coagulopathy (LIC) is an infrequent complication of VM, especially in children. Elevated D-dimer levels, thought to correlate with LIC, are found in 30% of pediatric venous malformation patients and are more

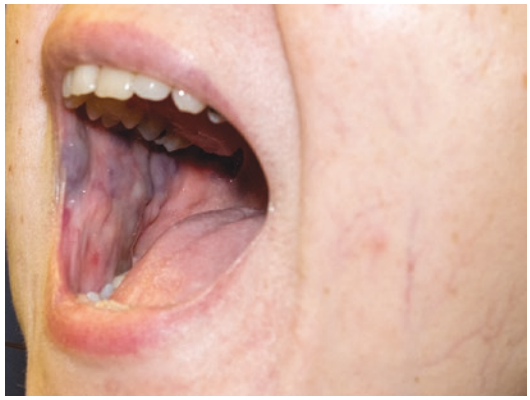

Fig. 21.1 A venous malformation located in the submucosal buccal region. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

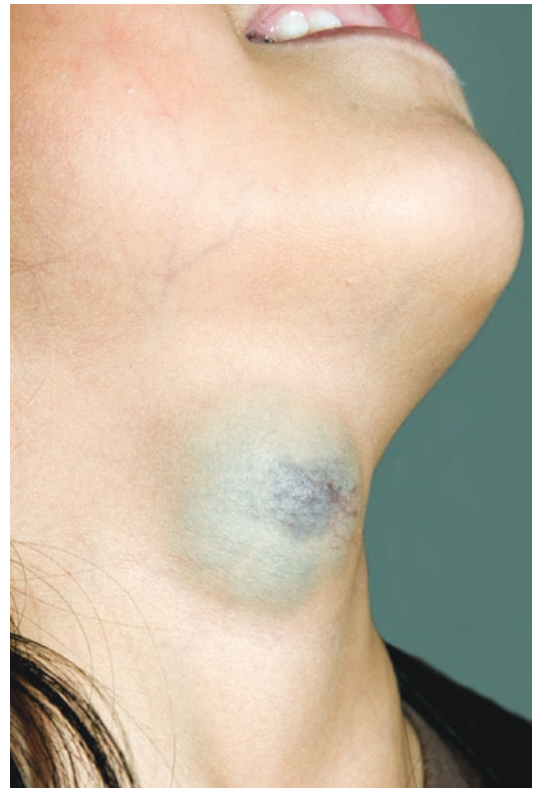

Fig. 21.3 Venous malformation right neck. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

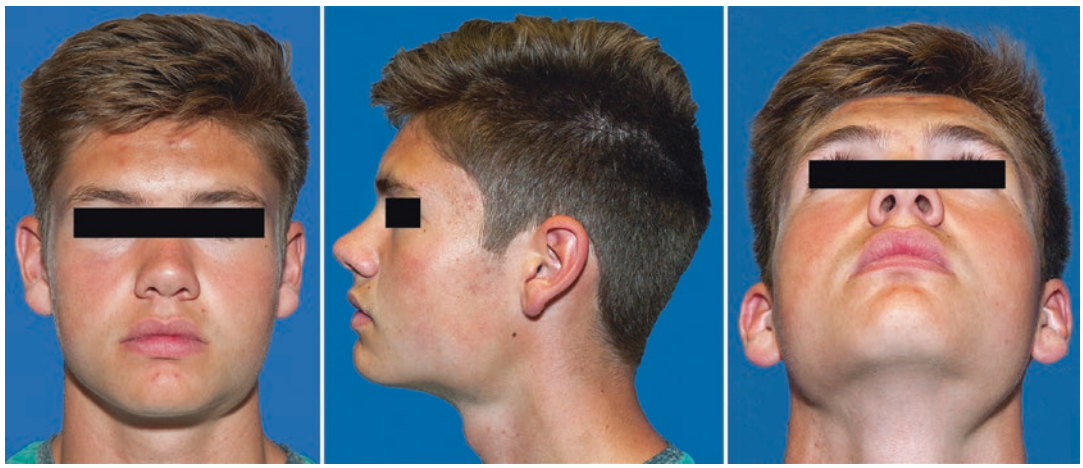

Fig. 21.2 Venous malformation located within the masseter muscle on the left side causing pain, swelling, and discomfort with exercise. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

frequently encountered in several circumstances: (1) large lesion volume (>10 mL), (2) presence of phleboliths, (3) multifocal disease, and (4) associated Klippel-Trenaunay syndrome [4]. Larger studies that include adults with VM have shown the incidence of LIC is even higher at 50% [5]. Although rare, LIC can lead to life-threatening disseminated intravascular coagulopathy (DIC). Because of this risk, some authors recommend perioperative treatment with low-molecular-weight heparin to prevent DIC if undergoing a procedure, as well as other medical treatments discussed in Management section.

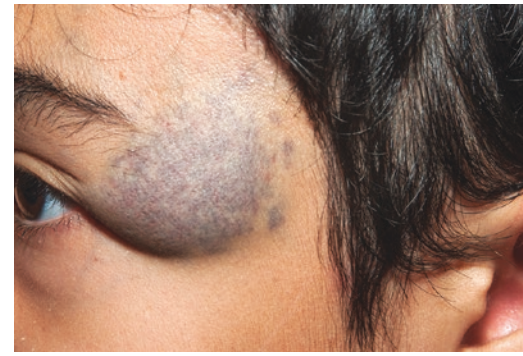

Fig. 21.4 Glomuvenous malformation of left temporal brow region. This was treated with surgical excision using facial nerve mapping and monitoring. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

Etiology

Genetic causes for VM have been described to account for the majority of cases [6]. The ISSVA classification subtypes of venous malformations with causal genes are shown in Table 21.1

VM may present in the context of multiple syndromes, some of which are germline mutations with autosomal dominant inheritance. For the more common sporadic VM, the most common somatic mutations are in *TEK/TIE2 and PIK3CA*. A loss of function mutation in *RASA1* was identified as the etiology, initially in familial cases [7–10]. Indeed, the loss of *RASA1* function has been shown in animal and in vitro studies to be essential for normal vascular development [11, 12]. A somatic mutation of *PIK3CA* has also been identified in venous malformations both in the context of KTS and isolated venous malformation [13, 14]. *PIK3CA* promotes overgrowth and cellular proliferation, and mutations are often found as the genetic etiology of lymphatic malformations.

Glomuvenous malformation (GVM) present clinically as a tender non-compressible mass-like lesion (Fig. 21.4). Histopathology in GVM is distinct in that it shows immature vascular smooth muscle cells, termed glomus cells. GVMs are caused by a loss-of-function mutation in glomulin germline gene, which regulates the development of mature vasculature [15]. A second somatic mutation (*GLMN*) within the affected tissue has also been identified [16]. Blue rubber bleb nevus (Bean) syndrome presents with mucocutaneous VMs that are compressible (please see Blue Rubber Bleb Nevus Chapter).

Table 21.1 ISSVA classification of VM and causal genes

Type	Causal gene
Common venous malformation	TEK/TIE2 somatic, RASA1, PIK3CA
Familial venous malformation cutaneo-mucosal (VMCM)	TIE2
Blue rubber bleb nevus (Bean) syndrome venous malformation	TEK/TIE2
Glomuvenous malformation (GVM)	Glomulin, GLMN
Cerebral cavernous malformation (CCM)	
CCM1	KRIT1
CCM2	Malcavernin
CCM3	PDCD10

Management

Central to the management of VM is the accurate diagnosis and determination if the lesion occurs in isolation or as part of a syndrome. Additionally, a VM must be differentiated from other vascular malformations and vascular masses. Many patients will be referred with a generic and inaccurate "hemangioma" diagnosis. In most cases, a clinical history, examination, and appropriate imaging modalities will generate an accurate diagnosis. Genetic testing is immensely helpful for molecular diagnosis, to confirm a clinical diagnosis, and to provide the necessary information for genetic counseling.

A variety of imaging modalities are available for the characterization of vascular malformations, each with its own strengths and limitations. Doppler ultrasound is widely available and free from ionizing radiation and requires no anesthesia. Ultrasound enables rapid differentiation of vascular malformations from true parenchymal vascular masses such as hemangioma. Assessment of internal flow provides a gross assessment of volumetric perfusion and may detect arterialized waveforms characteristic of a high-flow lesion such as an arteriovenous malformation. Partially or completely thrombosed venous malformations may create a diagnostic dilemma, however, as characteristic flow is no longer present and the lesion becomes difficult to differentiate from a true mass. Ultrasound may fail to characterize deep lesions or lesions interdigitating between osseous structures due to sonographic penetration limitations. CT and MR, while not as ubiquitous as ultrasound, are widely available. The addition of iodinated and gadolinium-based contrast agents, respectively, allows confirmation of perfusing intralesional channels. CT is rapid but exposes the patient to ionizing radiation and is more susceptible to poor contrast bolus timing which may be critical for the differentiation of high- from low-flow lesions. MR is non-radiating and provides added value of enhanced lesion characterization through a variety of sequences and noncontrast angiographic sequences. Images are highly susceptible to motion artifacts, however, and young patients may require anesthesia to tolerate the duration of the examination.

The treatment goals for localized intravascular coagulopathy (LIC) can be to relieve pain and swelling or to prevent DIC or thromboembolic events. Testing for LIC with prothrombin time, activated partial thromboplastin time, fibrinogen levels, D-dimer, and complete blood count should be performed in patients who have the following risk factors: (1) large volume malformation (>10 mL), (2) presence of phlebolith, (3) multifocal disease, and (4) in the context of Klippel-Trenaunay syndrome [4]. The specificity for LIC with an elevated D-dimer level is 96.5% [17].

Treatment decisions, including whether or not to treat, should be made with the patient and family after discussing the risks, benefits, and alternative options. Ideally, the patient and family meet with a team of providers that offer the diverse treatment options, typically provided by surgeons, interventional radiologists, dermatologist, therapists, and hematologists (Table 21.2).

Table 21.2 VM treatment modality summary

Medical management (systemic)	Sirolimus (rapamycin), aspirin, heparin (perioperatively), or other anticoagulation therapy
Compression therapy, lifestyle management	
Laser therapy	A variety of laser modalities (PDL, CO2, KTP, Nd:YAG) to treat both superficial and deep malformations
Surgical excision	
Intravascular injection/ percutaneous injection	Sclerotherapy (variety of medications), embolism with multiple agents (n-BCA, Onyx, etc.)

Medical and Conservative Management

VMs showing laboratory evidence of LIC and associated symptoms are candidates for treatment. Patients in this group are at risk of thrombosis causing hemorrhage into the lesion, as well as the development of painful phlebolith masses within the malformation. One worrisome sequela is a thromboembolic event, rare in the pediatric population but potentially devastating [18–20].

It is recommended that patients with VM and elevated D-dimer (greater than or equal to five times the normal level) who are undergoing a procedure with sedation should be treated perioperatively with LMWH [21]. The recommendation from the Vascular Anomalies Special Interest Group of the American Society of Pediatric Hematology and Oncology is to treat for 14 days pre- and post-procedure with LMWH.

The treatment plan should be individualized and may be best in a combination of medical therapy with additional modalities [22]. Compression therapy decreases blood pooling within the malformation and may relieve symptoms in extremities. Although well studied for deep vein thromboses in adults, the effectiveness for compression treatment of VM is not well established in the literature.

Aspirin therapy in the pediatric population may be effective in symptom relief and the treatment of LIC, but the specific indications and goals of treatment are not well defined [23]. In 1 retrospective study, 17 of 38 patients reported some improved symptoms. Side effects such as bruising, minor bleeding, and nausea were reported in greater than 20% of patients. Further, the D-dimer levels before and after treatment had little correlation with symptom severity. In severe cases, warfarin therapy may have similar potential benefits as aspirin [24].

Sirolimus (rapamycin) has been shown in small retrospective case series to improve symptoms in severe cases of VM refractory to alternative treatment [25, 26]. Sirolimus is an mTOR inhibitor, targeting the effect of a *PIK3CA* mutation. The utility of Sirolimus in treatment of VM is a topic on ongoing investigation.

Invasive Management (Laser Therapy, Sclerotherapy, Surgery, or Combination)

Multiple review articles have evaluated the evidence for laser treatment, sclerotherapy, and surgery. In general, the results show that interventions provide improvement either in the form of appearance, swelling, or pain reduction. However, there are no standards to compare results between the studies. Many of the studies lack a control group. One specific review article examined 35 such studies and found that all of the included studies contained, or likely contained, a significant bias based on the study design and reporting of data [27]. The data within the studies showed that an intervention was "successful" (definition of successful varied within the studies) at the rates listed in Table 21.3.

Table 21.3 Treatment modality and reported "success" rate in systematic review

Treatment modality	Reported "success" rate in systematic review (%)
Ethanol	74
Gelified ethanol	89
Bleomycin	88
Polidocanol	90
Sodium tetradecyl sulfate (STS)	86
Ethibloc	65
Surgery	90
Laser	94

Laser therapy is delivered via a variety of laser types with varying wavelengths and depth of penetration. Superficial lesions are often treated with a pulsed dye laser (PDL) in one or repeat treatments. Successful treatment of deep malformations can be achieved with interstitial laser therapy, often using Nd:YAG laser. Risks associated include edema, scarring, and skin ulceration and occur at a rate of 5–15%.

Surgical risks include bleeding, need for revision surgery, and damage to surrounding structures, including nerves. The complication rate for surgery is estimated to be less than 5%. In the review article, there were no major complications noted in the surgical treatment group [28].

Risks associated with sclerotherapy, in general, include risk for repeat procedures, chronic pain, skin ulceration or necrosis, nerve injury, and pulmonary vasospasm [29]. Mild complications such as skin discoloration, ulceration, and transient hemolytic hemoglobinuria have been reported at 10–20% (excluding absolute alcohol which is higher) [30]. Significant complications of nerve injury and pulmonary vasospasm occur rarely, estimated to be less than 5%. Because sclerotherapy is often administered over multiple anesthetics, in the pediatric population, it is important to consider the effects on brain development. There is mounting evidence that multiple exposures to general anesthesia in pediatric patients, especially under age 12 months, can result in permanent neurotoxicity [31].

There are reports of successful combined therapy methods. In severe cases, sirolimus has been used as an adjunctive treatment to any of the invasive modalities [32]. A combined single-stage method of injecting the malformation with n-BCA (glue) immediately followed by surgical resection has shown excellent results to treat cervicofacial malformations without complications [33]. For malformations located in the

region of the facial nerve, percutaneous nerve mapping was performed in coordination with a neurophysiologist [34]. This technique enables the otherwise amorphous venous malformation to be filled with n-BCA (glue) to form a cast and excised in its entirety (Fig. 21.5).

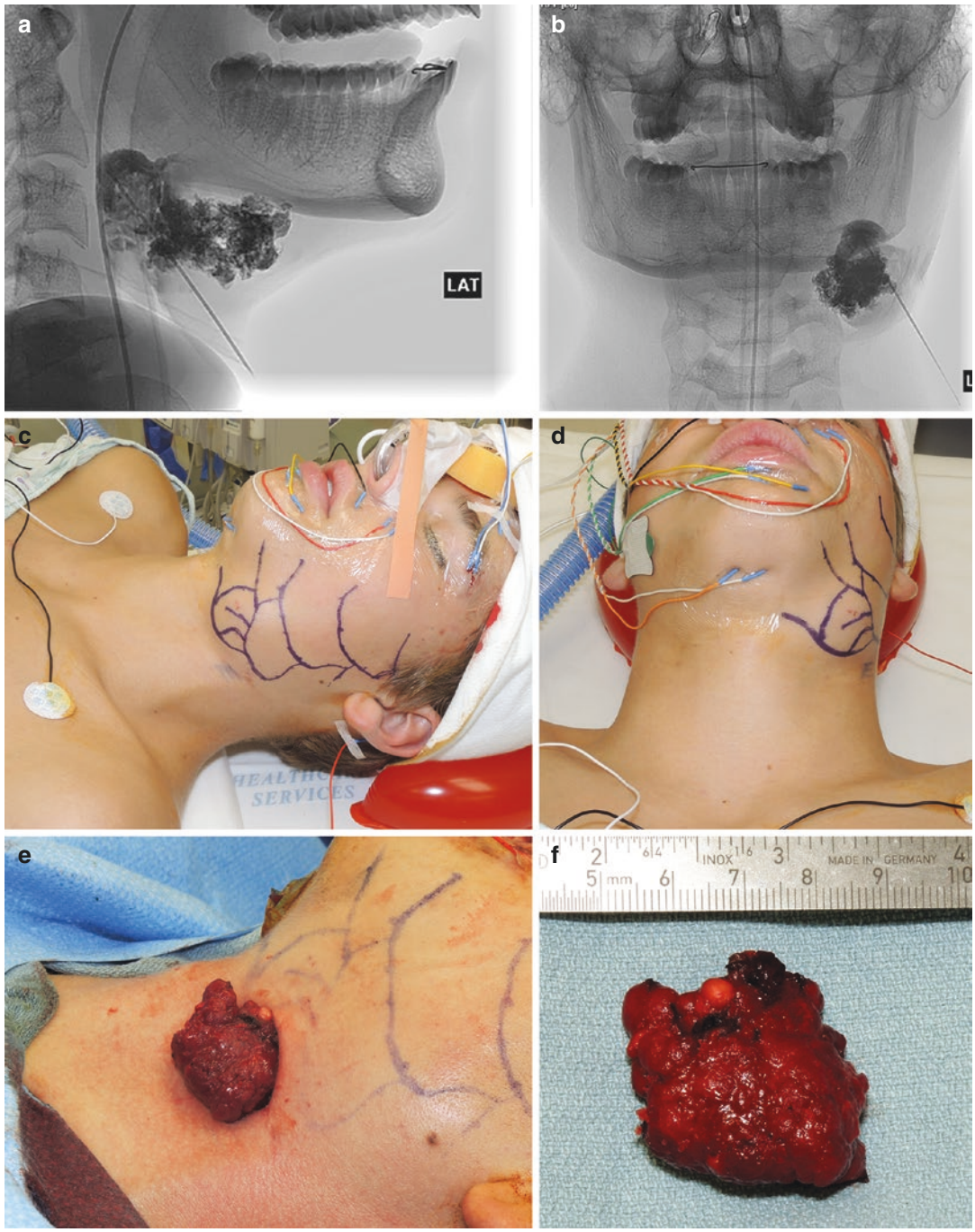

Fig. 21.5 Frontal and lateral intraprocedural radiographic images following percutaneous lesion embolization with n-butyl cyanoacrylate (**a**, **b**), preoperative facial nerve mapping (**c**, **d**), and surgical excision (**e**, **f**). (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

To assist the reader in gaining familiarity with available evidence, the following rating system has been used to indicate key references for each chapter's content:
***: Critical material. Anyone dealing with this condition should be familiar with this reference.
**: Useful material. Important information that is valuable in in clinical or scientific practice related to this condition.
*: Optional material. For readers with a strong interest in the chapter content or a desire to study it in greater depth.

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22 Intracranial Arteriovenous Malformations

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Diagnosis

Intracranial vascular malformations are broadly classified into four major categories and include arteriovenous malformations (AVM), cavernous malformations, capillary telangiectasias, and developmental venous anomalies. Intracranial AVMs are the most common of these vascular malformations with a prevalence of approximately 15–18 per 100,000 people. They do not show a gender predilection [1]. Most commonly, AVMs are first diagnosed with intracerebral hemorrhage (~75%) or, to a lesser extent, seizures (~30%). The risk of morbidity or mortality is significant, ranging from 40% to 50% after rupture [2].

Diagnostic imaging is key to the diagnosis and management of intracranial AVMs. In patients presenting with symptoms concerning for an intracranial hemorrhagic process, non-contrasted computed tomography (CT) is the preferred screening modality. Non-contrasted CT will show acute hemorrhage in an AVM that has ruptured. In addition, calcifications are often visible within the AVM nidus. Magnetic resonance imaging (MRI) will show hypointense flow voids on T2-weighted imaging, which can help identify the size of the AVM nidus, as well as a preliminary analysis of feeding arteries and draining veins. MR and CT angiograms are useful diagnostic studies to better image the presence of underlying vascular abnormalities and to rule out other causes of intracranial hemorrhage when present.

The gold standard for diagnosis of intracranial AVMs is digital subtraction angiography. This allows for identification and dynamic analysis of feeding arteries, draining veins, and the AVM nidus. In addition, flow-related aneurysms or other vascular anomalies that may require additional treatment can be identified. Angiography is limited by its inability to show its three-dimensional relationship to brain parenchyma. However, a thorough understanding of the dynamics of an AVM is critical to determine appropriate treatment.

While multiple classification schemes exist for intracranial AVMs, the Spetzler-Martin (SM) classification is the most ubiquitous. This scale grades AVMs from 1 to 5 based on eloquent or noneloquent location, size, and presence of deep venous drainage. Eloquent location

Would be helpful to have a table showing the different classification methods. There is too much text in this chapter dedicated to this.

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is defined as motor, sensory, and visual cortex, frontal and temporal cortex language centers, hypothalamus, thalamus, internal capsule, brain stem, cerebellar peduncles, and deep cerebellar nuclei. Deep venous drainage is defined as any draining vein not draining into a cortical vein or convexity sinus. This includes internal cerebral veins, basal veins, or the precentral cerebellar vein. The SM classification was developed to predict the risk of morbidity and mortality of microsurgical resection and has been applied as a surrogate to the severity of the AVM as it applies to treatment decision-making. In the original study, microsurgical outcomes were categorized into three categories of increasing neurological morbidity: no deficit, minor deficit, and major deficit. Grade I (n = 23) lesions had no minor or major neurological deficits nor any mortality associated with microsurgical resection, while grade II AVMs (n = 21) had a 5% incidence of a minor deficit. Comparatively, grade III–V AVMs were associated with higher levels of minor deficits (grade III, 12%; grade IV, 20%; grade V, 19%) as well as major deficits (grade III, 7%; grade IV, 12%; grade V, 4%) [3]. To guide management decisions, the five-tier grading system was placed into three classes (Table 22.1). Class A AVMs are thought to be best treated with microsurgery; class B with a combination of microsurgery, radiation, and/or embolization; and class C with nonsurgical methods, including embolization, radiotherapy, or conservative management [4].

Other patient factors that clearly effect surgical decision-making are not incorporated into the original SM criteria. Lawton et al. proposed a supplementary grading scale incorporating age, rupture status, and AVM nidus diffusivity. This grading system ranges from 0 to 5 and is aimed at supplementing the SM system. For example, in AVMs with low SM grades and low supplementary grades, microsurgery is associated with excellent outcomes, while AVMs with high SM grades and high supplementary scores are associated with higher levels of morbidity and mortality. In cases where the SM grade and supplementary grade are mismatched, the supplementary grade may be more accurate. For instance, high SM grade AVMs (grades IV–V) with low supplementary grades, surgical morbidity, and mortality were similar to that of a grade III AVM in the original SM scale, suggesting that these additional factors can assist treating physicians in surgical decision-making and counseling patients on operative risk with a higher degree of accuracy [5].

Table 22.1 The Spetzler-Martin and Spetzler-Ponce classifications for intracranial AVMs

Spetzler-Martin grading scale	Spetzler-Ponce grading scale
Location	A: SM Grade I/II
Noneloquent cortex: 0	
Eloquent cortex: 1	
Size	B = SM Grade III
<3 cm: 1	
3–6 cm: 2	
>6 cm: 3	
Deep venous drainage	C = SM IV and V
Not present: 0	
Present: 1	

Additional AVM classifications have been proposed and studied. Hollerhage et al. used feeding artery distribution (ACA, MCA, PCA, rolandic MCA branches) and Hunt and Hess score and correlated this with Glasgow Outcome Scale (GOS) scores [6]. The University of Toronto AVM study group proposed a classification scheme involving eloquent cortex, diffuseness of the AVM nidus, and deep venous drainage. This classification was able to accurately predict permanent disabling neurologic outcomes with an increased area under the curve (receiver operating characteristic of 0.79) as compared to the SM scale (0.69) [7]. These alternative classification schemes are rarely used, given the ubiquity and familiarity of the SM scale.

Etiology

AVMs consist of high-pressure abnormal connections (shunts) of arteries directly into draining veins without an intervening capillary network. Feeding arteries lack a muscularis layer, and, as a result of

the high-flow shunting of blood through these vessels, undergo smooth muscle hyperplasia. Unlike cavernous malformations (where there is no intervening brain parenchyma within the vascular lesion), AVMs contain gliotic parenchyma within the nidus. Because of high-pressure shunting, flow-related aneurysms and fistulas may develop.

Genomic analysis of AVM tissue has shown up to 900 differences in gene expression as compared to normal brain. Genes specifically related to angiogenesis in AVMs include angiopoietin-1, angiopoietin-2, matrix metalloproteases, fibroblast growth factor, vascular endothelial growth factor and its associated receptors, Tie-1 and 2, CD31, neuronal nitric oxide synthase, and $\alpha_v\beta_3$ integrin [8]. Mutations in endoglin and TGF-beta signaling have also been implicated in murine AVM models [9].

In addition to genetic predisposition to AVMs, evidence suggests that hemodynamic factors can lead to expression of proteins involved in vascular remodeling. An increase in wall shear stress induces endothelial cells to increase surface expression of proteins previously shown to be upregulated in AVMs. These proteins include matrix metalloproteinase-9, platelet-derived growth factor, and vascular endothelial growth factor [10, 11].

The most common presentation of intracranial AVMs is neurological deficit associated with hemorrhage. While neurological symptoms may vary, acute onset of headache is nearly universal. Hemorrhage is typically within the brain parenchyma. However, hemorrhages into the subarachnoid or the intraventricular spaces are possible with lesions adjacent to the cortical surface or near the ventricles. The second most common presentation is seizures, typically occurring as a result of AVMs located in the supratentorial compartment [12, 13].

AVMs are dynamic lesions capable of growth, remodeling, and re-formation, even after surgical or radiosurgical obliteration [14–17]. Some AVMs are congenital lesions, as observed in inherited clinical syndromes where AVMs have a high prevalence. These include hereditary hemorrhagic telangiectasia, Sturge-Weber, and von Hippel-Lindau syndromes.

Treatment

Unruptured AVMs

The decision to treat unruptured AVMs is based on comparing the risk of rupture over the course of a patient's lifetime with the risks of a proposed treatment. The natural history of intracranial AVMs suggests that the risk of rupture is approximately 2–4% per year [18]. In 2014, a prospective clinical trial, "A Randomized Trial of Unruptured Brain AVMs" (ARUBA), [19] was designed to determine if the risk of treatment differed from the natural history of intracranial AVMs. This study enrolled patients from 39 institutions in 9 countries with unruptured AVMs in a 1:1 design to either intervention (microsurgical resection, stereotactic radiosurgery, endovascular embolization, or a combination thereof) or medical management. If randomized to the intervention arm, the intervention was not prespecified, but rather determined by treating physicians at each center.

Notable inclusion criteria included patients older than 18 years, no previous hemorrhage, no previous interventions, and radiographic characteristics that were deemed suitable for intervention. The primary outcome was death or symptomatic stroke with a secondary outcome of clinical impairment, as defined by a modified Rankin scale (mRS) of 2 or higher at 5-year follow-up. A single study neurologist who was not involved in the interventional procedures performed the clinical outcome assessment.

ARUBA centers screened and enrolled patients as shown (Fig. 22.1). Of patients having interventions, 5 underwent microsurgical resection, 30 underwent embolization, and 31 underwent radiotherapy. Embolization was combined with microsurgical resection in 12 patients or radiotherapy in 15 patients. A single patient underwent embolization, radiation therapy, and microsurgical resection. At the time of trial analysis, 53 of the above patients had ongoing treatment plans, and the remaining 20 patients that were randomized to intervention had not yet initiated treatment.

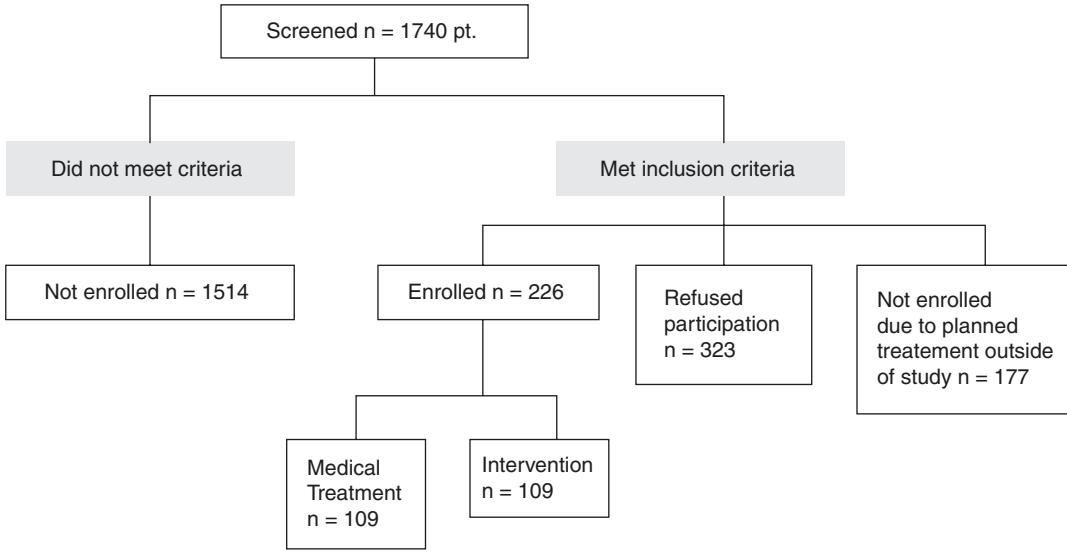

Fig. 22.1 ARUBA study patient enrollment flow

One hundred ten patients were allocated to the medical management arm, 109 of which were included in the final analysis. At the time of publication, the primary endpoint had been reached by 11 patients in the medical management arm and 35 patients in the interventional arm over a mean follow-up of 33.3 months. The study was halted prematurely as interim analysis showed that the risk of stroke or death in the medical management arm was significantly lower than the intervention arm. There were a higher number of strokes in the intervention arm (45 vs 12, $p < 0.0001$) and neurological deficits that were not related to stroke (14 vs 1, $p < 0.0001$) as compared to the medical management arm [19].

While there are multiple limitations to the ARUBA data, the randomized design of the study remains the highest level of evidence for guiding the treatment of intracranial AVMs. However, the study suffers from significant design constraints that limit its generalizability. The study design was significantly limited by a low number and heterogeneous group of enrolled patients. Of the 726 eligible patients, 323 patients refused entry into the trial and 226 were enrolled. Both the patients who refused enrollment and the 177 patients treated outside the study potentially caused a selection bias. In addition, the trial was halted early after an average follow-up of 33 months, which likely biased the results of both the primary and secondary outcome in favor of medical management, as such limited follow-up likely detected complications of those patients undergoing treatment while not detecting potential strokes or deaths as a result of the natural history of non-treated AVMs beyond the limited study period. Only 30.7% of patients randomized to treatment and 10.1% of patients randomized to medical management reached the primary endpoint of symptomatic stroke or death. The secondary endpoint of clinical impairment (mRS ≥ 2) was only reached by 38.6% of treated patients and 14% of patients randomized to medical management. The heterogeneity of patients included in the study also significantly limited analysis. While the study authors argued that heterogeneity of patients mimics that seen in actual clinical settings, it is clear that a SM IV or V AVM is more likely to have a poor outcome as compared to a SM I/II lesion, limiting the ability to detect a difference in low-grade AVMs compared to medical management.

Notably, there were no clear criteria for the application of specific interventions (i.e., microsurgical resection, embolization, or radiosurgery) which may have limited detecting a potential

helpful therapy when grouped with potentially harmful therapies. Optimal design would have considered each treatment separately when compared to medical management. However, in a rare pathology, this is challenging in the time it would require to enroll enough patients to power the study to detect a significant difference and long-term funding needed to continue to follow patients for an extended period of time [20, 21].

Current best practices for unruptured AVMs must factor patient age, AVM location, associated high-risk features (flow-related aneurysms, intranidal aneurysms, or venous outflow stenosis), and patient preference. A balanced assessment and treatment approach by experienced cerebrovascular centers remain the standard of care.

Microsurgical Resection

The results of the ARUBA study challenged treating neurosurgeons to assess unruptured AVM patients that would optimally benefit from microsurgical resection. Bervini et al. reported improved surgical outcomes in Spetzler-Ponce class A AVMs as compared to conservative management in a series of 427 patients that were retrospectively reviewed. They found a 5-year risk of hemorrhage of 11.5%, and, when hemorrhage occurred, 14 cases (88%) resulted in mRS >1. Following surgery, the risk of mRS >1 was 1.6%, while the risk of mRS >2 was 0.5% at postoperative follow-up. The risk for adverse outcomes with an mRS >1 at postoperative follow-up was increased in Spetzler-Ponce class B and C AVMs: 14.0 and 38.6%, respectively [22]. In a retrospective study of 61 ARUBA-eligible patients (31 SM I/II, 20 SM III, 10 SM IV/V) undergoing microsurgical resection, Nerva et al. reported that all patients had angiographic obliteration without any associated mortality [23]. Of these patients, impaired functional outcomes (mRS ≥2) occurred in 3% of grade I/II, 25% of grade III, and 20% of grade IV/V. Long-term outcomes were similarly better for patients with lower-grade AVMs. Rutledge et al. performed a similar retrospective analysis of 43 ARUBA-eligible patients who underwent microsurgical resection. Ninety-three percent of these patients had radiographic obliteration with a 11.6% rate of stroke or death. Impaired functional outcome was observed in 4.8% of patients [24]. Javadpour reported on 34 ARUBA-eligible patients, 24 of which were SM grade I/II. Of these patients 6% had an mRS ≥ 2 following microsurgical resection [25]. Schramm et al. reported on 104 ARUBA-eligible patients, 63 of which were SM grade I/II. Of these patients 3.2% had significant permanent neurological deficit and 14.3% had mRS scores ≥ 2 [26]. Finally, Wong et al. reported on 155 ARUBA-eligible patients who underwent microsurgery with or without preoperative embolization. Complete obliteration was achieved in 98.1% of patients and 99.2% of SM I/II AVMs. For SM grade I/II AVMs, early disabling deficits (mRS ≥ 1) occurred in 9.3% of patients and permanent debilitating deficits in 3.4% of patients [27]. These retrospective studies, which more effectively control for treatment modality compared to the ARUBA clinical trial, show that microsurgical resection for low-grade (SM I/II) AVMs can effectively treat unruptured AVMs with an acceptable safety profile that exceeds the risk of hemorrhage defined by the natural history of the disease. These data should frame the context of future AVM-related clinical trials.

While grade I and II AVMs are associated with low surgical risk and grade IV and V AVMs are associated with high risk, grade III AVMs represent a unique management challenge. For instance, in the original SM criteria report, large (>6 cm) AVMs located in noneloquent cortex carry the same risk as small AVMs located in eloquent cortex with deep venous drainage. Lawton et al. reported the outcomes of grade III AVMs and showed that small AVMs with deep venous drainage in eloquent cortex had the lowest rate of new deficit or death (2.9%) as compared to moderate-sized (3–6 cm) AVMs in either noneloquent cortex with deep venous drainage (7.1%) or eloquent cortex without deep venous drainage (14.8%) [28]. Thus, supplementary criteria may be used to better stratify the treatment risks of various grade III AVMs. A representative case of SM III AVM treated with staged embolization, followed by microsurgical resection, is shown (Fig. 22.2).

In addition to technical excellence needed for AVM resection, appropriate postoperative care is

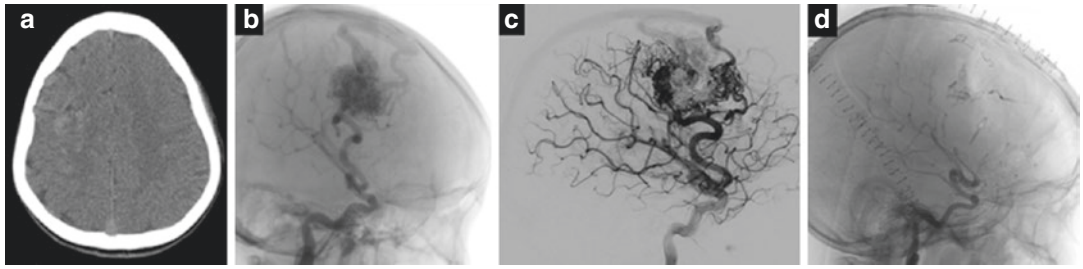

Fig. 22.2 A 13-year-old boy presented with recurrent seizures. (**a**) Non-contrast CT showed a hyperdensity within the right frontal lobe, consistent with an unruptured AVM. (**b**) Diagnostic angiography showed a SM III AVM fed primarily by the right anterior cerebral artery. (**c**) Staged embolization was performed. (**d**) Following microsurgical resection, no residual AVM was appreciated

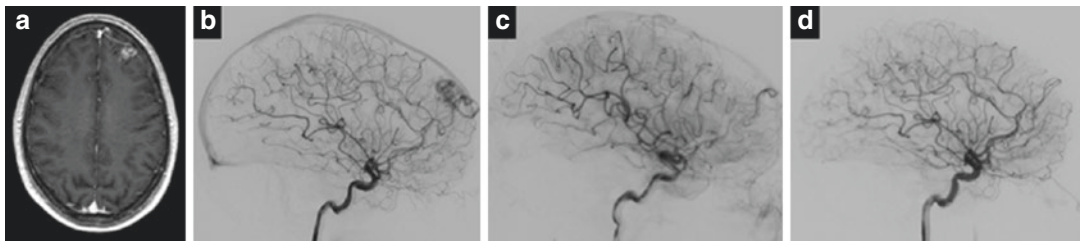

Fig. 22.3 A 49-year-old man presented with seizures. (**a**) Contrast-enhanced MRI showed a left frontal lobe SM I AVM. (**b**) The AVM nidus was fed primarily by branches of the anterior cerebral artery. (**c**) Embolization was performed with near obliteration of the AVM nidus. (**d**) Following microsurgical resection, no residual AVM was present

critical to the success of surgery. Patients are admitted to the intensive care unit postoperatively for hourly neurological exams and strict blood pressure management, typically reducing the systolic pressure by 10–20% of baseline until angiographic verification of complete AVM resection. This is important as elevated blood pressure through a small, residual AVM nidus could lead to AVM rupture. Potential postoperative complications directly associated with craniotomy and microsurgical resection can include seizure, hemorrhage, edema, stroke, and infection.

Endovascular Embolization

Endovascular embolization provides both a primary treatment and, more often, an adjuvant treatment option in patients undergoing microsurgical resection or radiosurgery. Current embolic agents include N-butyl cyanoacrylate (NBCA), ethylene-vinyl alcohol copolymer (Onyx), polyvinyl alcohol particles, or platinum coils. Embolization as monotherapy is rarely curative. In an extensive review of 1246 patients, a 5% cure rate was achieved with embolization alone [29]. More recent studies by Katsaridis et al. and Saatci et al. showed complete occlusion with embolization alone in 54% and 51% of patients, respectively [30, 31]. However, despite these cure rates, Saatci et al. reported a permanent morbidity rate of 7.1% and a mortality rate of 1.4%. Often, embolization is an adjunctive treatment with either microsurgical resection or radiosurgery (Fig. 22.3). Embolization can eliminate deep arterial pedicles that would either be difficult to access or would be encountered in the latter stages of microsurgical resection. In addition, high-risk features can be treated to theoretically decrease the risk of intraoperative rupture [32]. Similarly, in patients undergoing radiosurgery, preoperative embolization can eliminate high-risk features, as the curative effects of radiosurgery take several years to manifest. Notably, while embolization has previously been used to decrease the volume of the AVM nidus in patients undergoing radiosurgery, studies suggest that long-term obliteration rates are actually worse as compared

to patients who did not undergo preoperative embolization; partial embolization followed by radiosurgery alone is not recommended [33].

Radiosurgery

Stereotactic radiosurgery represents the only noninvasive method of treating intracranial AVMs. While different delivery platforms are available, including Gamma Knife, proton beam, and linear accelerator-based technologies, all aim to direct focused ionizing radiation to obliterate the AVM nidus. Radiosurgery is primarily implemented in high-grade AVMs that are deemed non-resectable due to significant risk to adjacent neural parenchyma or in patients with significant surgical comorbidities (Fig. 22.4). Compared to microsurgical resection which aims for an immediate cure, the preventative treatment effect of radiosurgery takes approximately 2–4 years to manifest. Thus, the patient is exposed to the standard 2–4% risk of rupture in the interval between radiosurgery and cure. In addition, the normal parenchyma near the AVM may be exposed to radiation with varying clinical effects including edema, radiation necrosis, or, rarely, radiation-induced neoplasms [34].

Obliteration of AVMs following radiosurgery occurs from endothelial proliferation and fibroblast proliferation of the intimal layer leading to progressive stenosis of the AVM and eventual resolution [35]. Typical radiation dose ranges from 12 to 30 Gy delivered to the margin of the AVM nidus [36, 37]. While the earliest radiological evidence of AVM obliteration can be seen 2–3 months following treatment, up to 3 years are typically allotted before assessing for complete obliteration and treatment success. Noninvasive imaging studies such as CTA or MRA may be used to evaluate treatment effects. However, angiography remains the gold standard to assess the response to treatment.

Obliteration rates following stereotactic radiosurgery range between 60% and 90% with negative predictors of obliteration being lower marginal dose, prior hemorrhage, eloquent location, larger nidus volume, and increased numbers of isocenters [38–40]. Treatment failure may be the result of insufficient dose, either

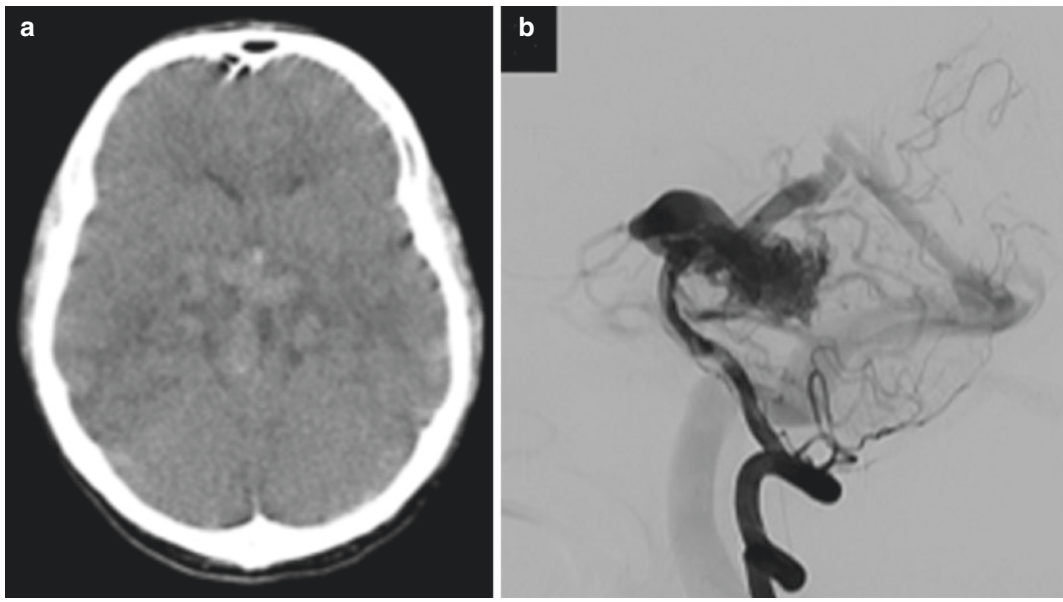

Fig. 22.4 A 43-year-old man presented with acute onset of headache. (**a**) Non-contrast CT showed intraventricular hemorrhage. (**b**) Diagnostic angiography showed a SM III AVM with dysplastic veins draining into the vein of Galen. Arterial supply was from the bilateral superior cerebellar arteries, left posterior cerebral artery, and right posterior communicating artery. This patient was referred for Gamma Knife radiosurgery

due to reduction of dose to important adjacent structures (such as the optic nerves or pituitary stalk) or recanalization of previously treated AVM not included in the original radiosurgical treatment plan.

Though the ARUBA study suggested that stereotactic radiosurgery for unruptured AVMs was inferior to medical management, multiple studies have demonstrated its safety and efficacy. Nerva et al. reported 30 patients (SM I/II, 12; SM III, 11; SM IV/V, 7) who underwent stereotactic radiosurgery. Complications were identified in 33% of grade I/II, 9% of grade III, and 14% of grade IV/V AVMs. Radiographic cure was shown in 80% of grade I/II, 67% of grade III, and 25% of grade IV/V AVMs [23]. In 174 ARUBA-eligible patients (SM I/II, 85; SM III, 55; SM IV/V, 34) treated with stereotactic radiosurgery, Pollock et al. reported an 8.7% rate of adverse radiation effects and 6.9% rate of posttreatment neurological deficit. The rate of stroke or death was 10.3% and 11.5% at 5 and 10 years, respectively, with a lower rate for lower-grade AVMs [41]. In a multicenter retrospective study of 509 ARUBA-eligible patients (SM I/II, 232; SM III, 245; SM IV/V, 32), complete AVM obliteration was obtained in 75% of cases [42]. Permanent neurological morbidity occurred in 4.5% and there was a 4.3% mortality rate. Of those patients that died, 22.7% (0.98% of overall patients) were related to posttreatment hemorrhage, whereas the remaining 77.3% of mortalities were due to other medical causes or remained unknown. While direct comparisons to the ARUBA study are difficult to make, these retrospective studies suggest a low rate of hemorrhage risk that is comparable to the medical treatment arm of patients in the ARUBA study, with the eventual advantage of AVM resolution and reduction in long-term annual hemorrhage risk.

Treatment of Ruptured AVMs

The primary management of a ruptured AVM focuses on managing intracranial pressure. In the setting of intraventricular hemorrhage, an external ventricular drain can be placed both for intracranial pressure monitoring and CSF diversion to prevent the development of hydrocephalus. Hypertonic and hyperosmolar solutions can be used as treatment for intermittent increases in intracranial pressure. However, once intracranial pressure is refractory to CSF diversion and hypertonic/hyperosmolar therapy, the treating physician must weigh the risks and benefits of decompressive hemicraniectomy and possible judicious implementation of hematoma evacuation in selected cases. If the underlying AVM angioarchitecture has not been well-characterized (typically by catheter angiography), emergency surgery for refractory intracranial pressure should consist of decompressive hemicraniectomy only, and AVM resection should be considered in a second-stage operation, if required.

Following optimization of intracranial pressure, a diagnostic cerebral angiogram is obtained to identify the size and location of the AVM nidus as well as identify feeding arteries, adjacent arteries, en passage vessels (arteries that both supply the AVM and normal brain parenchyma), and draining veins. High-risk features can also be identified.

Treatment of the AVM is based on the understanding of the natural history of ruptured lesions. Longitudinal studies suggest approximately a 6–7.5% risk of re-rupture within 1 year of initial rupture, decreasing to approximately 2–3% per year following 1 year after the initial rupture [43–45]. Both the options and rationale for each treatment option are similar to those in cases of unruptured AVMs.

Microsurgery is often recommended in low-grade (SM I/II) ruptured AVMs in noneloquent/superficial regions of the brain (Fig. 22.5). In many cases, embolization is often used to treat intranidal aneurysms (to protect against re-rupture during surgery) and deep feeding arterial pedicles (as these are generally the last vessels that can be seen during resection and are often the most complicated to dissect and ligate intraoperatively) (Fig. 22.6). In low-grade AVMs that are located deep within the brain or in patients that are poor candidates for surgery, radiosurgery is often recommended with adjuvant embolization of high-risk features if necessary.

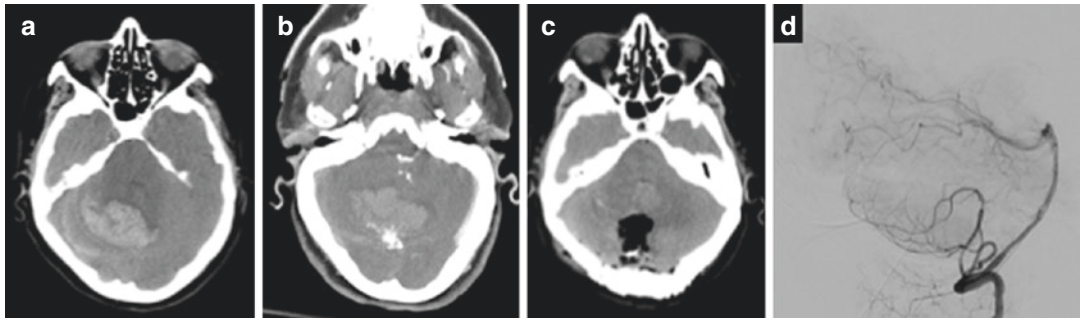

Fig. 22.5 A 73-year-old woman presented with acute decline in mental status. (**a**) Non-contrast CT showed a cerebellar intraparenchymal hemorrhage. (**b**) CT angiography showed a superficial SM I AVM. (**c**) A suboccipital craniotomy was performed for resection of the AVM and intraparenchymal clot. (**d**) Postoperative angiography showed no residual AVM

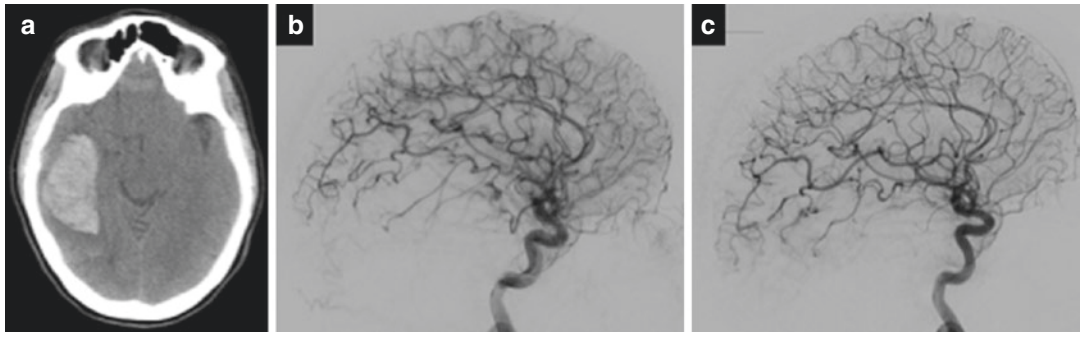

Fig. 22.6 A 35-year-old woman presented with an acute episode of worst headache of life. (**a**) Non-contrast CT showed a right temporal intraparenchymal hemorrhage. (**b**) Diagnostic angiography showed a superficial SM I AVM with feeding vessels from the inferior division of the middle cerebral artery. Embolization was performed followed immediately by microsurgical resection. (**c**) Postoperative angiography shows complete obliteration of the AVM

Ruptured SM III AVMs present a similar treatment challenge as microsurgery is associated with slightly higher risk of morbidity as compared to low-grade AVMs. However, microsurgery in this setting can provide an immediate cure of an AVM without a latent period that is seen with AVMs treated with radiosurgery. In general, superficial AVMs are treated with microsurgery and embolization. AVMs that are located deep in the brain or in eloquent cortex are often best treated with radiosurgery with embolization if high-risk features exist.

High-grade AVMs (SM IV/V) are most often observed unless high-risk features are present, in which case targeted therapy is performed. If repeat hemorrhages occur and treatment is necessary, then staged radiosurgery is considered. Partial treatment or surgical resection has not been proven to be an effective treatment strategy without high risk of permanent morbidity and mortality.

Adverse Treatment Effects

Postoperative Epilepsy

Seizures represent a common presenting symptom of patients with both unruptured and ruptured AVMs. Risk factors for developing preoperative epilepsy include younger age, cortical location, and increasing size. Following treatment, approximately 40% of patients will be seizure-free and approximately 70% will be seizure-free or have improvement

in their seizure frequency compared to pre-treatment [46].

Approximately 2% of patients will experience worsening of seizure frequency following treatment. Seizures often occur within 1 year of treatment, but 25% of seizures can occur beyond 1 year. In addition, approximately 5–20% of patients will develop new seizures after surgical resection [47, 48]. Anti-epileptic medications are commonly prescribed following treatment, and their discontinuation and recommendations regarding activities of daily living must take into account the risk of delayed seizures.

Re-rupture of Recently Treated AVMs

Hemorrhage remains an uncommon yet potentially devastating complication of AVM treatment. This can be due to rupture of sub-totally resected AVM, normal perfusion pressure breakthrough, arterial hemorrhage from feeding arteries, or occlusive hyperemia. These causes are grouped into a syndrome termed arterial-capillary-venous hypertensive (ACVH) syndrome and likely represent a constellation of pathological changes to surrounding vessels and the brain that can lead to postoperative hemorrhage. It reportedly occurs in less than 5% of AVMs undergoing microsurgical resection with risk factors including nidus size >4 cm and postoperative hypertension [49].

Normal perfusion pressure breakthrough was first described in 1978 in which Spetzler et al. postulated that small arteries that fed an AVM, and were located in adjacent normal brain, lost their cerebral autoregulatory properties causing them to become dilated due to hyperemia from the adjacent AVM [50]. Following AVM resection, these arteries would continue to experience perfusion but would be unable to autoregulate in the setting of hyper- or hypotension. Hyperemia through this compromised vasculature would lead to postoperative edema and hemorrhage. Clinical as well as rat models of hypoperfusion suggest that arteries can vasodilate but are unable to vasoconstrict, providing indirect evidence to alterations in vasomotor reactivity following changes in hemodynamics [51, 52]. However, this theory has been challenged. Young et al. showed intact autoregulation in adjacent parenchyma both pre- and post-AVM resection, while Ogasawara et al. showed impaired autoregulation in adjacent parenchyma in areas that had normal autoregulation prior to resection [53–55]. In addition, while Spetzler hypothesized that it was adjacent feeding arteries that had lost the ability to autoregulate, increases in cerebral blood flow maximally occur several centimeters from the AVM nidus and can be seen throughout the entire brain [49, 56].

Hemorrhage from feeding arteries is thought to occur from the loss of low-resistance vessels from the AVM nidus following resection resulting in an increase in arterial pressure as well as increased pulsatility in the feeding artery [56, 57]. These changes in hemodynamics can lead to significant stress on both feeding arteries and aneurysms associated with these vessels.

The theory of occlusive hyperemia postulates that slow or stagnant flow occurring in either the arterial or venous system leads to changes in intracranial hemodynamics and subsequent post-surgical edema and hemorrhage. Abnormalities in venous drainage are reported to occur in 30–100% of AVMs, and those with less than three draining veins and/or deep locations are at risk for hemorrhage [58, 59].

Vasospasm

Vasospasm is a rare complication of ruptured AVMs as compared to aneurysmal subarachnoid hemorrhage. Vasospasm from intraventricular or intraparenchymal hemorrhage is thought to arise via re-circulation of heme breakdown products via cerebrospinal fluid into the subarachnoid space [60, 61]. Of note, the treatment of ACVH syndrome can worsen the effects of cerebral vasospasm as the inability to elevate the patient's blood pressure can lead to ischemia. Treatment of delayed cerebral vasospasm includes hypertension, intra-arterial nicardipine, and balloon angioplasty.

Conclusion

Intracranial AVMs represent a complex lesion requiring the expertise of multiple clinical teams for optimal patient outcomes. While the optimal treatment depends on AVM-specific

factors such as rupture status, size, location within the brain, and the presence of deep venous drainage, the treating neurosurgeon must be able to synthesize the risks and benefits of multiple treatment options to best determine the safest treatment modality for each patient. While the ARUBA study concluded that medical management was superior to intervention, multiple limitations exist. In high-volume stroke centers, microsurgical resection is considered safe for low-grade and some intermediate-grade AVMs. What is clear is a multidisciplinary approach is needed to maximally treat intracranial AVMs to prevent rupture while limiting treatment-associated morbidity.

To assist the reader in gaining familiarity with available evidence, the following rating system has been used to indicate key references for each chapter's content:
***: Critical material. Anyone dealing with this condition should be familiar with this reference.
**: Useful material. Important information that is valuable in in clinical or scientific practice related to this condition.
*: Optional material. For readers with a strong interest in the chapter content or a desire to study it in greater depth.

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Arteriovenous Malformation

23

Adam B. Johnson and Gresham T. Richter

Genetic diagnosis	Yes
Genetic etiology	Multiple; RASA1 most common, MAP2K1
Level of evidence: treatment	Low
Evidence	Case series

Introduction

Arteriovenous malformations (AVM) are rare high-flow vascular malformations that arise from an aberrant connection between an artery and a vein without separation by a well-defined capillary bed. They consist of three components: (1) a radiographic nidus, (2) one or more feeding arteries, and (3) one or more draining veins. They may be focal or diffuse with approximately 50% of them occurring in the head and neck. They are generally present at birth but may not be noticed until later in life. They are notorious for expanding in pubescent years, during pregnancy, as well as with trauma [1–3]. These lesions are present for life, infiltrative, and progressive and can cause deformity, bleeding, and cardiovascular malfunction. They are difficult to treat and usually require a multidisciplinary team for complete care [4].

There have been multiple attempts to classify AVMs, but the most accepted scheme is the Schobinger classification (Table 23.1). These lesions are invasive and can be destructive in nature and leading to other classification schemes characterizing AVMs similar to cancer [5]. Yakes created an endovascular classification system that defines AVM by the arrangement of feeding and draining vessels [6]. Other attempts to classify AVMs have been suggested based on therapeutic outcomes [7]. A utilitarian and prognostic classification scheme for AVMs would be to divide them into either focal or diffuse lesions. Evidence suggests that cure may be achieved for focal lesions comprising a single feeding artery, while diffuse AVMs progress despite aggressive and repetitive management.

Table 23.1 Schobinger classification of AVM

Schobinger classification	
Stage I	Warm and mildly erythematous skin
Stage II	Expanding lesion with bruit
Stage III	Expanding lesion with bruit and bleeding, pain, or ulceration
Stage IV	High output causing cardiovascular overload

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Table 23.2 Summary of gene associations with AVM syndromes

Malformation	Locus name	Locus	Mutated gene
CV-AVM	5q13-22	CMC1	RASA1
HHT	9q33-34	HHT1	ENG
HHT	12q11-14	HHT2	ALK1
PHTS	10q23	PHTS	PTEN
Somatic AVM		MAP2K1	MEK1

Diagnosis is often difficult and requires imaging such as an arteriogram or magnetic resonance arteriography to confirm diagnosis and for therapeutic planning. The etiology of AVMs remains unclear, and animal models have been proposed for study [8, 9]. There are syndromes and genetic components that are not entirely understood at this current time, leaving much room for genetic and epigenetic research in this area (Table 23.2). Intracranial and brain AVMs have an extensive amount of literature dedicated to the origin and management of AVMs. Therefore, a large amount of extracranial AVM research, literature, diagnosis, and management protocols have been based on what we know about brain AVMs.

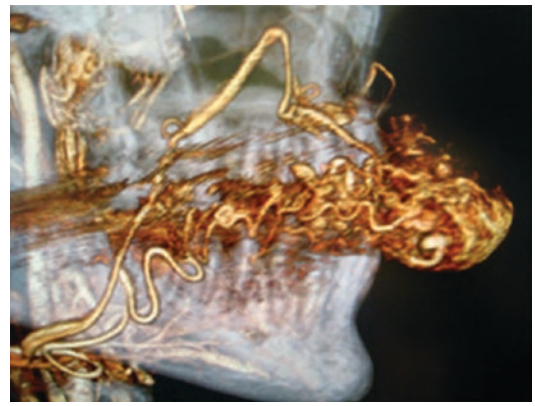

Fig. 23.1 3D CT angiographic volumetric rendering of upper lip AVM

Diagnosis

Early clinical diagnosis of AVMs can be challenging. During childhood these lesions can be noted as only an irregular red vascular blush that is warmer than the surrounding skin. Capillary malformations have a similar appearance but with well-defined borders and a temperature equal to adjacent skin. Compared to other vascular lesions AVMs may also have a palpable bruit or thrill that is noted in Schobinger stage II or greater. AVMs do not regress and continue to grow throughout life. It is common for them to have a burst of growth during periods of hormonal fluctuations or after incidental trauma. With growth, AVMs will demonstrate evidence of relentless soft tissue expansion, ulceration, and bleeding. Thorough physical examination can help determine the correct diagnosis.

Ultimately imaging is crucial for the diagnosis and treatment planning of AVMs. Ultrasound is very helpful in diagnosis but is somewhat limited in regard to defining the extent of the disease and involvement of bony structures. This is particular true for facial AVMs. Magnetic resonance imaging (MRI) and magnetic resonance arteriograms (MRA) are useful modalities to identify AVMs as well as the extent of the disease. Flow voids are easily identifiable in these high-flow lesions. An arteriogram is still the gold standard for imaging diagnostics for an AVM. Shunting with early venous filling is indicative of an AVM (Fig. 23.1).

Phenotype and Variations

There are multiple phenotypes and syndromes that incorporate AVMs into their description. Here we present a few of the more common, yet still rare, phenotypes of AVMs. One of the more notable hereditary AVM associations is Parkes Weber syndrome (PWS), a rare syndrome with an unknown prevalence. Originally described in 1907 by Frederick Parkes Weber, this syndrome is characterized by lymphatic malformations, venous malformation, and capillary malformations associated with arteriovenous malformations. It also associated with soft tissue and bony hypertrophy. There can be a genetic mutation

association known as RASA1 (Ras p21 protein activator 1) mutation. This mutation is generally associated with patients with multiple multifocal capillary malformations. This gene exists on chromosome 5. The features are expressed via haploinsufficiency, also known as a loss of function secondary to the loss of diploidy. The normal function of the product from RASA1, p120RasGAP, is to aid in proliferation and differentiation of cells. This protein has been shown to negatively regulate Ras, a signal transducer of vascular endothelial growth factor (VEGF)-mediated angiogenesis [10]. Particularly, it is speculated to be involved in vascular differentiation, but it is currently unclear how RASA1 controls vascular differentiation. Knockout mice have shown that alteration of this gene results in abnormal angiogenic remodeling suggesting RASA1s' involvement in vascular differentiation [11].

Capillary malformation-arteriovenous malformation (CM-AVM) syndrome has some overlap with Parkes Weber syndrome [12]. It is an autosomal dominant syndrome that, like PWS, can have the RASA1 mutation, although this is variable [13]. CM-AVM syndrome lacks the limb hypertrophy associated with PWS. AVMs are noted to only be associated with 30% of patients with CV-AVM syndrome. Orme et al. proposed key features to be indicative of CM-AVM: (1) capillary malformations that are 1–3 cm in diameter, round or oval pink macules with or without arterial flow on Doppler and with or without a blanched halo, (2) AVMs, (3) family history of capillary malformations with or without AVMs, or (4) RASA1 mutation [14].

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome, is another familial disorder associated with high-flow AVMs. There is an estimated prevalence of 1 in 5000 people. The AVMs associated with HHT are generally visceral with pulmonary, gastrointestinal, cerebral, hepatic, and spinal locations. Pulmonary AVMs are the most common and present in 50% of patients with HHT [15]. Three of the following four criteria must be met for diagnosis: epistaxis, telangiectasia, visceral lesions, or family history of HHT. The molecular basis of this disease is based on abnormal function of the transforming growth factor beta (TGF-β) pathway. The most common mutated genes found are those coding for endoglin (CD105) or the activin receptor-like kinase type 1 (ALKT1) in chromosomes 9 and 12, respectively. Both of these genes encode for receptors of the TGF-β pathway. Endoglin has been shown to be expressed exclusively on AVMs when compared to other vascular tumors and malformations [16]. Normally TGF-β aids in the formation of vessels. There is confirmation that these genes are related to HHT via transgenic mouse studies. Heterozygosity for these genes induces the features of HHT [17].

Bannayan-Riley-Ruvalcaba syndrome (BRRS) is one of four syndromes encompassed in the category of phosphate and tensin homologue hamartoma-tumor syndromes. Phosphatase and tensin homolog (PTEN), the mutated gene in BRRS, is located on chromosome 10. BRRS is the only one of the four syndromes that has associated AVMs, although there are descriptions of Cowden syndrome with AVMs present as well. The typical characteristics of BRRS are macrocephaly; developmental delay; penile freckling in males; benign lesions of primarily mesodermal origin, which include lipomas; and vascular lesions that are mainly found intramuscularly [18]. PTEN is normally an inhibitor of the PI3K/AKT/mTOR pathway. Mutation in this gene allows for formation of benign and malignant tumors including AVMS.

Summary of Evidence

Parkes Weber syndrome is accurately and clearly described in a meta-analysis by Banzic et al. This study was performed to clarify the diagnosis, as there is often confusion and misdiagnosis with Klippel-Trenaunay syndrome. The authors revealed 48 cases of PWS where a predominance between male and female was not found, and in 87% of patients, a lower extremity was involved without a clear site predilection. Thirty-one percent had high-output heart failure secondary to AVM shunting. This helped profile Parkes Weber syndrome patients as those with capillary malformation, venous malformation, lymphatic malformation, and arteriovenous malformation associated with limb hypertrophy [19].

A prospective and retrospective study from [13] was performed on 261 patients with the CM-AVM syndrome and the RASA1 mutation. The prospective portion of this study included 100 index patients with CM-AVM and resulted in 68 patients positive for the RASA1 mutation. Ninety of these patients' family members were genetically tested to reveal 70 with the RASA1 mutation. Forty (59%) of the families had high-flow lesions. Of note, not all RASA1 mutation patients or family members had a vascular malformation. They proposed a "two-hit" hypothesis in the development of CM-AVM and Parkes Weber phenotypes. This study underscored the physical findings in CM-AVM that should lead to the diagnosis of this disease.

Parambil [15] organized a concise review of AVM associated with HHT. TGF-β function and its receptors seem to be critical in understanding HHT. This review also describes the ALK-1 gene and its involvement with VEGF and AVM. Ultimately this report states that pulmonary AVMs in HHT can be present in up to 50% of patients.

Newer evidence suggests a somatic mutation associated with extracranial AVMs. Couto et al. [20] discovered *MAP2K1* mutations with AVMs via whole genome and whole exome sequencing. Using CD31 as a marker, they were able to also show that MAP2K1 mutant alleles were present only in endothelial cells [20]. Understanding these molecular and genetic mechanisms behind AVMs is important to help develop innovative treatments [7].

Natural History

AVMs are thought to be present at birth but are often not recognized until childhood. They are sensitive to hormonal changes and will have increased growth during puberty and prepubescent years. AVMs have a predilection for the midface, oral cavity, and limbs. As they progress, they will invade surrounding structures. Trauma may also influence the rate of AVM growth [1–3]. AVMs do not spontaneously regress. In contrast, they tend to continue to grow and infiltrate soft tissue to cause disfigurement, dysfunction, and life-threatening hemorrhage. As AVMs advance through Schobinger stages, elevated expression of vascular growth factors and extracellular matrix regulators help advance soft tissue degradation and disease progression [16].

Summary of Evidence

Liu and colleagues in 2010 explored the natural history of extracranial AVMs via a retrospective review of 272 untreated patients affected by AVMs. They defined progression by advancement through the Schobinger classification stages (I through IV) and discovered that the majority of AVMs advance with time. Each patient in this study presented in Schobinger stage I and was followed for disease progression as they aged. The authors defined childhood as birth to 8 (female) and 9 (male) years old, adolescence from 9 (female) to 10 (male) years old until 21 years of age, and adults as greater than 21 years old. They noted that 43.8% of AVM patients progressed before adolescence and that 82.6% progressed before adulthood. Progression was twice as likely to occur during adolescence as compared to childhood. Sex, location, and pregnancy did not significantly influence AVM growth [21].

Richter and Suen also examined the natural progression of extracranial AVM but specific to the head and neck. They reviewed the charts of ten patients (age 13–46) with cervical-facial AVMs. These patients had failed previous treatments at outside hospitals. AVM staging was documented clinically as well as photographically, and the patient's treatment regimen was analyzed. Patients presented to the tertiary care center with AVMs ranging from Schobinger stage II through IV. This study reinforced the notion that AVMs are aggressive lesions that progress relentlessly over time and invade critical structures. The authors also offered an alternative staging for head and neck disease [5].

Treatment

The goal of treating AVMs is to reduce the burden of disease without creating a problem worse

than the lesion itself. When patients are appropriately followed for many years, evidence suggests that cure is rarely achieved. The ideal therapeutic approach is to anticipate lesion control with repeated multimodal treatment and long-term vigilance at ever-increasing treatment intervals. Diffuse AVMs infiltrate and surround critical structures where resection can create significant morbidity and disfiguration. While the main goal is to cure, treatment paradigms must consider quality of life after management.

Observation

There is essentially no role for observation in AVM management. There are episodes of observation that take place between treatment intervals to observe for recurrence. A report in 2002 implicated spontaneous regression of an AVM in the lower extremity of a patient with Parkes Weber syndrome [22]. However, outside of this unlikely scenario, there is no evidence of spontaneous regression of an extracranial head and neck AVM. Thus, strategies to treat AVM should be employed when diagnosed, in recognition of expected progression and future complications. The goal shall remain to achieve disease control.

Pharmacotherapy

Increased expression of matrix metalloproteinase (MMP) is present in AVMs. MMPs function as collagenases to degrade extracellular matrix. It is hypothesized that through increased MMP activity, AVMs can invade surrounding tissues. MMP inhibitors have been reported to aid in control of AVMs. Specifically MMP-9 seems to be the most important MMP with regard to AVM progression [23, 30]. Doxycycline is a nonspecific MMP inhibitor and has been shown to be especially useful as an adjunct to therapy. This medication can be taken orally and has a known effect on the MMP-2 and MMP-9. Reports on brain AVMs have shown a decrease in MMP activity with the administration of doxycycline in vitro and in vivo [24, 25].

Sirolimus is a mammalian target of rapamycin (mTOR) inhibitor that inhibits immune function via interleukin 2 (IL-2), thus affecting the activation of T-cells and B-cells. Sirolimus has been shown to be effective in the treatment of capillary malformations, lymphatic malformations, and venous malformations with varying success. There are a handful of reports of using sirolimus in the management of AVMs. One case report demonstrated a patient with an AVM in the right upper extremity, a PTEN mutation, and penile freckling suggesting a BRRS diagnosis. He had multiple treatments without much success, but when sirolimus was administered, the patient's AVM and associated pain were reduced [26]. Despite some literature showing minimal to no response [27], this oral medication seems to be gaining popularity as a potential adjunct to current therapy. The authors currently have three patients with AVM on sirolimus with a promising response from the patient with a PTEN mutation.

Bleomycin is a chemotherapyutic drug used as a sclerotic agent on slow-flow lymphatic and venous malformations by inducing damage of the vascular endothelium [28]. There are few reports that implicate a benefit from bleomycin in the treatment of AVMs. The results remain inconclusive due to a limited volume of patients treated [29, 30]. Research on the use of bleomycin on fast-flow lesions is necessary before routine use can be advocated. There is promise however in the use of bleomycin as a single modality with demonstration of AVM improvement in small lesions (Fig. 23.2). Damage to the endothelium of the venous outflow tract is likely the mechanism.

Laser

Laser therapy is used to aid in AVM management via selective photothermolysis of small feeding vessels and draining veins. Flashlamp-pumped dye laser (FPDL) and neodymium-doped yttrium aluminum garnet (ND:YAG) laser therapy have been effective in helping to control superficial AVM disease. There is a small study of four patients with head and neck AVMs that were shown to be controlled with interstitial ND:YAG

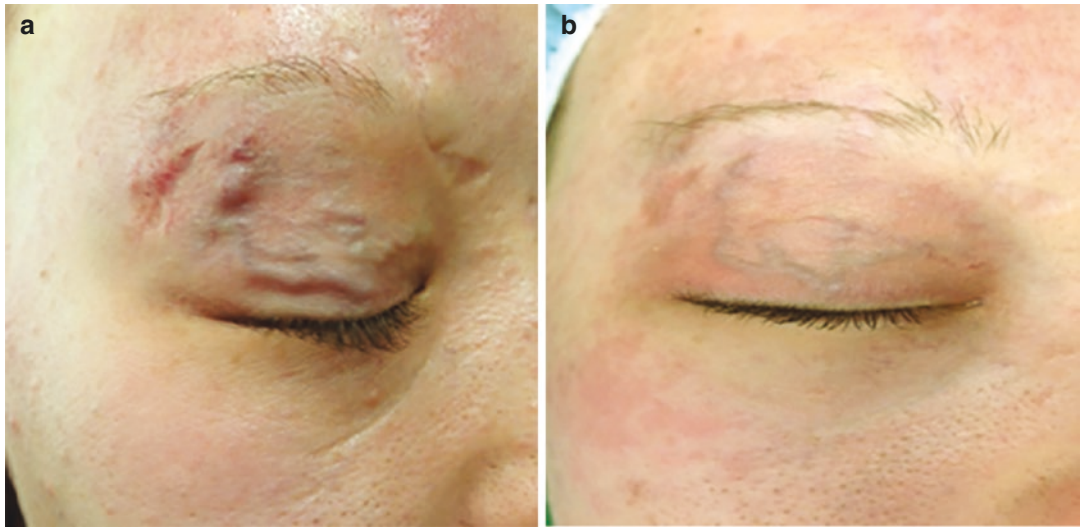

Fig. 23.2 Pre- and post-bleomycin sclerotherapy of small upper eyelid AVM

laser as shown by a reduction in size and a change from soft to a more solid lesion [30]. The lesions were infiltrated with the laser fiber to help manage the deep soft tissue disease. The use of lasers superficially helps to ablate draining veins within 8 mm of the skin surface. Similar to other modalities, and much like the treatment of port-wine stains, ND:YAG and FPDL laser should be repeated in order to achieve the desired benefit.

Embolization

Embolization is effective in controlling growth of extracranial AVMs. Multiple vectors have been used to obtain the desired embolization: Onyx, ethanol, and recently described N-butyl-2-cyanoacrylate (n-BCA). Complications of embolization include, but are not limited to, damage to surrounding structures that share a similar blood supply as the AVM, necrosis of the skin overlying the AVM, emboli causing cardiovascular problems, pain, neuropathy, skin or mucosal staining, and swelling. Each agent used for embolization comes with its own unique set of risks and complications [31].

Onyx is an ethylene-vinyl alcohol copolymer dissolved in dimethyl sulfoxide (DMSO) and mixed with micronized tantalum powder. It can be visualized fluoroscopically. It is FDA approved for presurgical embolization of central nervous system AVMs. Embolization can also be used alone as this helps to close off contributing channels to the AVM. The extracranial and brain AVM embolization protocol is similar. It is likely to be performed through femoral access and placed endovascularly with fluoroscopic visualization to increase accuracy. Complications with Onyx are comparable to other embolization techniques [32]. Unique to Onyx is skin discoloration that can occur if the injection is too superficial [33].

Absolute ethanol (99.7%) is another substance that can be used effectively for the management of AVMs [34]. It has been proposed to work through toxicity to the endothelial cells as well as clumping and denaturing of protein within the vascular lumen and stripping the endovascular wall causing occlusion of the vessel lumen. The damage to the endothelium is thought to prevent recanalization. Absolute ethanol contains no contrast, and therefore this method does require repeat administration of contrast in order to perform super-selective placement of the ethanol for embolization. A unique consequence of absolute ethanol embolization is hemoglobinuria that can be treated with fluid resuscitation. There are theoretical risks of liver and kidney dysfunction that at this time have not been supported by the literature. There have however been reports of skin and nerve damage. This is usually transient with full recovery, but can rarely

be permanent. The response to ethanol embolization is remarkable, with reports of up 68% cure as a single agent treatment [35]. Long-term follow-up is, however, critical.

N-butyl-2-cyanoacrylate (n-BCA) also known as GLUE is another embolization medium that is used mostly in intracranial AVMs. While this has been used as treatment in isolation [36], it may be best used as an adjunct to surgery allowing for an easily palpable mass to remove with decreased bleeding. There is a paucity of literature on this technique in extracranial head and neck AVMs. There are theoretical fears that GLUE embolism may occur, although to date there are none described in the literature. In brain AVMs, a meta-analysis showed increased cure rates and complications from absolute ethanol when compared to n-BCA [37].

Resection

Resection of AVM is technically challenging but is the most likely way of achieving cure [38]. However, with resection alone, there is still a reported 80% chance of recurrence [21]. While resection is an adequate method for cure of some AVMs, selection of which AVMs are amenable can be quite difficult; small isolated and focal AVMs seem most amenable to resection alone (Fig. 23.3) [39]. Other more complicated lesions (diffuse) usually require a multimodal technique. Combination therapy is not an uncommon practice for resection of AVMs. Presurgical treatment with embolization can decrease blood loss, define lesion borders, make intraoperative identification easier, and be therapeutic in unresectable parts of the lesion [39]. n-BCA is most effective preoperatively, in the authors' experience and in improving surgical approach and outcomes. Surgery has become a central element of management of even familial causes of AVM [40].

Multimodal

All treatment options for AVMs have advantages and disadvantages. Because AVMs infiltrate and destroy soft tissue, much like locally invasive malignancies, it may be wise to approach them similarly. This includes the use of multimodal therapy that selectively treats the AVM while protecting local tissue. The approach takes advantage of each therapeutic arm while reducing the risk of making the outcome worse than the disease. While the outcome for focal AVMs is frequently good regardless of treatment approach, most AVMs are diffuse and complex and involve important structures. Diffuse lesions often require embolization followed by site-specific surgical removal. This reduces the risk of intraoperative blood loss and damage to local structures. Follow-up at 2–4-month intervals with a variety of laser therapy, ethanol embolization, and interstitial and systemic pharmacotherapy is employed to ablate and

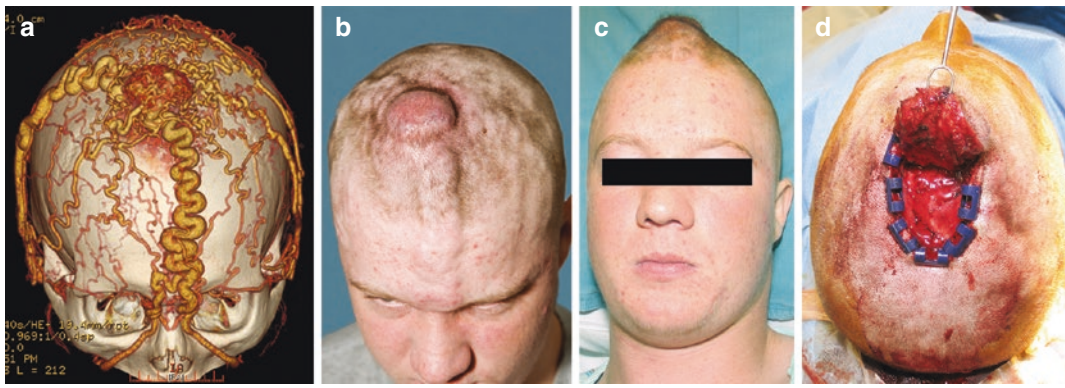

Fig. 23.3 Treatment of scalp AVM with glue embolization of nidus and surgical excision. Images from left to right: 3D CT angiographic volumetric rendering of scalp AVM nidus; feeding arteries and large serpiginous veins; preglue embolization, note the dilated forehead veins; postglue embolization, note the veins are collapsed; and intraoperative nidus resection. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer). (Images courtesy of Seattle Children's Radiology, Giridar Shivaram, Eric Monroe and Kevin Koo)

control the remaining disease. Recurrent therapy is necessary to control vascular recruitment and collateralization of the AVM. This process is conducted at gradually increasing treatment intervals with devout vigilance.

Regardless of therapeutic approach, it is apparent that AVM treatment requires targeted and sequential therapy. Ethanol embolization alone is effective at luminal and nidus ablation with the risk of necrosis or injury to local and superficial tissue. Both Onyx and n-BCA embolization are effective at obstructing and ablating the offending vessels but leave behind foreign material. The authors contend that targeted surgical resection of the embolized vessels with these agents is important to avert inflammation and recurrence at these sites. This can be staged with repeat therapy of large AVMs affecting more than one anatomic subunit, whereby parts of the AVM are addressed at 3-month intervals.

The most challenging portion of AVM management is disease that involves the skin and direct subcutaneous tissue. These sites are at risk for injury and necrosis with embolization and are not always cosmetically amenable to resection without creating deformity. In these scenarios, we utilize other tools to ablate and control disease. Lasers, such as ND:YAG and flash pulsed dye, can ablate small- and medium-sized arterial and vascular feeders to the lesions [39], while indirect sclerotherapy with bleomycin and doxycycline can disrupt the vascular endothelium. Unfortunately, due to the rarity of this condition, there is limited evidence of the impact of this therapeutic approach. We have constructed a rudimentary algorithm for the treatment of simple and complex AVMs (Fig. 23.4).

Summary of Evidence

Thiex and colleagues reported in 2011 the largest series on the safety and efficacy of Onyx embolization in extracranial head and neck AVMs. In their retrospective review, the authors report 3 years of 77 total treatments with specific indications for embolization such as acute hemorrhage, recurrent or episodic hemorrhage, pain, progressive enlargement, impending necrosis, or functional impairment. The patients were followed with a phone call at 2 weeks and then a clinic visit at 4 weeks and at 6 months after their embolization date. Hemostasis was achieved in 13 out of 14 patients with acute hemorrhage. Five patients went on to have their AVMs resected and were noted to have minimal blood loss and no need for transfusion as reported by the surgeons. The median number of treatments to obtain near complete embolization was 6, pointing to the need for repeat and vigilant therapy [32].

Ethanol embolization was reported by Do et al. in 2005 as a safe and effective method for treatment of extracranial AVMs. They performed a retrospective review of 40 patients who underwent a

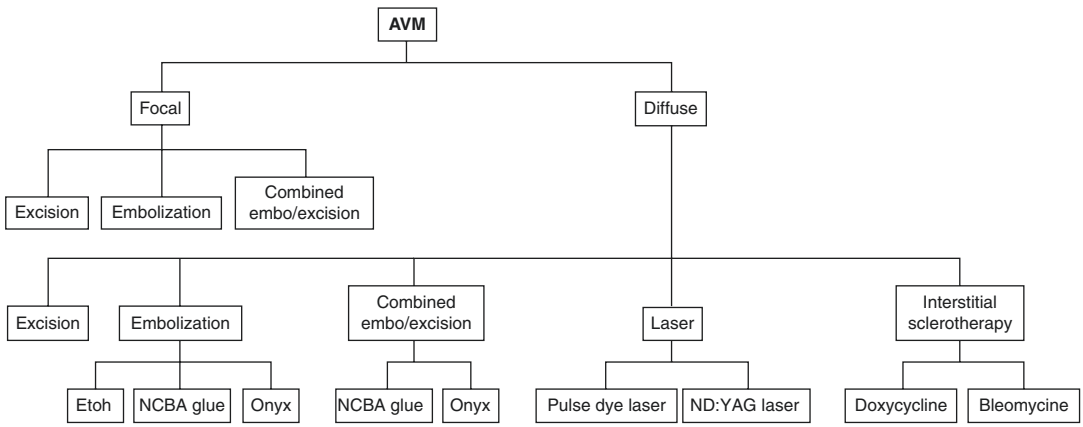

Fig. 23.4 Proposed AVM treatment decision algorithm

total of 175 ethanol embolizations. They reported a cure rate of 40% with a 28% partial remission. Fifty-two percent of these patients had complications, but almost all of them were transient. Out of the 175 procedures, only 15% resulted in minor complications, and 3% resulted in major complications with complete recovery except for one patient. They concluded that ethanol embolization has a potential for complete cure of body and limb AVMs, but also comes with some acceptable minor and major risks [35].

Visser et al. [39] reported on their experience with resection of as the primary treatment of AVMs. This group was able to compile 14 years' experience with resection of extracranial AVMs. They collected retrospective data on 53 patients. Twenty-two of these patients underwent embolization prior to resection. Seventeen patients required reconstructive surgery consisting of local regional flaps and free flaps. There was a low recurrence rate of only 8.7% for all 53 patients. This study shows the safety and effectiveness of resection of AVMs. Preoperative embolization seems to help with resection by decreasing bleeding. The use of the reconstructive ladder for complex and large AVM resections is imperative to have adequate outcomes [39].

To assist the reader in gaining familiarity with available evidence, the following rating system has been used to indicate key references for each chapter's content:
***: Critical material. Anyone dealing with this condition should be familiar with this reference.
**: Useful material. Important information that is valuable in in clinical or scientific practice related to this condition.
*: Optional material. For readers with a strong interest in the chapter content or a desire to study it in greater depth.

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Part V

Vascular Malformations: Site-Specific Considerations

Airway Vascular Malformations

24

Deanna C. Menapace and Karthik Balakrishnan

Level of evidence: treatment	Low
Evidence	Case series

Introduction

Vascular anomalies, both tumors and malformations, can occur anywhere in the body, including the airway. Airway involvement can be seen in the oral cavity, oropharynx, larynx, glottis and subglottis, and trachea as well as having extension into the retropharyngeal and parapharyngeal regions. Vascular malformations of the airway are less common than vascular tumors [1]. Slow-flow vascular malformations of the airway include capillary malformations (CMs), venous malformations (VMs), and lymphatic malformations (LMs), while arteriovenous malformations (AVM) are considered fast-flow lesions. Mixed lesions such as lymphovenous malformations (LVMs) of the airway can also be seen.

The larynx, trachea, and esophagus serve essential functions including voice, breathing, and swallow. Accordingly, in evaluation, it is important to evaluate for impairments in function including respiratory patterns, feeding patterns, dysphonia, vocal fold mobility, dysphagia, aspiration, and need for dietary modification. Indeed, many of these functions are not only important to evaluating providers but to the patients and their families as well. Symptoms of sleep-disordered breathing may be present as well and should be elucidated, although the impact of vascular malformation therapy on sleep-disordered breathing outcomes is yet to be determined. On physical exam, the provider should evaluate for signs of vascular malformations including drooling, speech distortions, anatomical asymmetry, difficulty swallowing, aspiration, and various levels of airway obstruction with or without associated stridor or retractions.

In general, stability of the airway must be determined clinically, followed by an awake flexible fiber-optic laryngoscopy if the airway is deemed stable and safe for endoscopic access in the outpatient setting. Work-up should also include planned, intraoperative rigid microdirect laryngoscopy and bronchoscopy (MLB) to examine the complete extent of involvement [2]. Adjunctively, both computed-tomography angiography (CTA) and MRI/MR angiography are used to elucidate lesion flow characteristics as well as the extent of involvement of the aerodigestive tract with the latter being the more commonly utilized imaging tool. Polysomnography should also be considered to rule out sleep-disordered breathing or frank obstructive sleep apnea if the history is consistent [3]. Vascular

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malformations of the airway are high risk for pain, thrombosis, and/or airway obstruction; therefore, they must be promptly identified and treatment strategies carefully considered.

Diagnostic Considerations

Venous Malformations

Venous malformations (VMs) are congenital collections of ectatic veins that grow with the child throughout life. They characteristically have a bluish hue and are compressible. VMs tend to occur in the post-cricoid region or on the epiglottis with symptoms of airway obstruction, dysphagia, and hemoptysis (Fig. 24.1) [1, 3, 4]. Post-cricoid VMs are not to be confused to posterior cricoid anatomic variants, which are thought to be a distention of the post-cricoid venous plexus causing intermittent obstruction in a dynamic manner (i.e., crying during flexible nasal endoscopy) [5]. VMs can be diagnosed by bedside flexible endoscopy or ultrasound, CT/CTA, or MRI. MRI with contrast can be helpful to identify relationship to the aerodigestive tract and to help locate thrombosis if present [2]. Importantly, enlargement or ulcer of VMs can occur with hormonal changes including pregnancy, trauma, or infection, which may cause intermittent symptoms. Airway involvement of a VM should be considered if a patient describes intermittent obstruction with or without hemoptysis.

Lymphatic Malformations

LMs tend to grow within the first few years of life and fluctuate with acute inflammation from infection or trauma. Of LMs in the head and neck, approximately 73% involve the aerodigestive tract above the glottis (Fig. 24.2). In a recent case series with chart review, 141 patients with airway LMs were studied for anatomic variations in location. Patients had involvement of multiple sites, but overall involvement was seen in the following prevalence: oral cavity (75%), oropharynx (36%), parapharynx (30%), retropharynx (9%), and hypopharynx (6%) [6]. LMs may cause airway compromise through compression from mass effect or occlusion. LMs that infiltrate into the supraglottic portion of the larynx may cause severe airway obstruction, whereas extensive cervicofacial lesions may cause obstruction and compression [2]. Involvement of the submandibular triangle and/or parotid space or extension into the parapharyngeal and retropharyngeal spaces can also be seen. Additionally, LMs may have mass effect associated with bony overgrowth and growth within bone [7].

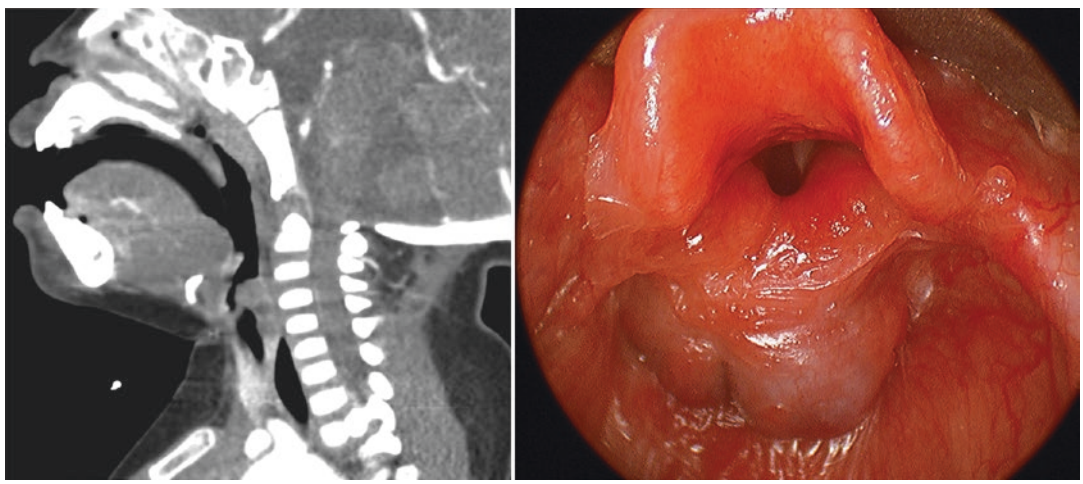

Fig. 24.1 Venous malformation of the larynx as seen on sagittal CT of airway, demonstrating poor enhancement of laryngeal venous malformation, and microlaryngoscopy. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer). (Images courtesy of Seattle Children's Radiology, Giridar Shivaram, Eric Monroe and Kevin Koo)

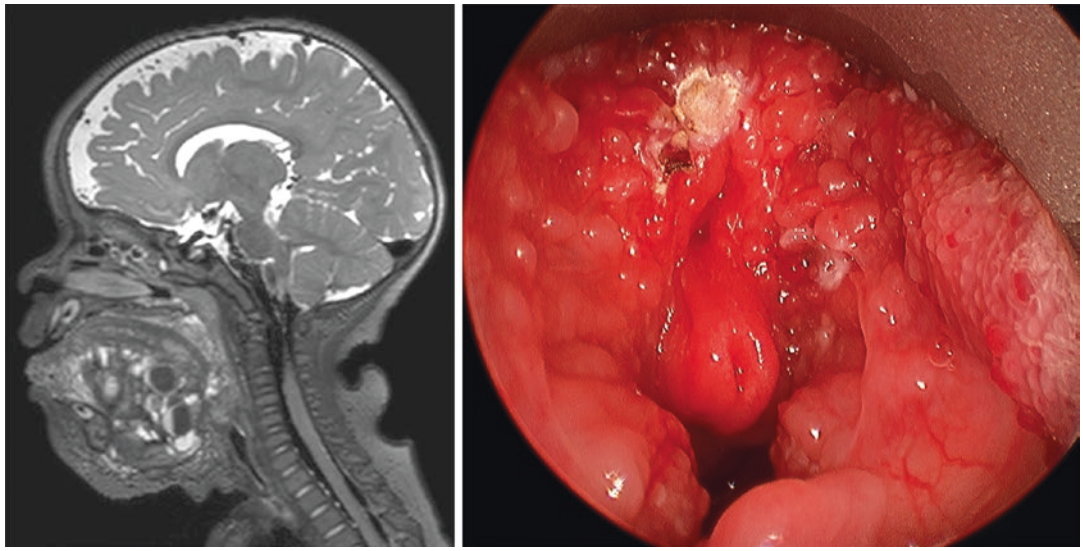

Fig. 24.2 Lymphatic malformation involving the tongue, pharynx, and supraglottis, as seen on sagittal MRI and endoscopy. Note the swollen epiglottis and large tonsils. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer). (Images courtesy of Seattle Children's Radiology, Giridar Shivaram, Eric Monroe and Kevin Koo)

With the increased use of ultrasound in the prenatal period, diagnosis of LM is often made in utero. Anterior and lateral neck swellings identified on repeat ultrasounds, likely represent congenital LMs. In new literature, an anatomic-based nomenclature has been described including the terms ventral LM (VLM) and dorsal LM (DLM). It is of importance in the prenatal period to distinguish between the two locations as VLM may be associated with airway obstruction, while DLM may be associated with chromosomal, renal, cardiac, or skeletal abnormalities [8]. Making this distinction is important as VLMs do not resolve before birth and may impact airway management in the post-partum period. If not diagnosed in utero, flexible endoscopy or direct laryngoscopy is needed to visualize the lesion [9]. Anatomic location of lymphatic malformations of the head and neck can be used to predict prognosis and outcome of surgical intervention via the De Serres classification [10]; however, it is important to keep in mind that the De Serres classification does not directly address laryngeal or extra- or intrathoracic tracheal disease burden. Currently, LMs are generally categorized based on their microcystic (<2 cm) or macrocystic (>2 cm) characteristics and where they are discrete or diffuse based on MRI [2]. Identification of microcystic disease is imperative in treatment strategies along with identification of diffuse or infiltrating lesions, as both phenotypic qualities can be more difficult to treat (Figs. 24.1 and 24.2).

Complications of LMs include swelling, pain, bleeding, ulceration, dysphagia, and odynophagia. The functional impact of these symptoms was revealed in a study from 2012, where in this study, breastfeeding alterations in infancy, the need for special positioning, and perceived prolonged sicknesses were of significant impact in this group [11]. The negative social stigmata of these lesions must also not be overlooked. In 2015, the Lymphatic Malformation Function (LMF) instrument was introduced in the literature in an attempt to establish a validated measure of LM disease burden incorporating functional criteria. The LMF instrument is a 12-item, 2-domain instrument that measures disease-specific, parent-reported factors with good internal consistency. The LMF instrument is a significant ($p < 0.05$) association with lesion stage. The LMF instrument or the Cologne Disease Score should be considered for use in longitudinal care and/or when treatments strategies are implemented [12, 13].

Lymphovenous Malformation

Similar considerations as airway LMs.

Capillary Malformations

Capillary malformations (CM) can involve the airway but are usually asymptomatic. The diagnosis can be challenging and is often missed. Symptomatic CMs are associated with Sturge-Weber, Klippel-Trenaunay, Parkes-Weber, hereditary hemorrhagic telangiectasia (HHT), macrocephaly-CM, and CLOVES (congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and spinal/skeletal anomalies/scoliosis), among many other syndromes. CMs can also lead to several respiratory complications including airway obstruction, bleeding, and chylous pleural effusion [14]. Patients with symptomatic capillary malformations should be screened (physical exam or imaging) for other synchronous vascular anomalies and if found should be sent for genetic evaluation. The diagnosis of HHT should be considered when there are vascular lesions of the skin and mucous membranes with visceral involvement.

Arteriovenous Malformations

AVMs are high-flow vascular lesions that can occur in the head and neck region. They most commonly occur in the lung parenchyma but have been rarely noted in the trachea, bronchi, and larynx [2]. AVMs are also associated with HHT. Screening for synchronous lesions is recommended, similar to management of symptomatic CMs.

Evidence-Based Treatment Approaches

Venous Malformations

Treatment options for airway VMs include observation, surgery alone, surgery with sclerotherapy, or adjunct treatments including sclerotherapy or laser therapy alone. Observation alone should be considered for asymptomatic lesions. Surgery alone (i.e., resection, suction diathermy, etc.) can be attempted as primary therapy even with lesions involving he airway [15]. Surgery, however, is not always feasible with extensive lesions. It is then appropriate to consider multimodal therapy including surgery with sclerotherapy for attempted cure. Serial sclerotherapy alone (i.e., ethanol, bleomycin) or laser therapy alone is used for symptom control in the setting of unresectable disease. In all operative treatment cases, pre- and postoperative endoscopy should be used to check for airway swelling [9]. Additionally, consideration may be given to performing an endotracheal cuff leak test to assess for extubation readiness although the evidence for its accuracy is variable [16–18]. If postoperative airway obstruction is a concern, the patient should remain intubated and monitored in the intensive care unit with appropriate anti-inflammatory medication, analgesic, and IV fluid regimen. Complications in treatment of VMs of the airway include postoperative swelling, obstruction, bleeding, pain, hoarseness, dysphagia, skin necrosis, transient facial nerve palsy, blistering, and pulmonary fibrosis (bleomycin) [9].

Recently, bleomycin sclerotherapy of airway venous malformations with image-guided needle placement or direct mucosal puncture has been shown to be safe and effective [9, 19]. Bleomycin is reported to have lower complication rate than other sclerosants. In a retrospective, single-center case series of 5 patients who underwent 16 treatments with foamed bleomycin (25% albumin suspended with bleomycin 0.5 mg/kg up to 30 units) for airway venous malformation, patients showed at least partial response in 15/16 treatments without significant airway swelling. When compared to ethanol, there was no difference in clinical response ($p = 0.30$), but foamed bleomycin had significantly shorter mean hospital stay ($p < 0.001$) and less swelling ($p < 0.0004$) [9]. Laser therapy also exists as adjunctive therapy (i.e., KTP, Nd:YAG, C02, Diode) [20–22]. In a recent retrospective review, 17 patients with laryngeal venous malformations were treated with Nd:YAG therapy (2.2 mm fiber, 0.3 to 0.7 s pulses from 18 to 30 W, pulsed). This cohort required an average of four serial treatments with each treatment showing both a marked reduction in size of the lesion as well as reduction in symptoms including obstruction [21]. The diode laser has also been used, with the added benefit of the 908-nm

laser's ability to treat deeper lesions [20]. The KTP laser (1.5 W continuous mode) has been used for more superficial photocoagulation of pharyngolaryngeal venous malformations [22].

Lymphatic Malformations

LMs engorge and cause various levels of obstruction of the airway. Management of airway obstruction however has been advanced by prenatal ultrasound and fetal MRI performed several weeks before birth. Significantly obstructive lesions should be managed by an otolaryngologist or other airway experts via fetal endoscopy during ex utero intrapartum treatment (EXIT) procedure for airway stabilization (rapid direct laryngoscopy and bronchoscopy with intubation versus tracheostomy), while fetal oxygenation is maintained via the utero-placental circulation with less mortality than standard delivery. In a recent retrospective, single-institution case series, three cases of airway lymphatic malformation diagnosed in utero were safely managed via EXIT procedure utilizing a combination of laryngotracheobronchoscopy techniques to secure the airway. EXIT-to-ECMO (extracorporeal membrane oxygenation) may also provide a bridge to definitive airway control, provided that the newborn is of sufficient gestational age and size. Overall, if prenatal airway obstruction is suspected, EXIT should be planned with a multidisciplinary team using a map of the OR and simulation [23]. During the EXIT procedure, it is crucial to have multidisciplinary involvement including otolaryngology, neonatology, maternal fetal medicine, and maternal fetal anesthesiology.

Structurally, LMs tend to cross tissue planes and involve multiple anatomic compartments, making surgical resection challenging secondary to morbidity. Airway access followed by massive dissection versus sclerotherapy needs to be discussed with the treatment planning team and family [14]. The best results are generally achieved in patients whose LM can be resected with minimal morbidity (isolated infrahyoid or posterior triangle of the neck). However, more extensive lesions require staged resection with adjunct laser or sclerotherapy with the goal of therapy being maximal relief of symptoms while minimizing morbidity. Sclerotherapy has been the treatment of choice for macrocystic lesions not amenable to surgical excision and for large cervicofacial lesions that are involving the skull base or parapharyngeal space [24]. In a large retrospective review, where primary surgery and primary sclerotherapy were compared controlling for disease stage, both treatments had similar effectiveness and hospital resource utilization including intensive care unit stay, total hospital days and total number of interventions, and need for subsequent tracheostomy [25]. Aerodigestive complications especially those involving these regions or patients with bilateral disease should be considered. These patients may require airway stabilization and gastrostomy tube for nutritional supplementation. It is important to keep in mind that extensive lesions are also associated with a 19% mortality and high rate of tracheostomy placement [26]. Complications in treatment of LMs of the airway are similar to those reported for VMs including postoperative swelling, airway obstruction, bleeding, pain, hoarseness, and dysphagia secondary to the location and close proximity of critical anatomy of the head and neck.

Sildenafil and sirolimus have been identified as treatment options for LMs, but limited evidence is available to support their use for lesions involving the airway [27].

Lymphovenous Malformations

Evidence-based treatment approach in the airway is lacking but is commonly treated similarly to airway LMs.

Capillary Malformations

Evidence-based treatment approach in the airway is lacking.

Arteriovenous Malformations

Evidence-based treatment approach in the airway is lacking.

Case

Thirty-five-year-old woman with a large lymphovenous malformation with microcystic lymphatic component that involves a large portion of the neck extending down into the mediastinum with laryngeal and tracheal involvement. Her symptoms include Eustachian tube dysfunction, dysphagia, drooling, obstructive sleep apnea, jaw pain, and fatigue. She has been managed using three applications of percutaneous sclerotherapy to lesion debulking and bilateral inferior turbinate reduction with hyoid suspension for airway optimization. She has undergone acetylcholine neuromodulator injections for sialorrhea as well as pressure equalization tube placement for Eustachian tube dysfunction. During her admissions, secondary to trachea involvement, her airway is managed using laryngeal mask airway techniques, perioperative high-dose steroids, and prophylactic antibiotic therapy (Figs. 24.3 and 24.4).

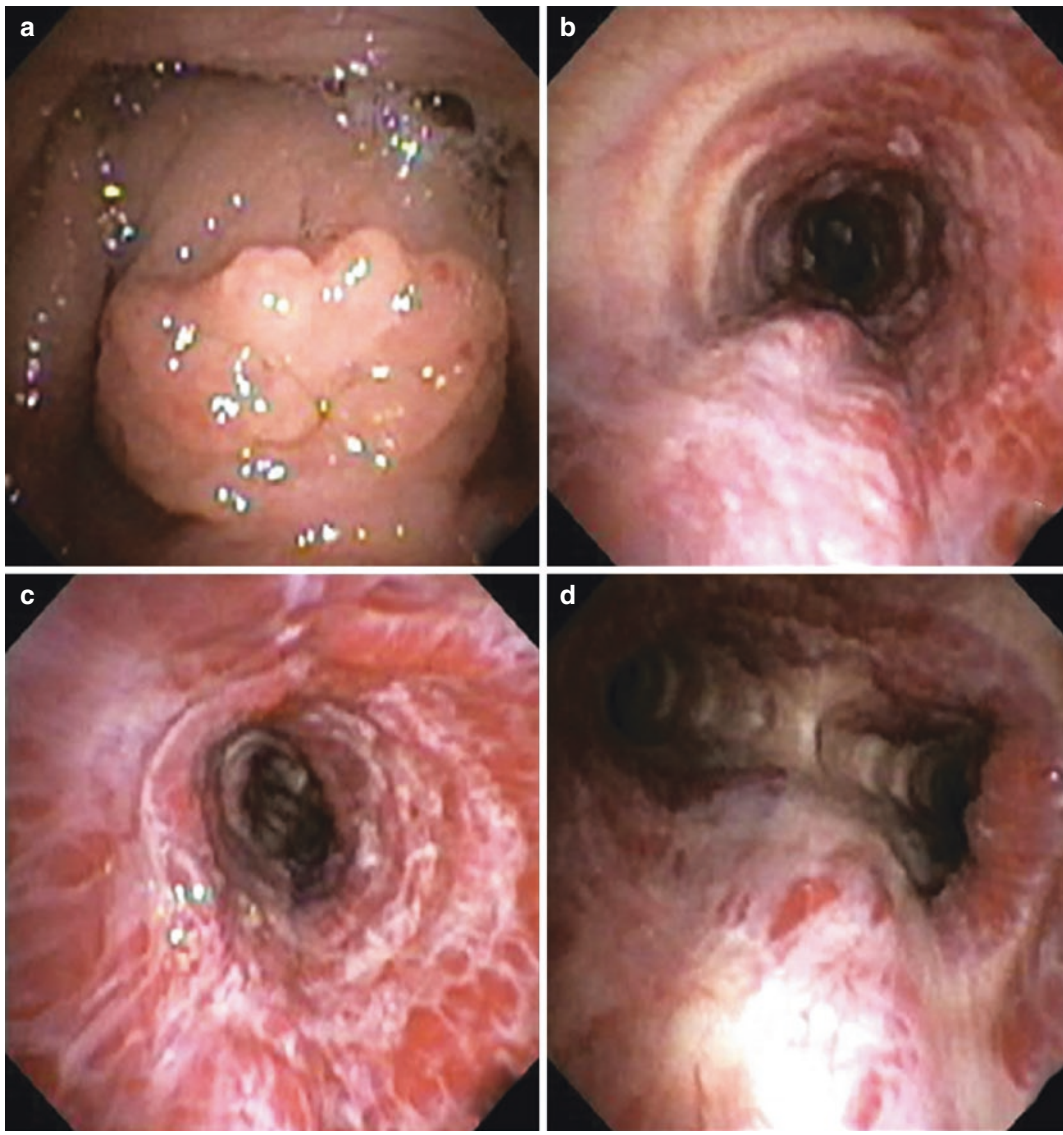

Fig. 24.3 *Microdirect laryngoscopy and rigid bronchoscopy findings* (**a**–**d**): (**a**) Microcystic LVM on the lingual surface of the epiglottis. (**b**) Trachealis and 270° involvement of trachea wall with microcystic LVM. (**c**) Distal circumferential tracheal involvement with blunting of tracheal ring anatomy. (**d**) Microcystic LVM down to and involving the mainstem bronchi

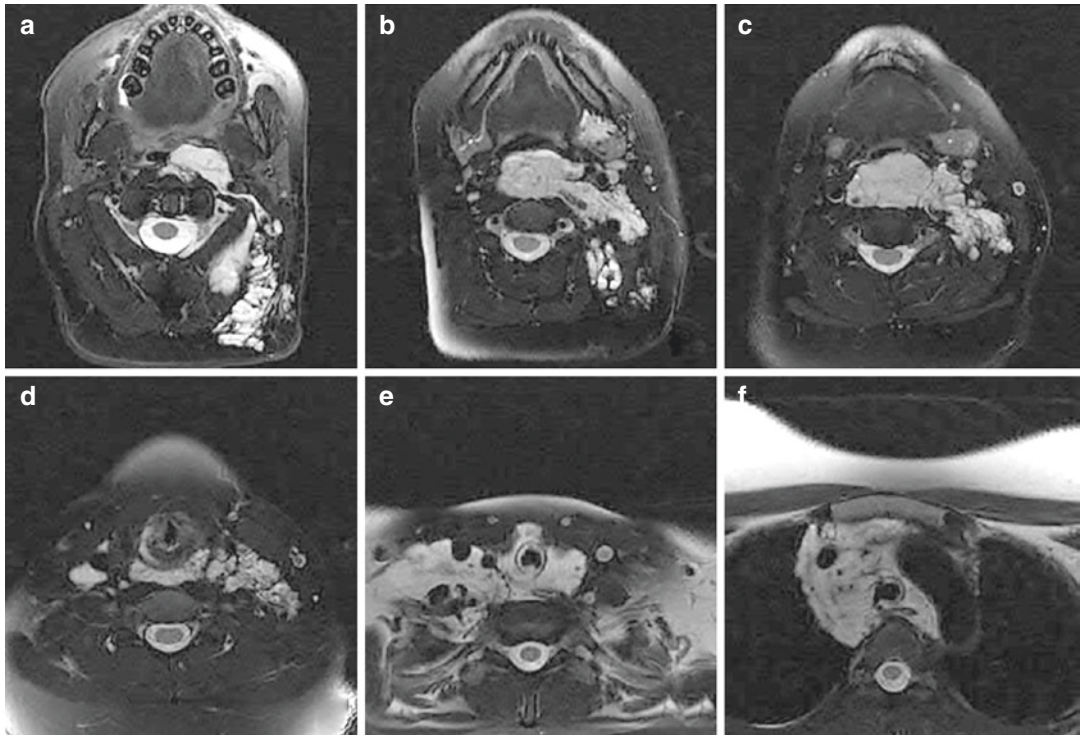

Fig. 24.4 *MRI imaging findings*: Axial T2 imaging demonstrating large lymphovenous malformation (**a**–**f**): (**a**) Level of the maxillary dentition. (**b**) Level of the mandibular dentition. (**c**) Level of the tongue base, demonstrating anterior-posterior airway narrowing, (**d**) Level of the larynx, (**e**) A cut through the cervical trachea, showing mucosal involvement; (**f**) A cut through the mediastinum, showing the unresectable LVM wrapping around the trachea and esophagus and filling the mediastinum

To assist the reader in gaining familiarity with available evidence, the following rating system has been used to indicate key references for each chapter's content:
***: Critical material. Anyone dealing with this condition should be familiar with this reference.
**: Useful material. Important information that is valuable in in clinical or scientific practice related to this condition.
*: Optional material. For readers with a strong interest in the chapter content or a desire to study it in greater depth.

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Dermatologic Considerations in Vascular Malformations

25

Megha M. Tollefson

Level of evidence: treatment	Moderate-high
Evidence	Case reports, case series, systematic reviews

Introduction

Vascular malformations often have some component of skin involvement, ranging from capillary malformations which are present entirely on the skin to lymphatic and venous malformations which may all have cutaneous involvement. Other than the visibility of the lesions, other complications involving the skin include atrophy, ulceration, dermatitis, and the growth of pyogenic granulomas. Practicing general skin care principles is important in all patients with vascular malformations with skin involvement. Pulsed dye and other lasers may be used for treatment in some patients.

Diagnostic Considerations

Vascular anomalies and malformations may involve any location of the body, but many have some manifestation on the skin. Port wine stains, or capillary malformations (CM), are the most common vascular malformation and are exclusively present on the skin, seen in 0.3–0.5% of all newborns. These vascular birthmarks are reticulate or homogeneous, red to violaceous patches that can occur on any location of the skin. As discussed in the Klippel-Trenaunay Syndrome chapter elsewhere in this book, CMs persist throughout life and can develop hypertrophy and "blebs" within them (Fig. 25.1) [1, 2]. CMs are also prone to overlying dermatitis, and these areas can be itchy and eczematous (Fig. 25.2) [3, 4]. CMs may also be more susceptible to developing allergic contact dermatitis, such as from adhesives

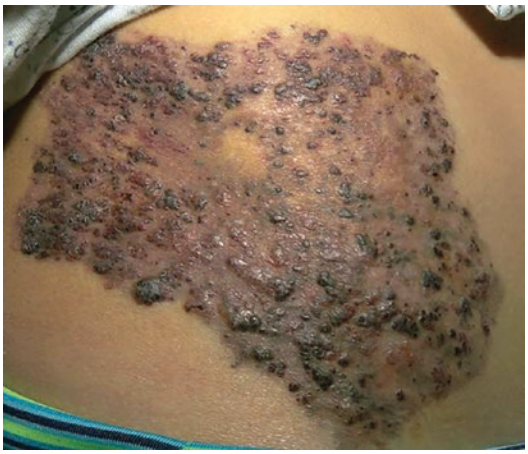

Fig. 25.1 Extensive vascular "blebs" within a capillary malformation

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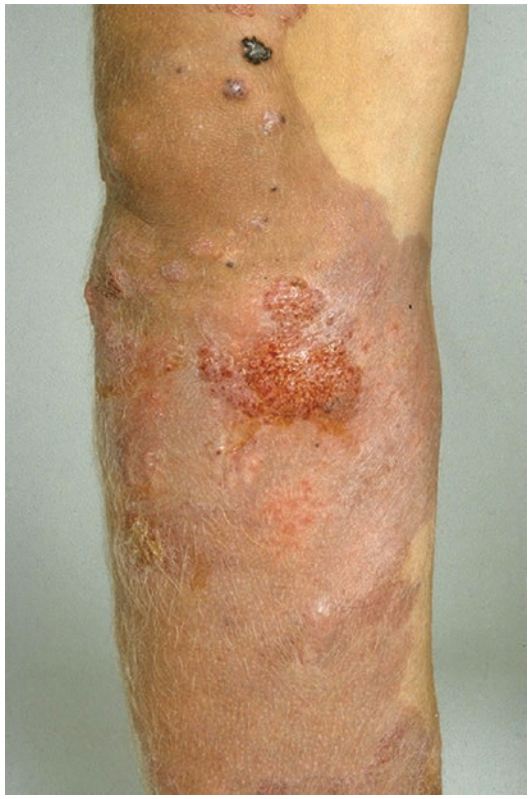

Fig. 25.2 Capillary malformation with overlying dermatitis

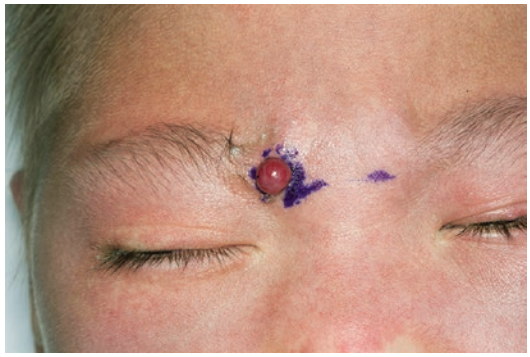

Fig. 25.3 Pyogenic granuloma within a capillary malformation

and dressings. In addition to dermatitis, CMs may develop pyogenic granulomas, which are friable benign vascular growths (Fig. 25.3).

Cutis marmorata telangiectatica congenita (CMTC) is considered to be a type of congenital capillary malformation that has a reticulate pattern or erythema and telangiectasia (Fig. 25.4), possibly with associated atrophy and ulceration. It most often involves an extremity but may be present anywhere on the body [5]. While the finding is most commonly seen in isolation, in some rare cases, associated signs such as limb and digital abnormalities and aplasia cutis may be present.

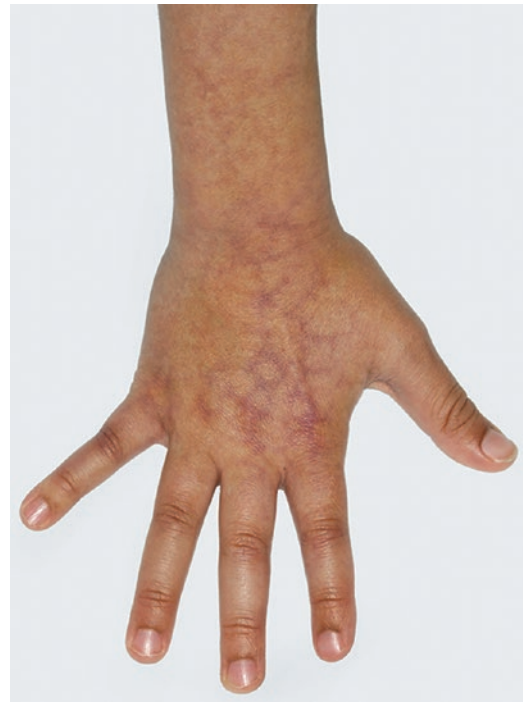

Fig. 25.4 Cutis marmorata telangiectatica (CMTC) of the hand

Venous malformations are another more common type of vascular malformation that may affect any location of the body but may commonly have skin manifestations. When visible upon skin examination, they appear as blue, soft, compressible masses just under the surface of the skin (Fig. 25.5); at times, firm papules called phleboliths may be palpable within the malformation, particularly in areas with more venous stagnation. There may be some overlying telangiectasias. Venous malformations are also prone to several complications. Inflammation of the superficial veins, known as superficial thrombophlebitis, may be a complication of superficial venous malformations [6]. These can be painful but are often

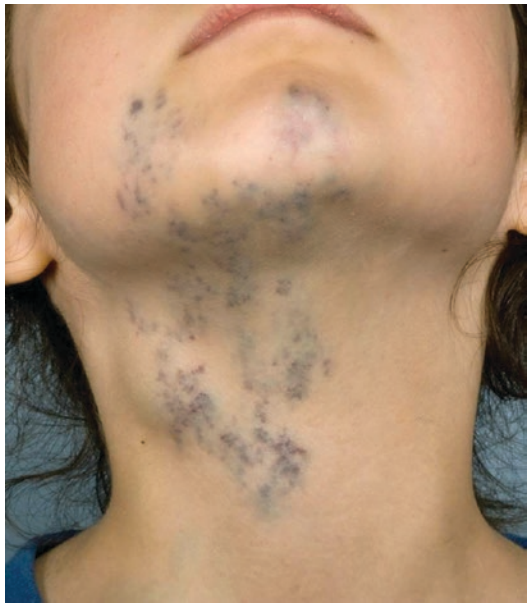

Fig. 25.5 Venous malformation on the neck with subcutaneous bluish hue

self-limited. Chronic venous insufficiency can coexist with venous malformations, especially those of the lower extremities. In cases of severe chronic venous insufficiency, changes of stasis dermatitis, as well as erosions and ulcerations, may occur [7–9]. In this situation, ulceration may be very difficult to heal and can predispose patients to developing cellulitis.

Lymphatic malformations may also have a cutaneous component. When present on the skin, lymphatic malformations consist of translucent "frog-spawn"-type of papules that may be isolated or that may form a cluster. Often, they have a "tip of the iceberg" quality, and there is a deeper associated portion of the lymphatic malformation. Cutaneous portions of lymphatic malformations may be transiently red to violaceous in color as there is often hemorrhage into them (Fig. 25.6). They may also intermittently or chronically leak fluid, predisposing the patient to developing cellulitis or soft tissue infections. In addition, when surgical excision is attempted on a lymphatic malformation, it is not uncommon for papules of lymphatic malformation to develop around the surgical site, whether or not there was any cutaneous involvement prior to surgery.

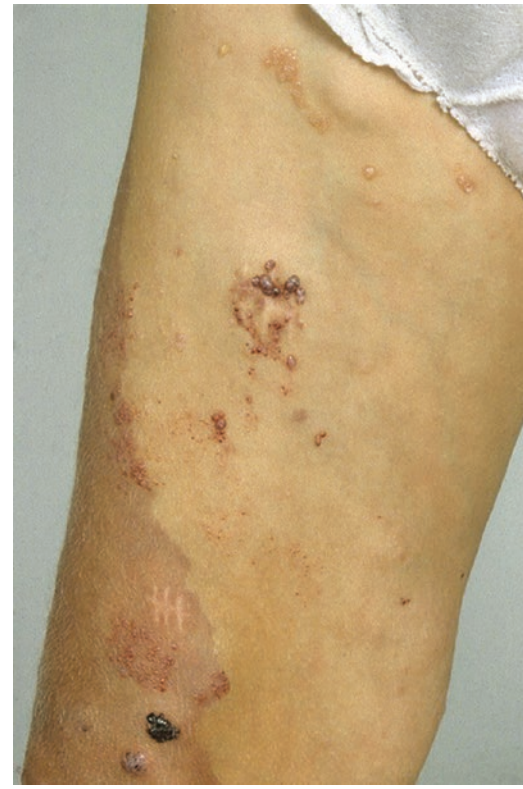

Fig. 25.6 Capillary venolymphatic malformation on the leg. Note the clustered translucent lesions of lymphatic malformation on the upper leg and hemorrhagic lesions more inferiorly

Arteriovenous malformations (AVMs) may also involve the skin. The most common scenario is in capillary malformation-arteriovenous malformation syndrome (CM-AVM), where the most common presentation is that of small, flat AVMs present on the skin (Fig. 25.7).

Skin cancer is a rare complication of vascular malformations but has been reported in a handful of cases. They may arise as a complication of long-standing ulceration or occur spontaneously within the malformation. Squamous cell carcinomas are more likely to arise in long-standing ulcers and in locations of prior radiation therapy [8]. Their diagnosis requires a high index of suspicion and may require multiple biopsies, a need that must be balanced with the tendency toward difficult healing. A handful of cases of basal cell carcinomas have been reported to have spontaneously developed within CMs [10, 11].

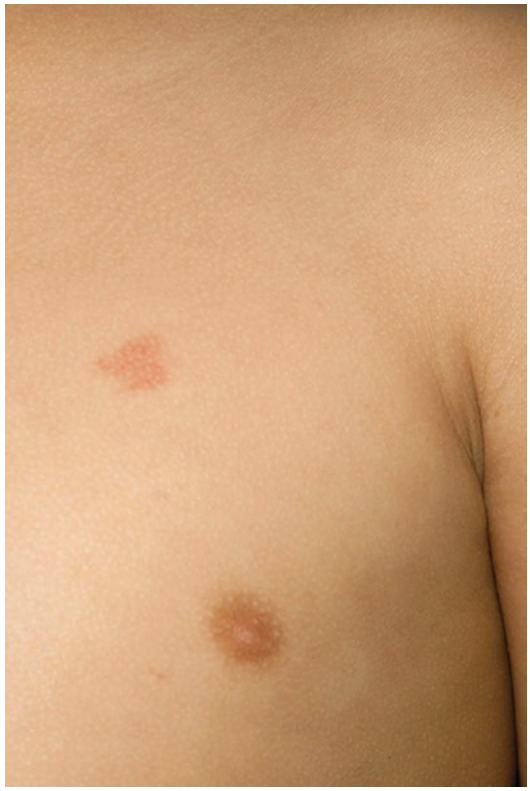

Fig. 25.7 Capillary malformation in CM-AVM syndrome

Angiosarcoma, an aggressive vascular tumor, has been described in one Klippel-Trenaunay patient [12]. Skin cancer in the setting of vascular anomalies should be managed by a surgeon experienced in managing these issues.

Treatment Considerations

All patients with vascular malformations involving some portion of the skin should be counseled on good general skin care practices. Bathing regularly with a gentle soap, in addition to once or twice weekly dilute bleach baths, can help to prevent infection in those that are prone to infection [13]. Additionally, the routine use of bland moisturizers can help to control xerosis and dermatitis that may be present overlying a CM. In some situations, a topical steroid medication may be necessary to treat dermatitis. Topical steroids are also effective, along with compression, in the treatment of venous stasis dermatitis. In addition, tinea pedis should be treated at the first sign of infection for those with lower extremity malformation as involved areas may be a nidus for the development of infection.

In some patients, the vascular malformation may be distressing because of its visibility and may result in poor quality of life This is especially true for malformations involving the head and neck [14, 15]. Cosmetic camouflage is a specialized type of cosmetic cover-up that can be very beneficial to those with changes on their skin that they wish to disguise. Children with facial vascular malformations noted significant improvement in quality of life with the use of cosmetic camouflage [16]. This should be considered in all patients with visible vascular malformations who are distressed by the appearance of their malformation.

In the case of pyogenic granulomas, surgical excision is most common. For smaller lesions, and especially those present on the head or neck of a child, surgical excision may not be optimal. In those situations, topical beta-blockers have been used successfully in the treatment of pyogenic granulomas [17].

For superficial thrombophlebitis, treatment is most commonly supportive as it is self-limited, usually resolving in 1–2 weeks. Compression and nonsteroidal anti-inflammatory medications are often sufficient. In recurrent cases, medications such as aspirin or anticoagulation have been used, in addition to sclerotherapy or vein stripping [18].

Pulsed dye laser (PDL) is the most common treatment for CMs [19–22]. The PDL targets hemoglobin. Its use is indicated to lighten PWS, treat blebs and bleeding, and treat or prevent hypertrophy of vascular lesions. Laser therapy with a PDL normally requires multiple treatments spaced 1–2 months apart. CMs that are thicker, on darker skin, and those that are not on the face or neck tend to respond less well than those which are thinner, on lighter pigmented skin, and are located on the face or neck; in the latter scenario, 70–90% lightening may be expected [19–22]. Complications of pulsed dye laser may include pain, crusting, blisters, and bruising in the short term and pigmentary changes or scarring in the long term [20]. The pres-

ence of inflammation and dermatitis can increase the risk of laser-associated side effects [3]. CMTC is not usually treated with the PDL as it can lead to complications of erosion, ulceration, and scar.

Some cutaneous malformations may not respond to the pulsed dye laser. In those cases, other lasers may be considered such as the neodymium:YAG [23], CO2 [24], and Alexandrite lasers, as well as intense pulsed light [25]. In lymphatic malformations that become thick and bulky, CO2 laser is often used and favored over surgical excision. However, this must be done with caution due to the risk of suboptimal healing and lymphatic fluid leakage [24]. Side effects of pigmentary changes and mild scarring may be seen with the CO2 laser.

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26

Facial, facial skeleton and dental considerations in vascular malformations

Teresa M. O

Level of evidence: treatment	Low
Evidence	Case series; case reports

Diagnostic and Treatment Considerations

Vascular malformations of the head and neck may affect all tissue layers including skin, subcutaneous fat, muscle, mucosa, and bone. These lesions are associated with:

- Soft tissue overgrowth and enlargement.
- Primary skeletal involvement with malformation.
- Vascular lesions may also mold or misshape skeletal structures by virtue of their mass. This is referred to as a secondary mass effect which leads to either thinning or hypertrophy of the adjacent bone.

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All vascular malformations – venous, lymphatic, capillary/port-wine stain, and arteriovenous – may present with associated soft tissue and skeletal abnormalities [1–5].

Soft Tissue Overgrowth

A discussion of skeletal changes would be incomplete without addressing the symbiotic relationship to the adjacent soft tissues. Soft tissue expansion of the vascular malformation may cause distortion of the adjacent skeletal structures due to a mass effect. This is especially common in lymphatic and venous malformations [2, 6]. Examples involving the mandible and dentition include:

- Glossoptosis preventing normal occlusion during the first few years of life will result in an open-bite deformity (the tongue and mandible have a symbiotic growth relationship).
- Long-standing glossoptosis will also affect the development of the lower jaw and lead to abnormal dentition.
- A large, long-standing lymphatic malformation of the parotid gland and parapharyngeal space will anteriorly displace the ramus of the

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mandible, increasing the distance between the mastoid process and the mandible. In extreme cases, the temporomandibular joint can be dislocated and displaced anteriorly out of the condylar fossa, and a pseudarthrosis will form at the site of the mandibular head.

- A large long-standing submandibular mass will displace and flare the angle of the mandible outward resulting in winging of the mandible [6].

Oral Cavity and Dental Considerations

Gingiva

The gingiva is affected in all types of vascular malformations.

Capillary malformations (CM, port-wine stains/PWS) cause erythematous staining and hypertrophy in the segmental distribution of the lesion [7]. For example, if the cutaneous V3/mandibular distribution is involved, there will likely also be mandibular gingival staining (Figs. 26.1). The discoloration itself is usually not a problem; however, patients with staining have a higher risk of future orodental issues [8]; approximately 47% of patients have gingival staining, and of these, 20% will report gingival hypertrophy in the same area of staining [9]. This leads to an increase in the depth of periodontal pockets leading to an inability to clean around the tooth and periodontal disease. One-third of patients also have spontaneous gingival bleeding. In addition to this, patients with Sturge-Weber syndrome (see separate chapter in this textbook) may require antiepileptic medication [10]; a common side effect of phenytoin and phenobarbital is gingival hypertrophy, which can further worsen symptoms [11, 12].

Other reported orodental concerns by patients and their dentists include malocclusion, widened interdental spacing, prolonged inflammation after dental procedures, gingivitis, ulcers, and maxillary and mandibular hyperplasia. No patients reported increased mobility of the teeth [8].

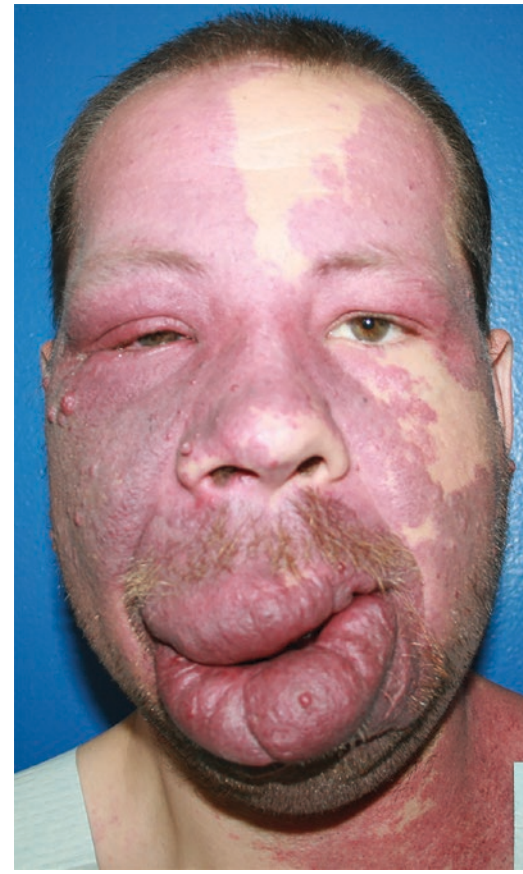

Fig. 26.1 Male with Sturge-Weber syndrome and bilateral facial CM. Both the upper and lower lips show soft tissue hypertrophy

Bony overgrowth tends to continue throughout the natural growth cycle of the bone, after which it may slow down. Soft tissue overgrowth, on the other hand, tends to continue into adulthood and even later. The underlying cause is most likely due to a somatic genetic abnormality leading to activation of downstream cellular growth pathways [13–15].

The principal goal is prevention of tooth loss and maintenance of good oral care, with emphasis on primary oral hygiene. Gingival hypertro-

phy may be treated with removal of the excess gum tissue around the tooth. This can be accomplished with surgical removal. Methods used have involved direct excision or CO2 laser ablation (Fig. 26.2). Laser has the added benefit of intraoperative hemostasis. Care should be taken not to damage the enamel of the tooth. Although CMs comprise small capillaries, bleeding is easily managed with local epinephrine. The erythematous stain itself is typically not treated.

Venous malformations of the gingiva may bleed with manipulation such as dental flossing, brushing, or during dental procedures. These lesions respond to neodymium-doped yttrium aluminum garnet laser (Nd:YAG) therapy. If more than one treatment is required, the sessions are spaced 4–6 weeks apart.

Microcystic lymphatic malformations involving gingiva and oral mucosa will manifest as small 1–2 mm clear or hemorrhagic vesicles. These areas can be treated with surgical excision, CO2 laser ablation (similar to PWS gingival removal), or transmucosal sclerotherapy such as bleomycin injections.

Arteriovenous malformation of the gingiva is typically seen with AVM involvement of the adjacent bone. There is secondary hyperemia of the overlying gingiva. The adjacent teeth are often loose, and gingival bleeding may occur spontaneously or during dental manipulation. Granulation tissue is often found in involved areas and may lead to hemorrhage, which can be severe at times. Small pyogenic granulomas may appear, and these should be ablated using bipolar electrocautery. These gingival changes will usually dissipate after successful treatment of the primary nidus (Fig. 26.3).

Oral Cavity Mucosa

Involvement of the buccal mucosa by all types of vascular malformations may produce a mass causing inadvertent biting and trauma to the inside of the mouth. Depending on the depth of the lesion, this area is treated with surgical excision, sclerotherapy, laser, or a combination of these modalities.

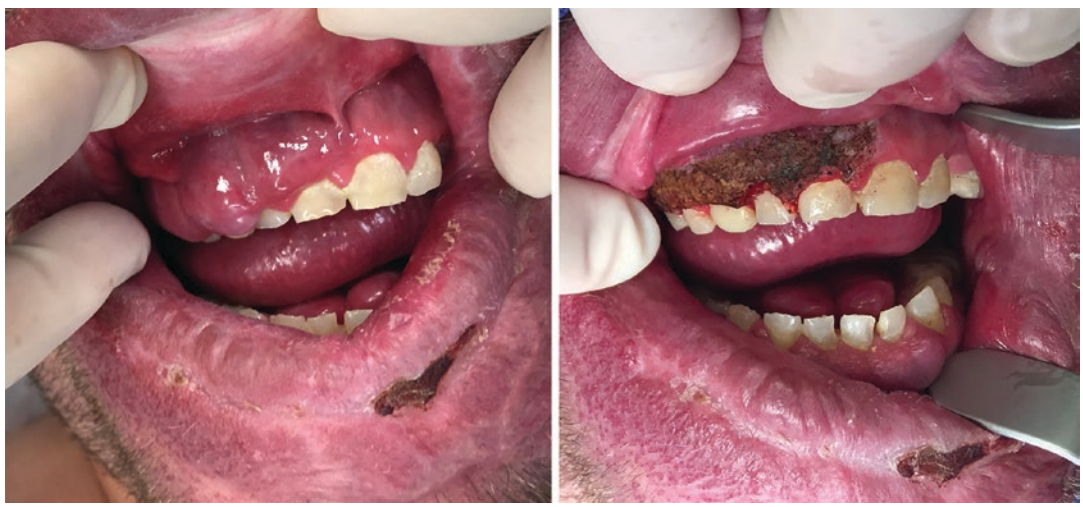

Fig. 26.2 Same patient from Figure 26.2. Right maxillary gingival hypertrophy secondary to port-wine stain. Immediately after CO2 laser ablation. Note emergent dental show and increased interdental spacing. Area will remucosalize over a 1–2 week period. Also evident is lower gingival, tongue, and floor of mouth hypertrophy with elevation of the tongue

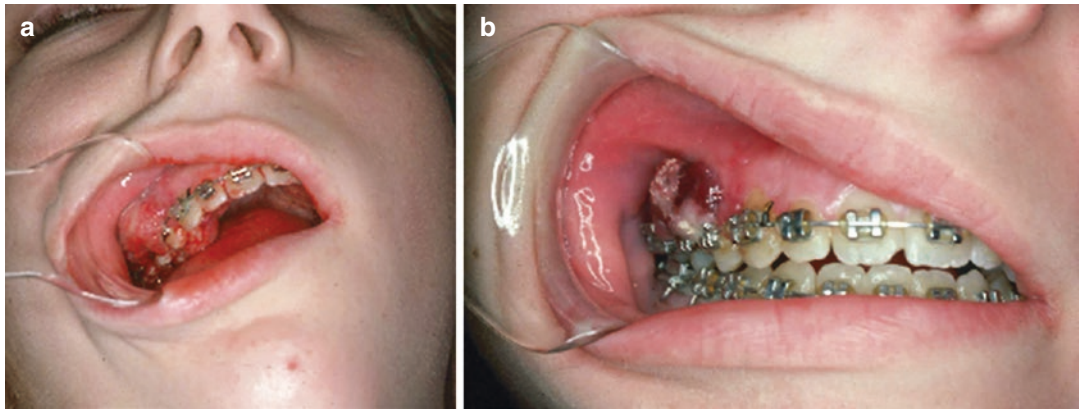

Fig. 26.3 (**a**) 15-year-old female presented with severe bleeding after placement of orthodontics. (**b**) After liquid embolic glue (n-BCA). Note the marked shrinkage of the AVM following embolization. (Photos courtesy of Alejandro Berenstein, MD)

Tongue

Capillary malformations (CM, port-wine stain, PWS). Sixty percent of patients with portwine stains will present with soft tissue overgrowth [9]. Port-wine stain involvement of the tongue may lead to partial macroglossia. This is treated with tongue reduction surgery. Oropharyngeal hypertrophy may lead to obstructive sleep apnea (OSA); surgical procedures used to treat OSA are appropriate here such as uvulopalatopharyngoplasty (UPPP), adenotonsillectomy, and tongue base reduction.

Venous malformations commonly involve the tongue. If the tongue is of a normal size with a focal area of involvement, Nd:YAG or direct transmucosal sclerotherapy is appropriate. In cases of frank macroglossia, tongue reduction surgery may be necessary [16]. In order to prevent massive intraoperative bleeding, atraumatic Satinsky clamps should be employed proximal to the lines of excision. Once the reduction has been completed and the edges of the resection sutured, the clamps can be released. Using this technique, a bloodless reduction can be accomplished. Once the macroglossia has been reduced, residual disease may be treated with a Nd:YAG laser or sclerotherapy (Fig. 26.4).

Lymphatic malformations of the tongue are typically microcystic. Macroglossia is a common finding. Tongue reduction will correct this and, if done early enough, prevent open-bite deformity and the dental problems that accompany macroglossia. In rare instances, there may also be macroglossia with mandibular hypertrophy and no malocclusion [17]. Active mucosal disease responds well to transmucosal sclerotherapy with bleomycin or ablative procedures such as coblation or CO2 laser ablation [18, 19]. Although there are no published data directly comparing sclerotherapy with ablative techniques, bleomycin sclerotherapy appears to have advantages including that there is no scarring or loss of taste buds and deeper, diffuse penetration [18].

Arteriovenous malformations (AVM) of the tongue are typically unilateral, though they may appear to expand across the midline. Patients initially present with dysarthria, dysphagia, and foreign body sensation in the pharynx. Eventually, ulceration and hemorrhage will ensue. Embolization has been proposed; however, embolization alone has not been shown to cure AVMs, temporizing them at best. Treatment should involve embolization followed by surgical resection via an intraoral or external approach. If a large segment is involved, reconstruction with microvascular free tissue transfer may be necessary [20, 21].

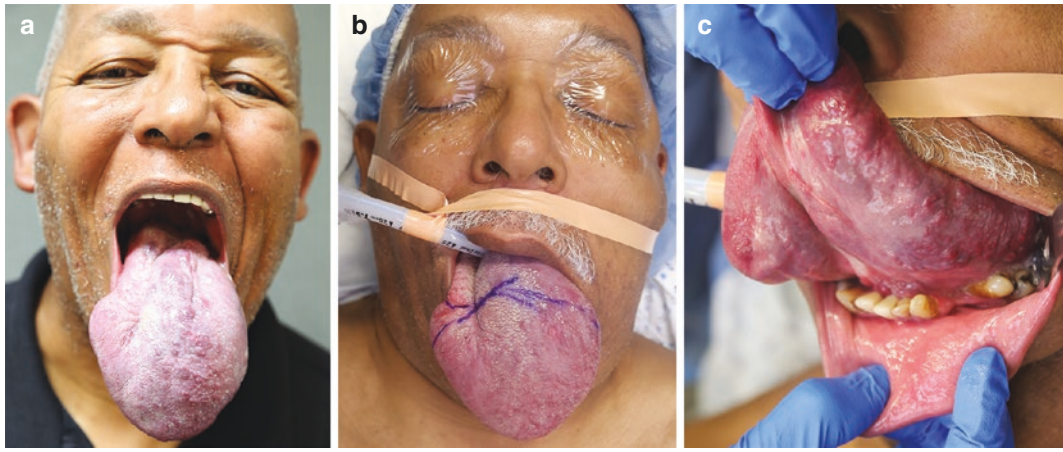

Fig. 26.4 60-year-old male with tongue VM causing macroglossia and mandibular skeletal remodeling. Anterior open-bite deformity and anteriorly canted dentition. (**a**) Macroglossia. (**b**) Planned midline wedge excision. The use of Satinsky clamps precludes bleeding during the procedure. (**c**) Anteriorly sloping dentition

Lip

The lip is the most commonly affected site in both capillary malformations and venous malformations [9]. AVMs and LMs may also involve the lip. A large, expanded lip may compromise oral competence, cause drooling, and affect speech intelligibility. In addition, expansion will cause asymmetry and aesthetic disfigurement. Techniques to correct these abnormalities include sclerotherapy and surgical reduction. Often, the lip is so expanded by the lesion that more than 30% of the horizontal dimension of the lip can be removed without microstomia.

Dentition

Alveolar bone hypertrophy leads to changes in dentition. The eruption pattern of the teeth may be affected by the hypervascular, enlarged milieu. Unilateral bony hypertrophy may lead to canting of the occlusal plane, malocclusion, and differential wear of the tooth surface. In some situations, there may be bony erosion and thinning with compromise of the dental roots, change in angle of teeth, and dental loss (Figs. 26.4c and 26.5c). As described above, interdental spacing may also be affected.

Direct Bony Involvement

The maxilla and mandible are derived from membrano-cartilaginous bone which ossifies partly into the cartilage and partly into the membranous bone. The bony layers include an external cortical bone and a layer of diploic cancellous bone. It is within this specialized vascular cancellous layer that an intraosseous vascular malformation will grow and expand.

Direct bony involvement is more commonly seen with arteriovenous malformations. Involvement of the cancellous bone will result in expansion of the bone (Fig. 26.6). Panoramic radiographs may show honeycombed radiolucency; CT will also show multicystic radiolucency [22]. The adjacent gingiva is often very vascular, and pyogenic granulomas are frequent. The teeth overlying the lesion are often loose. Hemorrhage from these areas is common and can be profuse (Figs. 26.7 and 26.8).

Patients with bony involvement suffer functional as well as psychosocial effects in the same way as other children with facial deformities. Malocclusion and open-bite deformities lead to oral incompetence with sialorrhea, difficulty with mastication, and dysarthria. Inability to close the mouth affects the protective effects of salivary flow over dentition, leading to changes in bacterial

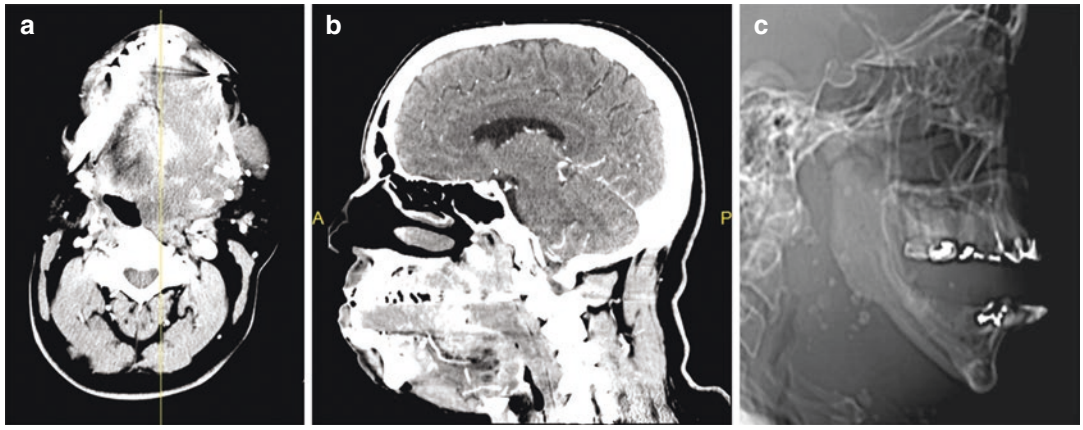

Fig. 26.5 (**a**, **b**) Axial and sagittal CT images show expanded tongue, submental, and submandibular VM with anterior displacement of left mandibular body and airway deviation to the right. Arrow denotes phlebolith which is pathognomonic for VM. (**c**) Lateral scout X-ray clearly shows obtuse gonial angle and anteriorly directed mandibular teeth (arrow)

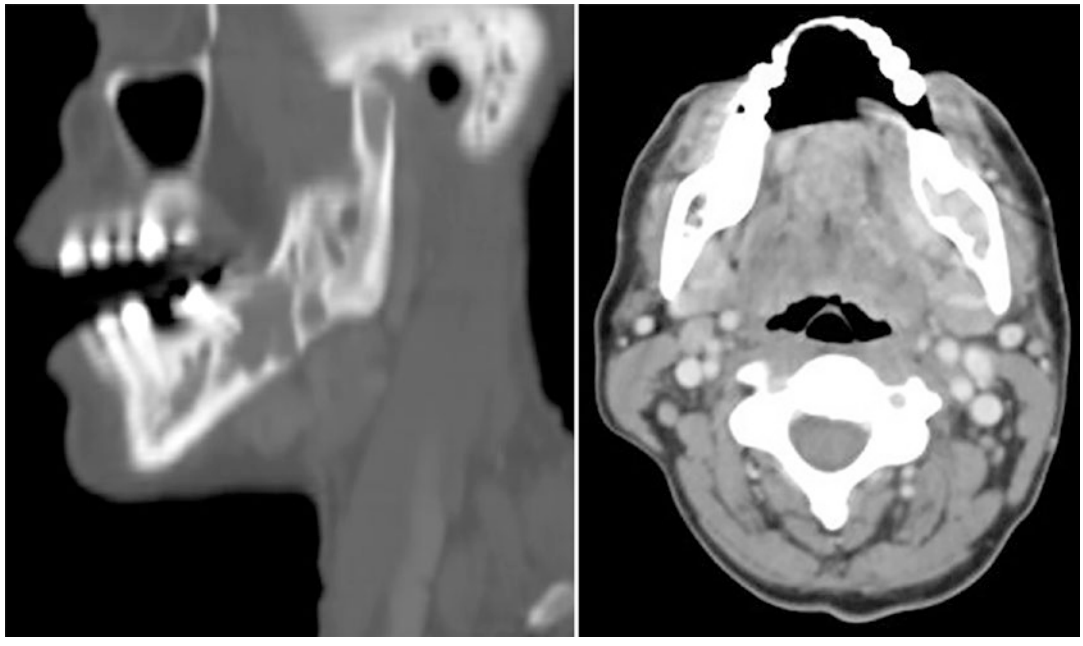

Fig. 26.6 Sagittal and axial CT of mandibular AVM showing radiolucency and lytic areas of the bone. Dental root disappears into body of AVM (Images courtesy of Jared Steinklein, MD, and Deborah Shatzkes, MD, Lenox Hill Hospital, New York, NY)

flora and dental caries. Difficulties with communication and physical appearance affect self-esteem and negatively impact psychosocial development. This negative impact can be profound.

Lymphatic malformations can sometimes involve adjacent bone although this is not common. The precise cause of bony hypertrophy is not fully understood. Padwa et al. showed evidence of abnormal lymphatic channels within hypertrophied cancellous mandibular bone in 67% of their surgical specimens [23]. PIK3CA gene mutations have been implicated in tissue overgrowth and have been found in LM specimens. Enlargement of the bone will create diastemata of the lower teeth with a "picket-fence" pattern (increase in the interdental spacing).

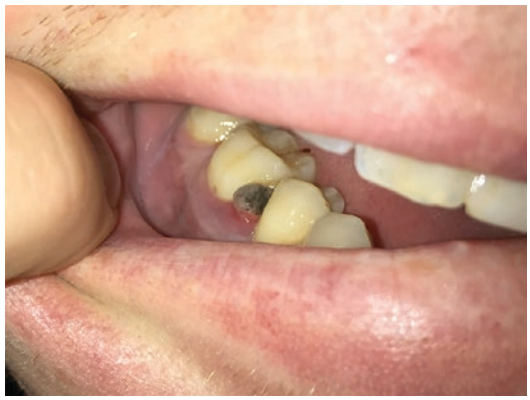

Fig. 26.7 Right mandibular AVM with hyperemic gingiva and pyogenic granuloma

Focal venous malformations can also be intraosseous. In a study of 115 patients with VM, 14% of patients had involvement of the bone, tendon, or joint. Five percent had sole bony involvement [24]. These are not common and are incorrectly referred to as "intraosseous or bony hemangiomas." Clearly this is a misnomer, because true hemangiomas are infantile or congenital hemangiomas found in children. Radiologically, panoramic radiographs may show an ill-defined, noncorticated, multilocular radiolucent area. Computed tomography (CT) may show expansion of the mandibular body with intact cortices. The radiographic appearance may vary from a multilocular appearance to a sunburst pattern and thus may incorrectly be misdiagnosed as a solid tumor [25].

If focal, and not causing a contour defect, these lesions may be treated with intraosseous sclerotherapy alone. However, if there is a contour deformity, surgical excision is necessary [26]. The resulting defect is repaired with either plating or bone grafts or a combination of these techniques [27]. Complete excision with recon-

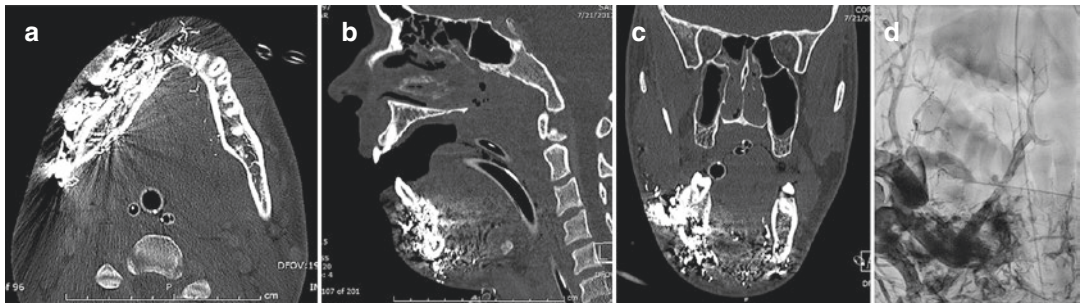

Fig. 26.8 CT imaging ((**a**) axial, (**b**) sagittal, (**c**) coronal) of same patient with right mandibular AVM immediately after embolization. Note extensive lytic disease in cortex and marrow of the bone. (**d**) Angiogram images of nidus. Patient presented with life-threatening bleed from right gingival pyogenic granuloma

struction is usually curative. However, if reconstructive options are not available, sclerotherapy with partial excision is an option, with the understanding that there is some risk of recurrence [2, 28]. Also, although sclerotherapy will inactivate vascular malformation, any bony expansion of the cortex and contour deformity will remain.

It is difficult to assess the primary cause of dental caries. In many cases, toothbrushing with minor bleeding, or fear of hemorrhage, will limit routine dental care leading to poor oral health [29]. Many dentists may also be reluctant to perform routine oral care. In high-flow AVMs, dental caries/abscesses may also be secondary to poor oral hygiene, steal syndrome (relative hypoxia of tissues), or embolization of the bone with secondary ischemia of dental roots.

In one series of 81 patients, 28% of patients with head and neck AVMs were noted to have bony involvement. The maxilla and mandible were the most common locations in the craniofacial skeleton. In one-third of these cases, the bone contained the nidus [30]. Imaging of mandibular AVM may show hypertrophy secondary to hyperemia or direct involvement with osteolysis and cortical thinning [31]. Patients with isolated bony disease may first present with life-threatening bleed during routine dental extraction [29]. Dental X-rays may indicate a radiolucency with lytic lesions. Vascular lesions should remain on the differential for lytic bony lesions (Fig. 26.6).

Similar strategies for treatment of soft tissue AVMs can be applied to bony AVMs [32, 33]. However, unlike focal AVMs which may be treated with surgical resection alone, embolization alone, or a combination, bony AVMs are treated with embolization alone or combined therapy. In preplanning treatment, an MRI/MRA or CTA gives an indication of the extent of disease and possibly location of the nidus. Preoperative or intent-to-treat angiography is the gold standard for mapping the AVM and treating the nidus. Focal mandibular AVMs respond well to super-selective embolization with glue or *n*-butyl cyanoacrylate (n-BCA). Evidence of new bone growth has been shown after treatment [31, 34]. Postembolization surgical excision 24–48 h later may be curative if only bony disease is present. Concomitant bony and soft tissue reconstruction may also be performed [27, 33]. Defects less than 5 cm may be repaired with nonvascular bone grafts (e.g., iliac crest). However, larger defects require vascularized bone grafts. Fibula grafts have been used widely in the adult and pediatric mandibular reconstruction literature as an ideal substitute due to long length and ability to be segmented and contoured [27]. Encouragingly, growth of the neomandible in a growing child has been reported [35].

Mandibular Skeletal Abnormalities with Orthognathic Deformities

Mandibular skeletal deformities secondary to vascular malformations have been most extensively reported in association with LMs. In a quantitative analysis of mandibular deformities in patients with cervicofacial LMs, the major deformities noted (Figs. 26.9 and 26.10) were:

1. Winging or flaring of the mandibular rami outward
2. Increase in the gonial angles leading to an open-bite deformity
3. Anterior displacement of the condylar process out of the temporomandibular fossa
4. Relative increase in anterior dentoalveolar height [6]

Mandibular prognathism and some of the above deformities have been noted in many other studies as well [1, 4, 6, 23, 37].

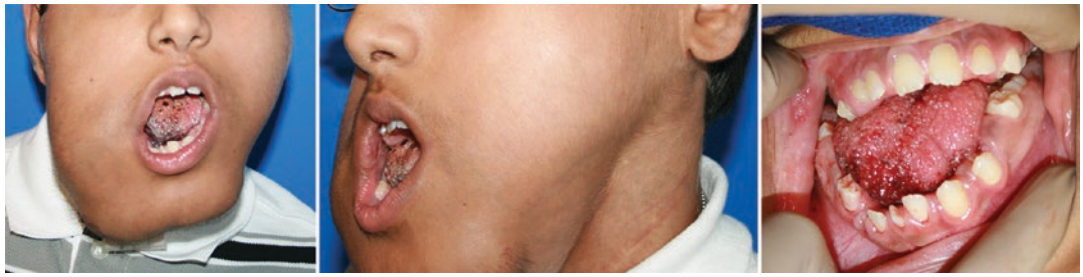

Fig. 26.9 Teenager with bilateral lower face LM. Note, multiplanar occlusal deformity with obvious open bite, widened dental spacing, and microcystic tongue disease. Tracheotomy is in place

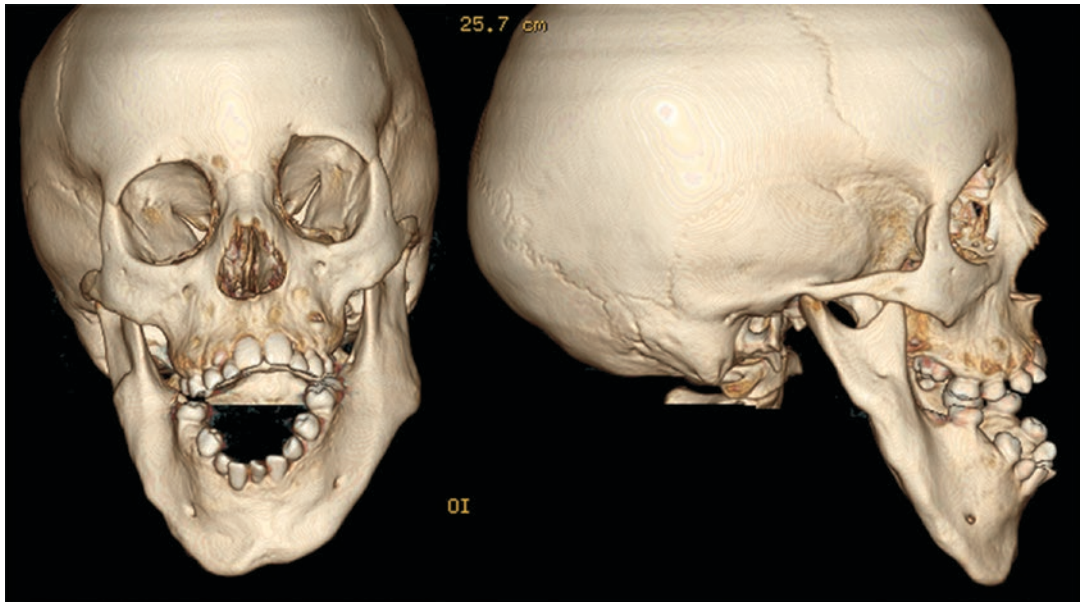

Fig. 26.10 Three-dimensional CT of same patient. Mandibular rami are winged outward, the gonial angles are obtuse, and there is a prominent open-bite deformity

Treatment of Orthognathic Abnormalities

Orthognathic surgery is necessary in a subset of patients with extreme skeletal changes, typically involving lymphatic or venous disease (Fig. 26.11) [36]. If there is evidence of malocclusion, or lateral bite deformities, complete dental X-rays, cephalometric studies, and 3D-CT and 3D modeling assist in orthodontic and orthognathic planning (Fig. 26.12). A 3D-CT is invaluable to assess the occlusal bony relationships of the maxilla and mandible. A three-dimensional medical model can be used to preplan osteotomies and shape plates prior to the surgery (Fig. 26.13).

Traditionally, orthognathic surgery is delayed until the dental roots have fully erupted and the

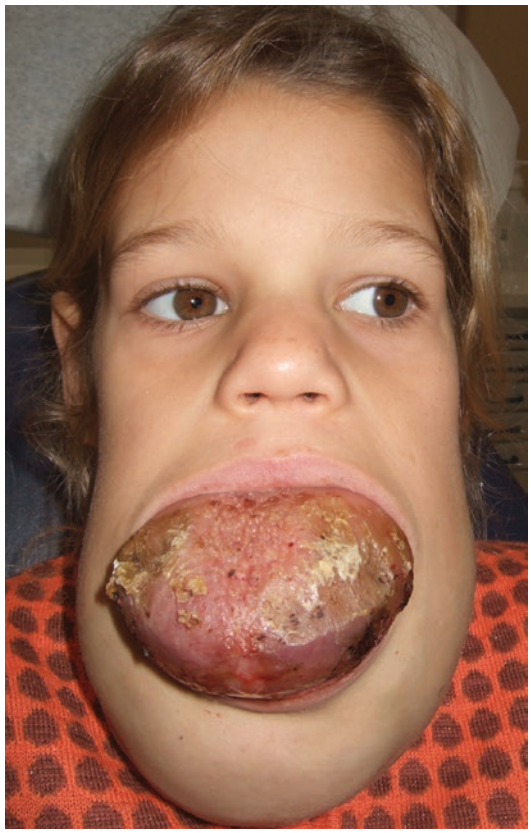

Fig. 26.11 11-year-old female with macroglossia (microcystic LM) after several sclerotherapy treatments

facial skeleton has completed its growth. In the case of congenital LM-related skeletal hypertrophy, the social and functional impacts are very high, and early intervention may be warranted. Surgery has been reported previously, with some recidivism [37]. It has been suggested that the failure of such surgeries might decrease with recent advances in plating technology [6]. Also, all soft tissues should be fully debulked prior to beginning skeletal reduction to decrease the impact of mass effect on regrowth of the bone.

If orthognathic surgery is contemplated, presurgical orthodontics may be helpful. The surgical approach will depend on the presentation. Mandibular prognathism alone can be treated with bilateral mandibular osteotomies. Depending on the amount of prognathism and open-bite deformity, the maxilla and mandible may both be addressed to "split the difference" and to lessen the distance for mandibular retrusion or maxillary advancement (Fig. 26.14). LeFort I maxillary osteotomy via an intraoral approach is combined with mandibular osteotomies (vertical ramus, gonial angle, or bilateral sagittal split). In advocating for early surgery, it is important to note that the growth center of the mandible is located at the condyle and not

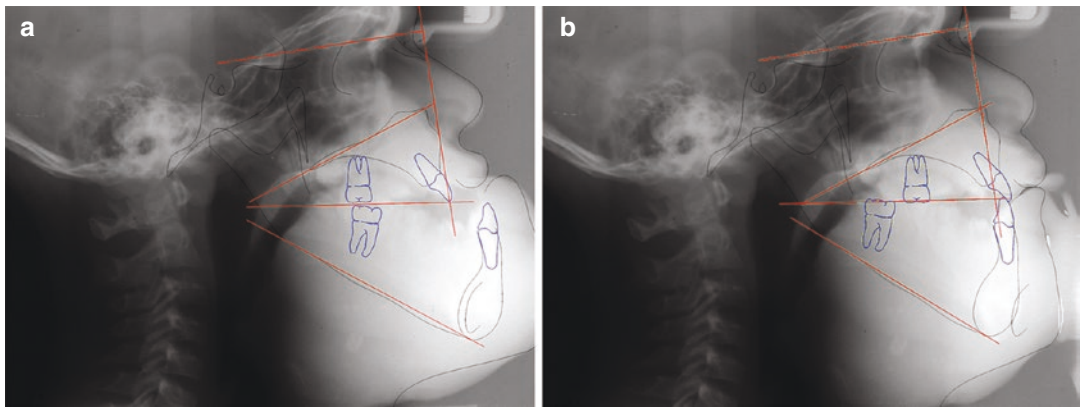

Fig. 26.12 Lateral X-rays show class III malocclusion and increased dentoalveolar height of lower third of the face, as well as anterior protrusion of maxillary teeth. (**a**) After tongue reduction, location of existing dental and skeletal structures. (**b**) Prior to soft tissue and bony correction. Lines show preplanning of maxillary advancement and mandibular retrusion

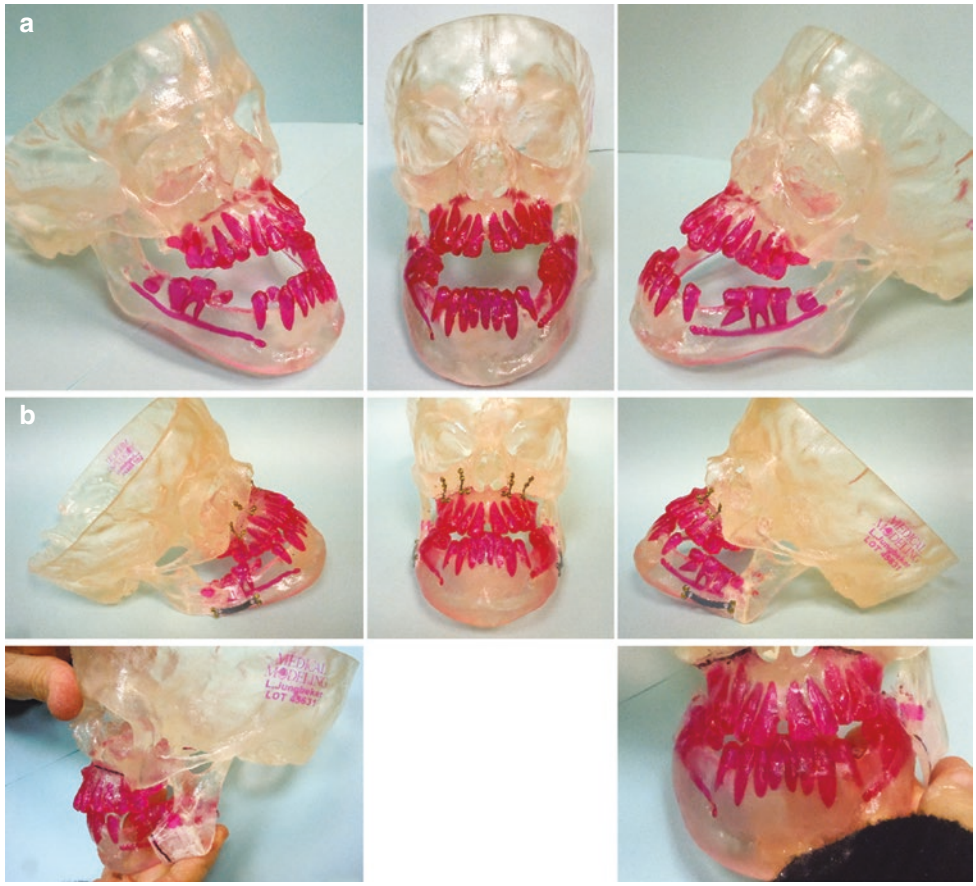

Fig. 26.13 (**a**) Three-dimensional medical model of same patient with class III malocclusion. (**b**) Preplanned osteotomies and initial location of plates resulting in improved class I occlusion

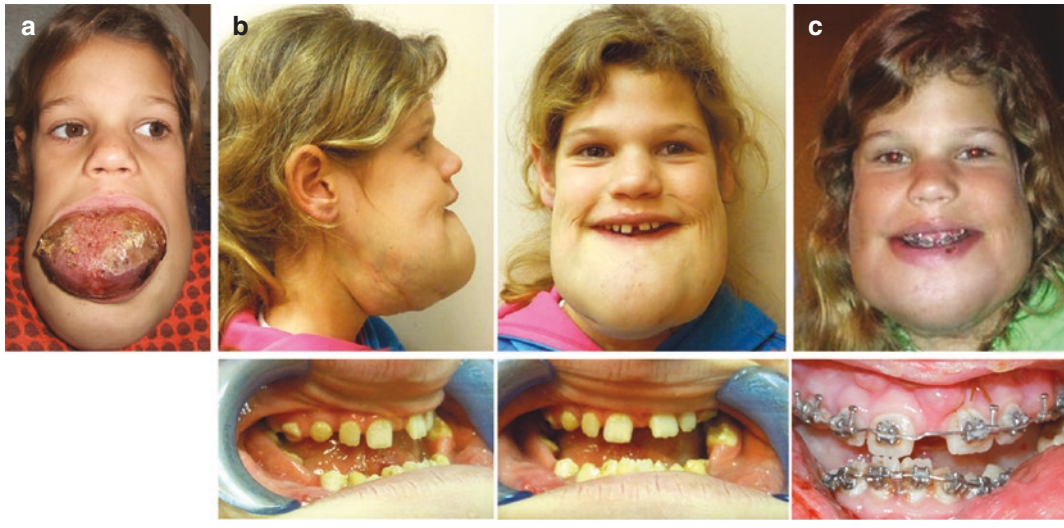

Fig. 26.14 (**a**) Same 11-year-old female with cervicofacial LM and macroglossia. (**b**) After tongue reduction. (**c**) After orthognathic surgery with LeFort I maxillary osteotomy and bilateral extraoral vertical ramus osteotomies. Patient requires further elastic therapy and more soft tissue surgery. She had been treated with presurgical orthodontics

the distal portions of the mandible. Also, many patients have widespread dental caries requiring dental restoration or even implants. In the case of AVM, dental loss is not uncommon. The functional advantages of normal occlusion on speech, feeding, and self-esteem are immeasurable.

In summary, vascular malformations of all types may directly or indirectly involve the craniofacial skeletal. The treatment is multidisciplinary and multimodal.

To assist the reader in gaining familiarity with available evidence, the following rating system has been used to indicate key references for each chapter's content:
***: Critical material. Anyone dealing with this condition should be familiar with this reference.
**: Useful material. Important information that is valuable in in clinical or scientific practice related to this condition.
*: Optional material. For readers with a strong interest in the chapter content or a desire to study it in greater depth.

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Oral Cavity and Oropharynx

27

Joseph L. Edmonds and Sheena Pimpalwar

Level of evidence: treatment	Low
Evidence	Case series, case reports, non-site-specific systematic reviews

Three vascular lesions are commonly encountered in the oropharynx. These are hemangioma, venous malformation, and lymphatic malformation. A fourth type of vascular anomaly, arteriovenous malformation, may also occur in the oropharynx but only as an extension of a nearby larger lesion. As such, it is better considered outside of the anatomic subsection of the oropharynx. Each of these three types will be discussed separately with respect to phenotype, etiology, natural history, and treatment.

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Hemangioma

Diagnostic Considerations

Hemangiomas are usually readily identified by the typical "strawberry" appearance; these are the so-called superficial hemangiomas (Fig. 27.1). A deep oropharyngeal hemangioma may have this typical appearance masked by intact mucosa and may appear as a mucosally covered bluish mass. In these unusual cases, MRI with contrast is likely the most useful radiologic evaluation to help diagnose a hemangioma, because it can differentiate a hemangioma from a vascular malformation. The ultimate method of differentiating all diagnostic possibilities is with a histologic study of the tissue. A biopsy should be done whenever there is a possibility that the lesion in question is a malignant tumor, though in most instances, a biopsy is not necessary as there is usually ample epidemiologic, clinical, and radiologic information that can facilitate a reliable diagnosis.

Another special diagnostic situation arises when a child presents with extensive hemangiomas, sometimes referred to as segmental hemangiomas. This term relates to the approximate distribution that may correspond to sensory innervation patterns and may also involve the oropharynx (Fig. 27.1) [1]. The acronym PHACE [2] can help the clinician recall the findings seen in these

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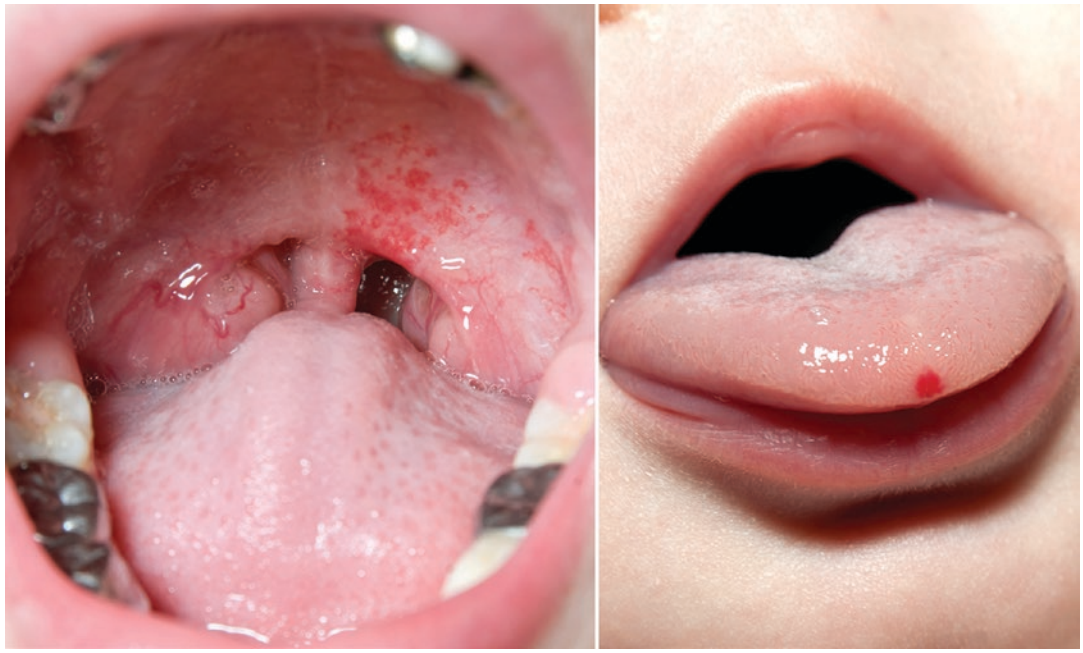

Fig. 27.1 Infantile hemangioma in the oral cavity. Left, large segmental lesion on left soft palate; right, small superficial infantile hemangioma on tongue. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

children. Please see Chap. 28 for further information on this syndrome and Chap. 6 for more details on segmental hemangiomas.

Oropharyngeal hemangiomas are often not seen initially and may not be clinically detected until well into the proliferative phase. The presenting symptom can often be poor oral intake and pain as these lesions frequently ulcerate largely because of the wet nature of the oral cavity and the mechanical irritation induced by feeding.

Special Considerations in Treatment of Oropharyngeal Hemangiomas

Local wound care consisting of topical and oral antibiotics, topical steroids, barrier creams, and wound dressings are the mainstay of treatment, though the latter two options are challenging in the oral cavity and oropharynx [3]. Treatment to minimize the ongoing proliferation of the hemangioma remains necessary. Management of pain is also very important, particularly while focusing on the ulceration as described below. Reports of the use of topical recombinant platelet-derived growth factor (beclapermin gel, Regranex) also seem promising, though site-specific evidence in the oral cavity and oropharynx is lacking and most studies of this drug are older [4].

Ulceration is a controversial indication for cutaneous and mucosal laser therapy. The yellow light emitted by pulsed dye lasers is selectively absorbed by hemoglobin and melanin. In an ulcerated hemangioma, the laser light does not need to pass through the skin and the melanin within the skin to reach the hemangioma; therefore, the risks of scarring due to absorption by melanin are considered lessened. Some series have demonstrated this benefit [5]. Recent advances in the flashlamp-pulsed dye laser include longer wavelengths, longer pulse durations, and the very important dynamic cooling of the surface tissues [6]. These advances have allowed for higher energy treatments, deeper penetration, fewer complications, and better overall responses. These advances have led to increased confidence in using flashlamp-pulsed dye laser for the treatment of select non-ulcerated cutaneous lesions. The KTP and Nd:YAG lasers have been employed for intralesional therapy by

using bare fibers to deliver high energies to the deep components of the lesions. One series of 22 infants demonstrated resolution in 91% of ulcerations within 2 weeks, using a dual-wavelength PDL and Nd:YAG laser [7]. These laser technologies are becoming more widely accepted and recognized for their usefulness. However, their application is not standardized and is limited by the experience of the practitioner.

Venous Malformation

Diagnostic Considerations

Craniofacial venous malformations cause symptoms dependent on location. They are almost always a cosmetic problem, and thrombosis often makes these lesions painful, impairing basic activities. MRI scanning is the single best modality to evaluate the three-dimensional complexity of a craniofacial venous malformation. Some patients will also have intracranial involvement; therefore, the initial study should always include an MRI of the brain. Coagulation studies should also be done, as these patients often have low-grade disseminated intravascular coagulopathy; however, this condition typically requires no therapy. Please see Chap. 21 for further general discussion of venous malformations.

Venous malformations are bluish-purple in color, raised, and easily compressible (Fig. 27.2). They may be confused on physical exam with a "deep" hemangioma, although an MRI should easily differentiate between the two. Often venous malformations will enlarge when dependent or straining/crying. Overtime they will gradually dilate, giving the appearance of a growing lesion. Pain is common with these lesions and is thought to be associated with formation of phleboliths.

Several syndromes are also included in the differential diagnoses of venous malformations:

1. Blue rubber bleb nevus syndrome. Affected patients have multiple cutaneous venous malformations and sometimes also have problematic

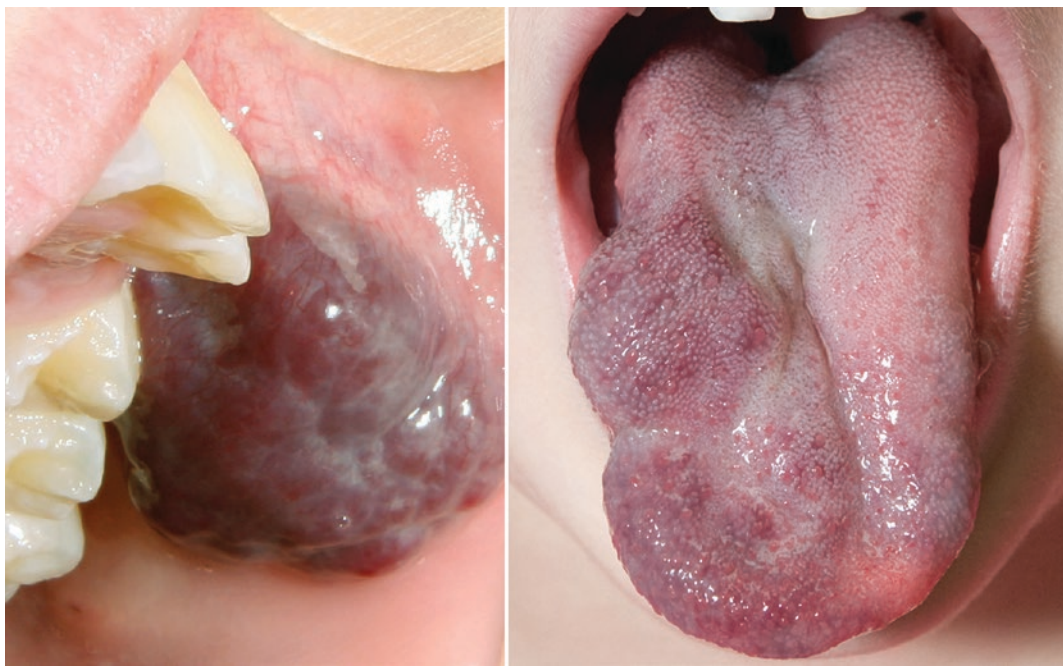

Fig. 27.2 Oral cavity venous malformations. Left, Localized venous malformation vestibulobuccal sulcus; right, venous malformation on oral tongue. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

gastrointestinal bleeding from intestinal lesions (please see Chap. 34 for details).
2. Maffucci syndrome. This syndrome of multiple venous malformations associated with enchondromas begins in adolescence. The skeletal lesions often degenerate into malignant tumors.

Treatment Considerations

Compression

Compression therapy is often used for venous malformations. It is possible to use compression therapy in the face with specially constructed garments, but they are expensive, and chronic use is a compliance problem. The oral cavity and oropharynx, in contrast, are not generally amenable sites for this treatment modality.

Sclerotherapy

Sclerotherapy is the mainstay of treatment for oropharyngeal venous malformations. Sclerosants are effective for these lesions because the sclerosant will stay in the lesion or can be made to stay in the lesion with compression of the outflow pathway. While a wide variety of sclerosants have been studied, alcohol-based agents are most commonly used. Sodium tetradecyl sulfate (STS) has been described as the most cost-effective [8]. The sclerosant, in any formulation, is intended to do extensive endothelial damage, inducing clotting and eventual vascular obliteration. Complications of sclerotherapy can occur, most commonly skin or mucosal necrosis. Previous case series have also demonstrated benefit for sclerotherapy combined with intralesional electrochemical therapy [9]. Bleomycin can be used instead of alcohol for venous malformations when swelling or necrosis is a concern. Its application has also been combined with electroporation in recent studies [10].

While response rates to sclerotherapy are often quite high, the concern for oral or pharyngeal edema and resulting airway compromise or dysphagia is real. Airway protection with temporary tracheostomy may be worth considering, particularly if several rounds of treatment are planned [11].

It is important to point out that while sclerotherapy is probably the best-studied treatment modality for venous malformations, systematic reviews have not been particularly revealing due to lack of standardized protocols or reporting [12].

Laser Therapy

Treatment with the Nd:YAG laser can be used in selected cases. The goal of laser therapy is also to cause endothelial injury sufficient to lead to coagulation and partial resolution. Transcutaneous therapy with dynamic cooling and percutaneous laser use avoids damaging the skin. It is very beneficial at the lip vermilion and in treating the cutaneous component of large buccal oropharyngeal lesions. This therapy can be used to eliminate the cutaneous component, while the deeper intraoral component can be managed with sclerotherapy. The mucosal component of lesions can also be effectively managed with the Nd:YAG laser. Improvements in color and size have been reported in uncontrolled case series, though response rates appear variable and some scarring has been reported [13]. This laser is likely best used in a noncontact fashion using the laser at 4–6 W. Replacing the thin venous malformation involved mucosa with a firmer layer of laser-induced scar which may be beneficial in and of itself, facilitating future dissection of the mucosa if resection is contemplated. Any bleeding encountered during laser work can usually be managed with pressure.

Surgical Therapy

Surgical therapy of oral and oropharyngeal venous malformations is generally reserved for resection of previously sclerosed areas for improved cosmesis or function, for lesions that respond poorly to sclerotherapy, or for recurrent lesions. Surgical therapy can be done in conjunction with sclerotherapy to decrease the incidence of recurrence. In this setting surgery is done 24–48 h after sclerotherapy and is typically bloodless. Surgical therapy may also be necessary for dental malocclusion or other secondary problems after primary sclerosant or laser management.

Lymphatic Malformation

Diagnostic Considerations

An MRI scan with contrast is the typical and best means for evaluating patients with a presumed lymphatic malformation. A lymphatic malformation is hyperintense on a T_2-weighted image and has only a slight increase in intensity on a T_1-weighted image. A lymphatic malformation does not enhance on gadolinium contrast images. Based on the radiographic appearance of the size of the lymphatic spaces located within the lesion, lymphatic malformations are then broadly categorized as either macrocystic or microcystic. Another clinically relevant descriptor of the lesion is "diffuse" or "localized" (confined to one anatomic region). These descriptors can be used in conjunction with the terms macrocystic or microcystic. Therefore one might describe the following phenotypes: localized macrocystic, diffuse macrocystic, localized microcystic, and diffuse microcystic. Figure 27.3 shows an example of localized microcystic disease. There are often patients that overlap these phenotypes, but if the lesion predominately fits the description, it remains clinically useful both prognostically and in assigning likely efficacious treatment.

The increased use of prenatal ultrasound has led to the diagnosis of patients with lymphatic malformations in utero. This development has led to some treatment dilemmas at very early stages of life, particularly with regard to airway and feeding concerns in children with oral cavity or oropharyngeal involvement. When children with massive lymphatic malformations are born, they may require an "EXIT procedure" (ex utero intrapartum treatment), in which the airway is stabilized by intubation, bronchoscopy, or tracheostomy. This approach has been described in several reports and is nicely laid out by Stefini and colleagues [14]. Immediate, extensive dissection or resection of the lymphatic malformation is not

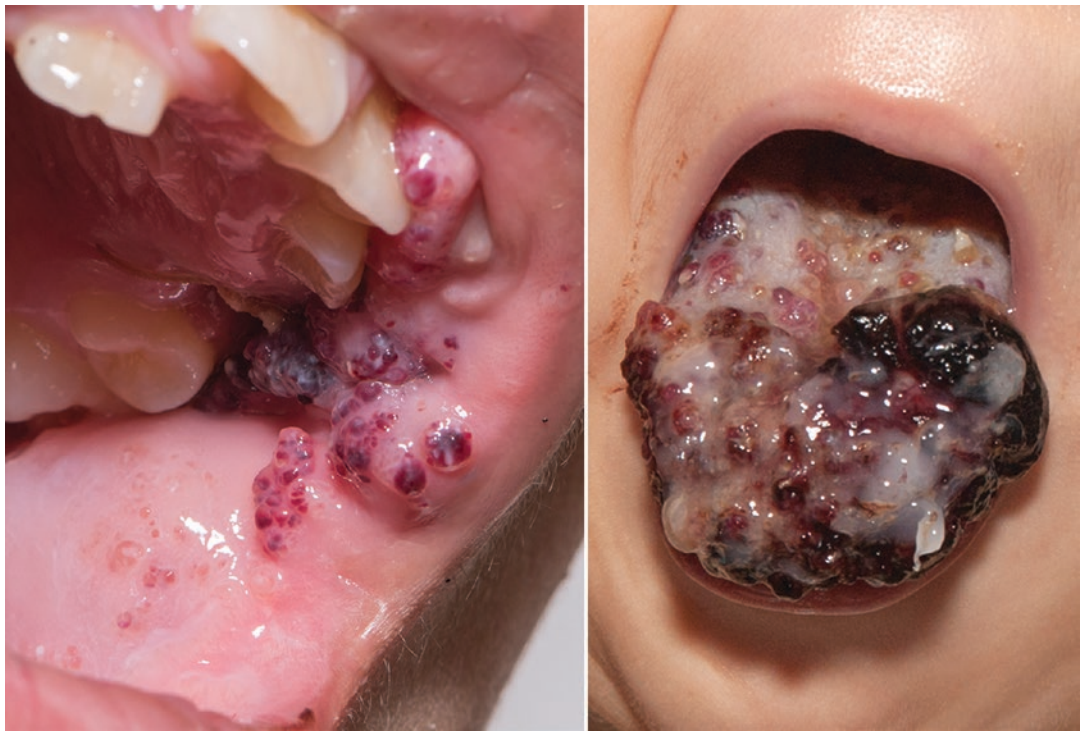

Fig. 27.3 Mucosal lymphatic malformation of the vestibulobuccal region and tongue. Both areas demonstrate tissue overgrowth. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

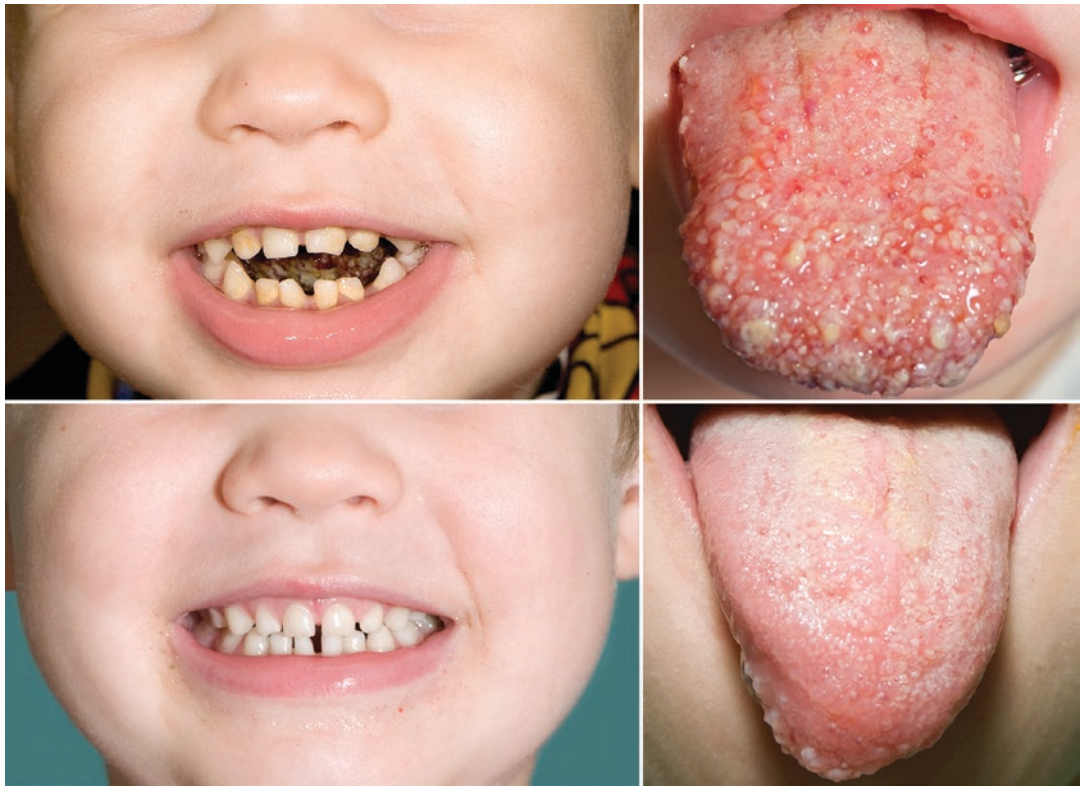

Fig. 27.4 Lymphatic malformation induced tongue overgrowth influenced dental bite (top). Tongue reduction surgery resulting in resolution of anterior open bite (bottom). (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer). (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Scott Manning)

preferred; such procedures may be more likely to result in surgical complications.

Diffuse microcystic cervicofacial and oropharyngeal disease often results in adjacent mandibulomaxillary bony hypertrophy, the mechanisms of which are discussed in Chap. 20. This may result in abnormalities such as malocclusion and an open bite (Fig. 27.4). After the child has matured, this hypertrophy can be managed with mandibular osteotomy and, if necessary, Le Fort osteotomies.

Treatment Considerations

Multiple treatments have been employed for the management of these lesions, which indicates that none have been demonstrated to be completely effective [15, 16]. It is helpful to consider treatment of the localized and diffuse groups separately. A secure airway is essential in patients with diffuse microcystic cervicofacial disease. It is often necessary to perform a tracheostomy to avoid acute respiratory problems, particularly for large obstructing lesions. Similarly, gastrostomy tube placement may be considered in children who experience feeding problems due to oral or oropharyngeal lymphatic malformations. As described below, these measures allow the child to grow and develop, providing time for planning and staged treatment of the malformation.

Localized Malformations

The treatment of localized lymphatic malformations relies essentially on sclerosis or surgery, except in some specialized locations. Both surgery and sclerosis are very effective for localized lesions; choosing between these two modalities depends on the surgeon's experience and the specifics of the patient's situation (Fig. 27.3).

1. *Oral care and dental hygiene*—Data in this area are lacking, but experience suggests that oral care is both challenging and important in these patients. Poor oral and dental health may precipitate local inflammation, which may lead to inflammation and enlargement of adjacent lymphatic malformation components as well. On the other hand, routine toothbrushing, flossing, and preventive dental care may induce pain or bleeding [17], particularly if the tongue or gingiva is involved. Common oral functions such as chewing may be impaired by poor dental health as well as bony overgrowth and malocclusion caused by these lesions. Furthermore, many dental care providers may be reluctant to manage these complex patients.
2. *Sclerosis*—Numerous agents have been used in an effort to sclerose these lesions, including boiling water, tetracycline, cyclophosphamide, sodium tetradecyl sulfate, bleomycin, doxycycline, alcohol, and OK-432. OK-432 is a medication developed in Japan with extensive worldwide use. In the United States, the medication remains under FDA investigation. The medication, a streptococcal culture treated and killed with penicillin, incites an immune response (delayed hypersensitivity reaction) in the location of the lymphatic malformation. Typically, after treatment with OK-432, the lesion swells and subsequently resolves. While it may be necessary to inject the medication several times for some lesions, an inflammatory response may predict better treatment outcomes [18]. Doxycycline, also a widely used an efficacious agent, may cause significant transient swelling and also typically is painful [19]. Bleomycin and its relative pingyangmycin are excellent choices for some oropharyngeal lesions as swelling is limited compared to other agents. Pain is usually not a significant component of the postinjection symptoms [20]. Bleomycin has been used successfully in small series for transmucosal treatment of parapharyngeal and retropharyngeal lymphatic malformations as well as for tongue lesions alone or in combination with other agents [21–23]. Similarly, the use of pingyangmycin has been described for microcystic tongue lesions [24].
3. *Laser or coblation resurfacing*—Other localized lesions may present within the tongue. The tongue may be involved with small blebs that bleed and become infected. An old term used to describe this type of lesion is "lymphangioma circumscriptum." These lesions can be managed with CO_2 laser resurfacing or the use of a coblator [25]. The effects are temporary.
4. *Tongue reduction surgery*—The tongue can also become massively enlarged due to lymphatic malformation. Children with this condition cannot be managed with laser and generally require tongue reduction surgery (Fig. 27.4) [26].
5. *CO_2 laser surgery*—Hypopharyngeal involvement may managed with a CO_2 laser to open lesions and debulk airway obstruction. Radiofrequency ablation has also been reported as an alternative to laser, particularly because it may allow submucosal reduction of the malformation [27, 28]. Sclerotherapy is another option but often requires collaboration with the ENT surgeon and the interventional radiologist for access to accurately inject. A tracheostomy tube should be considered for this type of airway surgery.

Diffuse Malformations

The management of diffuse cases is much more complex and may be a lifelong endeavor. For this reason, initial management decisions should not increase the morbidity of the disease by causing cranial nerve injury. The first goals of managing diffuse oropharyngeal disease are to allow for an adequate airway and feeding, which will often require a tracheostomy and possibly a gastrostomy. Surgical management is the mainstay of treatment for these lesions. If complete resection is not possible, it may be helpful to manage different anatomic areas as individual problems. The mylohyoid muscle is a typical boundary used to divide these massive lesions into several "zones." It is also advisable to approach the divided components of the total malformation from the "top down," if possible. For instance, the physician should attempt to deal with the tongue before

the floor of mouth and then approach the neck; this approach will prevent superior swelling of the untreated zone. Additionally, children with diffuse cervicofacial disease will also frequently require maxillo-mandibular reconstruction due to overgrowth of the facial bones.

It is also advisable in the care of children with diffuse disease to involve a child psychiatrist. It is likely that these children will have long-term morbidity, and a means for dealing with the psychosocial implications is essential. Previous studies have demonstrated significant functional impact of these lesions on critical areas such as breathing- and feeding-related functions, oral care, pain, and bleeding [29].

To assist the reader in gaining familiarity with available evidence, the following rating system has been used to indicate key references for each chapter's content:
***: Critical material. Anyone dealing with this condition should be familiar with this reference.
**: Useful material. Important information that is valuable in in clinical or scientific practice related to this condition.
*: Optional material. For readers with a strong interest in the chapter content or a desire to study it in greater depth.

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Part VI

Vascular Anomaly Syndromes

PHACE Syndrome

28

Deepti Gupta and Kristine Rosbe

Genetic diagnosis	No
Genetic etiology	Not known
Level of evidence: treatment	Medium
Evidence:	Case series, expert opinion

Diagnosis

Phenotype and Variation

A small number of children have large facial infantile hemangiomas (IH) with associated structural anomalies of the brain, cerebral vasculature, cardiovascular system, eyes, and chest wall (Fig. 28.1). In 1996, Frieden et al. proposed the acronym PHACE syndrome (OMIM no. 606519), to delineate a neurocutaneous disorder that is now diagnosed by published consensus criteria (Table 28.1) [1, 11]. IH associated with PHACE syndrome tend to have a characteristic appearance. They are large, greater than 5 cm in diameter, and segmental, meaning that they cover a territory rather than arise from a single focal point [2]. Segmental IH associated with PHACE syndrome involve four distinct facial patterns; segment 1 (frontotemporal), segment 2 (maxillary), segment 3 (mandibular), and segment 4 (frontonasal) [3]. These segments are embryologic patterns arising from the neuroectoderm and correspond to the development of specific areas of the skin and soft tissue. The various segments are associated with varying degrees of associated abnormalities, with frontotemporal segment, segment 1, being at highest risk for cerebrovascular and ocular abnormalities, segment 3 at highest risk for ventral defects, and segment 2 being at the lowest risk for associated PHACE anomalies [4–6]. The morphology of the segmental IH associated with PHACE syndrome can be a solitary confluent plaque or a cluster of smaller papules coalescing into a discrete plaque (Fig. 28.2). In the newborn period, there may be a faint pink/red patch resembling a capillary malformation or a pale vasoconstrictive area or telangiectatic patch. In some cases segmental IH can fail to proliferate, which can be described as reticular, abortive, or minimal growth [7]. Early on in the newborn period, IH can be misdiagnosed as capillary malformations due to their similar appearance (Fig. 28.2).

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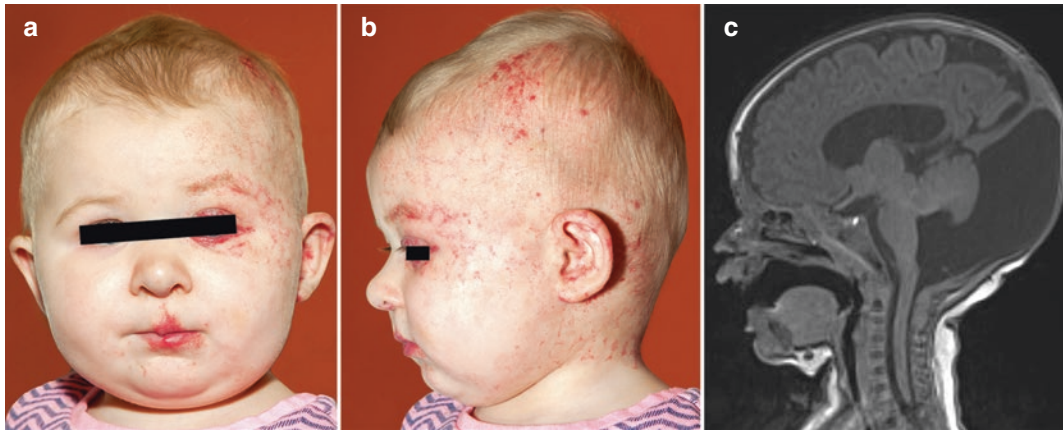

Fig. 28.1 Phenotypic features of PHACES: (**a**) and (**b**) large IH in segment 1, (**c**) cerebellar dysmorphology. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer). (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Scott Manning)

There has been increasing awareness that some patients meeting criteria for PHACE syndrome do not have characteristic large facial IH, but rather large segmental IH of the posterior scalp, neck, upper chest, and upper proximal extremity, no facial IH, or even small scalp IH [8, 9]. There have also been cases of large intraorbital IH without skin involvement that have been associated with PHACE syndrome [10]. Therefore, it has been recommended to screen all infants in the following groups for PHACE syndrome (Table 28.2) [11].

There have been over 300 cases of PHACE syndrome that have been described in the literature, and it is thought that PHACES occurs as frequently as the widely known neurocutaneous disorder, Sturge-Weber syndrome [5]. In a prospective study, infants with large cervicofacial IH (>22 cm^2) fully evaluated for PHACE had PHACE syndrome in 31% [6]. PHACE syndrome occurs more commonly in females at a rate of 9:1, Caucasian and Hispanic children, and term, singleton, and normal birth weight infants. Mothers of PHACE-affected infants do not have an increased incidence of placental abnormalities, preeclampsia, prior miscarriages, or other evidence of perinatal, prenatal, or demographic risk factors that was suggestive of environmental or other influences [5]. This differs from non-PHACE IH where risk factors include prematurity, low birth weight, and being the product of multiple gestations.

Etiology

Despite the known sex and race predilections, no specific genetic abnormality has been identified that causes PHACES. However, it is thought that the PHACES represents a developmental field defect occurring in early gestation with the hemangioma typically appearing ipsilateral to structural anomalies [12–18]. Further studies are needed to elucidate if there is a genetic basis associated with PHACE syndrome.

Natural History

While features of PHACE syndrome are well described, little is known about its natural history. Longitudinal study of PHACES patients has revealed new associated and long-term comorbidities; this has not generated evidenced-based screening and monitoring recommendations.

PHACE Syndrome and Arteriopathy and Risk of Stroke

Anatomic cerebral arterial variations (i.e., missing vessels, variable size, etc.) are the most common extracutaneous manifestation of PHACE syndrome occurring in 77% of all subjects [19]. This variation in cerebral arterial vascular structure detected with MRI or CT imaging is thought to potentially result in ischemic stroke. PHACE-associated stroke was ipsilateral to large cerebral

Table 28.1 Consensus criteria for PHACES diagnosis

PHACE diagnosis consensus		
Organ systems	Major criteria	Minor criteria
Arterial anomalies	Anomaly of major cerebral or cervical arteries[a]	Aneurysm of any of the cerebral arteries
	Dysplasia of the large cerebral arteries	
	Arterial stenosis or occlusion with or without moya-moya collaterals	
	Absence or moderate-severe hypoplasia of the large cerebral or cervical arteries	
	Aberrant origin or course of the large cerebral or cervical arteries except common arch variants such as bovine arch	
	Persistent carotid-vertebrobasilar anastomosis (proatlantal segmental, hypoglossal, otic, and/or trigeminal arteries)	
Structural brain	Posterior fossa brain anomalies	Midline brain anomalies
	Dandy-Walker complex	Malformation of cortical development
	Other hypoplasia/dysplasia of the mid- and/or hindbrain	
Cardiovascular	Aortic arch anomalies	Ventricular septal defect
	Coarctation of the aorta	Right aortic arch/double aortic arch
	Dysplasia[b]	Systemic venous anomalies
	Aneurysm	
	Aberrant origin of the subclavian artery with or without a vascular ring	
Ocular	Posterior segment abnormalities	Anterior segment abnormalities
	Persistent hyperplastic primary vitreous	Microphthalmia
	Persistent fetal vasculature	Sclerocornea
	Retinal vascular anomalies	Coloboma
	Morning glory disc anomaly	Cataracts
	Optic nerve hypoplasia	
	Peripapillary staphyloma	
Ventral/midline	Anomaly of the midline chest and abdomen	Ectopic thyroid hypopituitarism
	Sternal defect	Midline sternal papule/hamartoma
	Sternal pit	
	Sternal cleft	
	Supraumbilical raphe	
Definite PHACE		
Hemangioma >5 cm in diameter of the head including scalp		Hemangioma of the neck, upper trunk, and proximal upper extremity
Plus one major criteria or two minor criteria		Plus two major criteria
Possible PHACE		
Hemangioma >5 cm in diameter of the head including scalp	Hemangioma of the neck, upper trunk or trunk, and proximal upper extremity	No hemangioma
Plus one minor criteria	Plus one major or two minor criteria	Plus two major criteria

[a] Internal carotid artery, middle cerebral artery, anterior cerebral artery, posterior cerebral artery, or vertebrobasilar system
[b] Includes kinking, looping, tortuosity, or dolichoectasia

arteries. The incidence of acute ischemic stroke in PHACES is not known, but in a systematic review, they occurred on average at 13.6 months, with seizure and hemiparesis [20]. These patients usually had an incomplete circle of Willis and coexisting cardiac and aortic abnormalities, and 79% of patients had two or more abnormal cerebral arteries [20]. The consensus guideline group recommends categorizing PHACE patients based on initial MRA findings into three stratified risk

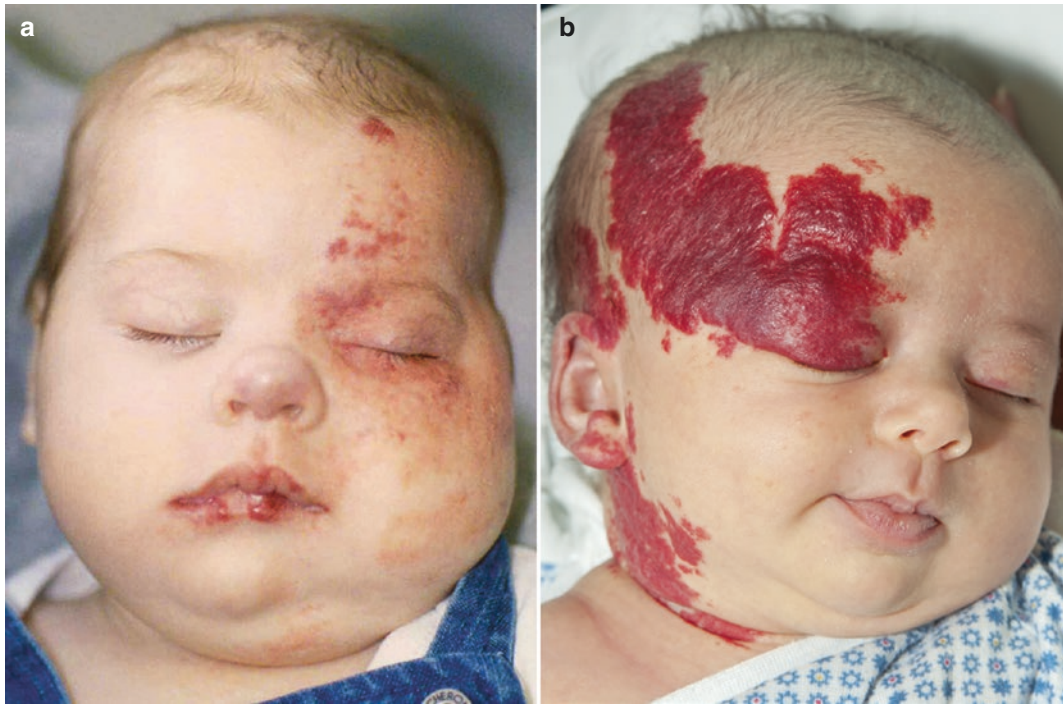

Fig. 28.2 Early (**a**) and late (**b**) appearance of IH in PHACES. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

Table 28.2 Infants that should have screening for PHACES

PHACE screening criteria
Segmental infantile hemangioma of the head
Infants with infantile hemangioma (smaller or lacking typical morphology or distribution) and characteristic anomalies found in PHACE (e.g., midline ventral defects, coarctation of the aorta, etc.)
Infants without cutaneous infantile hemangiomas with other characteristic anomalies found in PHACE (major criteria)

groups of low risk, intermediate risk, and high risk [11]. Controversy exists regarding systemic therapy with propranolol could be associated with a cerebral vascular accident, but there is no direct evidence to support this concern. In high-risk groups, consideration of lower doses and slower titration of propranolol has been suggested.

Headaches

Headaches are common in PHACE syndrome and can occur at an earlier age [21]. New onset of headaches should prompt an MRI looking for cerebral ischemia, and referral to neurology is recommended [11]. Consensus opinion is that the presence of cerebral arterial abnormalities in PHACE syndrome with headaches is a relative contraindication to headache medications with vasoconstrictive properties [11].

Hearing Loss, Speech, and Language

Conductive and sensorineural hearing loss has been associated with PHACE syndrome. Conductive hearing loss occurs when portions of large segmental IH involving the S1 and S3 segments extend into the ear canal, tympanic membrane, and middle ear. Sensorineural hearing loss is more common and can occur in the presence of normal newborn hearing screening; therefore PHACE patients should have behavioral hearing testing after 9 months of age and have assessment for normal receptive and expressive language development [22]. Hearing loss, sensorineural or conductive, if detected, should be evaluated by a pediatric otolaryngologist and audiologist and treated early to prevent developmental language delay [23, 49].

Airway Hemangiomas

The presence of segmental facial IH is associated with airway IH [5]. A recent study demonstrated that 29% of subjects with segmental IH arising in segment 3, also known as "beard distribution," had associated airway IH. Airway IH and PHACE syndrome have been present in 52% (12/23) of one cohort ($n = 23$) of PHACE patients. When patients had direct laryngoscopy, 86% of these PHACE patients had airway lesions, with 83% present in the subglottis, where 60% were circumferential and occupied over 50% of the airway lumen [25]. Medical treatment with propranolol was a sufficient treatment in 83% of airway IH, and one subject had surgical intervention.

A prospective multi-institutional study evaluated large facial IH ($n = 17$, defined as greater than 22 cm^2) and coexisting airway IH; eight (47%) subjects in this series had PHACE syndrome [26]. However, only 71% of subjects underwent rigid operative airway endoscopy, which is superior to flexible endoscopy for lower airway visualization. The airway IH findings were discussed in all 17 patients without a separate PHACE subset analysis. All symptomatic subjects who had operative endoscopy had subglottic involvement with two extending transglottically and one into the pharynx and oral cavity (Fig. 28.3). Additionally, these subjects had circumferential subglottic IH in 58% and focal lesions in the remaining 42%.

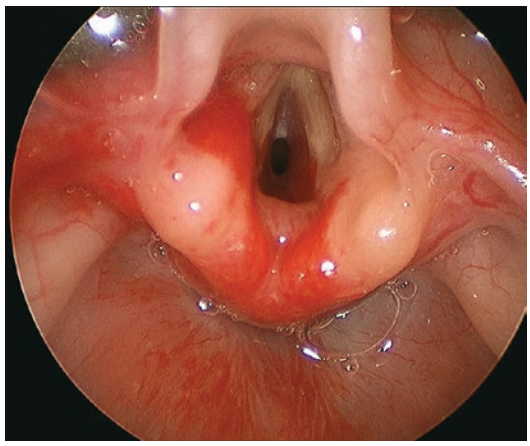

Fig. 28.3 Airway IH in PHACE patient extending transglottically and involving the subglottis circumferentially. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

A prepropranolol retrospective case series published in 2009 describes otolaryngologic considerations in PHACE syndrome and includes five subjects with PHACE, three of whom had airway IH [23]. These were hypopharyngeal and transglottic IH extending into the subglottis that were treated with CO2 laser destruction, intralesional steroid injection, and high-dose oral steroids.

There are currently no guidelines for airway evaluation in PHACE patients. Comprehensive airway evaluation should include operative direct laryngoscopy and bronchoscopy by a pediatric otolaryngologist with a pediatric anesthesiologist for PHACE patients with airway symptoms or for asymptomatic PHACE patients with large beard distribution cutaneous IH [27–30]. Office fiberoptic airway evaluation for PHACE patients can be performed, but critical areas frequently narrowed by IH are not adequately visualized with this technique [31]. Given the high rates of airway IH in symptomatic PHACE subjects, operative direct laryngoscopy and bronchoscopy in all PHACE patients with respiratory symptoms are recommended. It is also important to have a low threshold for airway evaluation in asymptomatic PHACE patients, especially those who are not receiving a systemic therapy for their cutaneous IH. More study is needed to identify the risk of airway IH in PHACE syndrome.

Endocrine Abnormalities

PHACE syndrome is associated with pituitary and thyroid disorders. Growth hormone deficiency is the most common, while hypothyroidism can occur in newborns or older patients, and hypopituitarism can cause delayed onset of puberty or late congenital adrenal insufficiency [32]. Therefore, changes in growth, height, and weight should be monitored in PHACES patients.

Dental Abnormalities

Dental enamel hypoplasia has been seen in PHACE syndrome, especially in the presence of intraoral IH, increasing risk of dental caries [33]. It is recommended that these individuals be referred to pediatric dentists by age 1 [11].

Psychological Impairment and Quality of Life

Adverse social and emotional impact of PHACE syndrome on parents and patients is real and should be followed longitudinally. Patient and family support groups can be an invaluable resource for families [34, 35].

Treatment

Evaluation for PHACE Syndrome

Formal guidelines for PHACE syndrome evaluation are not established; patients that have large head and neck IH or meet PHACE syndrome screening criteria should undergo a complete physical examination looking specifically for sternal defects or abdominal raphe. Contrast MRI of the brain will identify structural brain abnormalities in those patients not diagnosed on prenatal ultrasound. MRA of cerebral, head, neck, and aortic arch vessels will detect variation in vascular anatomy associated with PHACE syndrome. To avoid general anesthesia, echocardiogram can identify intracardiac or aortic arch abnormalities. As stated above appropriate airway, ear and eye evaluation is necessary [11]. Special consideration should be given to the frequency of MRI/MRA obtained with general anesthesia, due to potential anesthetic risks and impact on neurodevelopment in young children. A feed and wrap MRI/MRA, without anesthesia, could be considered.

Treatment of Hemangiomas

Propranolol is FDA approved for IH treatment and is first-line treatment for IH requiring treatment [36]. Side effects are covered in the IH chapter [37]. It has been recommended that propranolol be initiated cautiously in PHACE syndrome patients with arterial abnormalities [38]. Two PHACES patients at the beginning of the propranolol era treated with high-dose steroids and then propranolol experienced an acute ischemic stroke [20]. In another PHACES patient cohort ($n = 32$), in which seven were considered high risk for stroke, there were no problems with propranolol initiation or chronic administration [39]. In individuals with IH that are life-threatening or high risk for functional impairment, such as airway IH or periocular IH, propranolol could be considered prior brain imaging only after discussion with parents regarding potential risks. If needed, propranolol can be initiated at doses lower than 2 mg/kg/day and can be slowly up titrated in high-risk PHACE syndrome patients. Dividing the daily dose into three doses should be considered to minimize fluctuations in peak blood levels [11].

Airway Hemangiomas

Various treatment options exist for airway IH and sometimes multiple modalities are required. Observation with close monitoring is an option for asymptomatic IH [49]. Systemic steroids and propranolol are commonly used for airway-endangering lesions and can sometimes be used in combination when needed [24, 40–46]. Refractory airway IH may be treated with interferon or vincristine, but this has not been reported since propranolol has become a treatment option. Ablative carbon dioxide laser is beneficial for de-bulking of large airway IH but can lead to airway stenosis if multiple procedures are required [47]. Surgical excision and tracheotomy are generally reserved for cases that are resistant to other therapies [48, 49].

To assist the reader in gaining familiarity with available evidence, the following rating system has been used to indicate key references for each chapter's content:
***: Critical material. Anyone dealing with this condition should be familiar with this reference.
**: Useful material. Important information that is valuable in in clinical or scientific practice related to this condition.
*: Optional material. For readers with a strong interest in the chapter content or a desire to study it in greater depth.

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29 Hereditary Hemorrhagic Telangiectasia

Anthony B. Law and Greg E. Davis

Genetic diagnosis	Yes
Genetic etiology	Autosomal dominant, TGFbeta/BMP9 pathway (Endoglin, ACVL-1, SMAD4, GDF2/BMP9)
Level of evidence: treatment	Medium-high
Evidence:	Case series, randomized control trials, expert opinion

Diagnosis

Phenotype and Variation

Hereditary hemorrhagic telangiectasia (HHT), or Osler-Weber-Rendu disease, is an autosomal dominant disease characterized by multi-system telangiectasia, arteriovenous malformations (AVMs), and/or vascular dysplasia. The vascular anomalies of HHT are found as telangiectasia in the skin or mucosa of the aerodigestive tract. Aberrant vessels can also give rise to AVMs in visceral organs, such as the liver, lung, and brain. Mucosal telangiectasia usually leads to chronic often daily nose bleeds, while tissue-based AVMs can result in spontaneous aerodigestive tract or visceral organ hemorrhage. HHT clinical manifestations are heterogeneous within any given population, and lesions typically increase in severity with time. Severe presentations are particularly challenging for the provider and patient alike as symptoms are often refractory to traditional medical and/or surgical treatment regimens. In addition, the multi-system nature of HHT requires the coordination of many specialties including otolaryngology, hematology, pulmonology, hepatology, gastroenterology, neurological surgery, and dermatology.

Since its original description, the overall incidence has been reported to be between 1:10,000 and 1:1000. However, even the most liberal values are likely underestimates as subtle cases, often asymptomatic, evade clinical diagnosis. There is no preferential expression identified in regard to race, ethnicity, or gender. There are, however, small populations with increased incidence including Flyn County in Denmark, the Haut Jura region of France, and the Afro-Caribbean cohort in the Netherlands [1]. The allelic enrichment in these groups appears to be a consequence of their isolation and genetic homogeneity, i.e., the founder effect.

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Table 29.1 Diagnostic criteria for HHT

	Chromosomal locus	Protein	Comment
HHT type 1	9q33	Endoglin (ENG)	Higher incidence of cerebral and pulmonary AVM
HHT type 2	12q13	ALK-1	Increased incidence of GI and liver AVM. Increased incidence of PAH
HHT type 3	5	?	
HHT type 4	7	?	Extensive PAVM
JPHT*		SMAD4	Increased risk of colorectal and gastric cancer

? = unknown associated protein
* = juvenile polyposis-HHT

Table 29.2 Genetic mutations associated with HHT types

Criteria		
Epistaxis	Recurrent nosebleeds	1 point
Telangiectasia	Mucosal (nose, oral cavity) or cutaneous (lips, fingers, face)	1 point
Visceral lesions	Within the brain, lungs, liver, or gastrointestinal tract	1 point
Family history	Autosomal dominant inheritance pattern. Must have first-degree relative with disease	1 point

>3 points = HHT diagnosis is definite
2 points = possible/suspected HHT
1 point = unlikely that HHT is diagnosis

Diagnosis is made based on the Curacao criteria (Table 29.1) [2]. The algorithm considers the presence of recurrent epistaxis, mucocutaneous telangiectasias, visceral AVMs, and a positive family history of HHT. The presence of three or more of the aforementioned items confirms the diagnosis of HHT. Physicians should have high suspicion of a HHT diagnosis in patients with two positive items; in patients with less than two positive items, the diagnosis of HHT is unlikely. Once diagnosis is confirmed, a baseline contrast echocardiogram bubble study and brain magnetic resonance imaging should be completed to screen for intrapulmonary shunts and cerebral AVMs, respectively. Currently, with advances in next-generation sequencing, molecular genetic testing is recommended when HHT is suspected clinically and in at-risk family members who have an affected first-degree relative with prior determination of a molecular HHT subtype (Table 29.2) [3].

Etiology

Pathophysiology

It is fair to say that the exact mechanism resulting in HHT vascular dysplasia (telangiectasia, AVM) is unknown. Central to HHT lesions is abnormal blood flow between the venous and arterial systems, as well as aberrant angiogenesis. Traditionally enlargement and dilatation of telangiectasia were attributed to rapid shunting of blood from the arterial system to the venous system. Mutations in genes of the TGFbeta pathway are thought to cause abnormal signaling between blood vessel mural cells (pericytes) and endothelium. This signaling defect impairs vessel cellular function and adherence of mural cells to vascular endothelium, creating vascular instability and irregular vessel sizes in HHT lesions.

Molecular Mechanism

From a molecular standpoint, the vascular malformations in HHT are the result of dysregulation of the TGF-β/BMP cellular signaling pathway. Known loci are shown in Table 29.2. The TGF-β superfamily is central to vessel wall remodeling and is a well-established mediator of endothelial and smooth muscle cell growth [4, 5]. In HHT patients, two abnormal genes, endoglin and ACVRL-1, are present in ~80% of individuals. Both genes are involved with receptors that transduce their response to the cell nucleus via a series of intracellular secondary signaling proteins within the R-SMAD family. In both genes, the pathological state appears to be result of haplo-insufficiency as mutations cause either abortion of protein translation or nonfunctional proteins [6].

Endoglin (ENG) encodes for the endoglin protein, a type I membrane-bound receptor of TGF-β

receptor superfamily, which is found in high concentrations in endothelial cells. Studies demonstrate that endoglin has a significant role in vascular remodeling and angiogenesis [7]. Clinically patients with *endoglin* mutations, or HHT type 1, have a higher incidence of cerebral and pulmonary AVM.

Mutations in *ACVRL-1* and associated protein, ALK-1, have also been demonstrated to be responsible for the HHT phenotype (HHT type 2). Similar to endoglin, ALK-1 is a type 1 membrane-bound receptor that binds ligands from the TGF-β superfamily. It has been demonstrated that ALK-1 is involved in the angiogenesis and development of the mature arterial and venous superstructure. Studies with ALK-1 deficient mice suggest a lack of anatomical and molecular distinction between arterial and venous structures [8]. Clinically, patients with ALK-1 lesions appear to have a slightly higher incidence of GI bleeding and liver AVMs. The rare development of pulmonary hypertension (PH) also appears to correlate with ALK-1 mutations. Animal studies suggest that the predilection toward PH may be the result of the occlusive arteriopathy of precapillary pulmonary arteries [9]. This obstruction may lead to elevated pulmonary artery pressure, subsequent right ventricular heart failure, and ultimately death.

A third gene, SMAD4, has also been implicated in a syndrome which there is both juvenile gastrointestinal polyposis and HHT (JP/HHT) [10]. This gene encodes for the SMAD4 protein, a secondary signaling protein downstream in the pathway of both endoglin and ALK-1 receptors. Families with JP/HHT typically present with juvenile polyps as well as an early onset of HHT symptoms. The severity of lesions, including pulmonary, hepatic, and cerebral malformations, is often greater, and patients are more prone to the sequelae of the multi-system vascular dysplasias. In addition, the polyposis predisposes patients for gastrointestinal malignancy. GI screening is recommended for affected families [11].

There is a sizable cohort of patients that meet criteria for HHT but have no detectable mutations in *ENG*, *ACVRL-1*, or SMAD4. This has led many to posit the existence of additional genetic sources of the HHT phenotype. Indeed, recent familial linkage analyses suggest sites on chromosomes 5 and 6 as loci for genes contributing to a HHT3 and HHT4, respectively [12, 13]. Future studies will certainly continue to seek novel genes that contribute to the HHT phenotype.

Natural History

As with any unusual condition, accurate clinical diagnosis requires a careful appraisal of the patient's history and thorough physical examination. It is critical to understand the frequency and temporal progression of bleeding whether it be from the nose, oral cavity, or GI tract. Typically, spontaneous epistaxis is a presenting symptom, which over time increase in severity and frequency. Affected adolescent individuals often minimize the impact of epistaxis on their lives as they experience the bleeding so commonly. Careful assessment of the patient's family history is essential as, even within a family, the clinical phenotype can be variable, and mild cases of HHT (well controlled, recurrent epistaxis) may have previously gone undiagnosed. This is especially relevant as the frequency of genetic testing increasingly identifies patients without clinical disease [14].

Mucocutaneous

The most common and earliest manifestation of HHT is nasal telangiectasia and subsequent epistaxis. Mean age of first presentation is 12 years, and the symptoms, including the frequency and severity of bleeding, tend to increase with age [15]. By age 45, approximately 95% of HHT patients report recurrent epistaxis with a mean frequency of 18 episodes per month [16]. Like most manifestations of HHT, the severity of presentation is variable with the most severe cases experiencing chronic anemia, yet other patients experience only mild and infrequent epistaxis. In additional to vascular dysplasia of the nasal mucosa, telangiectasia may also be present in the oral cavity (including lips, tongue, and buccal mucosa) and oropharynx (most commonly the soft palate) (Fig. 29.1). While bleeding may be

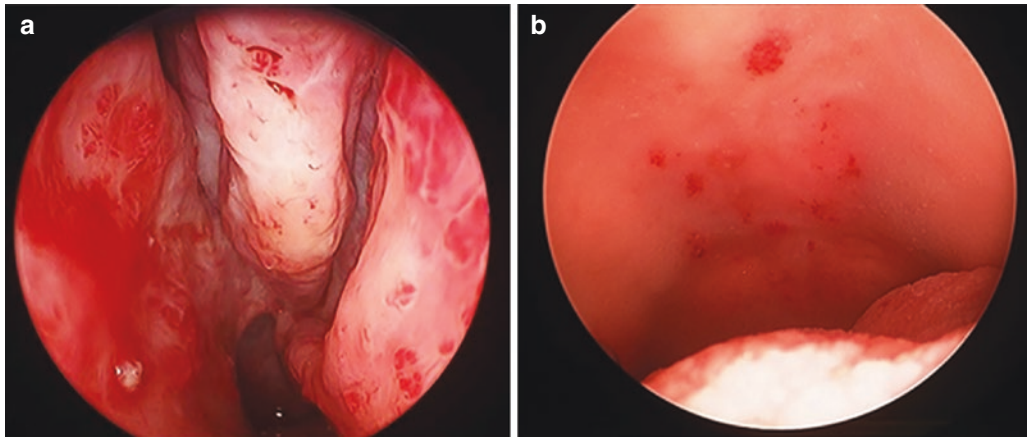

Fig. 29.1 Panel (**a**) Multiple telangiectasias of the nasal mucosa. Lesions are present within the mucosa posterior aspect of the inferior turbinate, middle turbinate, and lateral wall. Panel (**b**) Telangiectasias within the mucosa of the hard palate extending to the soft palate

present from these lesions, they are often asymptomatic and do not require treatment. Significant variability in clinical presentation exists within disease subtype (i.e., HHT1 vs HHT2) and within individual families.

Telangiectasias of the skin, specifically of the hands and face, are also quite common in the third or fourth decade for HHT patients. Unlike mucosal telangiectasias, bleeding for skin lesions is rare, and treatment is typically not necessary. Those who do seek treatment in the form of laser therapy commonly do so for cosmetic reasons alone.

Gastrointestinal

The vascular malformations of the nasal mucosa may be found at any point throughout the entirety of the aerodigestive tract in patients with HHT, from oral cavity to rectum. With regard to the gastrointestinal tract, the presence of lesions varies from 10% to 33% of patients and is most commonly found in the stomach and upper duodenum [17]. Like the telangiectasias of the nasal mucosa, gastrointestinal lesions are progressive in number with increased frequency of bleeding over time. By age 60, approximately 25% of individuals present with persistent melena, chronic blood loss anemia, or both [18]. Endoscopy is the most common diagnostic tool as it may demonstrate the presences of small telangiectasias and larger AVM, and it offers therapeutic options as well.

Lung

There are three pulmonary sequelae of HHT: (1) the classic pulmonary arteriovenous malformation (PAVM), (2) pulmonary hypertension secondary from high cardiac output from liver shunting, and (3) pulmonary arterial hypertension (PAH). PAVM is the most common pulmonary manifestation of HHT and is present in 15–45% of patients [19]. PAVM, however, is highly specific for HHT as 80% of patients with PAVM have HHT as an underlying cause. Like lesions in other organ systems, patients often have multiple vascular malformations in the lung and variable levels of expression and severity. Clinically, only 10% of patients with PAVM present with symptoms. The classic symptom triad for PAVM is cyanosis, pulmonary bruits, and digital clubbing. In addition to the classic symptoms which result from pulmonary vascular shunting, there are a number of well-documented and serious complications from PAVM. Recent studies have demonstrated stroke in 10–36%, transient ischemic attack in 6–37%, cerebral abscess in 8–19%, and massive hemoptysis and

spontaneous hemothorax in 4–20% of cases [20]. Risk is elevated in the cases of pregnant women with pulmonary AVMs as the high flow state of pregnancy is thought to increase pulmonary hemorrhage. Each of these complications is a consequence of right-to-left shunting via AVMs or in situ thrombus formation in PAVMs. Given the high rate of pulmonary manifestations, severe complications, and low incidence of classic symptoms, routine screening of HHT patients for pulmonary PAVM is recommended. The preferred study for screening is the contrast ECHO, while computed tomography (non-contrast) is often required for detailed visualization of lesions.

Liver

In contrast with pulmonary malformations, liver AVMs are relatively rare (4.6–8.6% of patients) and are typically asymptomatic. Given the low incidence and the relatively benign nature of AVMs when present, screening is currently not recommended. The symptoms of liver AVMs include bruits on liver auscultation and palpable thrill. Heart failure, portal hypertension, or both are only screen in advanced cases. Similarly, hepatic laboratory values are typically within normal ranges, except in advanced cases where abnormalities are indicative of an anicteric cholestasis (increased alkaline phosphatase and gamma-glutamyl transpeptidase). Heart failure seen in severe cases is a result of high-output flow from the hepatic artery/portal vein to hepatic vein shunting. As the hepatic artery is the sole arterial supply for the biliary tree, significant vascular shunting may result in chronic ischemia and severe cholestasis. Workup of liver manifestations of HHT typically begins with color Doppler of the liver. Dilation of the hepatic artery with tubular and tortuous intrahepatic channels suggests significant liver involvement. The gold standard for identifying complex lesions is angiography; however, helical CT imaging has demonstrated excellent sensitivity and specificity; thus, hepatic angiography is increasing limited in use [21].

Management of HHT-Related Epistaxis

Epistaxis is inevitable in nearly every person with HHT [22]. This leads to significant anemia and a substantial negative impact on quality of life [23–25]. Management of HHT-related epistaxis is fraught with challenges given the recurrent, persistent nature of the disease. Impressing upon patients with HHT that epistaxis is an expected part of their life is important for their understanding and for setting up appropriate expectations for treatment. Fortunately, there are recent innovations that have shown to decrease the frequency and duration of epistaxis. These treatments include a combination of medical and surgical innovations. Medical treatment can be administered topically, orally, or systemically. Surgical treatment can be delivered via office-based procedures or those procedures performed in the operating room.

Topically Applied Therapies

Humidification

The hallmark of managing the HHT nose begins with daily nasal hygiene and humidification. Nasal dryness and a buildup of nasal crusts can lead to damage of the telangiectasias present and engender bleeding. The use of room humidifiers, topical lubricants or ointments, and saline nasal lavages can be beneficial [26]. Many patients with non-HHT-related chronic epistaxis feel that using nasal saline gel is more helpful than liquid saline spray as the gel tends to coat the nasal mucosa lasting longer and providing more humidification [27]. One study investigated using compounded rose geranium oil and sesame oil intranasal drops in 20 patients with HHT [28], and 75% of subjects felt this treatment was beneficial. Objectively, the mean epistaxis severity scale (ESS) [28] decreased from 5.3 pretreatment to 3.5 posttreatment at a mean follow-up time of 183 days.

Topical Medications

Recently, a much anticipated double-blinded randomized trial investigated topically applied bevacizumab, estriol, tranexamic acid, or placebo [29]. One hundred twenty-one patients with HHT-related epistaxis were randomized to one of these four treatment arms. Epistaxis severity was assessed by frequency and duration as well as the ESS, hemoglobin level, ferritin level, need for transfusion, and visits for emergency care. Unfortunately, none of these study drugs showed any improvement in decreasing the frequency or duration of epistaxis or any of the other outcome measures when compared to the saline control arm.

Another double-blinded placebo-controlled study investigated bevacizumab, a VEGF inhibitor, in 80 randomized patients and applied the drug via nasal spray at three different concentrations for 6 months [30]. This study also showed no reduction in epistaxis duration and was terminated prior to initiation of a follow-up Phase 3 trial. A prior Phase 1 study by this group also showed no improvement in epistaxis frequency and duration in 40 patients [31]. Similarly, in an earlier study investigating topically applied tranexamic acid in a double-blinded randomized multicenter trial involving patients with any source of epistaxis, tranexamic acid again showed no improvement in controlling epistaxis [32].

Estrogen is thought to induce metaplasia of mucosal membranes, thus possibly leading to thickened layers of keratinized squamous epithelium in the nasal cavity. Presently, other than the study described above that showed no improvement, only three other studies have examined topical estrogen. One study involved 26 patients who underwent operative argon plasma coagulation followed by either topical estrogen or topical dexpanthenol applications [33]. In this prospective, randomized, non-blinded trial, patients in the topical estrogen group reported a significant decrease in frequency and duration of epistaxis compared to the dexpanthenol group. However, no comparative statistics were performed between the two cohorts, and both groups improved relatively similarly at the 4- and 12-month post-op time points reported. This group published a follow-up study reporting 18-month posttreatment data stating that 96% of patients had a significant reduction in epistaxis; however this conclusion is heavily confounded by the concomitant argon plasma treatment. The other study was a small case series of five patients who received topical estrogen ointment and reported a significant decrease in epistaxis frequency and severity as well as improvement in ESS compared to before treatment [34]. The lack of a rigorous appropriately powered trial, and the results of the negative JAMA study, sheds concern for the perceived efficacy of topical estrogen for HHT-related epistaxis.

Oral Medical Therapies

An encouraging randomized double-blinded placebo-controlled study investigated the short-term impact of the antiestrogen drug, tamoxifen, on HHT-related epistaxis [35]. Twenty-one subjects received oral tamoxifen for 6 months, and when compared to placebo controls, those on tamoxifen showed a significant improvement in frequency and duration of epistaxis and in hemoglobin levels. This group continued to follow the tamoxifen cohort out for 2 years [36]; 83% of the 46 subjects completed the 2-year study. Epistaxis severity, quality of life, and hemoglobin levels all improved. Despite these encouraging results, it is important to recognize the potential for side effects related to antiestrogen therapy, especially in women, and those risks should be discussed with the patient and a hematologist before considering therapy.

Tranexamic acid is an antifibrinolytic drug administered orally, commonly at 3 g divided daily. The first small case series using tranexamic acid published in 2001 showed a significant reduction in frequency of epistaxis [4]. Since then, two double-blinded placebo-controlled trials both showed an improvement in epistaxis with one reporting decreased epistaxis duration [36] and the other demonstrating improved subjective epistaxis but no improvement in hemoglobin levels [37].

Finally, thalidomide was recently demonstrated to improve telangiectasia maturation in a murine model followed by a small cohort study

of human subjects with HHT-related epistaxis [38]. Six of seven subjects reported decreased epistaxis frequency, and three of four subjects reported decreased duration of epistaxis. However, a follow-up study showed that 7 of the 12 patients discontinued treatment due to significant side effects (neuropathy, malaise, and drowsy/dizzy being the most common) [39]. Interestingly though, of the 12 patients available for follow-up, 9 patients reported they would recommend trying thalidomide to other patients with HHT.

Systemically Injected Medical Therapies

Systemic administration of bevacizumab has been investigated in a Phase 2 open-label non-randomized trial [40]. Further experience was summarized in a recent systematic review [41] and has shown promising results. The systematic review demonstrated an improvement in liver function, improved cardiac output, decreased need for blood transfusions, and improvement in epistaxis frequency and duration. The Phase 2 trial further demonstrated improved quality of life on SF-36 in both physical and emotional functions.

Procedural and Operative Therapies

Procedural Therapies

Sclerotherapy involves injecting a nasal telangiectasia with an agent that leads to obstruction of blood flow to the vessel and induces regression of the lesion. One study examined using injectable Aethoxysklerol in 45 patients and demonstrated decreased epistaxis frequency in 73.2% of subjects and significant improvement in daily quality of life as measured by the Euroqol-5D [42]. This study reported few complications including development of a septal perforation, enlargement of pre-existing septal perforation, and transient dizziness and blurred vision. More recently, a prospective randomized study compared standard treatment versus sclerotherapy using sodium tetradecyl sulfate (STS) in 17 subjects with recurrent HHT-related epistaxis [43]. The primary outcome measure, the epistaxis severity scale, revealed a statistically and clinically significant improvement with sclerotherapy (0.95 points). Furthermore, 13 out of 17 subjects reported they were "very likely" to consider future sclerotherapy. This last outcome is important given that one critique of sclerotherapy relates to patient discomfort [44].

Bevacizumab, a VEGF inhibitor discussed previously in the context of topical therapy, has also been studied as a local submucosal injection [45, 46]. These cohort studies do show benefit, with the majority of subjects reporting a significant reduction in their ESS following treatment for up to 9 months. Cautiously, nearly 10% of subjects self-reported sustaining a septal perforation following injection, leading the authors to recommend avoiding direct injection to the nasal septum.

Endovascular embolization of the internal maxillary artery and associated branches remains an option for severe, often emergent, HHT-related epistaxis. Unfortunately, one study showed 21.4% of subjects with HHT had telangiectasias originating off of the internal carotid artery, thus precluding safe embolization [47]. Furthermore, of the 14 subjects studied, half of those with follow-up data developed recurrent nasal bleeding by 6–24-month post-procedure. This relatively low success rate, coupled with the risks of embolization (distal necrosis of structures, stroke, vision loss, etc.) and significant cost, tempers enthusiasm for use to the point that a recent international guideline statement stated that "nasal artery embolization is generally not useful for treatment of chronic epistaxis since it is generally short term" [48].

Surgical Therapies

Once HHT-related epistaxis becomes moderate to severe, operative intervention is indicated. Endoscopic control of epistaxis with destruction of the nasal lesions has become the hallmark therapy for HHT-related epistaxis. Many types of cauterization procedures are available, and all strive to achieve the same goal of destruction of the telangiectasia. However, some techniques have shown superior results when they are able to

target the abnormal tissue and preserve as much healthy/normal tissue as possible.

Chemical cautery and electrocautery are effective by means of liquefaction necrosis of the tissue targeted. Unfortunately this destroys both abnormal and normal tissue, often leading to crusting and scar tissue. One advantage of monopolar suction cautery is the enhanced ability to see the discrete lesion with the application of suction. When less invasive methods of cautery are used to destroy a telangiectasia and the vessel ruptures, often suction cautery is needed to control the hemorrhage. However, bipolar cautery can be applied with less collateral soft tissue destruction leading to a lesser chance of septal perforation [49]. Additionally, some endoscopic bipolar devices also provide suction that significantly improves endoscopic visualization.

The KTP, argon, diode, and the Nd:YAG lasers are quite effective in controlling small telangiectasias [45, 51–54]. These treatments decrease the severity of epistaxis. Improvement can be short or long term, and all of these studies acknowledge that future treatments are needed. Fortunately with successive treatments, the duration between laser treatments is often extended. Additionally, health-related quality of life was shown to improve with Nd:YAG treatments [53]. The greatest challenge to using lasers for cauterization procedures is that once a vessel ruptures and blood flows on the field, the blood will absorb the laser energy and impair the energy from reaching the submucosal tissue, thus preventing destruction of the telangiectasia. When this occurs, a third hand holding suction or switching to a suction-assisted instrument needs to be used to clear the bloodied field prior to resuming laser treatments.

Coblation is a technology that delivers low thermal energy while also delivering saline and providing suction. The low thermal energy helps minimize the risk to non-telangiectasia tissue and as such should decrease the risk for septal perforation. The constant flow of saline and suction provides excellent endoscopic visualization. A recent study compared coblation versus KTP laser photocoagulation for HHT-related epistaxis [55]. Six patients received coblation and five patients received KTP therapy. Both techniques were effective in improving epistaxis though there was no difference in posttreatment epistaxis severity scale between the two techniques. However, subjects in the coblation cohort reported less nasal obstruction via visual analog scale compared to the KTP cohort.

Septodermatoplasty is an endoscopic-assisted or open approach procedure that involves removing the mucosa on the nasal septum and replacing it with a split thickness skin graft, often harvested from the thigh [50]. A retrospective review of this procedure yielded outcomes data (blood transfusion rates) in only 48% of the subjects enrolled [56]. These data showed a dramatic decrease in units transfused from 21 units of blood the year before septodermatoplasty down to only 1 unit transfused for the year following septodermatoplasty. A follow-up study showed 88% of subjects reported improved quality of life; however, they also developed significant consequences including nasal odor (78%), nasal crusting (72%), diminished smell function (58%), and worse sinus infections (30%). Therefore, septodermatoplasty remains an option but should be considered with reservation.

Finally, the Young's procedure involves surgical closure of both nostrils and was originally described for treatment of atrophic rhinitis [57]. Past studies applied this approach to patients with HHT [58, 59]. However, severe post-procedure epistaxis can occur and given the closure of the nostrils can be life threatening requiring emergent reversal [60, 61].

Emergent Care

Patients with HHT will exhibit frequent, even daily, epistaxis. Occasionally, the amount becomes severe and emergent intervention is indicated. Once the ABCs are established, a stepwise approach should be deployed with the intent to use hemostatic materials that are absorbable. Too often, well-intended emergency personnel use methods such as balloon devices or sponges to tamponade the bleeding. If the bleeding is life threatening, these devices can certainly be justified. However, if the bleeding is not life threatening as is often the case, the use of absorbable materials significantly

improves the treatment of these patients. When nonabsorbable materials are used, 2–3 days later, those devices need to be removed. Often they are adherent to the crusts within the nasal cavity, and removal quickly engenders recurrent bleeding. Using absorbable materials negates the need for removal. Saline sprays or irrigations are encouraged after applying absorbable materials to help them dissolve and avoid scar tissue. With proper training, newer absorbable materials originally intended for use in the operating room, such as Surgicel, Floseal, Arista, and many others, now can provide superior hemostasis with less patient discomfort and improved quality of life.

To assist the reader in gaining familiarity with available evidence, the following rating system has been used to indicate key references for each chapter's content:
***: Critical material. Anyone dealing with this condition should be familiar with this reference.
**: Useful material. Important information that is valuable in in clinical or scientific practice related to this condition.
*: Optional material. For readers with a strong interest in the chapter content or a desire to study it in greater depth.

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30

Lymphangiomatosis: Generalized Lymphatic Anomaly, Gorham-Stout Disease, and Kaposiform Lymphangiomatosis

Tara L. Wenger and Anne Hing

Genetic diagnosis	No, most forms
Genetic etiology	Unknown, most patients
Level of evidence, treatment	Poor
Evidence	Case series, expert opinion

Background

Lymphatic anomalies, including lymphatic malformations and lymphangiomatosis, result from the lymphatic system and have been classified by ISSVA, as described in Chap. 2 of this textbook. When functioning properly, the lymphatic system maintains fluid balance, produces lymphocytes which provide important defense against pathogens, and is crucial to the absorption of fats and fat-soluble vitamins (A, D, E, and K) from the small intestine into the bloodstream. Lymphatic channels develop early in gestation, and abnormalities of the lymphatic system often are present at the time of birth [1]. The age of onset of clinical symptoms of a lymphatic anomaly varies widely, with some being identified on prenatal ultrasonography, and others occurring late in adulthood, depending on the type. The age of onset, degree of organ involvement, clinical course, and treatment options vary depending on the type.

Lymphangiomatosis (including generalized lymphatic anomaly, Gorham-Stout disease, and kaposiform lymphangiomatosis), even when primarily manifesting in the head and neck, can cause widespread damage and be extremely challenging to treat.

Histology of lymphangiomatosis is best described in lung parenchyma where there are multiple benign-appearing lymphatic channels with stromal disorganized fascicles of spindle cells, associated with progressive bone loss. Although it is considered benign, the progressive change in lymphatic channels can cause significant morbidity and mortality. Approximately 75% of individuals with lymphangiomatosis will have multiple organ systems involved during the course of their disease, with the most common being the lung and bone [1]. Most individuals with lymphangiomatosis will be diagnosed during the first two decades, including a spike during puberty. As a general rule, the earlier the age of onset, the more aggressive the disease process will be.

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Up to 75% of individuals with generalized lymphangiomatosis develop bony involvement, which has led some to suggest that generalized lymphatic anomaly and Gorham-Stout disease are all manifestations of the same disease process [1, 2]. However, there are important clinical distinctions between patients with generalized lymphatic anomaly, including the presenting symptoms and multiorgan involvement. Others have suggested that generalized lymphatic anomaly and Gorham-Stout are pathophysiologically distinct entities, suggesting that both can include bone loss but that the pattern of bone loss and progression is unique to each disorder [3]. Patients with generalized lymphatic anomaly tend to have bony lesions that are nonprogressive and can be multifocal. The bony involvement in Gorham-Stout disease is characterized by progressive osteolysis. Additionally, patients with Gorham-Stout disease typically do not have involvement of their intestines and are free of enteric symptoms. A third entity, kaposiform lymphangiomatosis, has also been suggested as a unique entity among this group of disorders, being characterized by an aggressive course and mediastinal involvement and histopathologically characterized by clusters or sheets of spindled lymphatic endothelial cells accompanying malformed lymphatic channels [4, 5]. There is still a debate about the exact nature of these entities, especially for patients who do not classically fit into one of the diagnostic entities; current classification by ISSVA does describe them as unique disorders (Fig. 30.1).

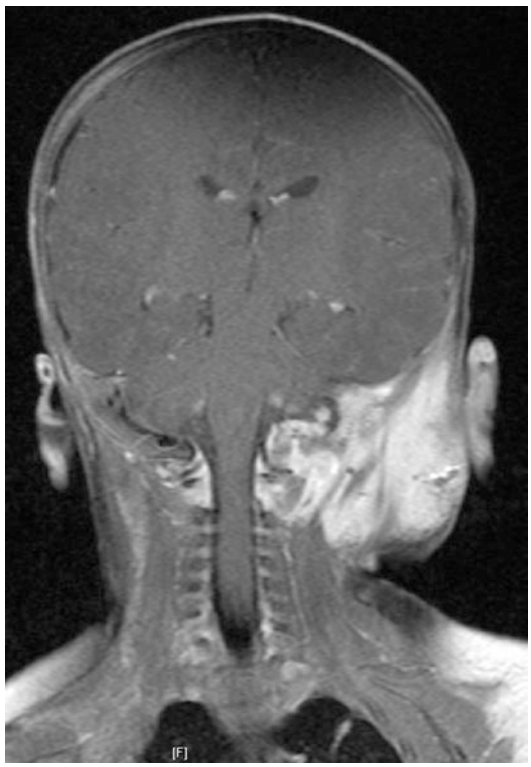

Fig. 30.1 Kaposiform tumor in young child with skull base bone resorption. (Images courtesy of Seattle Children's Radiology, Giridar Shivaram, Eric Monroe and Kevin Koo)

Phenotype and Variations

The presenting symptoms for each form of lymphangiomatosis depend on the location and extent of organ involvement. Most patients with Gorham-Stout disease will initially come to medical attention because of a fracture that does not heal. Subsequent imaging will reveal concern for lymphangiomatosis and loss of bone. Patients with generalized lymphatic anomaly and kaposiform lymphangiomatosis more often present with shortness of breath related to chylothorax due to the lung involvement. Shortness of breath can also occur due to chylopericardium. Some patients with generalized lymphatic anomaly will present because of pain or fracture associated with bony involvement, though it is a less common presentation. Similarly, some patients with Gorham-Stout will present with symptoms from chylothorax, when the lesion extends from the ribs into the adjacent lung. Although intestinal involvement is common in generalized lymphatic anomaly, it typically is asymptomatic until the disease is advanced, causing diarrhea, intolerance of fatty foods, and weight loss. Less common clinical presentations can result from lymphangiomatosis invading the kidneys (e.g., hematuria, flank pain, hypertension) or the liver (e.g., disseminated intravascular coagulation, ascites, liver failure).

The diagnosis of lymphangiomatosis will typically be suspected based on clinical characteristics and appearance on imaging. However, biopsy is required to formally establish the diagnosis. After lymphangiomatosis has been demonstrated, other clinical characteristics can help to distinguish between the three entities.

Table 30.1 Diagnosis: Gorham-Stout disease

Gorham-Stout disease criteria
Positive biopsy with the presence of angiomatous tissue
Absence of cellular atypia
Minimal or no osteoblastic response or dystrophic calcifications
Evidence of local bone progressive osseous resorption
Non-expansile, non-ulcerative lesions
No involvement of viscera
Osteolytic radiographic pattern
Negative heredity, metabolic, neoplastic, immunologic, or infectious etiology

Heffez and colleagues [6] proposed eight criteria for a definitive diagnosis of Gorham-Stout disease (Table 30.1). While these criteria are helpful, they require the clinician to combine information from histopathology, multiple imaging modalities, and a thorough family and personal medical history and to have a preliminary understanding of the natural history of the disease. For these reasons, it is extraordinarily difficult to diagnose early in the course of disease, and many patients will go through a prolonged diagnostic odyssey while awaiting a definitive diagnosis. Early in the course of the osteolytic lesions, it is difficult to distinguish Gorham-Stout disease from generalized lymphatic anomaly or kaposiform lymphangiomatosis. However, the bony lesions in Gorham-Stout disease are progressive, while the majority of osteolytic lesions in generalized lymphatic anomaly and kaposiform lymphangiomatosis are multifocal and nonprogressive [5]. Kaposiform lymphangiomatosis often presents in younger children (around age 6.5 years) but has been seen in patients as old as 44 years. It typically includes prominent mediastinal involvement and has a characteristic appearance on histopathology which can aid in the diagnosis [4].

Disease Progression

The symptoms experienced by individuals with Gorham-Stout depend on the organs involved and the extent of infiltration and are similar to those noted above in "diagnosis." There are some important differences between generalized lymphatic anomaly and Gorham-Stout disease involvement as the disease progresses.

Bony Involvement

The initial changes in the bone in Gorham-Stout disease include lucencies that resemble regions of osteoporosis. As the disease progresses, long bones become progressively thinner, with a "sucked candy" appearance (Fig. 30.2). There can be thinning of other bones, especially the skull base and affected facial bones (Fig. 30.3). The bone itself is lost through osteolysis and replacement with angiomatous or fibrous tissue [7–11]. In contrast, the bony lesions in generalized lymphatic anomaly are typically nonprogressive, though easily identifiable on imaging. According to a study of a large cohort of patients with different forms of lymphangiomatosis by Lala and colleagues [3], the average number of bones involved in generalized lymphatic anomaly was 30.7 with appendicular skeletal involvement in 88% of patients. In Gorham-Stout the average number of involved bones was 7.5, with appendicular skeletal involvement in only 26% of patients. The most common bones involved in Gorham-

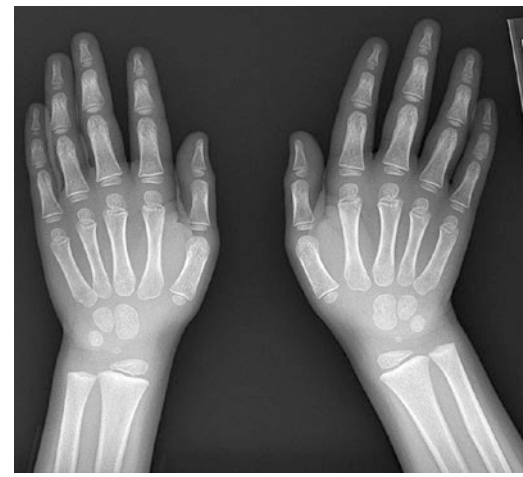

Fig. 30.2 Plain radiograph showing progressive thinning ("sucked candy") appearance of long bones. (Images courtesy of Seattle Children's Radiology, Giridar Shivaram, Eric Monroe and Kevin Koo)

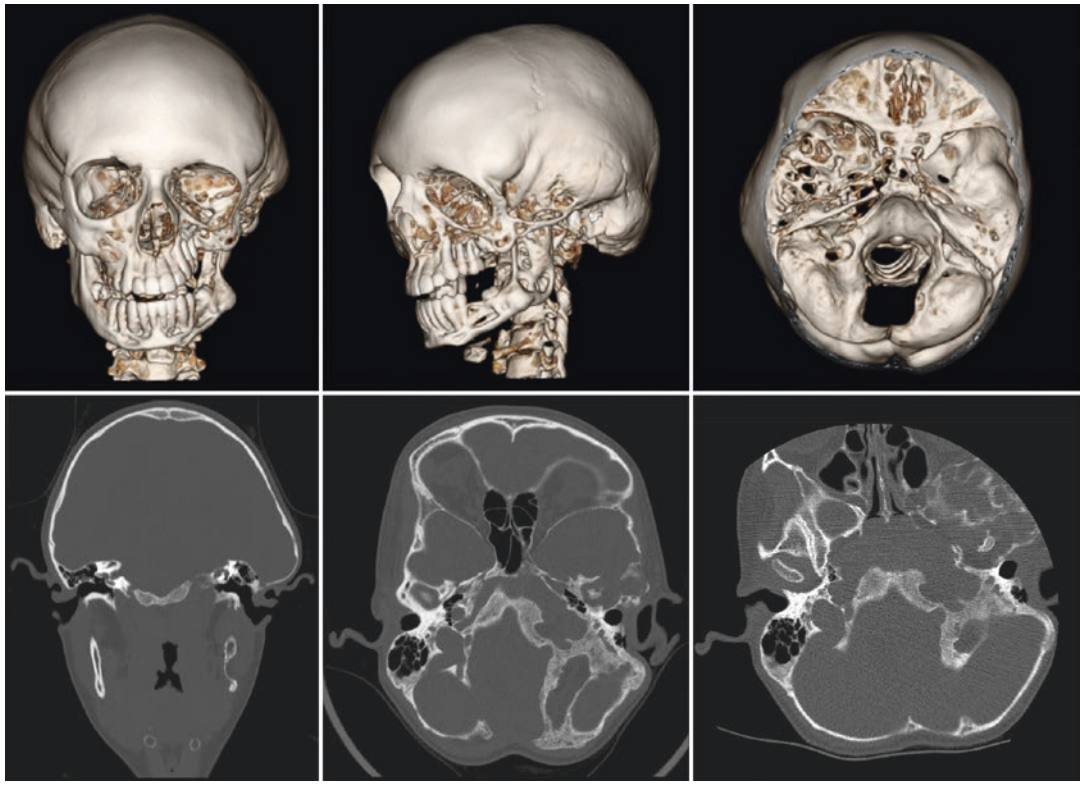

Fig. 30.3 Progressive bone loss in facial skeleton, lateral skull, and temporal bone extending into the skull base, as seen on 3D CT and axial CT sections. (Images courtesy of Seattle Children's Radiology, Giridar Shivaram, Eric Monroe and Kevin Koo)

Stout include the shoulder, skull, pelvic girdle, jaw, ribs, and spine [9, 12–14].

Soft Tissue Involvement

Lala and colleagues also evaluated the rate of soft tissue findings in patients with Gorham-Stout disease compared to generalized lymphatic anomaly [3]. The rate of splenic or hepatic cysts, pleural effusions, and macrocystic lymphatic malformation was similar in both groups. However, infiltrative soft tissue abnormalities were identified in 95% of patients with Gorham-Stout disease and only 19% of those with generalized lymphatic anomaly.

Progression of Symptoms

In addition to the symptoms that occur at the time of diagnosis, there are several features which are common in the progression of lymphangiomatosis (Table 30.2). Other variable symptoms depend on the organs and bones that are involved [3, 5, 9, 12–17]. The course of disease progression is unpredictable. There can be periods of rapid progression and periods of spontaneous stabilization [5, 15–17]. Patients may have varying clinical presentations, and also varying patterns of disease symptom involvement as noted in Table 30.2. Individual patients may have some or all features, and different levels of severity.

Table 30.2 Natural history of disease progression: Gorham-Stout disease

Gorham-Stout disease symptom progression
Depending on involved organs, impairments in kidney function and/or liver failure
Diarrhea, particularly with ingestion of fatty foods
Joint pain when disease involves adjacent bones
Liver, spleen, or kidney "cysts" (early lymphangiomatosis)
Multiple fractures with poor healing
Neurological complications if the skull base or spine is involved due to either fracture damaging the brain, brainstem, or spinal cord or invasion of lymphangiomatosis through the skull into the brain
Neuropathic pain due to nerve compression
Pericardial effusions
Pleural effusions
Recurrent, serious, or unusual infections due to lymphopenia
Restrictive lung disease due to long-standing chylothorax and scarring
Shortness of breath due to extension of lymphangiomatosis to the chest wall, pleural and/or pericardial effusions (note: can be misdiagnosed as asthma and pulmonary function tests are similar in pattern)
Vertebral compression fractures
Weight loss or poor weight gain

Etiology

Lymphangiomatosis is generally thought to be a sporadic disease, though there are reports of some families with apparently autosomal dominant transmission. In other cases, a mosaic mutation is suspected in the affected tissue, especially in cases where the disease is confined to an isolated anatomic location or is well circumscribed. Infants with lymphangiomatosis likely have developmental abnormalities that occur during embryonic and fetal development. Factors leading to progression or spontaneous stabilization are poorly understood. The process of osteolysis and the resulting pathophysiologic changes are well understood, but the triggers for the initiation of this process are not known. Osteoclasts typically break down bone, while osteoblasts lay down new bone. Unless the bone is growing (when osteoblast activity outweighs osteoclast activity), there is a relative balance between the activity of osteoclasts and osteoblasts. In Gorham-Stout disease, there is increased activity of osteoclasts compared to osteoblasts. There is some evidence that *VEGF* and *IL-6* may contribute to this imbalance [3, 6–10, 18, 19]. Autopsy studies have shown that the bony loss typically starts with proliferation of lymphatic and/or vascular channels in bone, followed by resorption and replacement of bone with angiomas and fibrosis. The mechanism for the increase in size and number of lymphatic channels and the mechanism for erosion into surrounding soft tissues and bones are not well understood. Moreover, it is not understood why different patients have a different distribution of organ and bone involvement; it is also not well understood why some patients have a self-limited course and in others it causes significant morbidity and/or mortality. Recent studies suggest pathogenic genetic variants may underlie some forms of lymphangiomatosis, which may have implications for understanding pathophysiology and identification of therapeutic targets. [20]

Treatment

There is no cure for lymphangiomatosis or Gorham-Stout disease. Treatments for lymphangiomatosis are generally targeted at alleviating symptoms. There are a number of different modalities that have been used for treatment, all with somewhat limited success. It is clear that some patients benefit greatly from specific treatments, while the same treatments are ineffective for other patients [21]. This may be due to variability in the underlying molecular mechanisms or triggering causes or because of palliative options for different manifestations of the disease across individuals. Despite uncertainty about the best initial steps of treatment, it is imperative that treating providers adopt an aggressive approach – Duffy and colleagues estimated that for patients with Gorham-Stout disease with chest wall involvement and resultant chylothorax, there is an estimated mortality rate of 64% without surgical intervention [12]. Some of the treatment options for patients with

Table 30.3 Treatment: Gorham-Stout disease

Gorham-Stout disease treatments
Dietary modifications: including low-fat diet with supplementation of medium-chain triglycerides and high-protein diet. Especially helpful for patients with involvement of the intestines. For some patients, low-fat diet can completely eradicate gastrointestinal symptoms
Medications: Interferon alpha 2b, pamidronate, rapamycin, thalidomide
Radiation therapy
Sclerotherapy
Surgery: Surgery may be used to stabilize bony lesions using bone cement, grafts, or scaffolding, surgical closure of channels allowing leakage of fluid from one body compartment to another (e.g., ligation of the thoracic duct; obliteration of the mastoid to close CSF leak), pleurocentesis, pericardiocentesis, removal of infiltrative lesions, pleurodesis, placement of central line for TPN administration, percutaneous bone cement, bone grafts, prosthesis, amputation
Total parenteral nutrition

lymphangiomatosis are summarized in Table 30.3. Patients may require a combination of these treatments to keep serious side effects at bay or halt progression, and in some patients, the disease may progress unremittingly despite best efforts at treatment [5, 12, 21–30]. Treatment options for lymphangiomatosis are summarized (Table 30.3).

Conclusions

Lymphangiomatosis, including generalized lymphatic anomaly, Gorham-Stout disease, and kaposiform lymphangiomatosis, are aggressive lymphatic malformations that can cause significant morbidity and mortality. Classification can help to guide likely disease progression for counseling, but as yet no targeted therapies have proven successful for all patients. Treatment is necessary in most cases because of worsened outcomes without intervention and may require a combination of surgery, dietary therapy, radiation, or medication (e.g., interferon, pamidronate, rapamycin, and/or thalidomide). Future research is needed to identify molecular mechanisms and targeted therapeutics to halt or reverse disease progression.

To assist the reader in gaining familiarity with available evidence, the following rating system has been used to indicate key references for each chapter's content:
***: Critical material. Anyone dealing with this condition should be familiar with this reference.
**: Useful material. Important information that is valuable in in clinical or scientific practice related to this condition.
*: Optional material. For readers with a strong interest in the chapter content or a desire to study it in greater depth.

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Klippel-Trenaunay Syndrome

31

Megha M. Tollefson

Genetic diagnosis	Yes
Genetic etiology	Mosaic activating mutations in PIK3CA
Level of evidence: treatment	Moderate
Evidence	Case series, single Phase 2 trial

Diagnosis

Phenotype and Variations

Klippel-Trenaunay Syndrome (KTS) is a disorder characterized by bone and/or soft tissue overgrowth and vascular malformations with or without other disease characteristics. KTS was described in 1900 and is extremely rare. It was classically described as a triad of capillary malformation, varicose veins and/or venous malformation, and soft tissue and/or bony overgrowth. Prior to the last several years, many vascular malformation overgrowth syndromes with features overlapping with KTS had often been diagnosed as KTS. Efforts to reclassify vascular anomalies, vascular malformations, and overgrowth syndromes are underway as more is learned about the different phenotypes and etiologies of these disorders. Recently, the International Society for the Study of Vascular Anomalies (ISSVA) has re-characterized KTS as the presence of a capillary malformation, venous malformation +/− lymphatic malformation, and limb overgrowth [1].

The capillary malformation (CM) in KTS is most commonly observed in an extremity, particularly the lower extremity. It is usually present at birth. The distribution is sometimes referred to as "blotchy" (Fig. 31.1) or "geographic" (Fig. 31.2). Those that are "blotchy" have poorly defined borders and appear "broken-up" and more muted in color than those that are geographic. Geographic stains are well-defined, fairly homogeneous, and dark red to purple in color. Geographic stains are associated with an increased risk of underlying lymphatic malformation and with increased complications in KTS, including pain, bleeding, and infection [2]. There is also an increased risk to develop tissue hypertrophy and "vascular blebs" within more geographic stains in KT (Fig. 31.3).

Venous malformations in KTS may manifest as significant varicosities, or as a more traditional venous malformation. While congenital, these are not always clinically evident at birth and often become more pronounced when a child starts walking [3]. Often, the presence of varicosities and venous malformations leads to complications of pain, feelings of throbbing, achiness,

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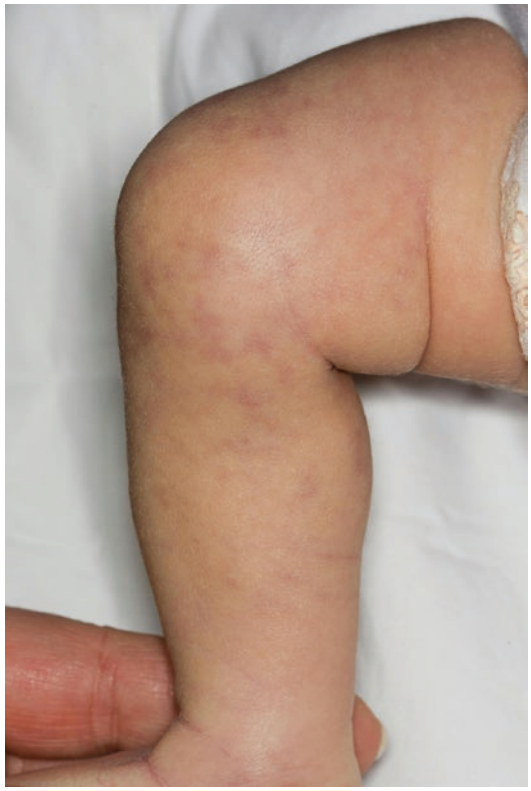

Fig. 31.1 Reticulate or "blotchy" capillary malformation

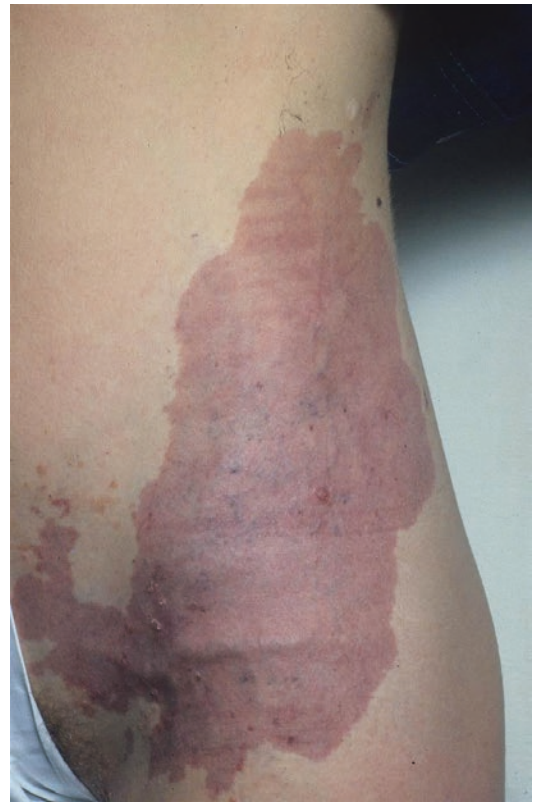

Fig. 31.2 Geographic or homogeneous capillary malformation

and even ulceration depending on the degree of venous valvular incompetence. Deep venous system abnormalities such as hypoplasia, aplasia, and duplications may also be seen, in addition to the persistence of the embryonic lateral marginal vein, contributing to these complications [4–6]. Lymphatic malformations may also be seen in conjunction with venous malformations in KTS [7]. The presence of vascular "blebs" in a CM indicates that a lymphatic component is present. Arteriovenous malformations (AVMs) are not a characteristic of KTS and are often erroneously attributed to the syndrome [8].

Overgrowth is a hallmark of KTS. The amount and location is variable; however, it is generally present in the affected extremity. The overgrowth is generally present at birth but may be progressive, especially until a child is done growing. The leg is the most commonly affected limb in KTS, and often the overgrowth involves the entire leg and foot. This may manifest as limb-length discrepancy, increased girth, or both. In the past, findings of overgrowth in other parts of the body such as the trunk, upper extremities, and face were also often referred to as KTS. However, as knowledge of the phenotypes and genotypes of overgrowth syndromes grows, there is increasing recognition that these are not all part of the same disorder.

Other findings including developmental dysplasia of the hip, digital abnormalities, and other skeletal abnormalities have been seen in patients with KTS, but these are not felt to be specific for the syndrome [8, 9]. Up to 30% of patients with KTS may have genitourinary involvement [10]. This may manifest as cutaneous or visceral genital abnormalities and difficulty with voiding and may also result in bleeding that can range from minor to life-threatening [10, 11]. Gastrointestinal involvement may be seen in 10–15% of patients, manifesting as intermittent

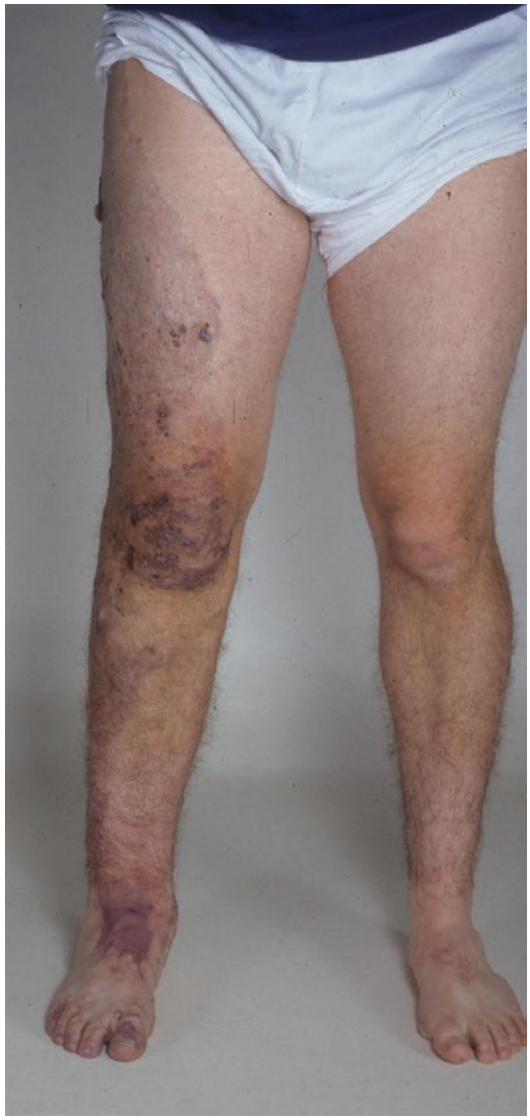

Fig. 31.3 Numerous vascular "blebs" within a homogeneous capillary malformation

bleeding or blood with stooling, which may range from minor to requiring regular blood transfusions [8].

Etiology

The etiology of KTS had long been elusive, with many proposed theories regarding its cause. It is a sporadic disorder; while other vascular anomalies have been reported in family members of patients with KTS and rare reports of similarly affected family members exist [12], KTS is usually not familial [8, 13]. Various gene mutations had been seen in isolated patients with KTS, including mutations in *AGGF1* and chromosomal translocations [14]. Mutations in *RASA1* have not been seen in KTS [15]. Physical causes including intrauterine injury and consequences from the deep venous anomalies have also been previously proposed as theories behind the development of KTS [16].

Recent insights into somatic mosaicism have led to a breakthrough in the discovery of the etiology of KTS. Somatic mosaicism is well-understood as a cause of cancer, and its involvement in other diseases is increasingly evident, including its role in KTS [17]. Most cases of KTS are caused by mosaic activating mutations in the *PIK3CA* gene, which is in the mTOR pathway. Mutations in *PIK3CA* also contribute to lymphatic malformations; congenital lipomatous overgrowth with vascular, epidermal, and skeletal anomalies (CLOVES) syndrome; other overgrowth syndromes; and also some venous malformations [18, 19]. This finding supports the idea that many vascular malformation overgrowth syndromes lie on a spectrum of disease referred to as the *PIK3CA*-related overgrowth spectrum (PROS) [18, 20]. These "PIK3CA-related overgrowth syndromes" are discussed in more detail later in this textbook.

The diagnosis of KTS is primarily clinical. Imaging is helpful for evaluating the extent of the disease. Magnetic resonance imaging (MRI) and angiography (A) is often helpful in evaluating the extent of overgrowth and involvement of underlying vasculature and associated malformations. These imaging studies are necessary for treatment planning [21]. Examination of venous insufficiency and vein mapping by ultrasound is done to assess deep venous developmental abnormalities and venous competency. Usually the entire limb and pelvis are imaged. Routine radiography and scanograms are used to evaluate and monitor limb-length discrepancy; however, they are rarely needed prior to early childhood. While lymphoscintigraphy can be useful in the evaluation of lymphatic vasculature, it is often not indicated as it is fairly invasive.

Natural History

The severity of clinical phenotype of KTS is extremely variable, and for that reason the natural history of the disease is also quite variable. The capillary malformation (CM) in KTS persists indefinitely, even with treatment. Many CMs in KTS may thicken and develop vascular "blebs" (Fig. 31.4) over time, especially if there is an associated lymphatic component. These blebs may bleed or ooze serous fluid and can be a risk factor for the development of cellulitis.

Hallmarks of KTS include venous and venolymphatic malformations and venous varicosities which may cause chronic venous insufficiency and significant edema (Fig. 31.5) that often progress throughout life if not managed adequately. These malformations are frequently associated with a dull, achy pain that is often worsens as the day goes on. Chronic venous congestion can also lead to cutaneous changes such as lipodermatosclerosis, stasis dermatitis, ulceration, and pigmentary changes [22, 23]. Treatment and prevention of chronic venous insufficiency is further discussed in the treatment section below.

The overgrowth (both length and girth) in patients with KTS may be slowly progressive, although the progression slows after the child has completed growth. Increases in girth may continue, but those increases occurring after a child is done growing can often be attributed to lymphedema. The overgrowth in KTS can sometimes be difficult to differentiate from Proteus syndrome. However, along with other distinguishing features, the overgrowth present in Proteus is typically distortive and more progressive [9].

The presence of venous stasis, ulceration, lymphatic leakage, and other cutaneous wounds predispose patients to the development of cellulitis, which is seen in approximately 15% of patients with KTS [8]. Severe episodes may require paren-

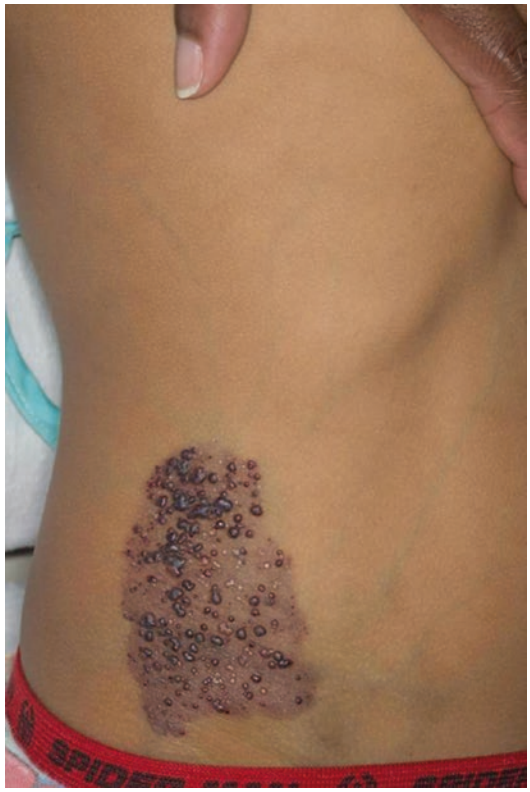

Fig. 31.4 Patient with KTS. Note the capillary malformation with blebs, cutaneous evidence of varicosities, and overgrowth of the leg

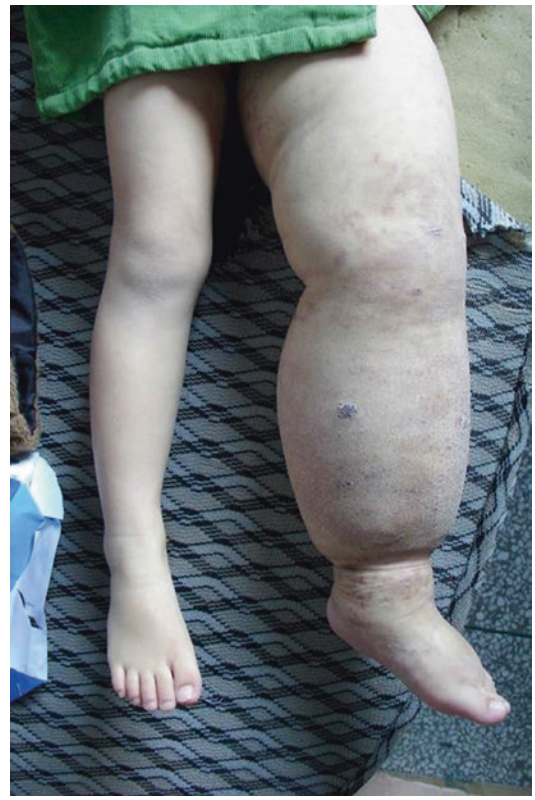

Fig. 31.5 Severe lymphedema associated with KTS

teral treatment. Often patients are able to recognize symptoms of cellulitis prior to it becoming clinically apparent.

Coagulopathy is an important concern in patients with KTS and some other overgrowth syndromes. Fifteen to 30% of patients with KTS often experience superficial thrombophlebitis and/or phleboliths, likely from venous stagnation in the varicose veins of the extremities [8, 24]. However, more serious coagulopathy is also concerning. Extensive vascular malformations may be associated with a low level, localized, intravascular coagulopathy, an entity which must be differentiated from Kasabach-Merritt phenomenon [25]. In KTS, localized consumptive coagulopathy within the malformation(s) leads to abnormalities in coagulation factors such as D-dimer and fibrinogen levels; the extent of the malformations seems to correlate with D-dimer levels [24]. While this is generally well-tolerated, surgical procedures, bone fractures, pregnancy, or trauma can lead to bleeding difficulties which could be life-threatening [26, 27]. Deep venous thrombosis (DVT) is more common in those who have KTS than those who do not, even in the presence of venous varicosities. Approximately 4–8% of patient with KTS experience DVT with or without pulmonary embolism (PE) [8, 24], and this must be treated immediately.

Pregnancy is a common concern for KT patients and for the physicians who take care of them. Successful and safe pregnancies can be achieved in patients with KTS, [10, 28]. Pregnancies are best managed with a multidisciplinary team with expertise in the management of vascular malformations in this setting, particularly in higher-risk situations such as vascular involvement of the uterus. Bleeding and coagulopathy, including increased risk of DVT, are often the largest concerns in pregnant patients with KTS, and appropriate peripartum management of those issues, including consideration of anticoagulation and surgical planning, is necessary. KTS symptoms such as pain and edema may also be increased during pregnancy [28] but often return to baseline after delivery and nursing.

Pain is a common symptom in patients with KTS. It may be due to aforementioned reasons such as chronic venous insufficiency, cellulitis, or coagulopathy but may also have other causes including arthritis and neuropathic pain [29]. In some KTS patients, there may be involvement of the vascular malformation within the joint. In this situation, intervention is often necessary at some point in life. Recurrent hemarthrosis increases the risk for joint destruction and results in arthritis and flexion contractures [25]. Another cause of pain in KTS patients is neuropathic pain. This pain can be quite disabling, and while the etiology can be unclear, it may result from nerve damage during surgical procedures and/or from direct compression of the nerve(s) from the malformation itself. As a result of all of these issues and potential complications, patients with KTS have been found to have a lower quality of life (QoL) as compared to unaffected people, particularly with regard to physical functioning and bodily pain [30].

Treatment

Treatment for KTS can be challenging and focuses on supportive care, prevention of complications, and improvement of quality of life, as there currently is no cure. Because of the complex nature of the disease, its manifestations, and potential complications, patients should ideally be cared for in a center with a multidisciplinary team-based approach with experience managing patients with KTS.

The capillary malformation (CM) in KTS may be treated with a vascular laser, most commonly the pulsed dye laser (PDL) [31]. When a CM involves an extremity, achieving appreciable lightening with the laser is more difficult and requires multiple sessions. For this reason, treatment of the CM for cosmetic reasons is usually not favored. In CMs starting to develop some hypertrophy or blebs, PDL therapy can be helpful for treatment and prevention. In CMs where significant thickening and "blebbing" have already developed, PDL treatment may not be as efficacious, and more destructive lasers such as the Neodynium:YAG and CO_2 lasers may be used.

Compression of the affected limb is a mainstay of therapy in KTS. Graduated compression

stockings of at least 20–30 mmHg, but higher if tolerated, should be used in all patients with KTS. Daily compression is useful for the treatment of pain caused by chronic venous congestion, to decrease lymphedema, and also helps to prevent episodes of superficial thrombophlebitis, cellulitis, and ulceration by improving vascular return [32, 33]. While compression will reduce the girth of the limb when lymphedema is present, it does not decrease soft tissue and/or bony overgrowth. Depending on the size of the affected extremity, custom-fit compression stockings may be indicated, and the expertise of a physical therapist specializing in lymphedema may also be helpful.

In patients who are prone to cellulitis, hospitalization with intravenous antibiotic therapy may be necessary. Many patients who have recurrent episodes of cellulitis are aware of their symptoms of infection prior to clinical appearance, and in those situations, having a standing prescription of antibiotics may allow the patient to initiate antibiotic therapy early, thereby avoiding hospitalization. Compression and good skin hygiene, including early treatment of athlete's foot, dilute bleach baths, and regular cleansing of the skin, can be useful to prevent cellulitis [29]. In patients where lymphatic or vascular leakage from "blebs" or other cutaneous involvement is a source for their infections, localized treatment of those areas can also prevent recurrent episodes of cellulitis.

Superficial thrombophlebitis is usually treated with anti-inflammatory agents, compression, and elevation. For more serious coagulopathy, specifically DVT and PE, anticoagulation should be done immediately. In those with a history of recurrent DVT and with a history of PE, prophylactic anticoagulation should be considered. Placement of inferior vena cava filters may also be beneficial. Anticoagulation, such as low-molecular-weight heparin (LMWH), is sometimes useful in cases of superficial thrombophlebitis and recurrent phleboliths. However, the risk of difficulty with bleeding should be considered. Anticoagulation therapy in patients with abnormal D-dimer and fibrinogen levels is somewhat controversial since clinical trials have not shown that this treatment reduces the risk of DVT or PE [34, 35]. Estrogen-containing medications should be avoided in all women with KTS.

Sclerotherapy is a commonly-used and effective treatment of the slow-flow vascular malformations and varicosities in KTS [36–43]. Some veins and malformations may not be amenable to sclerotherapy, and in those situations techniques including embolization, endovascular ablation, and surgical vein stripping should be considered [44–48]. Patients should be cautioned that the rate of recurrence is high, and even after these procedures, compression should continue to be a mainstay of therapy.

If the limb-length discrepancy is <2 cm, then active surgical intervention is usually unnecessary, and use of a shoe lift of the opposite shoe generally suffices. If a projected discrepancy is more than 2 cm, then epiphysiodesis of the longer extremity is usually indicated [8]. Synovectomy and sometimes even joint replacement, depending on the extent of destruction, are used to treat symptomatic intraarticular malformations in KTS [49–52]. In some patients, resection of a ray in the foot is sometimes indicated to improve ambulation. Debulking procedures have also been done, but the risk of these procedures is high and should only be done when the excess bulk severely limits function [53]. As a last resort, amputation of a limb may be necessary to improve overall function and QoL [8].

In patients who have chronic GI/rectal bleeding requiring blood transfusions, an endorectal pull-through procedure may be necessary if all other measure have failed [54]. Urologic surgical procedures may similarly be necessary in cases of severe hematuria that are unresponsive to conservative treatment approaches [10].

Recent advances into the genetics of overgrowth syndromes and medical treatments have led to the discovery that the mTOR-inhibitor, sirolimus, can be effective in patients with KTS. Because sirolimus is an immunosuppressant, it should be used with caution. The potential benefits and risks should be carefully weighed and discussed with each patient. In patients with significant morbidity, including difficult with pain and decreased QoL, sirolimus may be effective at eliciting at least a par-

tial response in as many as 85% of patients [55]. Its use in topical form for localized cutaneous areas of involvement has also been explored.

To assist the reader in gaining familiarity with available evidence, the following rating system has been used to indicate key references for each chapter's content:
***: Critical material. Anyone dealing with this condition should be familiar with this reference.
**: Useful material. Important information that is valuable in in clinical or scientific practice related to this condition.
*: Optional material. For readers with a strong interest in the chapter content or a desire to study it in greater depth.

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Choanal Atresia-Lymphedema

32

Graham Strub and Sanjay Parikh

Genetic diagnosis	Yes
Genetic etiology	Autosomal recessive, ?PTPN14
Level of evidence: treatment	Low
Evidence:	Single family

Diagnosis

Phenotype and Variations

Sustained accumulation of interstitial fluid, or lymphedema, can occur in animals and humans when the development of the lymphatic vascular network is disturbed [1]. The study of animal models as well as of several syndromic conditions in which lymphedema is a component has furthered our understanding of the genetic regulation of lymphatic development, maintenance, and function [2–6]. The unusual concurrence of lower extremity lymphedema and anatomical closure of the posterior choanae in the nasal cavity (posterior choanal atresia or PCA) has been reported, and analysis of this concurrence advanced our knowledge of lymphatic development.

In 1982, Qazi et al. [7] described three patients from a consanguineous Middle Eastern family who demonstrated an autosomal recessive inheritance of bilateral PCA (Fig. 32.1) (endoscopic views of choanal atresia and CT). The first patient (propositus), the child of first cousins once removed, presented with bilateral bony PCA, a narrow and highly arched palate, hypoplastic nipples, pectus excavatum, poor head control, delay in speech development, slightly enlarged lateral and third ventricles, and a normal karyotype. The propositus's younger sister was born with bilateral bony PCA and a highly arched palate but no other abnormalities. The propositus's paternal aunt, the child of first cousins, was born with bony bilateral PCA, a narrow and highly arched palate, and micrognathia and was otherwise normal.

In 1991, Har-El et al. [8] published a follow-up study of this family in which the original three patients had all developed hard, non-pitting bilateral lower extremity lymphedema between 4 and 5 years of age. In addition, five other family members were identified as having either unilateral or bilateral PCA, two of which also presented with unilateral or bilateral lower extremity lymphedema (Fig. 32.2 (lower extremity lymphedema)). Of the

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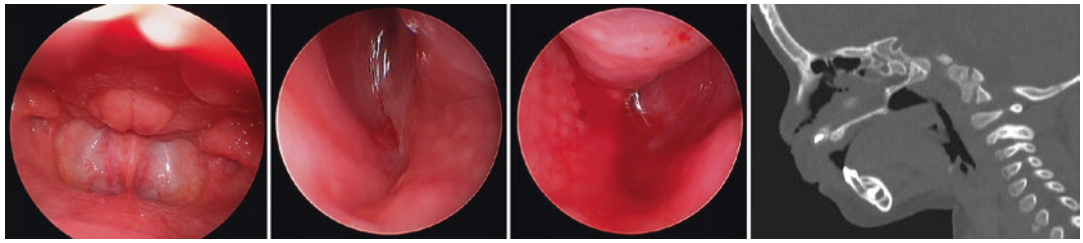

Fig. 32.1 Bilateral choanal atresia. Left-right: Posterior endoscopic view using a 120° telescope, right choana anterior, left choana anterior, sagittal CT demonstrating boney choanal atresia. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer). (Images courtesy of Seattle Children's Radiology, Giridar Shivaram, Eric Monroe and Kevin Koo)

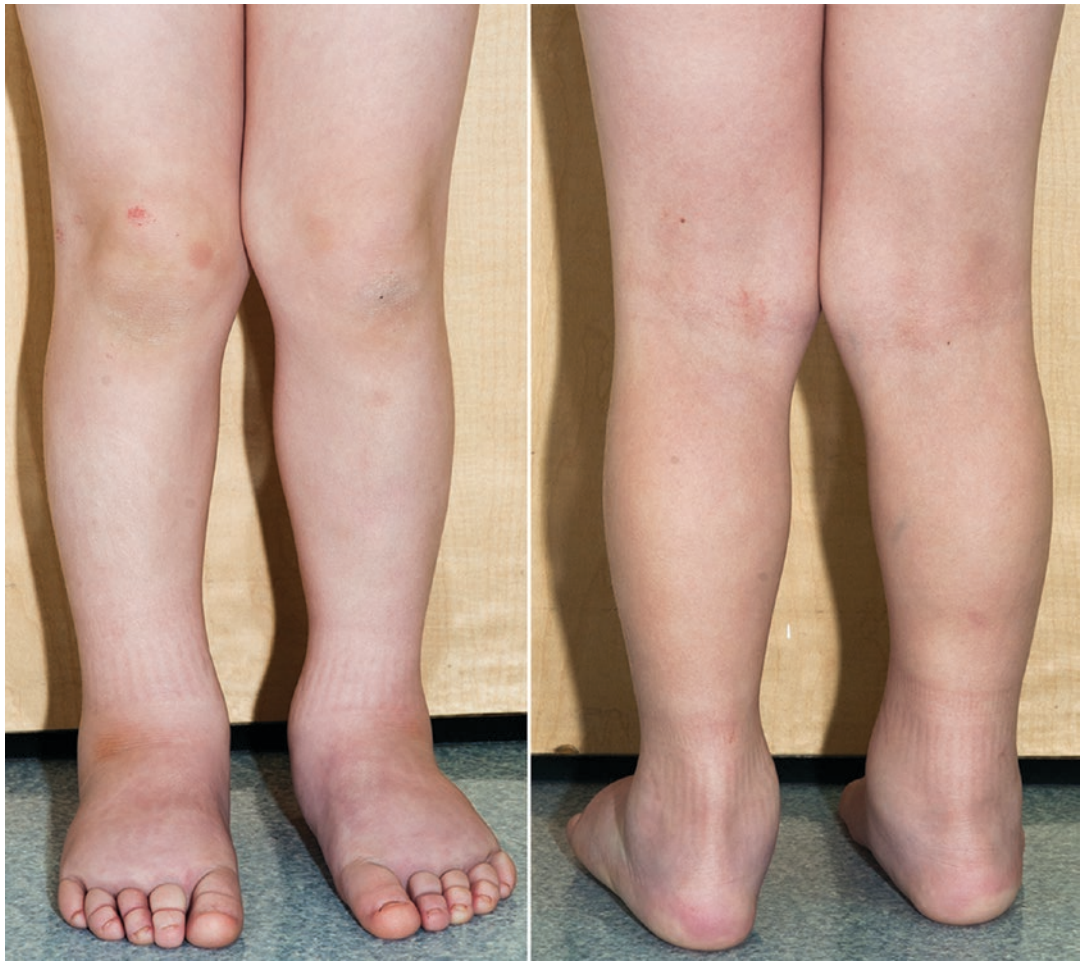

Fig. 32.2 Lower extremity lymphedema. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

three newly identified family members with PCA who did not have documented lymphedema, two had died before the age of 6 months (one was stillborn, and one died of measles), and one had unilateral PCA and spina bifida and was paraplegic.

Etiology

The etiologies of primary lymphedema and PCA are independently reviewed in the literature (reviewed respectively in Brouillard et al. [9] and

Kwong [10]); however, the concurrence of these two relatively rare conditions has only been reported in one family and analyzed in one study by Au et al. [11]. In that study, linkage analysis and genotyping of family members identified an interval on chromosome 1q32–q41 homozygous for all affected individuals and containing 52 predicted genes, including the protein tyrosine phosphatase (PTP) *PTPN14*. Because PTP mutations have been previously associated with lymphedema [12, 13], mutational analysis of *PTPN14* was performed and identified a 2016 bp deletion homozygous in all affected individuals not present in any Arab or mixed European control chromosomes. This mutation generates a truncated mRNA product resulting from a premature stop codon. The peptide product is unstable and catalytically inactive and has an altered amino-terminal domain preventing appropriate subcellular localization to the plasma membrane. Chimeric mice generated using exon-trapping to recapitulate the human mutation in *PTPN14* demonstrated limb and periorbital edema as well as hyperplastic lymphatic capillaries in 14% of the animals. However, no animals demonstrated PCA or other craniofacial abnormalities. The authors speculate that the absence of PCA may be due to limitations of their murine model, in that their animals were not truly null for *PTPN14*, so it is still unclear whether the concurrent PCA in the identified family is due to mutation of *PTPN14* or convergence of two recessive alleles. The precise mechanism by which mutant *PTPN14* results in lymphedema is also unclear. Au et al. [11] hypothesize that PTPN14 may function in signal transduction by forming a multi-protein complex and demonstrated co-immunoprecipitation of PTPN14 and VEGFR3 in a cell culture model using immortalized vein endothelial cells. VEGFR3 is a critical growth factor receptor essential for lymphangiogenesis. A mutation in this gene causes Milroy's disease in humans [14–16], a condition characterized by isolated lymphedema due to hypoplastic or absent lymphatic vessels [17, 18]. Alternative hypotheses of PTPN14's role in lymphatic function include maintenance of lymphatic capillary integrity due to PTPN14 accumulation at adherens junctions [19] and loss of the growth suppressor function of PTPN14 [20] in lymphatic endothelial cells.

Natural History

The natural history of concurrent PCA and lymphedema is limited to the one family described in the literature. Initial presentation is similar to the typical presentation of PCA and is dependent on whether the obstruction is unilateral or bilateral. Newborns are obligate nasal breathers until mouth breathing is established during the decent of the larynx at 4–6 weeks of life, and as such bilateral PCA presents with acute respiratory stress with intermittent cyanosis that is typically relieved by crying. Unilateral PCA is typically diagnosed later in life and manifests as chronic unilateral nasal obstruction, chronic sinusitis, and rhinorrhea. The development of the lower limb lymphedema associated with choanal atresia appears to occur later in childhood beginning at the age of 4 years. The presentation is that of slowly progressing, hard, non-pitting edema in one or both lower extremities. The lymphedema may be limited to below the ankle (as in one patient) or may extend up to the thighs.

Treatment

The treatment for choanal atresia with lymphedema is identical to managing these conditions independently. The first step is initial airway management, as bilateral PCA can present as an airway emergency. The primary goal is to establish an adequate oral airway, which can be accomplished by the use of a McGovern nipple, or in cases where this is inadequate, oral endotracheal intubation. In cases where patients have coexisting craniofacial abnormalities or other congenital malformations (such as is found in CHARGE syndrome), tracheotomy may be required as these patients often fail early PCA repair and may require multiple staged procedures for their other conditions [21]. The definitive treatment of PCA is surgical management to reestablish the nasal airway. This can be accomplished by several techniques including transnasal puncture, transpalatal repair, and transnasal endoscopic repair. For this last approach, adjuvant treatments such as postoperative stenting, laser assistance, image-guided surgery, and mitomycin

C treatment may be used in conjunction with surgery. Currently there exists no consensus on which of these options leads to the most favorable outcomes [22]. The treatment of primary lymphedema is intended to restore the function and physical appearance of the affected areas and reduce the risks of complications (reviewed by Murdaca et al. [23]). Nonsurgical management involves the use of compression bandage-centered decongestive lymphatic therapy (DLT) and manual lymphatic drainage (MLT), which function to stimulate the development of collateral lymphatics in an affected region. For patients who do not respond to nonsurgical interventions, surgical management including lympho-venous anastomosis, free lymph node transplantation, and debulking may be considered.

To assist the reader in gaining familiarity with available evidence, the following rating system has been used to indicate key references for each chapter's content:
***: Critical material. Anyone dealing with this condition should be familiar with this reference.
**: Useful material. Important information that is valuable in in clinical or scientific practice related to this condition.
*: Optional material. For readers with a strong interest in the chapter content or a desire to study it in greater depth.

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PIK3CA-Related Overgrowth Spectrum (PROS)

33

Erin Conboy, James T. Bennett, and David Deyle

Genetic diagnosis	Yes
Genetic etiology	PIK3CA
Level of evidence: treatment	Low-moderate
Evidence	Case series; retrospective reviews

Diagnosis

Phenotype and Variations

PIK3CA-related overgrowth spectrum (PROS) refers to a group of disorders of segmental overgrowth caused by mutations in phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*). PROS is an umbrella term that includes several diagnostic entities, some of which were independently described prior to the discovery that *PIK3CA* mutations were common to all [1, 2]. The mutations that cause PROS are typically, but not always, postzygotic, meaning that the mutation is not present in every cell in the body [3, 4]. The resulting mosaicism causes some of the phenotypic variation, although specific *PIK3CA* genotypes also contribute. The PROS diagnostic entities [5] include:

- Congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal and spinal (CLOVES) syndrome
- Fibroadipose hyperplasia or overgrowth (FAO)/hemihyperplasia multiple lipomatosis (HHML)
- Klippel-Trenaunay syndrome (KTS)
- Megalencephaly-capillary malformation syndrome (MCAP syndrome)
- Hemimegalencephaly (HMEG) and dysplastic megalencephaly (DMEG)
- Isolated macrodactyly
- Isolated lymphatic malformations (LM) [6]
- Facial infiltrating lipomatosis [7]
- Focal cortical dysplasia (FCD)

Although some of the above entities are clearly distinguishable from each other (e.g., HMEG and macrodactyly), there is significant overlap. For example, KTS and CLOVES syndromes tend to have hypertrophy and capillary malformations of

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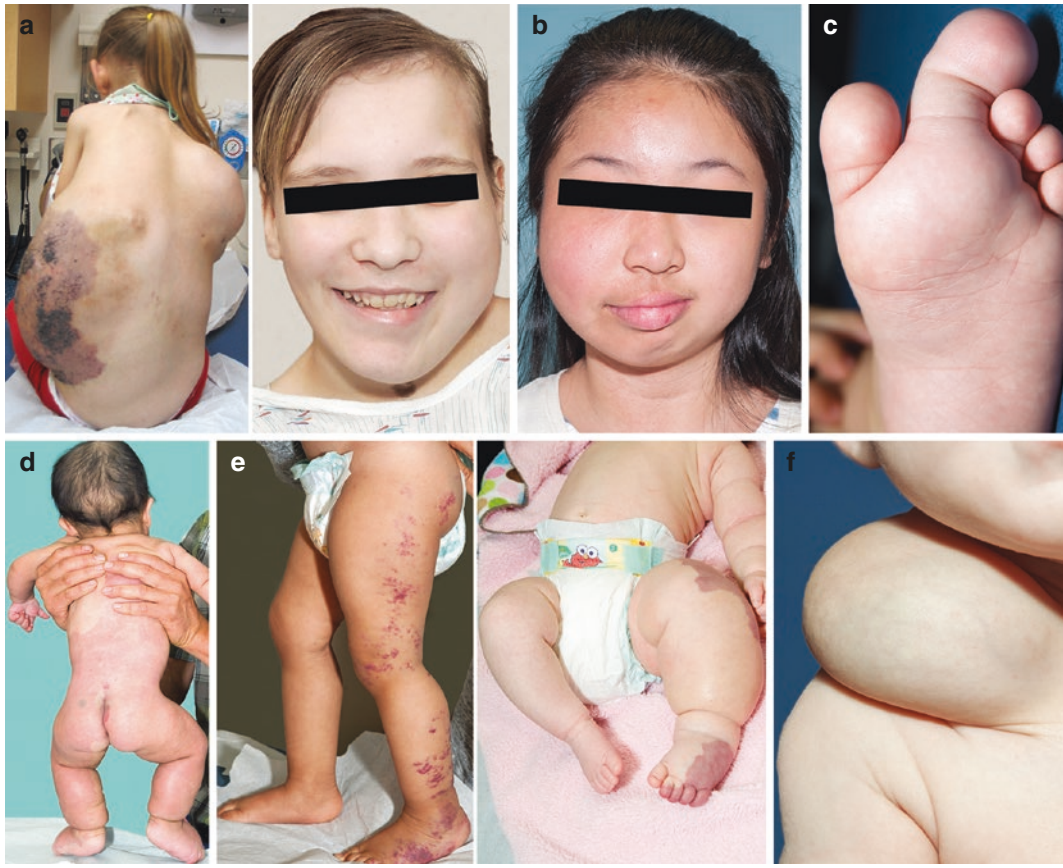


Fig. 33.1 Phenotypic spectrum of PROS: (**a**) CLOVES with facial hemihypertrophy, (**b**) FAVA, (**c**) macrodactyly, (**d**) megencephaly capillary malformation (MCAP), (**e**) two examples of Klippel-Trenaunay syndrome, (**f**) isolated stage one lymphatic malformation. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

a limb, but individuals with CLOVES syndrome have additional, more severe features (Fig. 33.1).

There has been some discussion about whether these diagnostic entities should be "lumped" or "split" into separate entities. Based on genetic and clinical data from a cohort of 61 individuals with overgrowth and *PIK3CA* mutations, Mirzaa et al. emphasize that *PIK3CA*-related overgrowth disorders comprise a discontinuous, rather than a continuous spectrum [2]. Their conclusion is based on the fact that the mutational spectrum and clinical phenotypes of patients with MCAP is distinct from CLOVES syndrome. MCAP-causing mutations are generally widespread across the *PIK3CA* gene, while the CLOVES-associated mutations are primarily located within three residues (amino acids 542, 545, and 1047), termed "hotspots" because they are also recurrently mutated in many sporadic human cancers. Most of the patients in their cohort were classified as having MCAP ($n = 50$), a disorder characterized primarily by large brain size with or without cortical developmental abnormalities (e.g., polymicrogyria) and with minimal body overgrowth that typically normalizes as the child ages. Patients with MCAP can also have cutaneous vascular malformations, connective tissue laxity, and digital anomalies (usually two to three syndactyly but also polydactyly). In addition to MCAP, two other clinical categories of *PIK3CA*-positive patients are described by Mirzaa et al.: "hotspot-associated phenotypes" ($n = 4$) and an

intermediate group ($n = 7$) that is between MCAP and the hotspot-associated phenotypes. The hotspot-associated phenotypes include CLOVES and dysplastic megalencephaly (DMEG). These patients typically have severe segmental body overgrowth that worsens with age, but head and brain size are usually normal (although one patient in this category had "bilateral hemimegalencephaly" and features of CLOVES syndrome). Port-wine stains and epidermal nevi are also commonly seen in patients with the hotspot-associated phenotypes. Patients with the intermediate phenotype exhibited features either overlapping MCAP but lacking megalencephaly or suggesting a milder variant of CLOVES.

Arguing in favor of *PIK3CA*-associated phenotypes as consisting of a single broad spectrum, Keppler-Noreuil et al. described 35 individuals with segmental overgrowth and somatic *PIK3CA* mutations; the overgrowth was described as asymmetric, disproportionate, and progressive [1]. They proposed the phenotypic designation of *PIK3CA-related overgrowth spectrum (PROS)* to describe the different but related phenotypes caused by *PIK3CA* mutations. In their cohort, more individuals (24/35) had overgrowth of the lower extremities as opposed to the upper extremities, and only two patients had unilateral involvement of the orbit and cheek. Interestingly, the asymmetric overgrowth in their cohort was predominantly left-sided, for reasons that remain unclear. They proposed that fibroadipose overgrowth (FAO), hemihyperplasia multiple lipomatosis (HHML), macrodactyly, and CLOVES syndrome represent a single *PIK3CA*-related phenotypic spectrum, with CLOVES syndrome representing the most severe end. They emphasize that the overgrowth in PROS is primarily congenital, and that, in most patients, the postnatal progression is mild. This distinguishes PROS from another overgrowth syndrome, Proteus syndrome, in which the overgrowth is typically not present at birth and is usually progressive postnatally. They also emphasize that all PROS patients have some form of adipose dysregulation. Similarly to Mirzaa et al., they describe a single patient (#33) described as having both hemimegalencaphaly and the body overgrowth of CLOVES syndrome, though this seems to be the exception and not the rule. It should be noted that the patients within the Keppler-Noreuil et al. cohort were primarily ascertained via non-CNS phenotypes, while those of Mirzaa et al. were primarily ascertained via brain abnormalities.

Lumping these disorders under the term PROS is useful as it describes the underlying genetic mechanism well. However, it should be recognized that within this term are distinct clinical entities, with a fairly clear genotype and phenotype distinction between patients with features of MCAP (who tend to have broader spectrum of mutations within the PIK3CA gene) and patients with primarily non-CNS overgrowth features (who tend to have "hotspot" *PIK3CA* mutations).

A National Institutes of Health workshop [5] suggests useful clinical diagnostic criteria for PROS disorders (Table 33.1).

Table 33.1 NIH clinical diagnostic criteria for PROS disorders

Required
Presence of somatic *PIK3CA* mutation (if this is not detected, then a presumptive PROS diagnosis is considered)
Congenital or early childhood onset
Overgrowth sporadic and mosaic (other terms: patchy, irregular)
Features as described in either A or B
A. Spectrum (two or more features)
1. Overgrowth: Adipose, muscle, nerve, skeletal
2. Vascular malformations: capillary, venous, arteriovenous malformation, lymphatic
3. Epidermal nevus
B. Isolated features
1. Large isolated lymphatic malformation
2. Isolated macrodactyly *or* overgrown splayed feet/hands, overgrown limbs
3. Truncal adipose overgrowth
4. Hemimegalencephaly (bilateral)/dysplastic megalencephaly/focal cortical dysplasia
5. Epidermal nevus
6. Seborrheic keratoses
7. Benign lichenoid keratoses

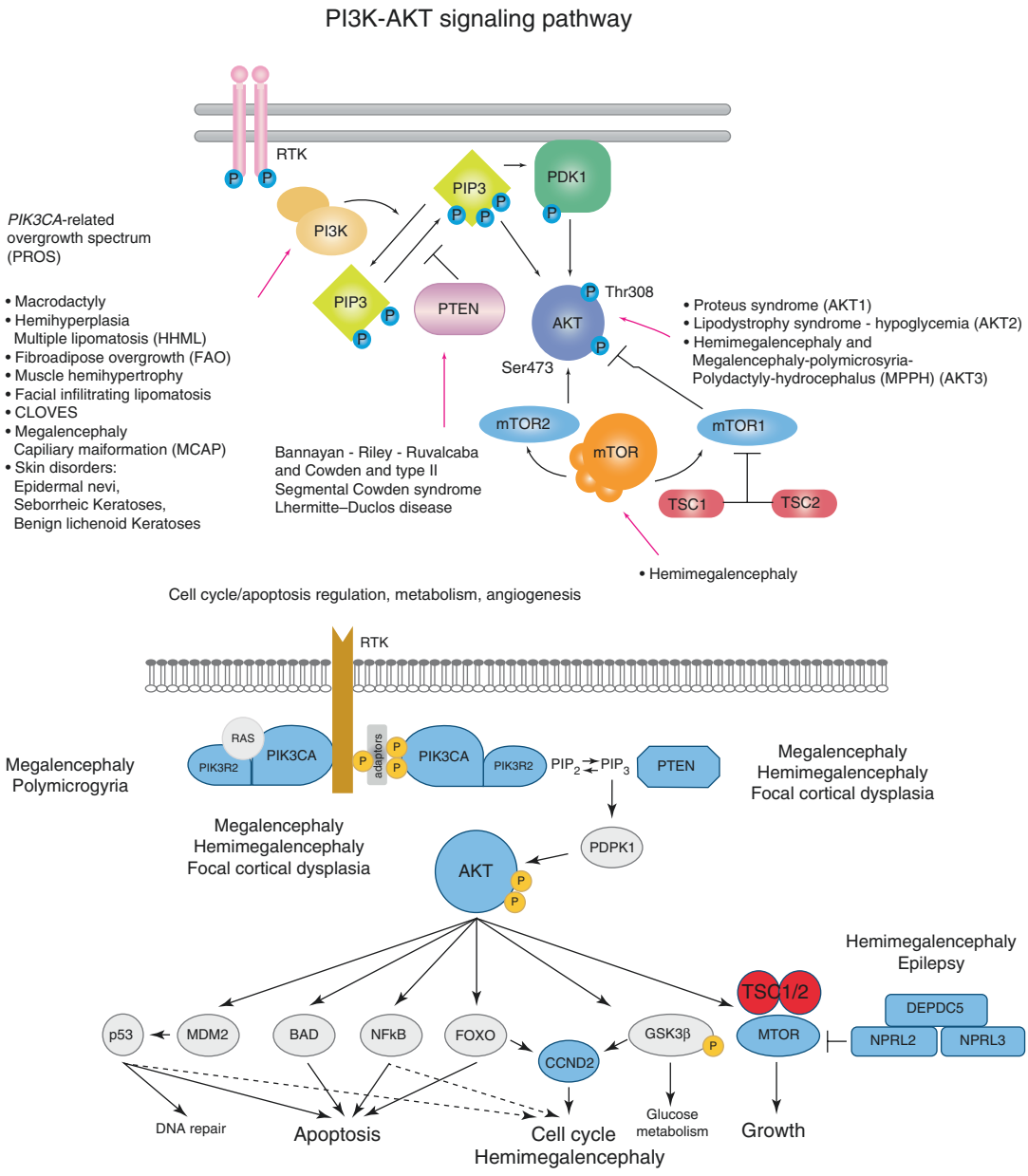
Diagnostic Genetic Testing

Recommendations about diagnostic genetic testing for patients with PROS come from a panel of experts that convened at the NIH in 2014 [5]. Pathogenic *PIK3CA* mutations are not usually present in every cell in the body but are mosaic, meaning that only a subset of tissues carries the mutation at detectable levels. Thus the primary issues to deal with in molecular diagnostic testing for PROS are *which tissues to test* and *which molecular methodology to use* to maximize sensitivity for detection of low-frequency (subclonal) variants.

The NIH panel suggests the use of clinically affected tissue, preferably a fresh, uncultured, surgically resected sample or dermal biopsy whenever possible. *PIK3CA* mutations can be detected in affected tissues or fibroblasts from skin biopsies to varying degrees. Levels of mutation detected from cultured fibroblasts should be interpreted with caution, as the presence of a *PIK3CA* mutation can lead to a growth advantage among fibroblasts in vitro, falsely elevating measured levels of *PIK3CA* mutation. Attempting to detect *PIK3CA* mutations in blood or saliva is not preferred, as constitutional, or germline, mutations of *PIK3CA* causing PROS are rare, and the absence of detected *PIK3CA* mutation in the blood or saliva does not rule out its presence in other tissues. Testing is also possible on formalin-fixed paraffin-embedded tissue, particularly when this type of sample represents the most "affected" tissue. Allele-specific methods, such as restriction fragment length polymorphism (RFLP) or droplet digital PCR (ddPCR), are effective methods for mutation detection. They are relatively easy to develop and inexpensive and have a high sensitivity of detection (0.1–1% alternate allele fraction detected, sometimes lower). Screening for recurrent hotspot mutations using these allele-specific methods is a very reasonable approach. However, allele-specific methods suffer from an inability to detect mutations outside of the three to four hotspot alleles. Methods that sequence entire exons are required for full *PIK3CA* gene sequencing. These methods include Sanger and next-generation sequencing (NGS)-based methods. Sanger sequencing is relatively inexpensive, and most labs have a great deal of experience with this method, but it suffers from limited sensitivity. Typically Sanger sequencing cannot detect mutations at lower than ~20% alternate allele fraction. Depending on the coverage, NGS-based methods maximize sensitivity (as low as ~1%) and breadth of sequencing; at present, *targeted capture and next-generation sequencing of all the exons of PIK3CA is the method of choice for molecular diagnosis of PROS* [5, 8].

Etiology

Figures from Mirzaa [2], Keppler-Noreuil [5]; reproduced with permission


PI3K-AKT signaling pathway
RTK
PIP3
PDK1
PI3K
PIP3
PTEN
AKT
Thr308
Ser473
mTOR2
mTOR
mTOR1
TSC1
TSC2
PIK3CA-related overgrowth spectrum (PROS)
• Macrodactyly
• Hemihyperplasia Multiple lipomatosis (HHML)
• Fibroadipose overgrowth (FAO)
• Muscle hemihypertrophy
• Facial infilitrating lipomatosis
• CLOVES
• Megalencephaly Capiliary maiformation (MCAP)
• Skin disorders: Epidermal nevi, Seborrheic Keratoses, Benign lichenoid Keratoses
Bannayan - Riley - Ruvalcaba and Cowden and type II Segmental Cowden syndrome Lhermitte–Duclos disease
• Proteus syndrome (AKT1)
• Lipodystrophy syndrome - hypoglycemia (AKT2)
• Hemimegalencephaly and Megalencephaly-polymicrosyria-Polydactyly-hydrocephalus (MPPH) (AKT3)
• Hemimegalencephaly
Cell cycle/apoptosis regulation, metabolism, angiogenesis
RTK
RAS
PIK3R2
PIK3CA
adaptors
PIK3CA
PIK3R2
PIP2 PIP3
PTEN
Megalencephaly Polymicrogyria
Megalencephaly Hemimegalencephaly Focal cortical dysplasia
Megalencephaly Hemimegalencephaly Focal cortical dysplasia
PDPK1
AKT
Hemimegalencephaly Epilepsy
TSC1/2
DEPDC5
NPRL2
NPRL3
MTOR
p53
MDM2
BAD
NFkB
FOXO
CCND2
GSK3β
DNA repair
Apoptosis
Cell cycle Hemimegalencephaly
Glucose metabolism
Growth

Genetics

PIK3CA is located on chromosome 3p26.32 and has 23 exons. *PIK3CA* encodes the 110 kD catalytic subunit of phosphatidylinositol-4,5-bisphospate 3-kinase (PI3K). With ATP, PI3K converts phosphatidylinositol (3,4)-bisphosphate (PIP2) to phosphatidylinositol (3,4,5)-triphosphate (PIP3) when activated by a tyrosine kinase receptor ligand. PIP3 causes phosphorylation and translocation of PDK1 at the cellular membrane, which in turn phosphorylates the serine/threonine kinase, AKT. Activated AKT leads to increased downstream cellular effects and cell proliferation through the mTOR1 pathway. Activating heterozygous *PIK3CA* mutations produce abnormal upregulation of the PI3K-AKT-mTOR pathway, leading to the overgrowth symptoms of PROS. Both postzygotic (mosaic) and constitutional activating mutations in *PIK3CA* lead to PROS, though postzygotic mutations are far more common [9].

Pathophysiology

Although numerous studies have investigated the mechanisms by which activating PIK3CA mutations cause cancer [10–12], the mechanisms underlying *PIK3CA*-related developmental abnormalities have only begun to be explored [13, 14]. Three recent publications showed that the brain and vascular malformation phenotypes seen in patients with PROS could be produced and studied in mice engineered to express mutated forms of *PIK3CA* in mosaic tissue distributions [15–17]. In each of these papers, aspects of the mouse phenotypes could be normalized by treatment with rapamycin or other PI3K-AKT-mTOR pathway inhibitors.

Castillo et al. generated a mouse in which an activated form of *PIK3CA* (with the p.H1047R "hotspot" mutation) was expressed in a mosaic distribution within embryonic mesodermal cells [16]. These mice (termed MosMes-*Pik3ca*^{H1047R}) developed subcutaneous vascular malformations in different body sites. As more cells with the mutated form of *PIK3CA* were induced, the phenotypes became more severe, with multifocal and diffuse lesions. At the highest levels of mutation induction, embryonic lethality occurred. Notably, none of the mice showed any evidence of overgrowth. The vascular lesions in these mice showed expression of both venous and lymphatic markers, though lymphatic markers (PROX-1 and LYVE1) were less prominent. Venous malformations were also induced postnatally by expression of the same activated form of *PIK3CA* (p.H1047R) within endothelial cells within the retina. In addition to inducing endothelial cell hyperproliferation, endothelial cell expression of *PIK3CA*^{H1047R} produced vessels with decreased pericyte coverage – a key pathological finding in human venous malformations [18]. Aspects of both the retinal endothelial cell and the embryonic mesodermal *PIK3CA*^{H1047R} phenotypes were normalized upon treatment with rapamycin.

Castel et al. generated mice that express an activated form of *PIK3CA* (*Pik3ca*^{H1047R}) in all cell types after tamoxifen-based induction at age 6–8 weeks [15]. These mice developed venous malformations with 100% penetrance. In contrast to the results of Castillo et al., there was no evidence for lymphatic markers (PROX-1 or LYVE-1) in the malformations, which may reflect differences in timing of PIK3CA activation between the two studies. When *PIK3CA*^{H1047R} was driven in embryonic endothelial cells using a Tie2-Cre strain, embryonic lethality was induced. Similar to the results of Castillo et al., aspects of the *PIK3CA*^{H1047R} phenotypes could be normalized by suppression of the pathway using the mTOR inhibitor everolimus. Treatment with

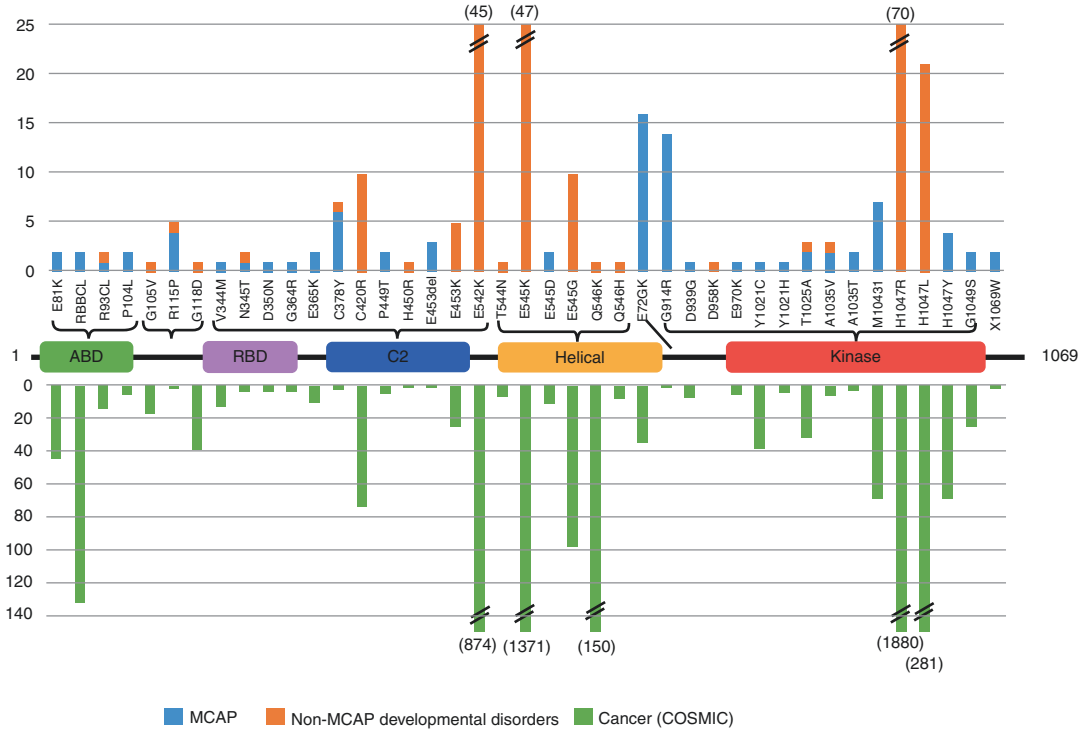
everolimus led to a reduction in the volume of venous malformations and a reduction in cell division in a *PIK3CA*^{H1047R} allotransplantation assay. However, a specific PI3Kα selective inhibitor (BYL719) led to more significant volume reduction than everolimus, as well as an increase in cell death within the lesion. The results of Castel suggest that treatment with selective PI3K inhibitors may be more effective in the treatment of some vascular malformations than inhibition of mTOR with everolimus or sirolimus.

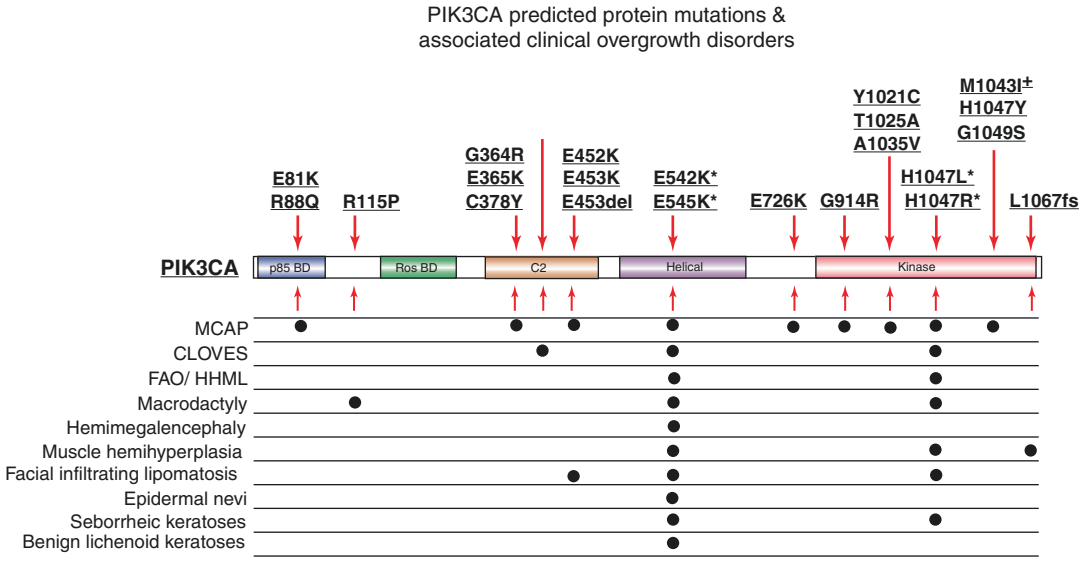
Roy et al. generated mice that expressed activating *PIK3CA* mutations in neural progenitor cells, to study brain-specific aspects of the PROS phenotype (i.e., MCAP, hemimegalencephaly, and focal cortical dysplasias) [17]. They engineered two different *PIK3CA* mutations (p.H1047R and p.E545K) to be induced at different developmental time points (embryonic versus perinatal). Brain-specific embryonic *PIK3CA* activation resulted in mice with megalencephaly, hydrocephaly, cortical malformation, and epilepsy, while perinatal *PIK3CA* activation resulted in mice with epilepsy but without structural brain defects. This is an important finding because it suggests that the epilepsy seen in patients with PROS is not only due to structural brain defects but also caused by ongoing cellular signaling abnormalities (i.e., elevated PI3K-AKT-mTOR signaling). In support of this, acute treatment of these mice with the PI3K inhibitor BKM120 decreased seizure number and duration in both megalencephalic and normocephalic mice. Patients with PROS who have primary brain involvement can have intractable epilepsy that frequently only responds to resection of the epileptogenic region of the brain. The study of Roy et al. suggests that PI3K inhibitors may provide novel antiepileptic therapy for these patients [17].

An important but so far unanswered question in understanding the pathophysiology of PROS is: why do activating mutations in PIK3CA that occur in a lung epithelial cell in an adult contribute to lung carcinoma [10], while the exact same mutation occurring in a mesodermal stem cell leads to somatic overgrowth? It is likely that the developmental location (mesodermal stem cell versus alveolar epithelial cell) and developmental time (embryogenesis versus postnatal, adult life) contribute to the different clinical outcomes of the exact same mutation. Further studies are needed to address this question.

Figures from Mirzaa [2] JCI Insight and Keppler-Noreuil [5], AJMG Part A; reproduced with permission

JCI insight RESEARCH ARTICLE





Management

Patients with PROS require a multidisciplinary approach tailored to the specific organ systems involved in each patient. These patients are ideally treated at a center that has experience managing these relatively rare disorders, with a team featuring dermatologists, geneticists, neurologists, interventional radiologists, as well as surgical specialties including otolaryngology, orthopedics, plastic surgery, and neurosurgery.

Because activating mutations in *PIK3CA* are frequently reported in numerous sporadic cancers [19, 20], there has been concern that patients with PROS are at increased risk of developing cancer. However, at present there is insufficient evidence to assess the magnitude of this risk or the benefit of tumor surveillance. Although a handful of patients with PROS have been reported to develop cancers, most have not. Among the 35 patients in Keppler-Noreuil's cohort, there were no true malignancies, though one benign neoplasm (ovarian cystadenoma) and one possible premalignacy (nephrogenic rest) were reported [1]. Among six patients with CLOVES reported by Kurek et al., one was reported with Wilms tumor [21]. Among 48 patients with MCAP, 2 were reported with meningiomas, 1 with leukemia (diagnosed at age 18), and 2 with Wilms tumor [22–25]. Altogether it seems that the chance of patients with PROS developing Wilms tumor is significantly less than the chance in Beckwith-Wiedemann syndrome (4–20%) [26–28] and also less than the chance in isolated hemihyperplasia (~6%) [29]. The consensus of the 2014 NIH panel was to *consider* serial abdominal ultrasounds every 3–4 months until the age of 8 in all patients with somatic *PIK3CA* mutations, akin to the recommendations for patients with overgrowth associated with Beckwith-Wiedemann syndrome [30]. In addition, the negative burden of serial imaging every 3–4 months for 8 years needs to be considered. It is reasonable to consider that patients with PROS limited to a very small part of the body (e.g., isolated lymphatic malformation or macrodactyly) are likely at lower risk than those with widespread somatic involvement (e.g., CLOVES). Further investigation into the risk/benefit of intense tumor surveillance in this patient population is needed.

Neuroimaging should be performed in all patients with PROS with brain involvement (MCAP, MPPH, HMEG) at the time of diagnosis, to evaluate for cortical dysplasia, ventriculomegaly, and cerebellar tonsillar ectopia/Chiari I malformation. Imaging should include both brain and spinal cord. Spine MRI should also be considered in patients with significant truncal involvement due to the risk of lipomatous or vascular lesions involving the spine [1]. Treatment of segmental overgrowth, which is usually primarily fibroadipose in nature, currently relies on surgical debulking and orthopedic corrections [1]. Pulsed dye laser can be used for treatment of capillary malformations, and sclerotherapy or embolization of ectatic veins can be considered for venous and lymphatic malformations. When vascular malformations are very large or associated with thoracoabdominal lipomatous masses, surgical excision may be combined with embolization, but in each case the management depends on the type and anatomic location and extension. Patients with CLOVES syndrome may be at increased risk of coagulopathies, with pulmonary embolism, spinal thrombosis, and neonatal cerebral infarcts reported [1, 31]. Anticoagulation is therefore an important perioperative consideration in these patients [1].

As described in the pathophysiology section, small molecule inhibitors of the PI3K-AKT-mTOR pathway hold great promise for the management of patients with PROS. The best known inhibitors of this type are sirolimus (aka rapamycin) as well as the "rapalogs" (temsirolimus, everolimus, and deforolimus), created to improve the pharmacodynamics of sirolimus. The safety profile of sirolimus is well known as it has been used for over 15 years as an immunosuppressant in transplant patients [32–34]. Due to its safety, availability, and biological evidence of overactivation of the PI3K-AKT-mTOR pathway in patients with PROS, there have been numerous reports of the efficacy of sirolimus in single case reports or, at most, ret-

rospective reviews of handful of patients, usually with vascular anomalies [35–37]. None of these studies included genetic sequencing data from their cohorts, so the fraction of patients in these studies with *PIK3CA* mutations is unknown. Several studies report some level of positive clinical response and few adverse effects, when sirolimus is given orally at doses equivalent to that in renal transplantation (typically 0.8 mg/m^2 twice per day). However, only a single prospective Phase II efficacy and safety trial of sirolimus has been completed [38]. In this study, 57 patients were treated with oral sirolimus for 6 months. In addition to monitoring for toxicities and adverse effects, the primary outcome measure was efficacy of sirolimus as defined by partial or complete response. Disease response was measured in three spheres: radiologic response, functional impairment score response, and by health-related quality of life (QOL) response. A complete radiologic response required no evidence of disease on imaging, while partial response required >20% reduction in size on imaging. A complete functional response required no evidence of organ dysfunction, and partial required improvement in target organ dysfunction by at least one grade. A complete quality of life response required normalization of QOL scores, while partial response required an improvement in QOL score as compared to the baseline. None of the 57 patients showed a complete response, although most (82%) had a partial response in at least one of the three spheres [38]. It is important to recognize that the natural history of at least some of these vascular anomalies is to improve with time even in the absence of any treatment. Thus, a randomized controlled trial is still needed to conclude that treatment of PROS patients with sirolimus is superior to non-treatment. In addition, because sirolimus' effects are cytostatic and not cytotoxic, and treatment with sirolimus can lead to compensatory upregulation of the PI3K-AKT-mTOR pathway, it is likely that other small molecule inhibitors of the PI3K-AKT-mTOR pathway will ultimately be more effective for patients with PROS.

To assist the reader in gaining familiarity with available evidence, the following rating system has been used to indicate key references for each chapter's content:
***: Critical material. Anyone dealing with this condition should be familiar with this reference.
**: Useful material. Important information that is valuable in in clinical or scientific practice related to this condition.
*: Optional material. For readers with a strong interest in the chapter content or a desire to study it in greater depth.

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Blue Rubber Bleb Nevus Syndrome

34

Janice E. Ma and Jennifer L. Hand

Genetic diagnosis	Yes
Genetic etiology	Spontaneous or autosomal dominant, TEK
Level of evidence: treatment	Low
Evidence:	Case reports and case series

Diagnosis

Phenotype and Variations

Blue rubber bleb nevus syndrome (BRBNS), also known as Bean syndrome, is a rare multisystem disease typically involving venous malformations of the skin and visceral organs, particularly the gastrointestinal tract (Fig. 34.1). The constellation of these findings was first reported by Gascoyne in 1860 but was delineated and officially termed BRBNS by William Bennett Bean in 1958. As described by Bean, characteristics of this condition may include (1) easily compressible, blood-filled sacs; (2) irregular, macular blue lesions potentially with black stippling; and (3) large hemangiomas that may compromise vital structures [1]. Only about 200 cases of BRBNS have been reported in the literature. Though the gastrointestinal tract is most commonly involved, lesions have been reported to involve the eye, lung, thyroid, spleen, liver, kidney, bladder, musculoskeletal, and central nervous system. There is no predilection for sex. The condition has been reported in all races; though it appears that Caucasians are most frequently affected. Lesions can be present as early as birth; cutaneous manifestations typically precede visceral organ involvement.

While lesions can occur anywhere from the mouth to anus along the gastrointestinal tract, the small intestine is most frequently affected. Various imaging modalities including endoscopy, barium studies, contrast-enhanced CT, and technetium-99m-labeled RBC nuclear scintigraphy can be used in visualizing lesions of BRBNS involving the visceral organs [2]. Barium studies may be useful in evaluating the small bowel, though it cannot be used singlehandedly to differentiate vascular BRBNS lesions from other polyps. Meanwhile, endoscopy has higher sensitivity in evaluating for smaller lesions of the stomach, duodenum, and

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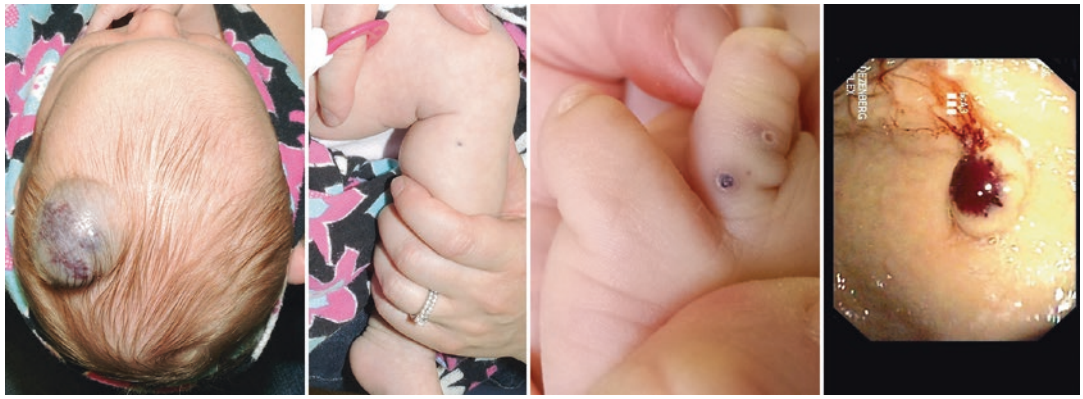

Fig. 34.1 Appearance of blue rubber bleb nevus syndrome. Left–right: scalp venous lesions, small venous lesion on leg and toe, endoscopic view of intestinal venous lesion. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

colon. Technetium-99-m-labeled RBC nuclear scintigraphy may be utilized to identify active sites of gastrointestinal hemorrhage, a very serious and potentially fatal complication of BRBNS. Contrast-enhanced CT is useful in identifying potential complications of BRBNS, which include mucosal necrosis, intussusception, and volvulus. Finally, MRI with fat-suppression techniques is valuable in evaluating lesions within solid organs such as the liver and spleen, as well as the musculoskeletal system. A combination of multiple studies may be required in identification of cutaneous, visceral, and musculoskeletal BRBNS lesions.

Oral cavity involvement has been estimated to affect over half of BRBNS cases [3]. Complications of oral cavity venous malformations include dysphagia and airway compromise. In these cases, flexible laryngoscopy may be utilized to identify lesions. The most common site of gastrointestinal tract involvement is the small intestine. Orbital vascular lesions are characterized by small orbital calcifications and dispensability with increased venous pressure. Presenting symptoms of ocular involvement include intermittent or sudden onset proptosis as well as orbital or retrobulbar pain. Contrast-enhanced CT and MRI are useful in visualizing ocular involvement of BRBNS [4]. Orthopedic involvement may result in complications including pathologic fractures, bony overgrowth, and bowing of skeletal structures.

Etiology

Like other vascular malformations, BRBNS is result of faulty development of vessels during embryogenesis. While some cases of autosomal dominant inheritance have been reported, the vast majority of BRBNS arise spontaneously. Recently, double (cis) somatic mutations of TEK, the gene encoding TIE2, an endothelial cell tyrosine kinase receptor, have been identified as the cause of the majority of sporadic BRBNS cases [5].

Cutaneous lesions often occur on the upper extremities and trunk. They can range in appearance from punctate papules to larger verrucous and pedunculated lesions and vary in coloration from red-purple to bluish-black. On palpation, these lesions have a rubbery consistency and are readily compressible, with instant vascular refill upon release of pressure. Histopathology of these lesions show dilated vascular spaces, lined with a single layer of cuboidal or flattened endothelial cells, surrounded by connective tissue. Increased sweat glands may be observed, accounting for hyperhidrosis in afflicted patients. There is no unique immunohistochemical marker used in the diagnosis of BRBNS. Dermoscopy, a noninvasive visual modality, has been implemented in visualizing cutaneous BRBNS lesions. Dermoscopic features of BRBNS include various hallmarks of venous malformation including

arborizing venous pattern or dilatation of vessels and red-purple nodules with lacunae separated by white linear structures representing fibrous demarcations [6].

Natural History

In addition to a complete history and physical, evaluation should include a complete blood count and stool guaiac test to evaluate for occult gastrointestinal bleeding. Patients may be chronically anemic due to blood loss. Consequently, iron replacement and occasionally transfusions may be warranted. Regular blood tests monitoring for iron deficiency anemia as well as localized intravascular coagulopathy are valuable. Patients may have high D-dimer and low-normal fibrinogen levels [7].

While this syndrome is rare, it is important for providers to recognize symptoms and complications of this potentially debilitating and life-threatening condition. Anemia and melena are the more common presenting symptoms of this condition, particularly if characteristic vascular lesions of the skin are also apparent [8]. Nevertheless, given the many organs that BRBNS can involve, symptoms can be highly variable and also include, but not limited to, hemoptysis, hematuria, dysphagia, and neurologic manifestations such as visual changes, paralysis, and epilepsy. Due to the wide variety of manifestations and potential complications, a multidisciplinary team is typically recommended for optimal management of this systemic condition.

BRBNS lesions may appear very similar to multiple glomangiomas, making it easy to confuse the two (Fig. 34.2). Of note, multiple glomangiomas are not congenital and do not involve the gastrointestinal or nervous systems. However, they appear clinically similar on the skin and can make accurate diagnosis challenging. An editorial letter expressed that cases of glomangiomas are mistakenly assumed to be BRBNS before a biopsy is performed [9]. The authors illuminated that the reluctance to biopsy these vascular lesions due to concerns of bleeding ultimately lead to misdiagnosis and improper management of these patients.

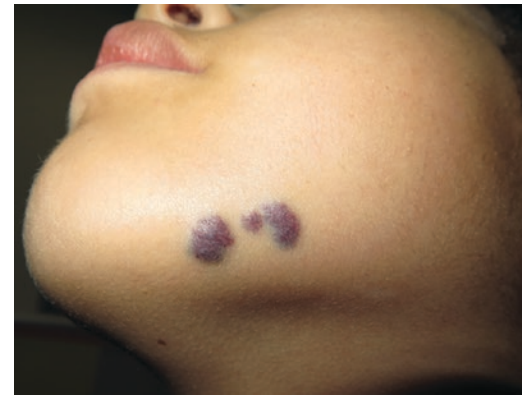

Fig. 34.2 Facial glomangioma. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

Both BRBNS and glomangiomas involve bluish lesions that are typically non-tender and present in a variety of sizes and even share similarities on histopathology. However, the distinguishing feature unique to glomangiomas is the presence of glomus cells lining the endothelium, which stain positive for vimentin and smooth-muscle cell alpha-actin [10].

Treatment

Unfortunately, there is no curative treatment for BRBNS, making treatment especially challenging. Cutaneous lesions are not typically treated, unless they become symptomatic or a cosmetic concern. Pulsed-dye laser has been successfully utilized in the removal of multifocal superficial lesions. The first-line approach for managing gastrointestinal involvement complicated by bleeding is typically conservative and symptomatic management with iron supplementation and blood transfusions [13]. If conservative management is not enough, sclerotherapy and surgical resection are traditionally considered the mainstay management options for BRBNS. Management also varies based on the organ systems afflicted; neurologic involvement may call for use of antiepileptics and/or a ventriculoperitoneal shunt, while orthopedic involvement may merit the use of physical therapy, casting, and/or surgery [7].

Recent case reports have proposed that low-dose sirolimus may be a safe, effective, and promising treatment option in refractory cases of BRBNS [12]. A recent study reported a lymphatic malformation phenotype confirmed with PROX-1 immunostaining in BRBNS, serving as the basis for the authors' hypothesis on the efficacy of sirolimus, a cytostatic agent, in this condition [11]. In contrast solely antiangiogenic medications such as prednisolone, interferon-alpha, and propranolol have not been successfully demonstrated in achieving remission of BRBNS lesions. Side effects of sirolimus include neutropenia and mucositis; however, it appears to be generally well-tolerated by patients. Prospective studies are warranted to assess for long-term side effects as well as optimal dose.

To assist the reader in gaining familiarity with available evidence, the following rating system has been used to indicate key references for each chapter's content:
***: Critical material. Anyone dealing with this condition should be familiar with this reference.
**: Useful material. Important information that is valuable in in clinical or scientific practice related to this condition.
*: Optional material. For readers with a strong interest in the chapter content or a desire to study it in greater depth.

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Sturge-Weber Syndrome

35

Catherine Amlie-Lefond

Genetic diagnosis	Yes
Genetic etiology	Postzygotic somatic mosaic, GNAQ
Level of evidence: treatment	Medium
Evidence	Case series, expert opinion

Diagnosis

Phenotype and Variations

Sturge-Weber syndrome (SWS) is characterized by the association of capillary malformation of the face (CM), leptomeningeal angiomatosis, and glaucoma (Fig. 35.1). SWS is classified into three types (Table 35.1) [1].

Type I: Facial CM and leptomeningeal angiomatosis; glaucoma may be present
Type II: Facial CM without leptomeningeal angiomatosis; glaucoma may be present
Type III: Leptomeningeal angiomatosis without facial CM; glaucoma is usually absent

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Facial CM occurs in approximately 0.3% of newborns [2]. Most patients with facial CM, approximately 80–90%, do not develop leptomeningeal angiomatosis and SWS. CM, involving the forehead, is bilateral or is distributed in all three divisions (V1, V2, V3) of the trigeminal nerve and increases the risk of glaucoma and SWS (Fig. 35.1) [3]. The incidence of leptomeningeal angiomatosis in patients with a facial CM is increased among CM in a V1 distribution/upper face, and there is no risk among isolated CM with V3 distribution [4, 5]. Among 55 patients with type 1 SWS with leptomeningeal angioma, the facial CM was unilateral in 63.5% patients, bilateral in 31%, and absent in 5.5% [6].

Glaucoma may be present at birth or early infancy, at times presenting with buphthalmos and corneal enlargement. Central nervous system involvement usually presents in the 1st year of life, with seizures, hemiparesis, and developmental delays. Diagnosis of central nervous system involvement may be confirmed if head computerized tomography (CT) shows cortical "tram-track" calcifications associated with leptomeningeal angiomatosis, although these are not always present in infancy and early childhood. Head CT can also detect brain atrophy and enlargement of the ipsilateral choroid plexus which is common in SWS. Imaging with MRI (magnetic resonance imaging) is more sensitive than CT in detecting leptomeningeal angiomatosis; however, MRI, like CT, very early in life

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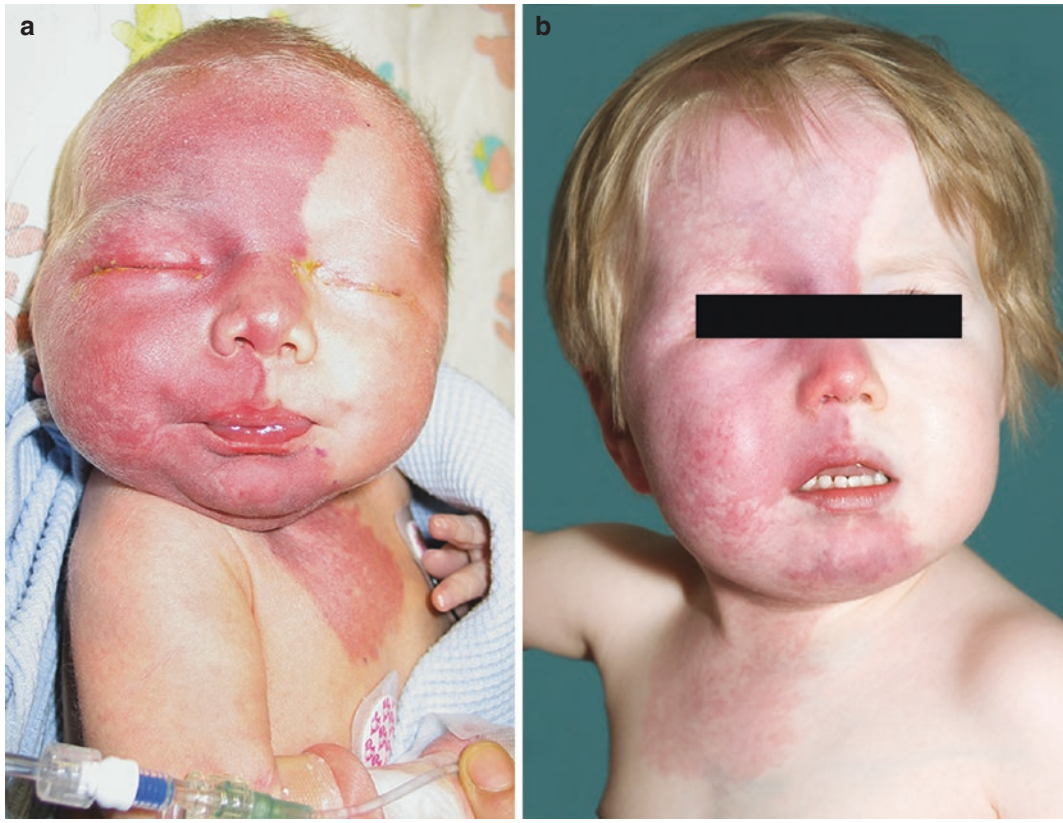

Fig. 35.1 (**a**) SWS in infant, (**b**) SWS in child. (Photos and illustrations courtesy of Seattle Children's Vascular Anomalies Program, Jonathan A. Perkins and Eden Palmer)

Table 35.1 Sturge-Weber syndrome subtypes

	Type I	Type II	Type III
Facial CM	Yes	Yes	No
Leptomeningeal angiomatosis	Yes	No	Yes
Glaucoma	Possible	Possible	Usually absent

may also miss leptomeningeal angiomatosis (Fig. 35.2) [7]. The use of gadolinium enhancement, particularly contrast-enhanced T2-weighted fluid-attenuated inversion recovery (FLAIR) sequences, and susceptibility-weighted imaging sequences increase detection of leptomeningeal angiomatosis. Head MRI can detect brain atrophy as well as choroidal enlargement ipsilateral to the leptomeningeal angiomatosis. MRI may detect ocular angiomas as well. MR perfusion may reveal hyperperfusion in the abnormal cortex during the first year of life, with hypoperfusion developing later in association with atrophy and epilepsy, although it is not routinely used for diagnosis [8].

The diagnostic yield of electroencephalography (EEG) is not known, but detection of posterior predominant asymmetric slowing, attenuation of background activity, and epileptiform discharges may suggest the diagnosis of SWS. Epileptiform activity can also occur in the contralateral hemisphere later in the course. EEG may be useful to screen infants with facial CM for central nervous system involvement of type 1 SWS as it may identify infants at greatest risk for seizures.

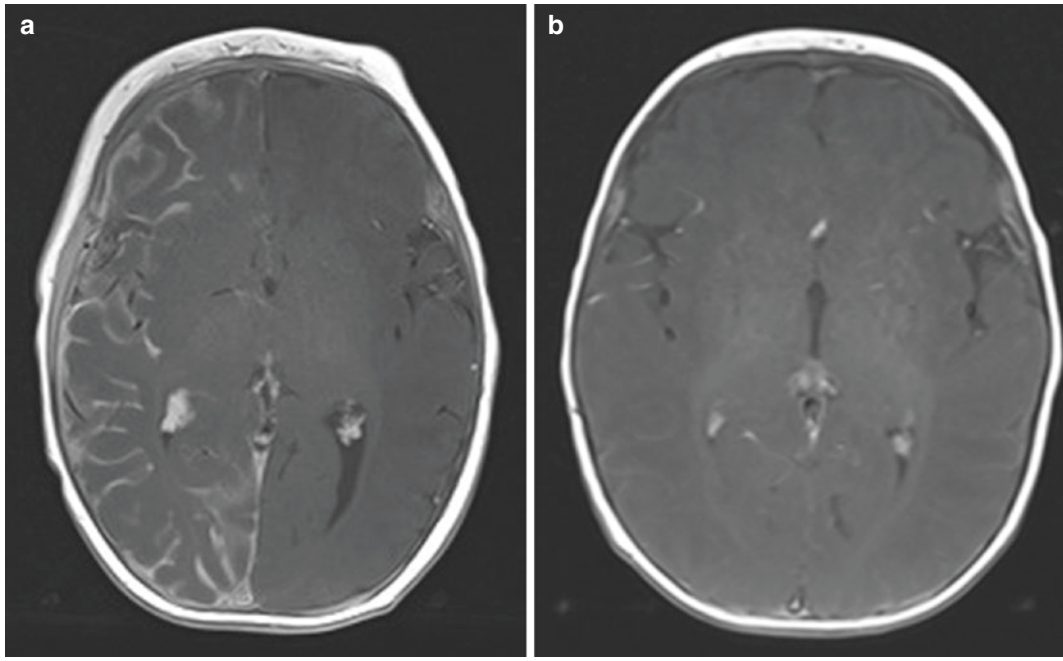

Fig. 35.2 (**a**) Axial T1 MRI with contrast in a 3-month-old infant with right facial port-wine stain and glaucoma of the right eye who presented with left-sided tonic-clonic seizures. Right-sided pial angiomatosis is present along with right choroid plexus hypertrophy and mild asymmetric volume loss of the right cerebrum. (**b**) Normal axial T1 MRI with contrast of brain in 3 months old with bilateral extensive facial port-wine stain and glaucoma of the right eye who has no history of seizures. (Images courtesy of Seattle Children's Radiology, Giridar Shivaram, Eric Monroe and Kevin Koo)

Etiology

SWS occurs sporadically in localized regions and has been shown to be caused by a postzygotic somatic mosaic mutation c.548G>A in *guanine nucleotide-binding protein alpha-q (GNAQ, detected in affected tissues of up to 80% of SWS patients)* [9, 10]. The GNAQ mutation was detected in affected skin and brain tissue from patients with type 1 Sturge-Weber syndrome as well as affected skin in clinically isolated CM tissue. The mutant allele frequencies in affected tissue ranged from 1.0% to 18.1% [9]. The *GNAQ* mutation activates downstream MAPK signaling which in turn increases cell proliferation and inhibits apoptosis due to increased downstream signaling through the RAS effector pathways [9]. The exact biologic mechanisms through which GNAQ causes SWS distribution, tissue malformation, and disease remain to be determined. It is now thought that the CM distribution in SWS corresponds to areas of somatic mosaicism not divisions of the trigeminal nerve [5, 11].

Natural History

Sturge-Weber syndrome can be associated with multiple comorbidities, including dermatologic, ophthalmologic, neurodevelopmental, and endocrinologic sequelae.

Capillary Malformation

Please see Chap. 19.

Ophthalmologic

Glaucoma and its sequelae occur in 1/3–2/3 of patients with SWS, typically occurring when the CM involves the eyelid. Glaucoma can occur ipsilateral to the facial CM or involve both eyes or very rarely the contralateral eye. Glaucoma

may be present at birth, with rapid progression in infancy. However, glaucoma usually presents in early childhood with a significant percentage presenting later in life. If untreated, persistent increased intraocular pressure can result in damage to the optic nerve and permanent vision loss. Glaucoma can also induce buphthalmos and anisometropia, at times resulting in amblyopia. In addition to glaucoma, conjunctival, episcleral, and choroidal hemangiomas may also be seen. Iris heterochromia has been reported, with the darker iris ipsilateral to the CM. Over time, degenerative changes in the outer retina also can occur. In addition, leptomeningeal angiomas in the occipital cortex can lead to central vision loss.

Neurologic and Neurodevelopmental Sequelae

The neurologic sequelae of SWS are typically absent at birth, present during the first year of life, and progress over time. The most common neurologic presentation is epilepsy, with bilateral leptomeningeal angiomas predicting earlier onset of seizures compared with unilateral involvement [12]. Seizures, usually onset during infancy, are initially usually focal, with subsequent progression to secondary generalized seizures. Pascual-Castroviejo et al. found epilepsy occurred in 85.5% of patients with type 1 SWS, over half of whom had intractable seizures [6]. Iimura and colleagues reported medically refractory epilepsy in 63% of patients [13]. Although three-quarters of children with SWS will have seizure onset during the first year of life, seizure onset can occur through adulthood, with one series reporting a range of onset age from birth to 23 years [14]. In this series, onset of seizures prior to age 2 years increases the risk of refractory epilepsy and developmental disability. The age of onset of seizures ranged from birth to 23 years; 75% had onset of seizures before 1 year of age; these children had an 83% incidence of developmental and academic problems [14]. Subclinical seizures are not infrequent. Status epilepticus can occur, leading to further injury in already compromise brain.

Over half of patients with SWS have developmental disabilities, with the risk increased in children with epilepsy [14, 15]. Bilateral leptomeningeal angiomas not only predict earlier onset of seizures but also greater neurodevelopmental sequelae compared with unilateral involvement [12]. Learning disabilities are common and ADHD are also reported. Behavioral difficulties including poor social skills are also seen.

Focal and diffuse neurologic deficit can accrue in a "stroke-like pattern," particularly after seizures, although the postictal deficit is usually more prolonged than with typical seizures, lasting days to even weeks. Initially, postictal deficit is transient; however, unilateral or bilateral hemiparesis develops in up to one-half of patients. Hemianopsia can occur as well. Neurodevelopmental delay, plateauing, and regression can occur with resultant developmental disability. Progressive focal and diffuse cortical atrophy occurs.

Headache

Headache is common in SWS and often refractory. Migrainous features are common, and migraine is reported more often in children with SWS than in the general population, often with associated neurologic deficits [16].

Endocrine

The incidence of growth hormone deficiency and central hypothyroidism are increased in patients with SWS [17, 18]. The use of oxcarbazepine may unmask or induce hypothyroidism.

Treatment

Although CM and glaucoma can be treated, effective treatments to prevent the neurocognitive sequelae of SWS are not known.

Capillary Malformation/Port-Wine Stain

(Please see Chap. 19).

Ophthalmologic

Any infant with a facial CM should be evaluated by an ophthalmologist to rule out glaucoma and followed closely particularly during the first year

of life when damage from elevated intraocular pressure can develop rapidly. Initial treatment is usually medical, with eyedrops such as timolol and latanoprost, but surgical intervention is often needed. Glaucoma can induce myopia, and screening for amblyopia is important in young children with SWS. Avoidance of medications that may increase intraocular pressure, including those used for anesthesia, may be necessary.

Neurologic and Neurodevelopmental Sequelae

To maintain optimal brain perfusion, stroke prevention strategies including encouraging optimal hydration, treating anemia, and receiving appropriate immunizations, including annual flu vaccines, are recommended. Antipyretics during febrile illness to decrease metabolic demands on the brain are often used as well.

Aspirin use in SWS has been advocated by experts to decrease seizures, stroke-like episodes, and possibly even venous hypertension contributing to glaucoma [19]. Lance et al. reported on 58 patients with SWS on low-dose aspirin since early childhood, with 84% reporting no significant side effects. One child developed a subdural hematoma after a minor head injury, one developed hematemesis during a viral illness, and one had an allergic reaction. The authors note that aspirin appeared to improve seizure control and neurologic outcome although no control group was available [20]. Using an Internet-based questionnaire, Bay and colleagues reported decreased self-reported seizure frequency and stroke-like episodes after starting aspirin among 34 patients with SWS, ranging from age 2 months to 34 years, among whom 40% had been on aspirin for more than 4 years at the time of survey [21]. Although aspirin is commonly recommended in SWS, definitive efficacy data is currently lacking. Subdural hemorrhages, intracranial hemorrhage, and subgaleal hemorrhages are reported on SWS [22–24].

Most patients with leptomeningeal angiomas will develop epilepsy. Seizures typically present with unilateral signs, including visual symptoms, and may generalize as well. Over time, seizures often become refractory to medications and subsequently intractable. Subclinical seizures are not infrequent. Epilepsy occurs earlier and more often in bilateral than unilateral leptomeningeal angiomatosis, and onset prior to 2 years of age predicts intractability.

Status epilepticus is common, resulting in further injury to an already compromised brain. Prolonged seizures may promote brain injury particularly in the setting of decreased perfusion. Broad-spectrum anticonvulsants, such as levetiracetam, as well as anticonvulsants targeting focal onset seizures, such as oxcarbazepine, are often used as first-line treatments. Oxcarbazepine can rarely induce hyponatremia and hypothyroidism. Unfortunately, epilepsy in SWS can be intractable.

A single-institution retrospective analysis of patients with SWS and epilepsy suggests that oxcarbazepine and carbamazepine may be more effective than levetiracetam [25].

Epilepsy surgery including focal cortical resection, hemispherectomy, and corpus callosotomy may be indicated for intractable epilepsy. Most children become seizure-free following hemispherectomy or cortical resection [26, 27]. Surgical treatment options are more limited for patients with bilateral leptomeningeal angiomas, although seizure control has been reported following unilateral hemispherectomy [28]. Resective and disconnection epilepsy surgery can be beneficial in terms of seizure control and development, even in some patients with bilateral leptomeningeal angiomatosis [26, 29, 30]. Subdural electrocorticography may detect and localize seizure activity not detectable on surface electroencephalography. Although hemispherectomy is more effective than focal surgery for seizure control [26], hemispherectomy can increase neurologic deficit particularly in younger patients with milder deficit, although it may not impair function long term. Optimal timing and type of surgical treatment of epilepsy in SWS remain to be established.

Attention deficit hyperactivity disorder is not uncommon in children with SWS. Stimulants have been used for attention deficit hyperactivity disorder without significant side effects in a series of 12 children with SWS obtained retrospectively from a research database [31].

Dr. Anne Comi, an expert in SWS, suggests that children with extensive bilateral leptomeningeal angiomatosis should be considered for presymptomatic treatment with anticonvulsant and aspirin [19]. As confirmation of diagnosis in SWS requires neuroimaging, usually MRI requiring sedation, and both anticonvulsants and aspirin have potential side effects, the safety and efficacy of presymptomatic therapies need to be established prior to making routine recommendations. Although diagnostic head MRI may be offered to all families of infants with PWS, many families do not wish to sedate their child in the absence of compelling evidence that the disease course can be altered. Facial distribution of PWS and EEG may be useful to stratify risk; however, families may express the desire to not know whether there is associated central nervous system involvement.

As children with type 1 SWS are at risk for progressive and emerging neurocognitive sequelae, neurodevelopmental monitoring is critical, with referral for appropriate developmental services.

Headache

Although headaches associated with SWS may have migrainous features, the safety of triptans in headache in SWS has not been established. Prophylactic rather than symptomatic treatment should be considered when necessary, although headaches can remain intractable. Lamotrigine has been reported to be effective in migraine-like headaches in a single case report [32].

Endocrine

The incidence of central hypothyroidism and growth hormone deficiency is increased in patients with SWS. Anticonvulsants, especially oxcarbazepine, may exacerbate this. Detection of hypothyroidism requires free thyroxine assay as opposed to thyroid-stimulating hormone, particularly if the patient is on a seizure medication associated with hypothyroidism such as oxcarbazepine [33]. Growth hormone can be screened using serum insulin-like growth factor-1 [19].

To assist the reader in gaining familiarity with available evidence, the following rating system has been used to indicate key references for each chapter's content:
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