Clinical Decision-Making in Oral Medicine

A Concise Guide to Diagnosis and Treatment

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Márcio Ajudarte Lopes
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Foreword

Oral Medicine is a complex, fascinating, and challenging clinical field that occupies the blurred interface between medicine and dentistry. Conditions as diverse as salivary gland dysfunction, oral mucosal vesiculobullous disease, jaw osteonecrosis, neurosensory dysesthesia, and neoplasm can all uniquely affect the oral cavity and orofacial region, causing pain, suffering, disability, and reduced quality of life. Oral medicine conditions may be uniquely limited to the oral cavity, or may be manifestations of systemic diseases, or even complications of medical interventions and therapies. Patients with oral medicine conditions may present to their primary care physician, general dentist, urgent care clinic, or emergency department; therefore, a broad constituency of healthcare providers must be sufficiently familiar with their basic evaluation, diagnosis, and management. Yet there are few clinicians who have the training and expertise to provide specialty oral medicine care, and overall, recognition and familiarity throughout the healthcare system, even in countries and regions where oral medicine is a recognized specialty, remains generally inadequate. It is therefore not uncommon for unnecessary, or even inappropriate testing to be ordered, or for incorrect, or even counterproductive therapies to be prescribed, and patients often see multiple providers prior to receiving the correct diagnosis and effective management. Dr. Santos-Silva has assembled an esteemed international team of oral medicine experts who collectively provide a concise, efficient, clinically relevant, and evidence-based approach to clinical decision-making in oral medicine that any clinician can easily follow and apply to their own practice. For example, oral ulceration is a common condition, but the diagnosis may be related to trauma, immune activation, infection, or malignancy. The treating clinician must have a logical and sequential approach to ensure both proper diagnosis and appropriate management. The authors achieve this by reducing the complex field of oral medicine down to basic elements of evaluation, work-up, and management that can be readily adapted to a wide variety of healthcare settings. As the clinical practice of oral medicine frequently requires interprofessional coordinated care across the healthcare system, this reference can serve as a common touchstone and guidepost for dentists, physicians, nurses, pharmacists, and other invested healthcare providers and stakeholders. From a broader perspective, this approach highlights and

reinforces the importance of interprofessional and international collaboration and cooperation in continuing to advance and expand the field of oral medicine internationally, with the ultimate goal of ensuring that all patients have access to and receive the highest quality of oral medicine care available.

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History Taking and Physical Examination

João Figueira Scarini, Alan Roger Santos-Silva, Márcio Ajudarte Lopes, Mariana de Pauli Paglioni, Oslei Paes de Almeida, Rogério de Andrade Elias, and Pablo Agustin Vargas

The clinical examination of the patient is the most important step in a dental appointment. It is essential to develop diagnostic hypotheses about the diseases that can affect the oral and maxillofacial complex. Dental surgeons and professionals involved must follow a logical sequence and complete a detailed anamnesis, to identify potential "clues" that can assist the diagnosis and treatment decision-making.

The clinical examination is divided into two moments: history taking and physical examination.

1 History Taking

The anamnesis must follow a chronological sequence:

1. Patient identification.
2. Main complaint and time evolution of disease (most important symptom and time elapsed from the beginning of the symptom to the present moment).
3. History of the current disease (record of the natural history of the disease: onset and its evolution until the present date):

   Investigate the presence of general symptoms: pain, fever, discomfort, upper airway infection, malaise, weight loss, and pruritus, among others.

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Investigate exposure and contact with cats (or cat feces), wild animals, ticks, and sick family members, travel, and continuous use of medication.
4. Hereditary background.
5. Personal history (allergies, medication in use, diseases that have affected the patient, systemic disorders, sexually transmitted infections, cancer, and surgeries performed).
6. Habits (repetitive/compulsive manifestations) and addictions (harmful habits, such as smoking tobacco, alcohol intake, and use of illicit drugs).

2 Physical Examination

The examiner must obtain consent from the patient to proceed with the examination. If the patient has dentures or oral and maxillofacial prosthetic devices, these should be removed. Good lighting is essential to ensure a good physical examination.

The physical examination should be complete and, whenever possible, done in an orderly manner after the anamnesis. All structures of the oral and maxillofacial complex should be analyzed using semitechnical maneuvers by visual inspection, palpation, and auscultation. The procedure should not take more than 5 min to complete, ensuring the patient's comfort. If the patient is in severe pain, the evaluation should be done sparingly.

The American Dental Association recommends that clinicians perform a visual oral examination (VOE) in all adult patients during initial, routine, or emergency visits. The physical examination can be divided into extraoral and intraoral:

2.1 Extraoral Physical Examination

1. Evaluate facies (appearance and facial expression), observing symmetry, coloration, pigmentary changes, hair distribution, sweating, and changes in skin volume and texture, as well as eyes, nose, and ears.
2. Assess head and neck ganglion chains. To do this, the examiner should relax the muscles of the patient's area that will be examined. A ganglion of the submandibular chain on the left side should be palpated with the patient's head flexed downward and to the left with four fingers (without the thumb).

   Didactically, the neck can be divided into six levels, and these should be evaluated in an orderly manner (Fig. 1):
   - Level I: formed by the submental and submandibular chains.
   - Level II: upper internal jugular (deep cervical) chain.
   - Level III: middle internal jugular (deep cervical) chain.
   - Level IV: lower internal jugular (deep cervical) chain.
   - Level V: posterior triangle.
   - Level VI: anterior compartment of the neck.
   - The accessory nerve subdivides levels II and V into "a" and "b."

   Every time the patient presents an abnormality in the lymph nodes, the number, size, consistency, tenderness, mobility, and location should be analyzed.

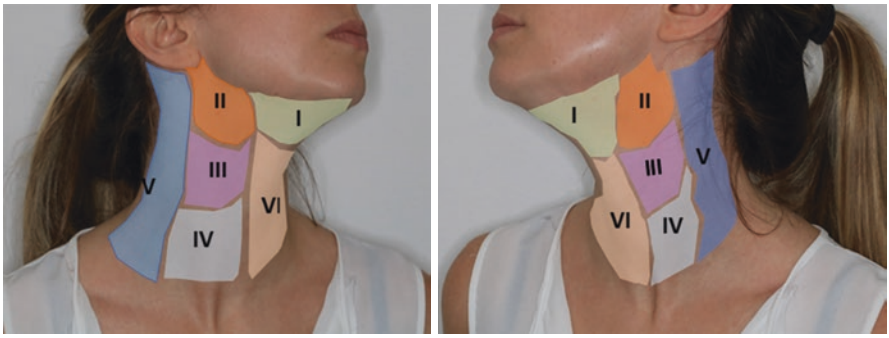

Fig. 1 Different levels of cervical lymph nodes

Normal lymph node	Inflammatory lymph node	Tumor lymph node
Painless	Painful	Painless
Flaccid	Not very consistent	Consistent
Not palpable	Mobile	Fixed
	Smooth	Irregular

3. Evaluate the anterior cervical region. Look for fixed or mobile cervical nodules in the region of the thyroid gland and parathyroid.
4. Evaluate the temporomandibular joint and major salivary glands (parotid, submandibular, and sublingual). Look for the presence of acute or chronic signs of infection, swelling, or nodules.
5. Evaluate bones for augmentations, depressions, or asymmetries.
6. Evaluate innervations of the region for painful sensitivity to touch, as well as signs of facial paralysis.

2.2 Intraoral Physical Examination (VOE)

The oral examination should be performed through visual inspection and bidigital palpation (with the index finger and thumb) or in a digitopalmar way, following the order suggested below. Whenever there is any change from normal, the type of abnormality, size, color, location, surface texture, consistency, and location should be noted on the patient's chart:

1. Lips (vermillion and labial mucosa).
2. Vestibule (brakes and emergence point of the parotid gland).
3. Alveolar mucosa.
4. Inserted gingival, free gingival, and interdental papilla (or alveolar ridge).
5. Buccal mucosa and vestibular mucosa (labial commissural and retro commissural).
6. Tongue and lingual papillae (tip, lateral border, dorsal surface, and ventral surface).

7. The floor of the mouth (and the ducts and emergence points of the submandibular and sublingual glands).
8. Hard palate.
9. Soft palate.
10. Tonsils and tonsillar crypt, pharyngeal arches, and uvula.
11. Oropharynx.
12. Teeth and periodontium.
13. Salivary flow and consistency.

With the mouth open, the examiner should traction the lip in the opposite direction of its insertion and laterally to check the color, texture, tenacity, and relationship of the lips with the vestibules (Fig. 2). In the vermillion, evaluate if there are hyperkeratosis, ulcers, small fissures, or pigmentation. In the labial mucosa, we evaluated whether there were nodules, scars, or ulcers.

After that, the examiner should examine the alveolar mucosa, followed by the inserted gingival, free gingival, and interdental papillae (Fig. 3). In edentulous patients, the alveolar ridge should be carefully evaluated. Examination of the buccal mucosa should begin at the labial commissural (which includes the retrocomissural mucosa) and extend to the anterior tonsillar (Fig. 3). For VOE, two wooden or plastic spatulas converging from the lips can be used.

Only the anterior two-thirds of the tongue (called the oral tongue) are normally seen on oral examination. The lateral borders of the tongue examination should be

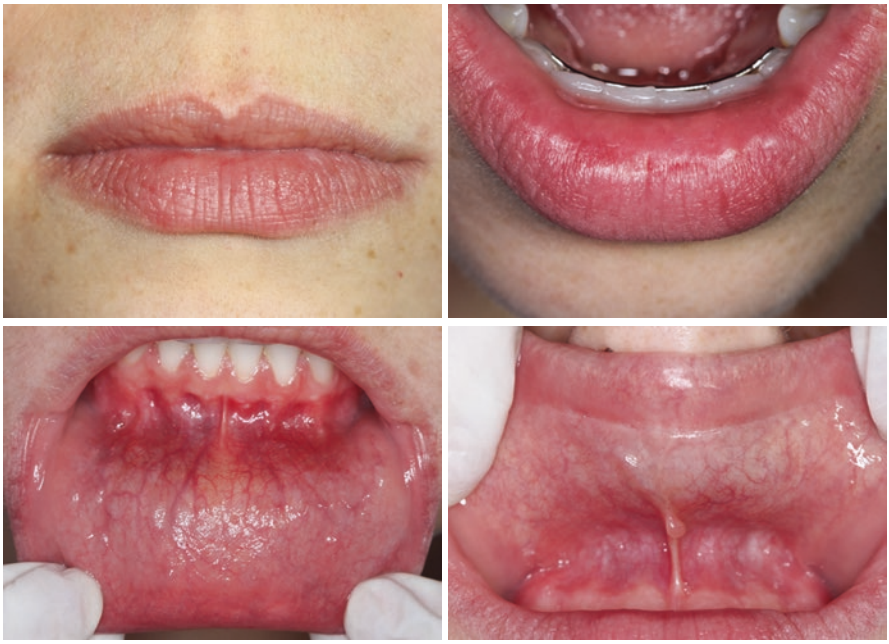

Fig. 2 Normal aspect of lips and vestibule

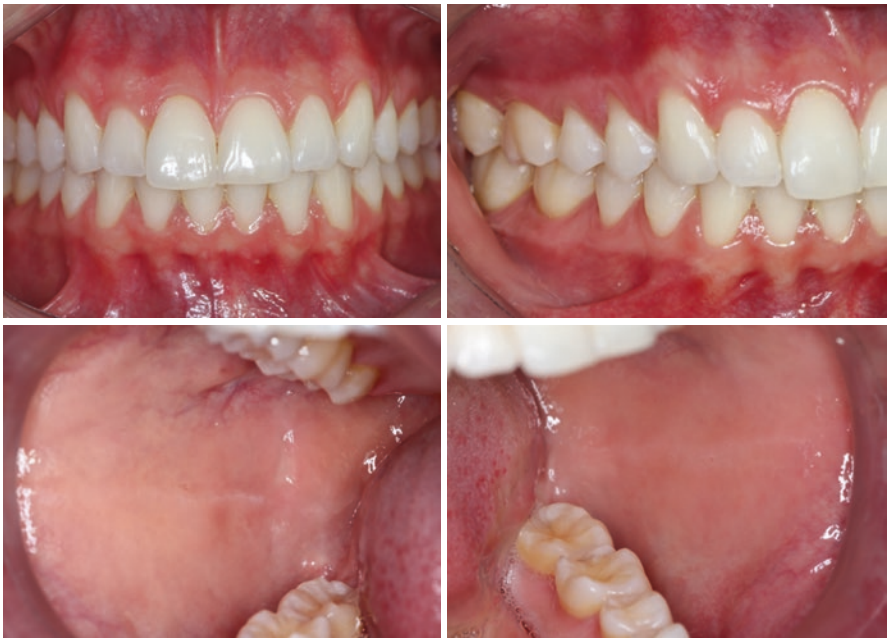

Fig. 3 Normal aspect of the gingiva and buccal mucosa. Note the healthy aspect of the dental papillae and normochromic patterns of the oral mucosa lining the oral cavity

done with the aid of a gauze pad. The dorsum of the tongue should be examined first. It is important that, in addition to VOE and palpation, the examiner observes the natural movement of the tongue. Tumors in this region tend to compromise the movement of the organ (Fig. 4).

Palpation of the floor of the mouth should be done carefully, and all its component structures should also be analyzed (Fig. 5). The submandibular ducts (Wharton's ducts) should be examined. For examination of the hard palate, the patient's head must be flexed backward (Fig. 6).

For examination of the soft palate and visible portion of the oropharynx, the pronunciation of vowels "e" and "I" may aid VOE (Fig. 7). The tongue should be protruded or pressed against the oral floor with the aid of a wooden/plastic spatula.

The examiner should look for missing teeth and/or supernumerary teeth. Signs of poor oral hygiene, occlusal caries, and caries at the gingival margins should also be noted. Hot or cold stimuli can help identify pulpitis. Sensitivity to firm percussion of individual teeth using a metal object may denote the progression of infection to the periodontal tissue. Mobility, extrusion, or reduced sensation of the teeth should also be investigated.

Regarding the periodontal examination, clinical attachment loss, amount and percentage of bone loss, probing depth, presence and extent of angular bone defects, furcation involvement, tooth mobility, and tooth loss due to periodontitis were assessed. The patient's general health status (such as diabetes control) and habits (such as smoking) must be considered.

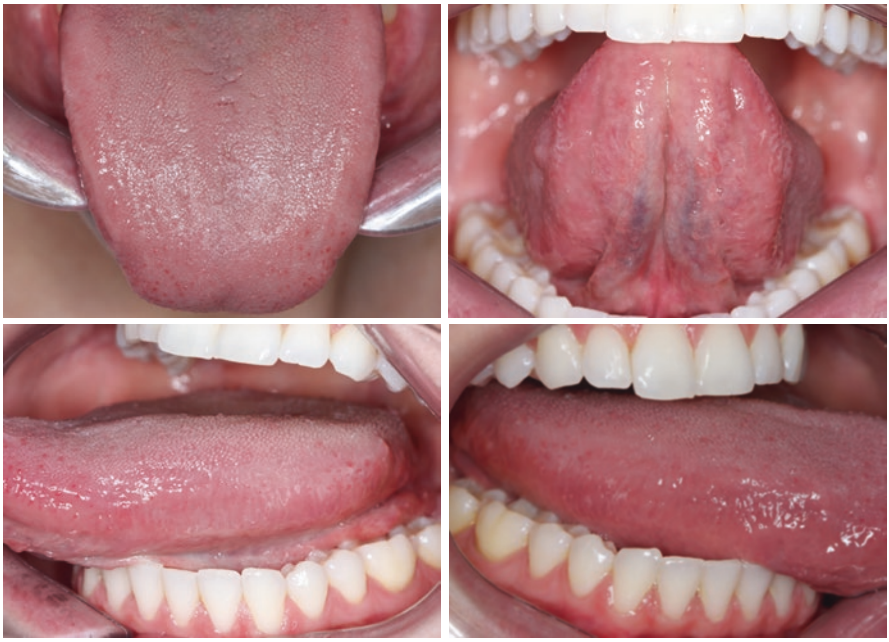

Fig. 4 Normal appearance of the tongue. Note color, texture, and movement

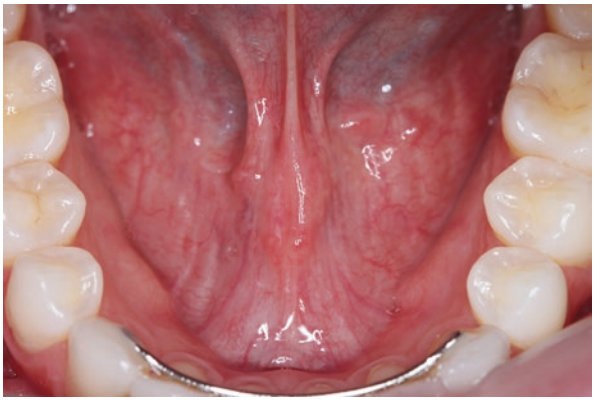

Fig. 5 Normal aspect of the structures that constitute the sublingual caruncle, located on the floor of the mouth

In implant-rehabilitated patients, there is no probing depth range to assess peri-implant health. In these cases, the presence of visual signs of inflammation and bleeding on probing is compatible with peri-implant mucositis. Peri-implant integrity can be evaluated through bone support. Reduced levels may be associated with peri-implantitis.

Examination of salivary flow and consistency should be the final part of the oral examination. Look for changes such as frothy saliva or thick saliva. Hyposalivation should be suspected based on the information collected during the examination.

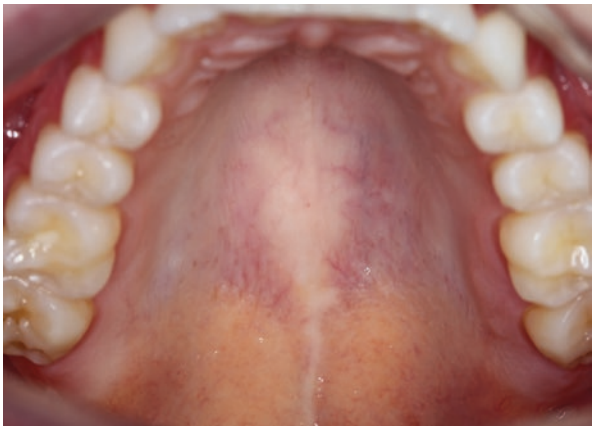

Fig. 6 Normal aspect of the hard palate and transition region to the soft palate

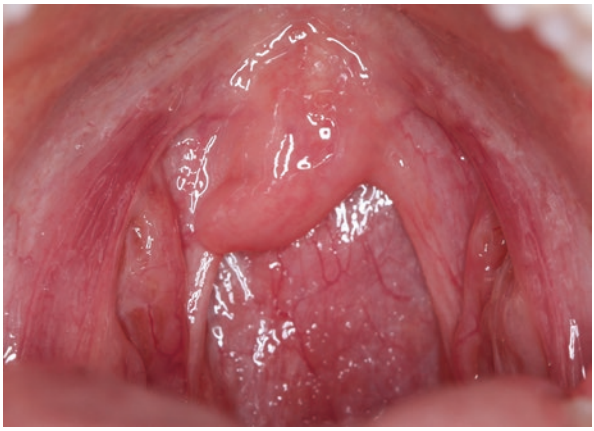

Fig. 7 Structures that make up the anterior region of the oropharynx: soft palate, palatoglossal and palatopharyngeal arches, uvula, and palatine tonsils

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Standardization in Oral Photography

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Digital photographs in dentistry are indispensable tools during clinical practice, especially in oral medicine. Photographs are used for a multitude of functions, among which are the recording of oral diseases – legal documentation (a medicolegal record), communication with patients, follow-up of the lesions, academic use (education and research), marketing, and communication between professionals.

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It is important that the image obtained accurately reproduces the oral scenario and has sufficient quality for the smallest details to be perceived. High-quality and standardized images can aid in the diagnosis of oral diseases as well as monitoring their clinical course because they allow the visualization of details not seen with the naked eye.

1 Fundamentals

1.1 General

1.1.1 Color

It is critical that a dental photograph accurately records the color observed by the eye during the dental examination. Therefore, the influence of different light sources or illuminators must be eliminated.

With the correct capture of the oral structure colors, it is possible to observe, in detail, important characteristics that distinguish healthy from pathological tissues.

In soft tissues, for example, changes in color and volume suggestive of inflammation, transitions between keratinized and nonkeratinized mucosa and attached gingiva, and the difference between ulcerated, eroded, verrucous, or plaque-covered surfaces can be observed.

In hard tissues, note translucency, pigmentation, porosity, cracks and fractures, noncarious lesions, restorative materials, and caries lesions.

1.1.2 Resolution

Good-quality photography should have enough detail to portray shape, texture, volume, and proportion. High-resolution and consequently good-quality images are only obtained by high-quality lenses. The number of pixels does not indicate the quality of the image but its size and detail.

1.1.3 Lighting

Good photography requires quality lighting and, especially dental photography, must be done with flashes, as ambient lighting is not enough. Electronic flashes allow the primary colors (red, green, and blue) to appear in equal proportions. There are two ideal types of flashes for dentistry: macro ring flash and twin flash. Despite having some specificities, both flashes produce high-quality images:

- *Macro ring flash*: more versatile, practical, and at a lower cost. It evenly illuminates the back of the oral cavity. It can produce images of anterior teeth or lesions in this region with less texture and volume by excessively removing shadows.
- *Twin flash*: ideal for anterior regions of the oral cavity giving more texture and volume. This may produce excessive shadows in lesions located at the back of the oral cavity. It costs more and requires more skill from the photographer.

Avoid using the dental chair light reflector because it has a different color temperature than the flash, which may alter the color in the photograph.

1.2 Equipment and Accessories

The most indicated are the following:

- DSLR or mirrorless camera.
- 100 mm macro lens (1:1 magnification)
- Macro ring flash or macro twin flash.
- Camera stands (tripods).
- Macro flash support.
- Remote release handle (for cross infection control during surgery, for example).
- Uni or bilateral cheek and lip retractors.
- Intraoral photographic mirrors (for occlusal, lingual/palatal, and lateral view of teeth).
- Black card/mirror (as background for focusing on teeth).
- The backdrop for extraoral photos.
- Cotton rolls, saliva suckers, and rubber dikes for humidity control.
- Astringents for controlling bleeding.
- The periodontal probe or millimetric scale for assessing the size of any lesion (should be placed adjacent to the lesion at the time of photographing).

1.3 Camera Setup and Calibration

Each camera has specific settings; however, these settings are similar across the categories, allowing the use of a standardized setup for dental photography (Table 1).

Table 1 Suggestions for camera setup and calibration

Camera mode	Manual
Focus	Spot or center fix
Lens aperture (which controls light intensity)	Intraoral: From f/22 to f/27 Extraoral: From f/8 to f/11
Shutter speed (which controls the duration of light)	From 1/160 to 1/125
ISO (which prevents grainy images)	Intraoral: 100 or 200 Extraoral: 200 or 400
Measurement type (if available)	Spot or center-weighted
Color space (domains)	Adobe RGB (ideal for publishing) Adobe sRGB (ideal for display in presentations)
White balance	*Flash*, *sunlight*, or *daylight*
Picture style/control	Neutral
Moiré filter (if available, which prevents checkered patterns)	On
File format	RAW—Highest quality and requires software for image processing TIFF—Good quality JPEG—Unsuitable for archiving
Lens focus control	Autofocus In cases where the specific focus is needed, switch to manual focus
Setting the flash	TTL mode

1.4 Image Standardization

1.4.1 Extraoral Photographs

Patients should be at rest and relaxed, preferably standing or sitting. The camera should be in front of and at the same height as the patient:

- Front face.
- Front face during smile (if necessary).
- Front face with an exaggerated smile (if necessary).
- Submentovertex (if necessary)—patient's positioning is similar to submentovetex radiography.
- Resting profile.
- Profile during a relaxed smile (if necessary).
- Profile with an exaggerated smile (if necessary).
- Dentofacial images (framing only lips and teeth in the required poses according to the clinical objective).

1.4.2 Intraoral Photographs

- Frontal image of the arches in occlusion, including the buccal corridor.
- Occlusal image of the total maxillary arch (addressing the hard and soft palate and bilateral tuber)*.
- Occlusal image of the complete mandibular arch, addressing the floor of the mouth. The tongue must be pulled back with the mirror*.
- Teeth and gingivae – lingual, palatal, and lateral views, per quadrant*.
- Right and left buccal mucosa.
- Lingual dorsum (patient with the tongue out).
- Ventral tongue.
- Lateral tongue edge on the right side (position of the tongue apex outside the retractor on the same side).
- Lateral tongue edge on the left side (position of the tongue apex outside the retractor on the same side).
- Oropharynx.

* Intraoral photographic mirrors should be used.

2 Technical Sequence for Photographing Oral Lesions

- Put the retractors in the correct position.
- Dry the region to be photographed with a gauze pad to avoid saliva glare when exposed to flashlight.
- Frame the lesion in the center of the photograph.

- Photograph a more open plane framing nearby anatomical structures, allowing the localization of the lesion and a closer plane to highlight details.
- Photograph from more than one angle to record all the characteristics of the lesion.
- Whenever possible, the horizontal plane of the photograph should be parallel to the occlusal plane of the patient, although depending on the location and lesion (such as lesions located on the tongue), the vertical plane may be used.
- Whenever possible, avoid visual interference (retractors, mirrors, and fingers).
- To prevent the mirror from fogging up, ask the patient to breathe through the nose or blow an airflow across the mirror.
- Removable dentures must be removed before taking photographs, except when the lesion is closely related to the denture. In this case, two photos should be taken: with and without dentures.

3 Care

- Ensure cross infection control.
- Avoid trauma when positioning mirrors and retractors. The use of a lip lubricant is encouraged before positioning oral retractors.
- Position the patient so that he/she is as comfortable as possible.

4 Storage

- The obtained images must be carefully stored to avoid losses. All data should be ideally stored on cloud based servers.
- It is preferred that the original file be securely archived for future retrieval without edits.
- If you need to do any editing, do it on a copy of the original file.
- A folder with the patient's name or registration number should be created. Organizations by year and month of the appointment are suggested.
- Within the folder, subfolders can be created according to the preference of each professional. We suggest a folder with images of the pretreatment and another for different moments of the follow-up and management (follow-up).
- Each file must be named with a name that identifies its true origin in case it is eventually misplaced or lost.
- Whenever possible, all images should be backed up by hardware and/or cloud storage, which in turn should be periodically updated.

Acknowledgments The São Paulo State Research Foundation (FAPESP, São Paulo, Brazil, grant number JFS 19/09419-0) and the Coordination of Training of Higher Education Graduate Foundation (CAPES, Brasilia, Brazil, finance code 001).

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Fine-Needle Aspiration Cytology and Exfoliative Cytology

Pablo Agustin Vargas, Janete Dias Almeida, and João Figueira Scarini

1 Exfoliative Cytology

1.1 General Principles

- Obtaining surface cells for subsequent evaluation by conventional microscopy.
- Easy and quick to perform, low cost, and noninvasive method.
- Technique well accepted by patients.
- No need for local anesthesia.
- Rapid diagnosis.
- It can be repeated several times and used in population screening and clinical studies.

1.2 Indications

Although not commonly used in these groups, they can be useful and indicated (Figs. 1 and 2) in the following:

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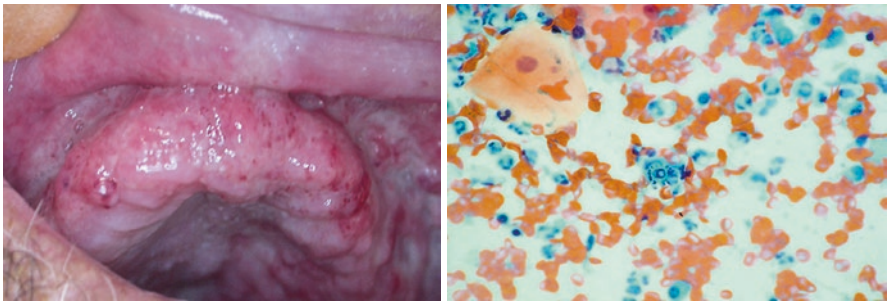

Fig. 1 Paracoccidioidomycosis. Ulcerated lesion of mulberry-like appearance with hemorrhagic spots located in the alveolar ridge that extends to the sulcus and hard palate. Multinucleated giant cells containing birefringent yeast-like structures are characteristic of the fungus *Paracoccidioides brasiliensis* (Papanicolaou, 630×). In detail, rounded cells presented cryptosporulation with a "steering wheel" appearance of the fungus *Paracoccidioides brasiliensis* (Papanicolaou, 630×)

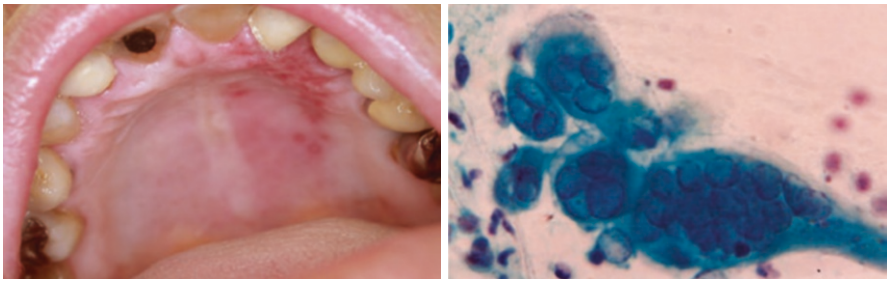

Fig. 2 Herpes simplex. Shallow, punctate ulcers with an erythematous halo, located on the hard palate. In addition, parasitized epithelial cells had enlarged nuclei and scattered chromatin, multinucleation, and giant cell formation (Papanicolaou stain, 630×)

- Diagnostic aid in autoimmune diseases, such as pemphigus vulgaris.
- Identification of bacterial (abscesses, actinomycosis), fungal (candidiasis, paracoccidioidomycosis), and viral herpes simplex and human papillomavirus infectious lesions.

1.3 Materials

Materials included (Fig. 3) are the following:

- Disposable cytobrush (cervical brush) or sterile metal spatula.
- Clean and dry microscopy glass slides with frosted ends.
- Fixed: 95% ethyl alcohol (96°GL) or cytological spray fixative.
- Slide mailer or microscope slide jar to keep the slides.

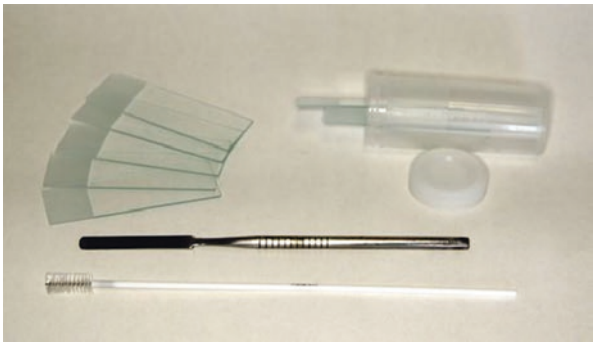

Fig. 3 Material needed for the cytopathological exam. Metallic spatula and cytobrush for sample collection. Glass slides with the frosted end where the sample is distended. The frosted end can be labeled with the patient's name and date or place of sample collection. Microscope slide jar with fixing solution

1.4 Technique

The technique (Fig. 4) consists of the following:

- Rotate the cytobrush in the lesion to be analyzed or scrape the area with a metal spatula. In the case of vesicular lesions, rupture the vesicle for material collection.
- The cells are transferred to a glass slide previously dried and cleaned.
- The material must be spread on the glass slide with rotational movements with the cytobrush or in a thin layer with the metal spatula, usually three slides for each staining.
- Fix immediately with cytological spray fixative or condition the slides in a slide holder containing 95% ethyl alcohol (96°GL).
- Staining: Papanicolaou, Hematoxylin and Eosin (HE), Periodic acid–Schiff (PAS).

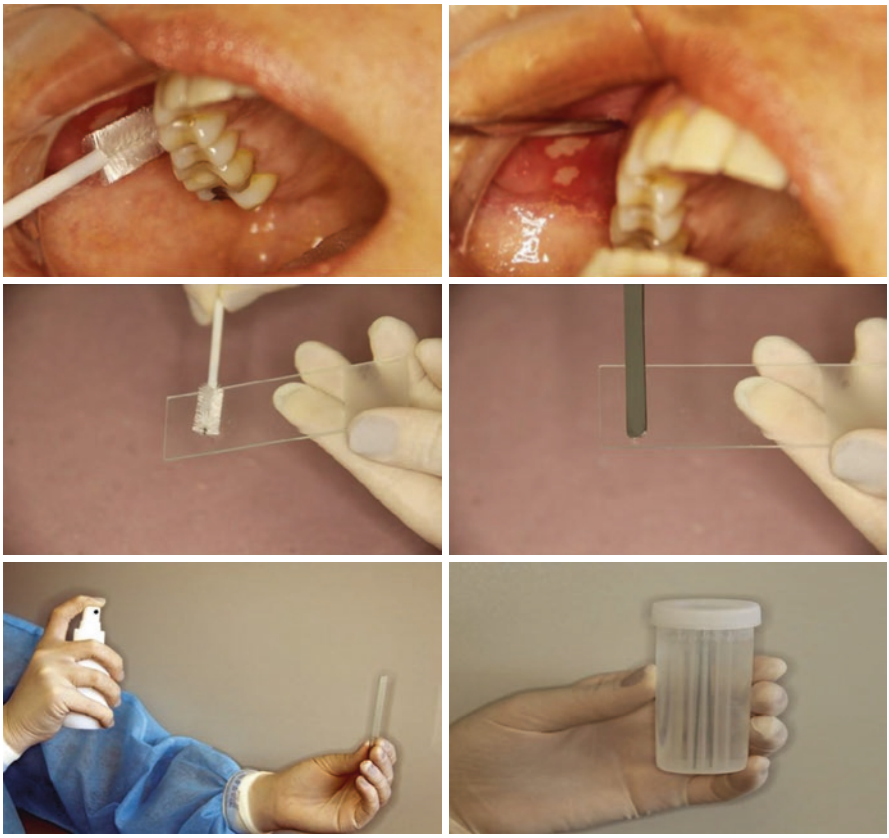

Fig. 4 Collection of material with a cytobrush or metallic spatula, followed by smearing of the collected material on a glass slide with frosted edge. When performed with cytobrush, in rotating movements and with a metallic spatula, in a unidirectional motion. Smear fixation with cytological spray fixative at a distance of approximately 40 cm or place slides in a microscope slide jar with a screw cap containing 95% ethyl alcohol (96°GL) for fixation and subsequent sending to the cytopathology laboratory

2 Fine-Needle Aspiration (FNA)

2.1 General Principles

- It contributes to diagnosis and treatment planning, as it allows the cytological study of a wide group of intra−/extraoral nodular diseases.
- Simple, fast, safe, inexpensive, and accurate technique.
- Well tolerated by patients.
- The patient may present with hematoma, local pain, and infection following FNA.

2.2 Indications

- Diagnosis of nodular diseases, lymph node enlargement or metastases in the head and neck region.
- Cancer staging and monitoring of recurrences.
- Diagnosis of salivary gland tumors.
- Diagnosis of infectious diseases such as paracoccidioidomycosis, tuberculosis, actinomycosis, leprosy, and toxoplasmosis involving lymph nodes among others.
- Diagnosis of lymphomas.
- Diagnosis of adverse reactions to aesthetic fillers, dermoid, epidermoid, and branchial cleft cysts, and other soft tissue diseases.

2.3 Contraindications

Carefully evaluate the indication of FNA for patients using anticoagulants or presenting coagulation disorders.

2.4 Materials

Materials used (Fig. 5) are the following:

- Sterile gauze, sterile gloves, and antiseptic solution.
- 24 G disposable fine needle (20 × 5.5 mm)
- Disposable syringe of 10 mL or 20 mL supported on syringe mechanical support to facilitate aspiration.
- Clean and dry microscope glass slides with frosted ends.
- Fixative: 95% ethyl alcohol (96°GL), cytological spray fixative, or dry fixation.

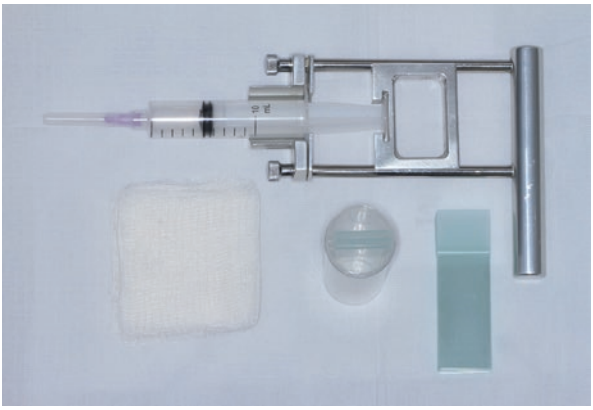

Fig. 5 Material needed for the FNA exam. The disposable syringe was supported on a aspiration gun to facilitate aspiration. Glass slides with the frosted end where the sample is distended. The patient's name and date or place of sample collection may be identified on the frosted end with a pencil. Slide holder case with fixing solution

2.5 Technique

The technique (Fig. 6) consists of the following:

- Local antisepsis with 0.1% iodinated alcohol, 10% povidone-iodine (topical PVP-I), or 2% chlorhexidine digluconate solution.
- Choose the best site for needle penetration before starting the procedure. In the case of the intraosseous lesion, introduce the needle in the cavity lumen through a thin area of cortical bone or perforation point, if present.
- Insert the needle almost perpendicularly toward the lesion site.
- Conduct quick and accurate forays in multiple directions for diverse sampling.
- Pull the plunger and observe the presence of material.
- Release the plunger, withdraw the needle, and press the site with gauze.
- Deposit a small amount of material directly on the slide for swab preparation, 2–3 mm in diameter, near the frosted end of the slide.
- With the tip of another slide inclined at 45 degrees, perform the distension of the material in a single movement in a uniform and smooth manner, generally, three slides for each staining.
- Fix by air-drying to be stained by the rapid panoptic technique and in 95% ethyl alcohol (96°GL) for Papanicolaou's technique and HE.
- Staining: Panoptic, Papanicolaou, and HE.
- Immunohistochemistry can be performed on paraffin-embedded material.

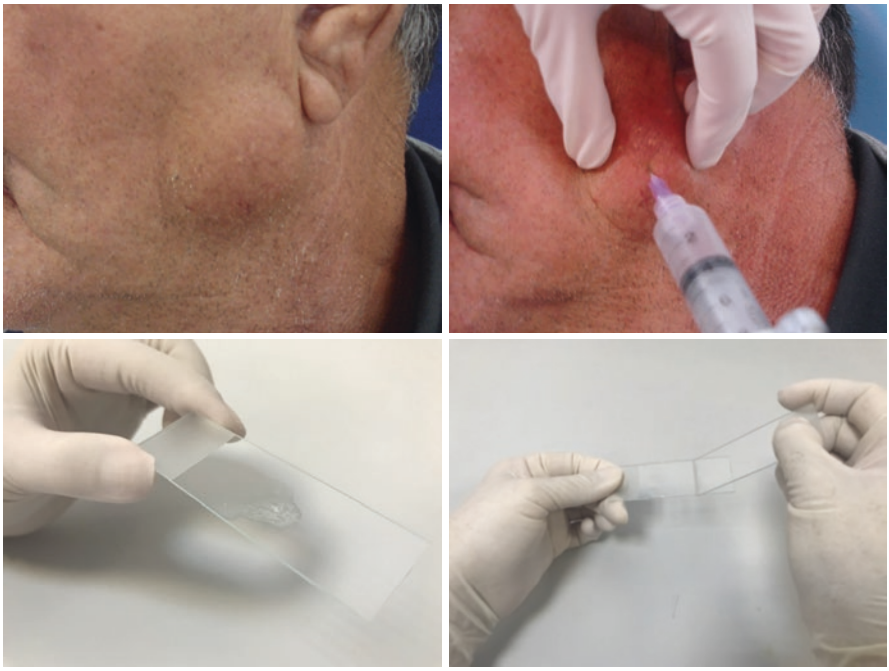

Fig. 6 Nodular lesion in the parotid region submitted to FNA. It is important to note that a small amount of aspirated material should be placed close to the frosted end of the slide. With the tip of another slide inclined at 45 degrees, a movement must be done until it touches the material. Slide the glass slide over the other slide in the direction opposite to the frosted end

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Biopsy of the Oral Mucosa and Histological Assessment

Mário José Romañach, André Caroli Rocha, Felipe Paiva Fonseca, João Figueira Scarini, Lara Maria Alencar Ramos Innocentini, and Michelle Agostini

The word "biopsy", from the Greek *Bios* (life) and *Opsis* (sight), was created by the French dermatologist Ernest Besnier in 1879 to designate procedures consisting of the removal of a fragment of living tissue to study its histological characteristics for diagnostic purposes.

Initially, the patient should be informed about the following points:

- The request for a biopsy does not mean suspicion of cancer.
- Biopsy is a relatively simple procedure that is usually performed under local anesthesia in the dental office. In children, general anesthesia may be needed.

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- The size and location from which the sample will be removed are important.
- The sample will be sent to an oral pathology laboratory, and the oral pathologist will perform a thorough analysis of the samples with the naked eye (macroscopy) and under the microscope (microscopy).

1 General Aspects

- The time to arrive at a diagnosis may vary. It is not an automated diagnosis printed quickly by a machine.
- The activity requires years of professional trainning, experience and study to interpret the cells and issue their opinion through a histopathological report.
- Chemical processes for tissue preservation and staining and cutting will be performed so that histological slides can be analyzed.
- The slides and the sample are safely stored for a certain period to aid in future treatments, prognostic information, or even scientific research.
- The oral pathologist usually correlates clinical data with microscopic analysis to determine the disease in question, contributing to the choice of the best treatment for the patient.
- In the oral and maxillofacial region, a biopsy is contraindicated in situations where:
  - The patient has complex systemic diseases.
  - The clinical diagnosis is sufficient.
  - The lesion regresses or disappears after 2 weeks of clinical follow-up.
  - The lesion shows a probable high-flow vascular origin.
  - The lesion is in the major salivary gland, producing an extraoral volume increase.
- Oral biopsies are indicated in situations where:
  - The lesion shows clinical features of malignancy.
  - The lesion without apparent etiology persists for more than 2 weeks.
  - The lesion of inflammatory origin does not respond to local treatment.
  - The lesion produces progressive growth in volume.
  - The lesion interferes with local function.
  - The intraosseous lesion cannot be diagnosed radiographically.
- There are two types of biopsies. The excisional biopsy (Fig. 1) consists of the total removal of the lesion, is usually indicated for clinically benign lesions, is pedunculated, and is smaller than 2 cm. An incisional biopsy consists of the removal of part of the lesion and is indicated mainly in lesions with suspected malignancy or larger than 2 cm.

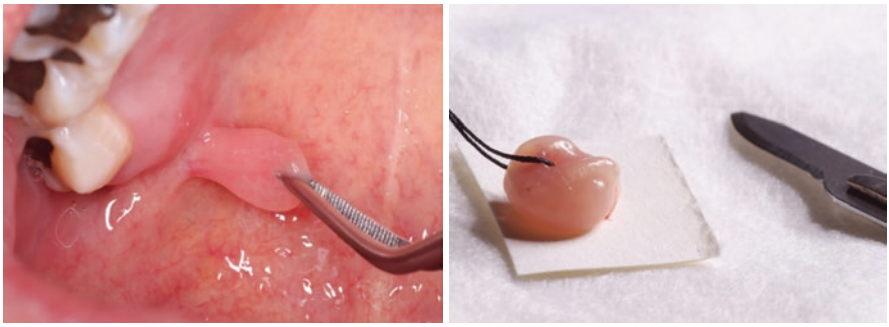

Fig. 1 Excisional biopsy of a pedunculated nodule smaller than 2 cm. Courtesy of Dr. Diego Tetzner Fernandes

2 Instruments and Materials

- The materials usually used are gauze, suture thread, scalpel blade, short or long needle (selected according to the anesthetic technique of choice), surgical suction device, table and fenestrated drapes, focus protector, surgical gloves, chlorhexidine digluconate 0.12% (alcohol-free), and povidone-iodine (or 2% chlorhexidine) for extraoral antisepsis and saline solution.
- Instruments such as curettes, chisels, or motor-driven surgical burs should be used only in cases of intraosseous lesions. Every intraosseous lesion, should be submitted previously to exploratory aspiration to rule out the possibility of a vascular lesion, a situation in which biopsy in an ambulatory environment should be avoided.
- In the case of very small biopsies, it is suggested to place them on filter paper before introducing them into the vial. This procedure guarantees a better orientation of the fragments, facilizing their manipulation in the laboratory (Fig. 2).
- Biopsy container containing 10% buffered formaldehyde should be properly identified and sent to the oral pathology laboratory (Fig. 3). In cases of multiple lesions in different locations of the oral cavity, when removed, they should be packaged in different biopsy containers, which should be properly identified through a label containing the name of the patient and the location of the fragment removed.
- The arsenal to perform the biopsy and the choice of the most appropriate instrument is mainly related to the nature and location of the lesion and the experience of the professional.

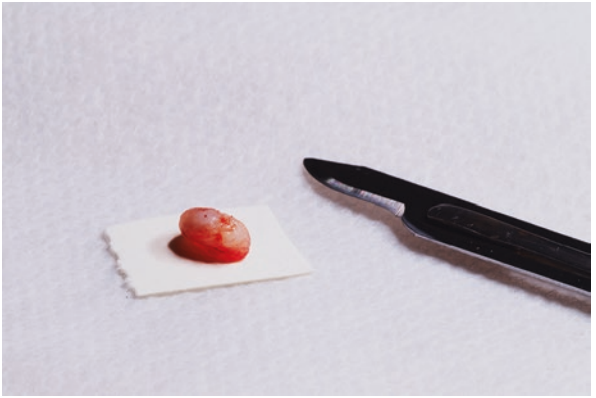

Fig. 2 Small biopsy placed on filter paper before introducing them into the specimen container. Courtesy of Dr. Diego Tetzner Fernandes

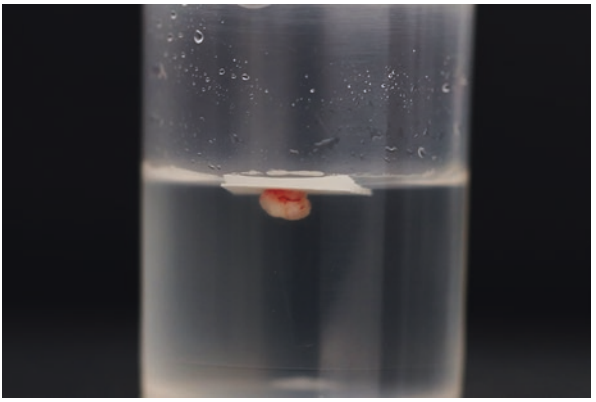

Fig. 3 Fragment of soft tissue placed in a transparent specimen container with a volume of formalin 20 times the size of the sample. Courtesy of Dr. Diego Tetzner Fernandes

3 Guidelines

- Incisional biopsy are mandatory in the suspicion of malignant tumors.
- Make an incision that is preferably elliptical or wedge-shaped to facilitate suturing and deep enough to include enough tissue for analysis.
- Perilesional tissue have to be included to ensure the inclusion of healthy tissue in the analysis of vesiculobullous lesion samples.
- Involve multiple areas in heterogeneous lesions (with leukoplakia and erythroplakia areas, for example) because histological features may vary in these regions.
- Avoid areas of necrosis.
- Never split the sample to send to two different pathologists.
- Be careful when manipulating the tissues, avoiding traumatizing them with forceps and/or sucker (Figs. 4 and 5).

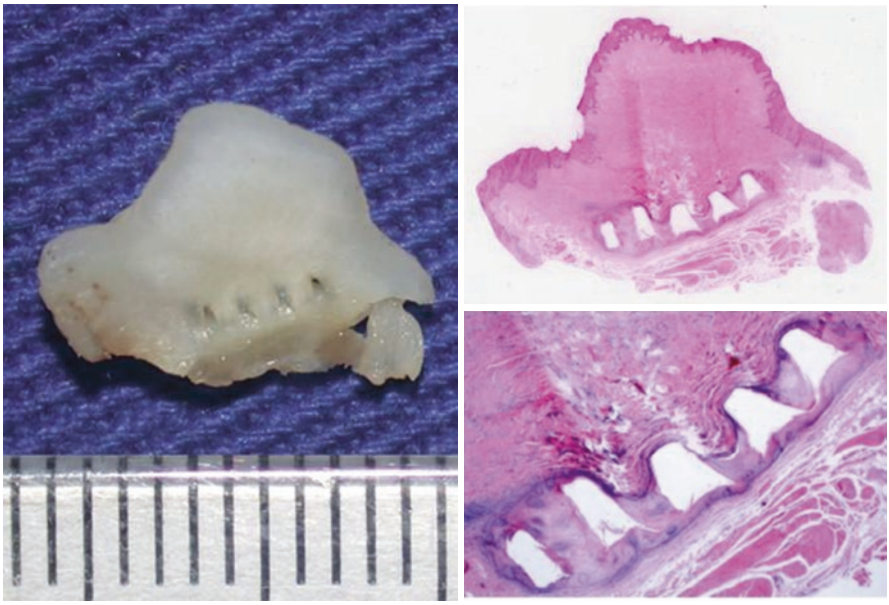

Fig. 4 Sample damaged by inappropriate use of the Allis forceps. Note that the base of the specimen was damaged by the shape of the forceps, resulting in a microscopic impression of epithelial tissue in the connective tissue depth

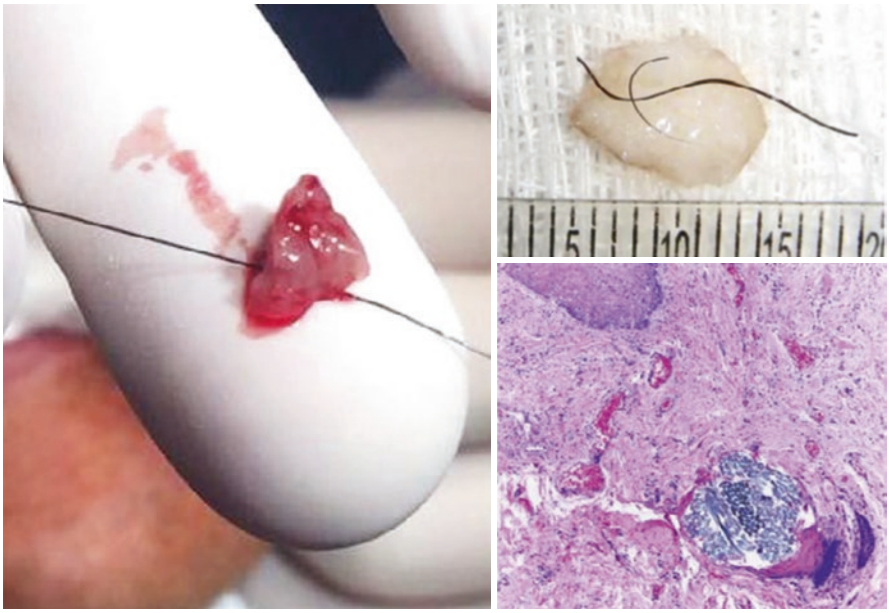

Fig. 5 Sample manipulated in the clinic with the aid of suture thread (left). The suture thread can be observed in the oral pathology laboratory (right) in the macroscopy (top) and microscopy (bottom) exams

4 Surgical Technique

- Place the tissue immediately into a sample container with a volume of formalin 20 times the size of the sample.
- Photographic documentation of the lesion (more details in Chap. 2) and election of the area to be removed.
- Preparation of the surgical field.
- Local anesthesia.
- Incision and manipulation of the removed sample (Fig. 6).
- Removal of excess blood with gauze without macerating the tissue.
- Suturing the surgical wound.

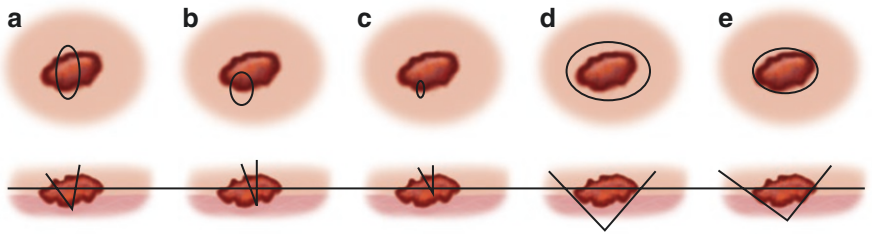

Fig. 6 Diagram showing different surgical approaches in a biopsy. (**a**) Correct incisional biopsy. (**b** and **c**) Incisional biopsy that will result in insufficient material. (**d**) Correct excisional biopsy. (**e**) Excisional biopsy in which the lesion was not completely removed

5 Bone Biopsy

Intraosseous lesions that do not allow a radiographic clinical diagnosis may also be submitted to incisional or excisional biopsy (Fig. 7). The decision will depend on the size of the lesion and the diagnostic hypotheses. After the evaluation of imaging exams (radiographs and computed tomography), the best surgical access is chosen (region of least resistance), followed by incision and detachment of soft tissues until the bone is exposed, proceeding with the removal of any remaining cortical bone (which should not be included in the same specimen container as the material to be examined) and collection of intraosseous pathological tissue, finishing with suture.

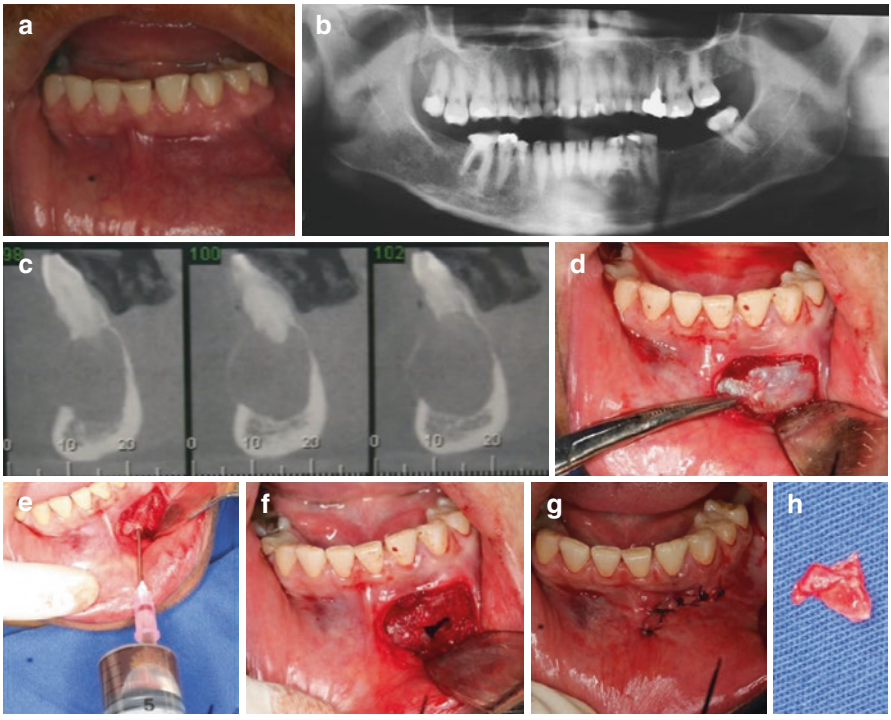

Fig. 7 (**a**) Volume increase in the anterior region of the mandible, (**b**) panoramic radiograph, radiolucent image extending from 35 to 43; (**c**) cone-beam computed tomography, the image of the osteolytic lesion, causing erosion of the buccal cortex; (**d**) incision and exposure of the lesion; (**e**) exploratory puncture; (**f**) removal of the lesion fragment (incisional biopsy); (**g**) suture of the mucosa; and (**h**) collected specimen

6 Information Shared with the Oral Pathologist

The oral medicinist or oral & maxillofacial surgeon must send the clinical information to the oral pathology laboratory, including at least the full name and date of birth of the patient, the description of the clinical and/or radiographic appearance of the lesion, the clinical hypotheses of diagnosis, and a brief medical history of the patient, including consumption of medication, alcohol, and tobacco. Sending clinical photos and radiographic exams contributes to a better clinicopathological correlation. The information can be sent in the histopathological exam request form along with the specimen container containing the sample or digitally by e-mail or smartphone apps.

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Protocol for Breaking Bad News

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and João Figueira Scarini

Communication is an essential element of the professional-patient relationship. More than just transmitting information, the act of communicating involves relational aspects between the interlocutors, which are fundamental to the understanding of the message. In clinical practice, communication should be understood as a process and not as a procedure. Such a process begins from the first contact and must consider both what the patient needs to know and his understanding of the information, his capacity to retain it, and, especially, the affective repercussions that it brings to him. Keeping these aspects of communication in mind is especially important when it is necessary to inform bad news.

Any information with the potential to generate drastic and negative changes in the perception of an individual about his/her present and future can be characterized as bad news. In health, it can be represented by the revelation of a life-threatening diagnosis, treatment failures, a dismal prognosis, and unfavorable test results, among other examples. This type of news is particularly common in oncology, whose diagnoses carry a stigma of death and suffering. Receiving bad news, such as the diagnosis of cancer, in addition to being a very particular and challenging

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moment for patients, triggers a series of negative feelings and emotions, which are often difficult to control. Giving this news is, equally, a complex task and can be a stressful moment for many health professionals.

In our area, patients diagnosed with oral cancer will be faced with challenging lifestyle changes. Depending on the treatment used, several vital functions (eating, breathing, and communication) may be affected. Body image and appearance, on the other hand, may affect another portion of these patients and reflect negatively on their self-esteem and quality of life. With impaired social interactions, many patients may develop anxiety, depression, and even symptoms of posttraumatic stress disorder. In addition, the increased incidence of HPV-related oropharyngeal cancer, especially among younger populations, can bring consequences linked to the cause of the disease (sexually transmitted diseases) and bring significant consequences not only for patients but also for their partners.

In this context, the way bad news is transmitted is as important as the message itself and can have important clinical and psycho-emotional consequences. Studies indicate that the high quality of communication between the health professional and the patient directly influences the understanding of information, levels of suffering, psychological stress, and even treatment adherence (Fig. 1). Adequate preparation of the professional—theoretical and emotional—provides both a more effective communication with the patient and a reduction in the degree of anxiety of both during the sharing of bad news.

Often, health professionals are inserted directly into clinical practice without any training for this type of communication, which can lead to embarrassing and

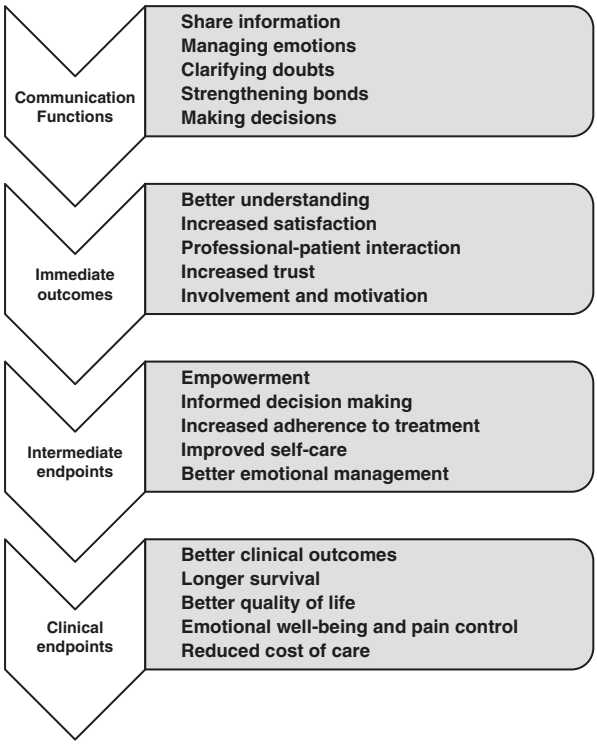

Fig. 1 Relationship between communication and health outcomes

emotionally charged situations. The unpreparedness begins in university education, where there is a poor focus on psychic issues associated with illness and management of borderline situations. Many develop their style of communicating based on observation of other coworkers or learning from experience. Although the intuition and common sense of the professional are important in the process of delivering bad news, it is essential to have a scientific basis to achieve greater clarity and effectiveness in communication, greater safety of the professional in his daily practice, and better patient care. Delivering bad news requires careful planning and execution through validated strategies. Like other competencies, such skills can be developed and improved with training and practice.

Several protocols available in the scientific literature are useful tools to facilitate this type of communication, such as the SPIKES, VOICE, SHARE, and ABCDE strategies. In general, they guide the clinician in the process of collecting and transmitting information, providing support, and involving the patient in the development of a care plan. Due to the complexity of interpersonal communications, this is not a

Table 1 Protocol for breaking bad news

Get ready to deliver the bad news
• Prepare yourself emotionally • Determine what and how much the patient wants to know • Allow sufficient time to provide information and explore the patient's response • Ensure privacy and make sure there are no interruptions (turn off your phone or put it on silent mode) • Have as much information as possible, as you may be questioned, and provide written materials that the patient can refer to after the service • Evaluate the need for a companion, as having family members or people to support can be important to the patient at this time
Discuss the bad news
• Introduce yourself to everyone • Sit down, do not stand up • Analyze what the patient/family already knows and what the real expectation is for the conversation • Find out how much information they would like and at what level of detail • Let the patient/family know that bad news is coming • Provide information in small chunks • Use language that is frank, simple, and direct but still compassionate. • Check that the content is understood and respond to the patient's reactions throughout, without euphemisms and jargon • Be empathic and show support. Acknowledge the patient's feelings, and allow silences (pauses) and tears; use touch when appropriate • Proceed at the patient's pace; explore their fears about the news given • Provide treatment and prognostic information that offers hope and reassurance according to your goals/needs/reality • Offer realistic hope according to the patient's goals • Do not discuss or criticize colleagues. Consider providing some contact phone numbers for the patient • Schedule follow-up appointments • Summarize the discussion and check the patient's understanding
Review the situation
• Recognize the impact that bad news has had on you and your patient • Reflect on what went right and what perhaps should be improved in a similar situation that could happen again • Document important discussions in the medical record

linear process but a dynamic one, which presents itself differently at each new contact. For didactic purposes, we will describe in sequence the fundamental elements for the transmission of bad news based on globally established protocols (Table 1).

1 Planning the Consultation

The professional must prepare rationally and emotionally for the meeting. It is important to review the clinical case, keeping in mind the patient's history and general information, procedures performed and their results, and treatments instituted, that is, all information that supports the bad news to be transmitted. Anticipating questions and mentally rehearsing your answers can help to identify words or phrases to be used and avoided during dialog with patients and their families.

The place of communication should be private and quiet. The reactions of patients and family members to bad news are variable, and it is important to allow them to show them in private. Depending on the context, this may mean reducing the number of people in the office, requesting that no interruptions be made for a certain period, silencing electronic equipment such as cell phones, using screens to provide privacy in a hospital setting or outpatient clinics with multiple visits.

Ensure the presence of people important to the patient, if this is their wish. After greeting them, it is recommended that the clinician sit with the patient, demonstrating an unhurried demeanor. Maintaining eye contact, in addition to conveying honesty and integrity, helps establish a connection during conversation and observation of patients' nonverbal reactions.

2 Understanding Patient Perception

Exploring the patient's perception of his diagnosis allows the professional to shape the bad news to his capacity of understanding and absorption. What has he been told about his clinical condition? What is their understanding of the reasons why tests were carried out? What other sources of information—professional or common sense—have been accessed? Understanding the patient's view will enable the clinician to correct misinformation, clarify unrealistic expectations, and minimize the shock of bad news since its impact is proportional to the gap between the patient's perception and the reality of his condition.

Bad news means different things to different people. In this context, before informing, ask. Start the dialog with open questions, avoiding interrupting the patients in their responses. This will provide some hints about how the patients may react and give a starting point to begin the explanation and offer support later. Listening and hearing are not synonymous. Listening involves an active process of engagement. The patient may perceive that the professional is actively listening when the professional paraphrases or summarizes what has been said.

Facilitation techniques such as nodding, smiling, or saying "Yes, I understand" are encouraged. Noting the words used by the patients in their response to the situation also helps the clinician avoid technical jargon at the time of further discussion.

3 Assessing the Patient's Desire to Know

From the first meetings, professionals should evaluate the desire for information expressed by their patients. When complementary exams are requested, such as imaging exams or biopsies, for example, it is opportune to negotiate the transmission of information about their results. Does the patient want detailed information about the diagnosis, prognosis, and treatment? Or does he/she prefer to receive information gradually? Or does he/she prefer that the clinical details be informed to his/her companion and only want to be informed about the next steps? Taking into account each individual's desire for information and shared responsibility and responding appropriately to that desire is part of the person-centered care model, not the disease-centered care model.

4 Transmitting the Information

To facilitate the understanding of the facts, the clinician can use a brief evaluative narrative, in simple language, about the events up to that moment: the symptoms, the clinical examination, the tests performed, and their results, always being available to clarify any questions expressed by the patient. After that, some protocols recommend a careful warning statement, such as "Unfortunately, I have no good news to tell you." This warning aims to announce the type of information that is coming, giving time for the patient to be willing to listen to them and emotionally preparing him for the impact of the bad news.

Information should be conveyed in simple and clear language to the patient, avoiding the use of overly technical terminology. The use of medical jargon creates a communication barrier that may result in the patient's fear of asking questions that may seem silly or inappropriate. The focus, however, should be on ensuring that the patient fully understands the problem and can understand the decisions to be made. Therefore, the professional must deliver the bad news clearly, regularly checking the patient's understanding of what is being talked about.

The patient should not be alarmed by large amounts of information, as this overload can be an additional stressor. In addition, it can hinder the patient's understanding of his condition. Information should be passed in short and manageable follow-ups, respecting the assimilation capacity of each patient. The understanding of the message by the recipient reflects the quality of the way it was reported.

5 Management of Emotions

The patient's initial reaction to bad news may include negative feelings such as anger, sadness, fear, and worry. They are projections of a new understanding of reality. No matter how carefully it is delivered, bad news does not become positive. On the other hand, clinicians can facilitate the patient's ability to manage their emotions by presenting diagnostic and treatment information clearly and honestly, listening carefully, and validating patients' expressions of feelings.

Patients should feel comfortable demonstrating their emotions, which is essential to support and validate them empathically. The professional does not need to experience the same feelings as the patient, but it is very important to recognize them, expressing, for example, "I know this is very difficult for you" but never: "I know how you feel." Allowing silence when it presents itself also has immense value, as it offers the patient time to cognitively process the emotional implications of the news.

Whenever possible, the professional should expect a movement from the patient indicating that he or she is ready to continue, which may occur when the patient asks a question or resumes eye contact. Providing clear explanations about the continuity of care also helps patients gain a greater sense of control, have more hope, and manage uncertainty. In addition, communication that privileges the patient's sense of value can confer hope, meaning, motivation, and the energy needed to perform activities of daily living and allow the patient to enjoy a higher quality of life despite his/her new condition.

6 Summarize and Strategize

At the end of the meeting, a plan of action must be developed according to the patient's goals, needs, and reality. This plan provides the individual with a sense of control over the situation and allows for a new starting point. The clinician must involve and share responsibilities with the patients in this decision-making about the next steps. One should explain in understandable language and approach planning from the patient's perspective, providing explanations simply and honestly but avoiding excessive candor. One of the dilemmas when communicating bad news lies in being honest without destroying patient's hope.

Assessing the patients' understanding of the discussion prevents the tendency to overestimate or not understand the purpose of the planning. One strategy to check their understanding is to ask the patient to briefly summarize what was agreed upon, allowing the professional to highlight the most relevant points. Conveniently, the professional makes him/her accessible for the clarification of doubts after the consultation, providing a contact number and informative support brochures when available.

Protocols that value patient-centered communication skills tend to obtain better treatment outcomes. This means that the health professional will achieve success when adapting his communication style to the patient's way of reasoning,

understanding, feeling, and behaving. Communication processes must begin since the first consultation and permeate throughout the treatment/follow-up of the disease. A patient is more than a clinical case or a statistical number of pathologies. Above all, he/she is a person who, in this delicate moment, needs our attention, compassion, and empathy.

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Part II

Reactive Lesions and Non-Neoplastic Proliferative Processes

Traumatic Oral Ulcer

Felipe Paiva Fonseca, João Figueira Scarini, and Lara Maria Alencar Ramos Innocentini

Traumatic ulcers are lesions caused by external factors (mechanical, thermal, or chemical) associated with occasional or continuous trauma to the oral mucosa. Ulcerations caused by mechanical or thermal factors are more frequent and only regress when the traumatic factor is removed. On the other hand, ulcerations caused by chemical factors are less common.

Traumatic ulcers due to mechanical factors are usually associated with constant trauma of total removable prostheses, especially in elderly patients, but can also be seen as eosinophilic ulcers of the oral mucosa, which is a rare, benign, and self-limited condition and can often be confused as malignant ulcers. In these cases, histopathological findings after an incisional biopsy can confirm the diagnosis.

It is important to note, however, that when seen in neonates, these lesions have been called Riga-Fede disease. They are seen on the tongue of infants with

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(neonatal) teeth and develop by continuous contact between the tongue and teeth during physiological activities, such as breastfeeding and swallowing. They require intervention because they can interfere with the quality of feeding and cause a risk of nutritional deficiencies for the newborn.

1 Clinical Characteristics

1.1 Traumatic Ulcers

- Erythematous edges.
- A central region with fibrinopurulent membrane (Figs. 1 and 2).
- Symptomatic.
- Present in areas related to direct traumatic factors.
- The time of evolution depends on the intensity and frequency of these factors.

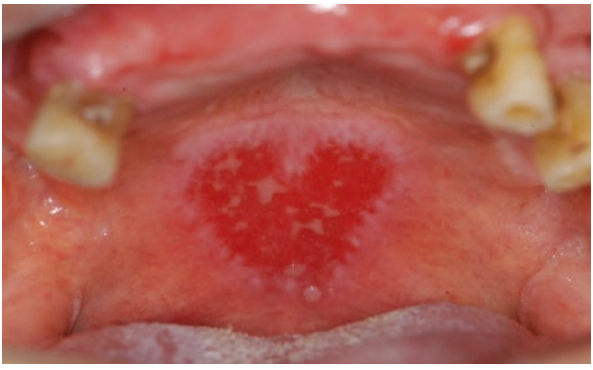

Fig. 1 Traumatic ulceration. Ulceration of the soft palate mucosa with the hyperkeratotic halo

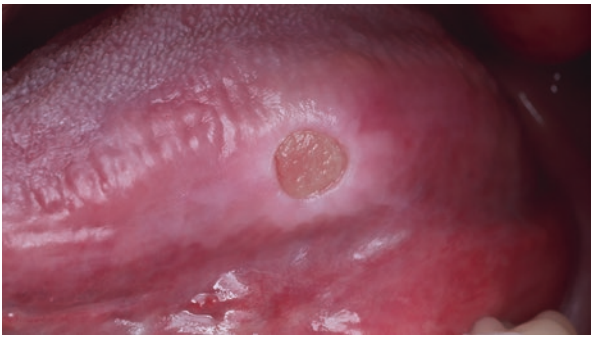

Fig. 2 Traumatic ulceration. Ulceration of the lateral border of the tongue with the hyperkeratotic halo. Courtesy of Dr. Diego Tetzner Fernandes

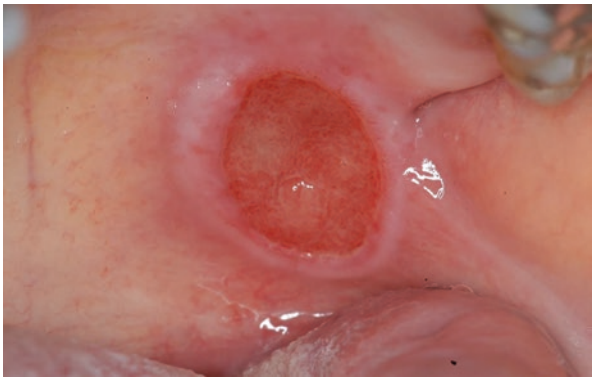

Fig. 3 Eosinophilic ulcer. Extensive mucosal ulceration of the soft palate on the left

1.2 Eosinophilic Ulcer

- Raised and hardened edges.
- White–yellowish background.
- Usually asymptomatic.
- It can remain for weeks to months.
- Frequently in the tongue, although some cases can be observed in the lip, palate (Fig. 3), buccal gingival mucosa, and floor.

1.3 Riga-Fede Disease

- Prominently raised border ulcer.
- Persistent.
- Often in the anterior ventral tongue.
- It may evolve into an enlarged fibrous mass.

2 Diagnosis

- Clinical features are the primary means of reaching a diagnosis.
- Some patients complain of altered sensation before the development of the ulcer.
- Investigate the use of drugs that can induce ulceration in oral mucosa:
  - Beta-blockers (labetalol).
  - Immunosuppressants (mycophenolate).
  - Anticholinergic bronchodilators (tiotropium).
  - Platelet aggregation inhibitors (clopidogrel).
  - Vasodilators (nicorandil).
  - Bisphosphonates (alendronate).
  - Protease inhibitors.

  - Antibiotics.
  - Nonsteroidal anti-inflammatory drugs.
  - Antirheumatics.
  - Antiretrovirals.
  - Antihypertensives (captopril, enalapril).
- Anemia, blood dyscrasias, autoimmune diseases, and diabetes were excluded.

3 Treatment

- Reinforce removal of removable prostheses.
- Incisional biopsy is indicated to exclude the possibility of malignant tumors in cases of eosinophilic ulcers of dubious appearance and nonobvious causes.
- Restoration and polishing of teeth associated with trauma (special attention when they are deciduous and not supernumerary, in Riga-Fede disease).
- Photobiomodulation.

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Recurrent Aphthous Stomatitis

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Recurrent aphthous stomatitis (RAS) is the most common oral mucosa disease. The clinical picture of RAS is characterized by recurrent episodes of painful, solitary, or multiple ulcerations, without association with systemic diseases. Since aphthous ulcerations (or RAS-like ulcerations) have a systemic etiology, they ought to be regarded as a separate medical disorder. Population-based studies show prevalence rates of RAS ranging from 0.9 to 78% in different examined groups. Due to the episodic nature of RAS, its true prevalence may be underreported. The onset of RAS occurs between 10 and 19 years of age, and its frequency decreases with aging.

Although the clinical features of RAS are well defined, the etiology remains unclear. Multiple factors are associated with the setting of RAS (all of which alter the composition of microbiota living on oral mucosa), including family history, food hypersensitivity, smoking cessation, psychological stress, and immunological disorders. However, for this evidence, there is often an absence of statistical risk

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analysis, and despite a large number of factors examined, the triggering cause of ulcer episodes remains to be elucidated.

The stages of RAS progression are as follows: pre-ulcerative (erythema and mild edema), ulcerative (active ulceration), healing (a decrease in symptoms and progressive healing); and remission (there is no evidence of ulcers). Currently, three clinical variants of aphthous stomatitis are recognized: (1) minor (most common), (2) major (chronic process), and (3) herpetiform (which is unrelated to the herpes virus).

1 Clinical Characteristics

1.1 Minor RAS

- Ulcers less than 1 cm in diameter.
- Round or oval.
- Usually with the presence of yellowish–white pseudomembranes.
- There may be an erythematous halo (Figs. 1 and 2).

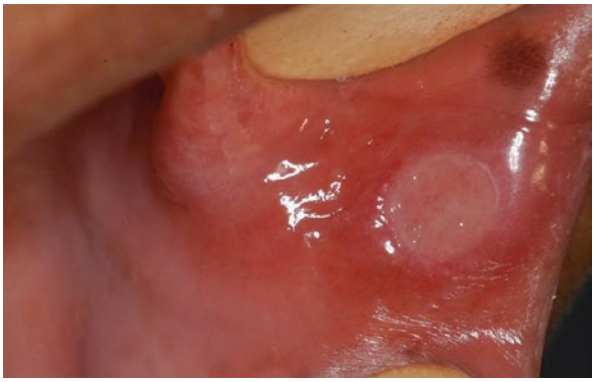

Fig. 1 Minor RAS. Ulceration is surrounded by an erythematous halo in the jugal mucosa, near the labial commissure

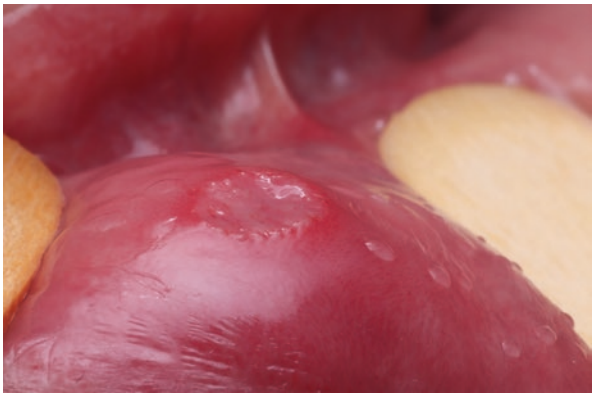

Fig. 2 Minor RAS. Deep ulceration on the labial mucosa. Courtesy of Dr. Diego Tetzner Fernandes

- Uncommon on keratinized surfaces (gingiva, hard palate, or dorsum of the tongue).
- Regression in up to 2 weeks, without leaving a scar.

1.2 Major RAS

- They may be more than 1 cm in diameter (Fig. 3).
- They occur in lips, soft palate, and tonsillar pillars.
- They may persist for more than 3 weeks and leave a scar.

1.3 Herpetiform Ulceration

- Multiple small (2–3 mm) ulcers that may coalesce and form larger areas of ulceration (Fig. 4).
- Disseminated.
- Painful.

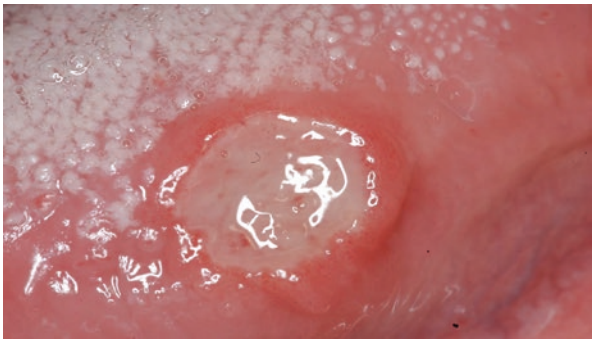

Fig. 3 Major RAS. Deep ulceration on the lateral border of the tongue

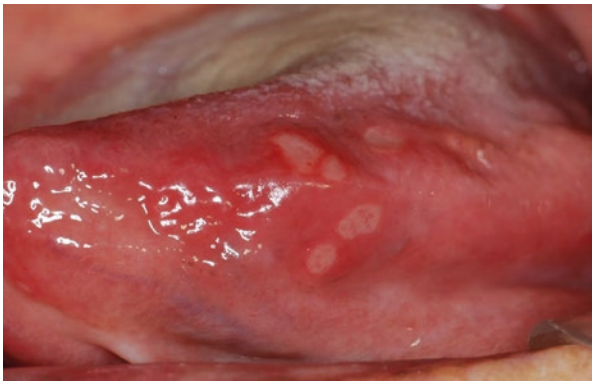

Fig. 4 Herpetiform ulceration. Numerous ulcerations on the lateral border of the tongue, of which some coalesce to form larger lesions

2 Diagnosis

- Clinical features are the primary means of reaching a diagnosis.
- Perform biopsy in cases of minor ulcers lasting more than 2 weeks.
- Perform culture and specific tests to exclude infection with herpes simplex virus, cytomegalovirus, and HIV.
- Assess clinical history and physical examination to rule out food allergy, in which case perform specific serological tests for IgE and for the antigen of the suspected food and skin tests.
- Assess deficiency of iron (iron deficiency anemia), folic acid, and vitamins B and C, as well as absorption problems.
- Systemic disorders such as Crohn's disease, celiac disease, cyclic neutropenia, HIV infection, Behçet's syndrome and periodic fever syndrome, herpetic gingivostomatitis, pharyngitis, and adenitis have to be excluded.

3 Treatment

- In the case of food allergies, food should be substituted with the monitoring of nutritionists. The topical and systemic use of corticoids will be evaluated.
- Recurrent ulcers:
  First Line of Treatment
  - Triamcinolone 0.1% mouth ointment—Apply a small amount in the affected area up to four times a day until remission of ulcers occurs, besides lidocaine 2% viscous solution, maximum eight doses a day, and as an adjuvant, alcohol-free chlorhexidine 0.12%, 15 mL as a mouthwash twice a day.

  Second Line of Treatment
  - Systemic corticotherapy with oral prednisone (20 mg/day) administered for 7 days. After that, reassess the patient.[1]

  Third Line of Treatment
  - *Photobiomodulation for wound healing:* A single session of diode laser (wavelength 810 nm, power 0.5 W) 2–3 mm away from the border of the ulcerative lesion (four times with an interval of 30–40 s between each application in continuous mode).
  - *Photobiomodulation for pain relief:* Laser (wavelength of 810 nm, power of 0.06 W) applied once a day for 2 days in pulsed mode and direct contact with the lesion (80 s per application).

[1] This therapy is more effective against pain and accelerates ulcer healing. Long-term and repeated use should be avoided to prevent adrenal suppression.

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Desquamative Gingivitis

Lara Maria Alencar Ramos Innocentini,
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The term desquamative gingivitis, initially described by Prinz in 1932 and originally associated with hormonal disorders, refers to a clinical manifestation triggered by a variety of disorders, including vesiculobullous diseases up to adverse reactions to a variety of chemicals or allergens, being characterized by the presence of erythema, epithelial peeling, and erosion of the marginal and inserted gums, regardless of the etiopathogenesis involved.

The etiological agents responsible for activating the different mechanisms that culminate in the onset of desquamative gingivitis in genetically predisposed patients are not known. There is no evidence that desquamative gingivitis per se causes the loss of alveolar bone and periodontal insertion; however, it may compromise the ability of patients to perform adequate oral hygiene, which would potentially lead to the development of chronic periodontitis due to the accumulation of biofilm and calculus.

Because most cases of desquamative gingivitis are associated with systemic conditions, its oral and extraoral manifestations eventually cause great morbidity to affected patients. Moreover, the wide variation in therapeutic approaches among the various underlying conditions further increases the importance of an accurate

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diagnosis. Among the conditions most frequently associated with the onset of desquamative gingivitis, lichen planus (45–70%) and mucous membranous pemphigoid (14–48%) can be highlighted, and these disorders may be the only clinical presentation, in addition to pemphigus vulgaris (13–24%).

1 Clinical Characteristics

- A predilection for female gender with a peak incidence between the fifth and sixth decades of life reflecting the epidemiology of associated diseases.
- The upper anterior inserted gingiva is the most affected site.
- Erythematous, erosive, and rarely ulcerated areas (Figs. 1 and 2).
- Burning sensation and pain in a significant portion of cases.
- Very rarely, the presence of easily ruptured blisters and vesicles may be observed.

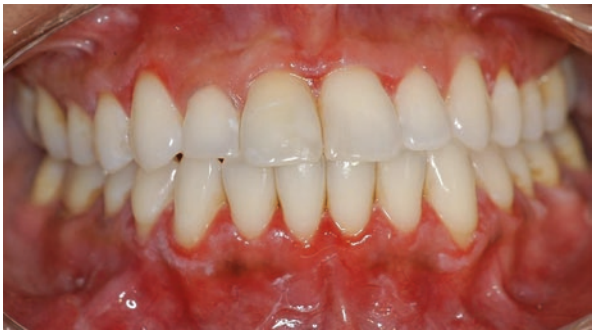

Fig. 1 Gingival lesions presenting as "desquamative gingivitis"

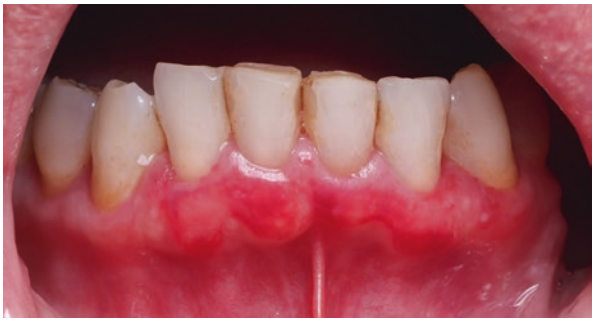

Fig. 2 Gingival lesion in the mandible presenting as an erythematous area. Courtesy of Dr. Diego Tetzner Fernandes

2 Diagnosis

- Identification of the desquamative gingival lesion.
- Clinical history (onset, chief complaint, infections, use of topical substances, drug intake, general health of the patient).
- Intraoral clinical examination (presence of other lesions outside gingival sites).
- Assessment of extraoral involvement (another mucosae, skin, internal organs).
- Incisional biopsy and histopathological evaluation (inflammatory infiltrate, epithelial modification). Biopsy of these lesions is challenging, and the site of choice is usually adjacent to the desquamated area.
- Immunopathological evolution (direct immunofluorescence for tissue involvement, indirect immunofluorescence for serological assessement).
- Differential diagnoses:
  - Lichen planus.
  - Mucous membranous pemphigoid.
  - Pemphigus vulgaris.
  - Paraneoplastic pemphigus.
  - Erythema multiforme.
  - Graft-versus-host disease.
  - Systemic/discoid lupus erythematosus.
  - Chronic ulcerative stomatitis.
  - Plasmacytic gingivitis.
  - Linear IgA disease.
  - Dermatitis herpetiformis.
  - Congenital dyskeratosis.
  - Dermatomyositis.
  - Acquired epidermolysis bullosa.
  - Psoriasis.
  - Ulcerative colitis.
  - Foreign body gingivitis.
  - Gingivitis induced by drugs or chemicals (sodium lauryl sulfate, magnesium monoperoxifalate).
- Establishment of final diagnosis and treatment.

3 Treatment

The appropriate treatment for desquamative gingivitis depends on the exact diagnosis of the underlying disease, and the description of its therapeutic protocols can be found in their respective chapters.

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Non-neoplastic Proliferative Processes

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The oral cavity is a constant site of stimuli and constitutes a vast biological environment favorable to the development of alterations and diseases. The presence of mucous membranes together with the teeth and the intense and perennial participation of several categories of microorganisms make the metabolism of this anatomical region unique. In addition to local interactions, this complex biological system is susceptible to systemic conditions, such as endocrine, genetic, hematological, and immunological conditions.

The oral mucosa, in particular, is constantly exposed to local irritating factors and may respond to such aggressions by developing different reactive lesions,

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benign and non-neoplastic. These conditions are frequent in daily clinical practice and are easily visualized during oral examination. In this group of lesions, pyogenic granuloma, peripheral ossifying fibroma, fibrous hyperplasia, and giant cell lesion (which will be discussed in a separate chapter) stand out. Although all these lesions have significant clinical occurrence, it is important to pay attention to differential diagnoses, including malignant conditions that mimic the clinical presentations of the mentioned group.

Nonneoplastic proliferative processes commonly arise as a result of common and chronic stimuli, such as bacterial biofilms, dental calculus, appliances, and prostheses with installation deficiencies, and have a marked anatomical predilection for gingival tissue. On physical examination of the lesion, non-neoplastic proliferative processes may mimic benign neoplasms presenting as nodules. It is noteworthy that the interaction of irritating factor(s) with the oral mucosa enables, through cell proliferation, degradation of extracellular matrix proteins, with the mediation of cytokines and the appearance of clinical lesions, commonly slow-growing and asymptomatic, with similar coloration to the mucosa, or hyperchromic, such as dark red and purplish.

Pyogenic granuloma is a predominantly nodular lesion with possible morphological variations and exuberant vascular components. Contrary to what one might assume, in this lesion, there is no production of purulent infiltrate or evidence of a granulomatous condition. The majority (75%) of pyogenic granulomas are located in the gingiva, but other areas, such as the tongue and lips may also be involved. They are usually pedunculated, asymptomatic, and predominantly female. They are observed more frequently in young adults, and in addition to the evident participation of local irritant agents, the contribution of hormonal changes stands out, for example, during pregnancy, oral contraceptives, and hormonal repositions. When it occurs in pregnant women due to the vascular effects of female hormones, the name used is granuloma gravidarum. When the levels of estrogen and progesterone return to normal after the end of pregnancy, a decrease in the inflammatory component or even involution of the lesion may occur. Molecular studies have been performed, but the biological events and the actual mechanisms involved in the etiology of the lesion remain uncertain. There are also studies considering the possibility of pyogenic granuloma constituting clinical stages of fibrous hyperplasia (fibroma) development.

Pregnancy tumor or granuloma gravidarum

- A pyogenic granuloma that develops during pregnancy.
- Especially in the third trimester of pregnancy.
- The increasing levels of estrogen and progesterone during pregnancy have a direct influence on its pathogenesis.

Fibrous hyperplasia represents the most common exophytic alteration of the oral mucosa and affects patients in a wide age range. They have no predilection for gender and vary in size. They result from chronic localized stimuli, especially trauma from ill-fitting prostheses or fractured teeth. When associated with ill-fitting

prostheses, the edges of dentures stimulate the formation of inflammatory hyperplasia in the buccal fornix of the alveolar ridge, also called fissured epulis. They are asymptomatic, but when ulcerations are present, they may present pain.

Peripheral ossifying fibroma is a benign mesenchymal lesion with collagen deposition capacity and a calcified component in its stroma. The genesis of this lesion probably involves modifications in undifferentiated cells of the periosteum and/or periodontal ligament. Peripheral ossifying fibroma occurs in the gingiva, with a predilection for the anterior region of the maxilla, in adolescent and young female patients. Similarly, certain studies continue to suggest that the lesion may be the result of maturation of a long-standing pyogenic granuloma and therefore another stage of fibrous hyperplasia. The first line of treatment is the removal of possible local irritants, such as bacterial plaque and incorrect tooth positioning, total excision of the lesion associated with scaling, and coronoradicular smoothing to remove the periodontal ligament involved in the formation of the lesion.

Tirelessly, it is worth reinforcing that all the mentioned conditions represent only a response to chronic stimuli and thus are not truly neoplastic processes. It also emphasizes that the diagnosis of these lesions is always the sum of the clinical-epidemiological characteristics and radiographic and histopathological findings.

1 Clinical Characteristics

1.1 Pyogenic Granuloma

- Asymptomatic nodule with a sessile base and reddish-purple coloration (Figs. 1 and 2).
- Secondary superficial ulcerations may be present.
- Tendency to bleed upon contact.
- A whitish-yellow pseudomembrane may be present.
- It is located mainly on the gums but can also be seen on the lower lip, buccal mucosa, and tongue.

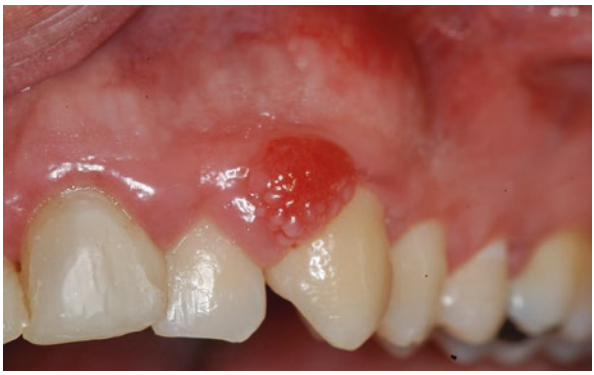

Fig. 1 Pyogenic granuloma. Erythematous and hemorrhagic volume increase in the gingiva of the anterior region of the maxilla

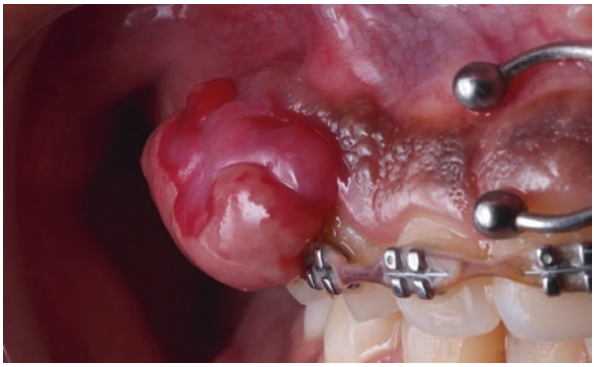

Fig. 2 Pyogenic granuloma. Erythematous and hemorrhagic volume increase in the gingiva of the anterior region of the maxilla. Note the whitish-yellow pseudomembrane on the surface

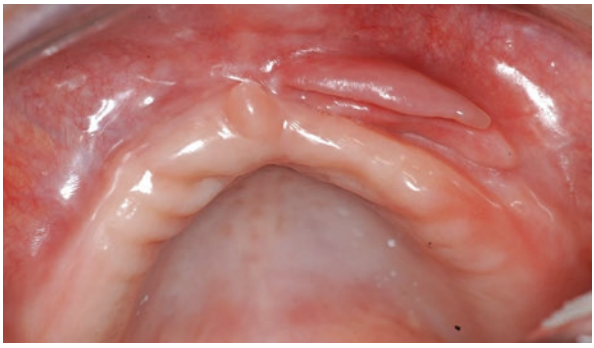

Fig. 3 Pleats of hyperplastic tissue in the anterior maxillary vestibule associated with a removable total prosthesis

1.2 Fibrous Hyperplasia

- A normochromic or pinkish pink, sessile, or pedunculated nodule.
- Rounded, elongated, or ovoid.
- The surface may be hyperkeratotic or ulcerated due to secondary trauma.
- Usually, asymptomatic.
- It was mainly located on the alveolar ridge (Fig. 3) and buccal mucosa (Fig. 4).

1.3 Peripheral Ossifying Fibroma

- Reddish-purple or normochromic sessile or pedunculated nodule (Fig. 5 and 6).
- The surface may be ulcerated.
- It can reach the expressive diameter.
- Exclusive of gum.
- It often originates in the interdental papilla.

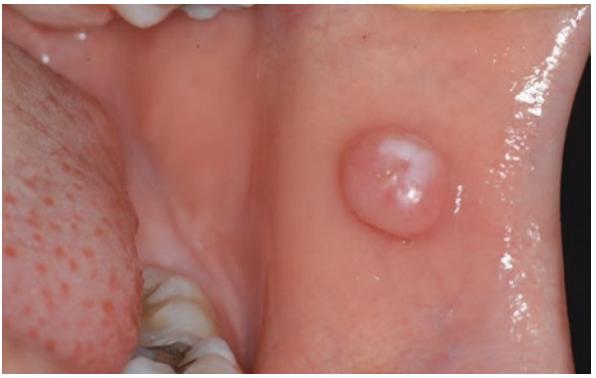

Fig. 4 Fibrous hyperplasia. Pink nodule in the anterior region of the buccal mucosa, near the labial commissure and at the level of the occlusal line

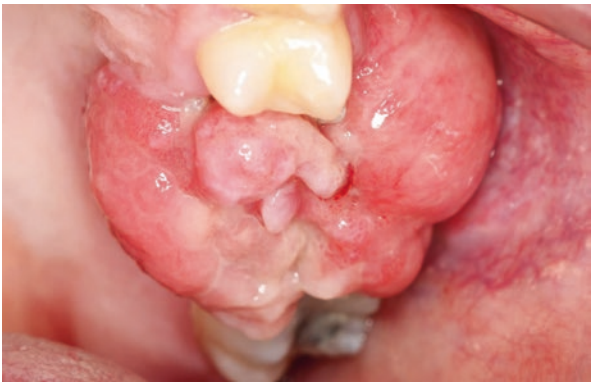

Fig. 5 Peripheral ossifying fibroma. Ulcerated and normochromic lesion originating in the maxillary gingiva

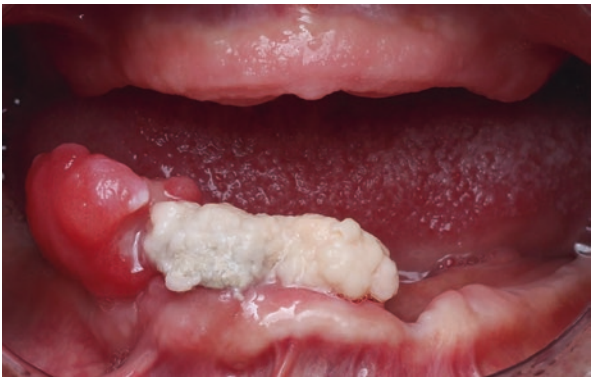

Fig. 6 Peripheral ossifying fibroma. Ulcerated and normochromic lesion originating in the maxillary gingiva. Note the extensive area of necrosis

1.4 Diagnosis

- Clinical evaluation.
- Radiographic evaluation.
- Incisional or excisional biopsy.

1.5 Treatment

- Removal of the local irritant.
- Surgical removal.
- Basic periodontal treatment (scaling and root planning) in cases of peripheral ossifying fibroma.
- Patient education and clinical follow-up showed a favorable prognosis.
- Maintenance of oral hygiene with the teaching of brushing technique.

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Giant Cell Granuloma

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Peripheral giant cell granulomas represent a relatively common hyperplastic connective tissue response to chronic and low-intensity local irritants in periodontal tissues, constituting an exuberant reparative process. It presents microscopic features very similar to those of the central giant cell lesion, a benign nonneoplastic condition that occurs almost exclusively in gnathic bones and accounts for approximately 7% of benign bone lesions diagnosed in these anatomical sites.

1 Clinical Characteristics

1.1 Peripheral Giant Cell Granuloma

- Discrete predominance in the female gender.
- Wide age range.

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- Located exclusively in the gingiva.
- Usually, between molars or incisors.
- Asymptomatic nodule with a sessile base and purplish coloration (Fig. 1).
- Secondary superficial ulcerations may be present.
- Possible "cup resorption" of the underlying bone.

1.2 Central Giant Cell Granuloma

- Young adults before the age of 30.
- A predilection for the female gender.
- Anterior mandible region (Fig. 2).
- Occasionally crosses the midline.
- Multilocular radiolucent image with well-defined margins.
- Occasionally unilocular.
- Nonaggressive variant:
  - Slow, painless bone expansion and swelling.
  - Absence of cortical perforation.

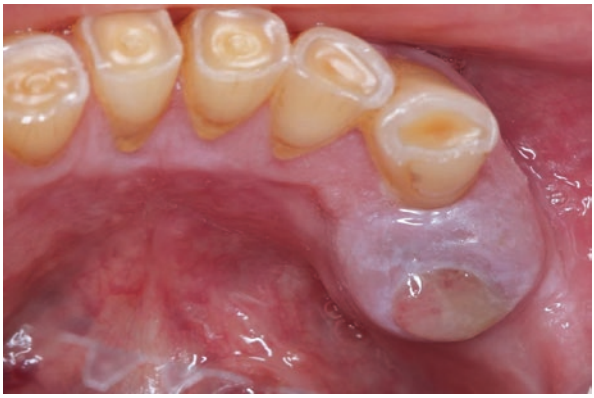

Fig. 1 Peripheral giant cell granuloma. Nodular, ulcerated, purplish-blue lesion in the mandibular gingiva

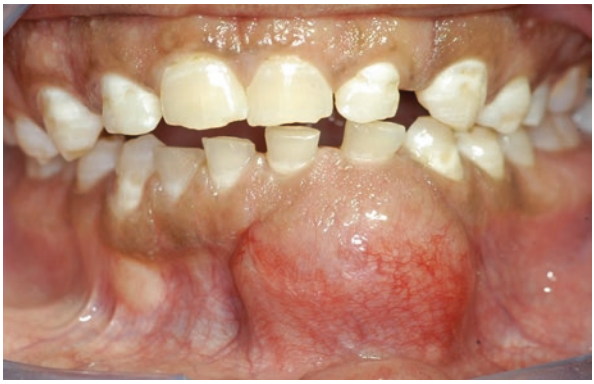

Fig. 2 Central giant cell granuloma. Nodular lesion in the anterior region of the mandible

  - Absence of root resorption.
  - Low relapse rate.
- Aggressive variant:
  - Rapid bone expansion.
  - Cortical bone rupture.
  - Obvious root resorption.
  - High relapse rate.

2 Diagnosis

- Clinical evaluation.
- Radiographic evaluation.
- Incisional biopsy.
- Complementary examinations in the case of central giant cell granulomas to exclude brown tumors from hyperparathyroidism:
  - Dosage of parathormone.
  - Serum calcium dosage.
  - Serum phosphorus dosage.
  - Alkaline phosphatase dosage.

3 Differential Diagnoses

In the presence of two or more concomitant lesions, consider possible association syndromes or other conditions:

- Cherubism.
- Brown tumor of hyperparathyroidism.
- Noonan syndrome.
  - Neurofibromatosis.

4 Treatment

4.1 Peripheral Giant Cell Granuloma

- Surgical removal.
- Basic periodontal treatment (scaling and root planning) or exodontia.

4.2 Central Giant Cell Granuloma

- Surgical removal: curettage or resection.
- Or intralesional injection of corticosteroid:
  - Triamcinolone (Theracort 40 mg/ml) and lidocaine 2% (epinephrine 1:200,000), combined in a 1:1 ratio, total of 0.3 mL or compatible with the size of the radiolucent lesion, applied every 2 weeks for 12 weeks or depending on the clinical response observed.
  - Triamcinolone (Theracort 40 mg/mL) and Ethamolin 5%, combined in a 1:1 ratio, total of 0.3 mL or compatible with the size of the radiolucent lesion, applied after local anesthesia every 2 weeks for 12 weeks or depending on the clinical response observed.

Acknowledgments The São Paulo State Research Foundation (FAPESP, São Paulo, Brazil, grant number JFS 19/09419-0) and the Coordination of Training of Higher Education Graduate Foundation (CAPES, Brasilia, Brazil, finance code 001).

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Part III

Common Oral Infections

Oral Candidiasis

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Candidiasis is a disease caused primarily by the fungus *Candida albicans* and is of particular clinical importance in oral infections. The microorganisms take advantage of poor oral hygiene or immunodeficiency to multiply and spread beyond normal levels (Table 1). Despite relative therapeutic progress in the treatment of opportunistic fungal infectious diseases of the oral mucosa, the prevalence of these lesions has increased, especially in users of total dentures and patients with poor oral hygiene, transient immunodeficiencies, and chronic diseases, polypharmacy, oncology patients, and carriers of other systemic factors. The advent of new medical practices, such as immunosuppressive therapies, the use of broad-spectrum antibiotics, and invasive surgical procedures such as solid organ and bone marrow transplantation, has also contributed to this increase.

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Table 1 Host predisposing factors

Local predisposing factors
Prosthesis users
Use of inhaled/topical steroids
Hyposalivation
Systemic predisposing factors
Elderly
Endocrine disorders (diabetes)
Immunosuppression (HIV, transplanted)
Corticosteroids
Broad-spectrum antibiotics
Oncological patients

1 Clinical Characteristics

1.1 Pseudomembranous Candidiasis

- White pseudomembranes that are removed by scraping and exposing an underlying erythematous mucosa (Figs. 1 and 2).
- On labial and buccal mucosa, gingiva, tongue, hard and soft palates, and oropharynx.
- Predisposing factors:
  - Age (neonates/infants/elderly).
  - Diabetes mellitus.
  - Patients with HIV/AIDS.
  - Leukemia.
  - Users of steroid aerosol inhalers.
  - Systemic corticosteroids.
  - Broad-spectrum antibiotics and psychotropic drugs.
  - Terminally ill patients.

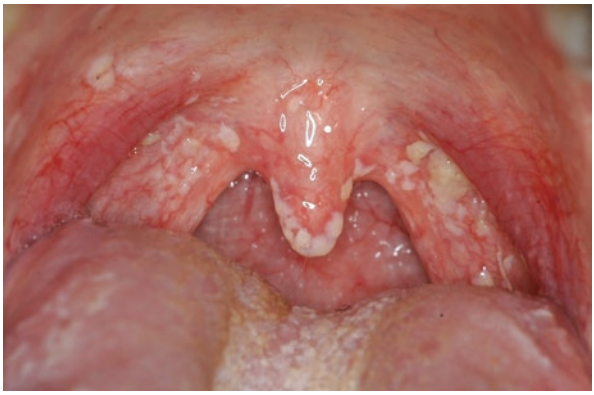

Fig. 1 Pseudomembranous candidiasis: detachable white plaques on the soft palate and tonsillar pillar

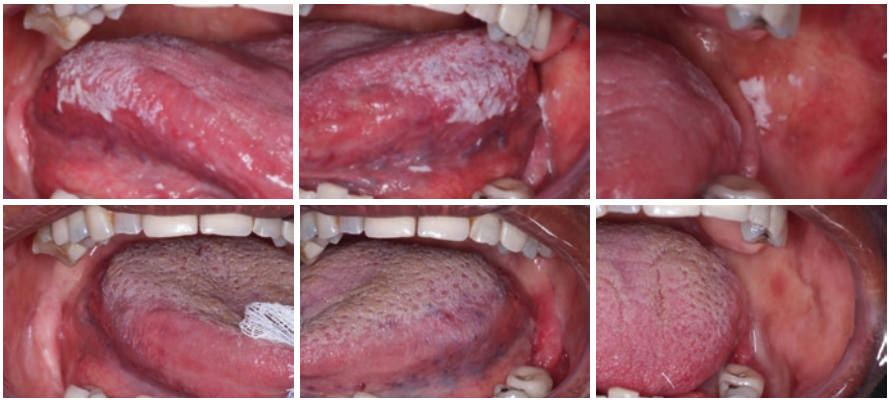

Fig. 2 Pseudomembranous candidiasis before and after treatment. Courtesy of Dr. Diego Tetzner Fernandes

1.2 Erythematous candidiasis

1.2.1 Acute Atrophic Candidiasis

- After a prolonged course of broad-spectrum antibiotic therapy.
- It may be seen in xerostomia patients.
- Often associated with a burning sensation in the oral cavity or on the tongue.
- The tongue appears bright red and with depapillation.

1.2.2 Chronic Atrophic Candidiasis

- Additionally, known as "denture stomatitis".
- Chronic erythema accompanied by petechial hemorrhage (Fig. 3 and 4).
- In palatal and gingival tissues.

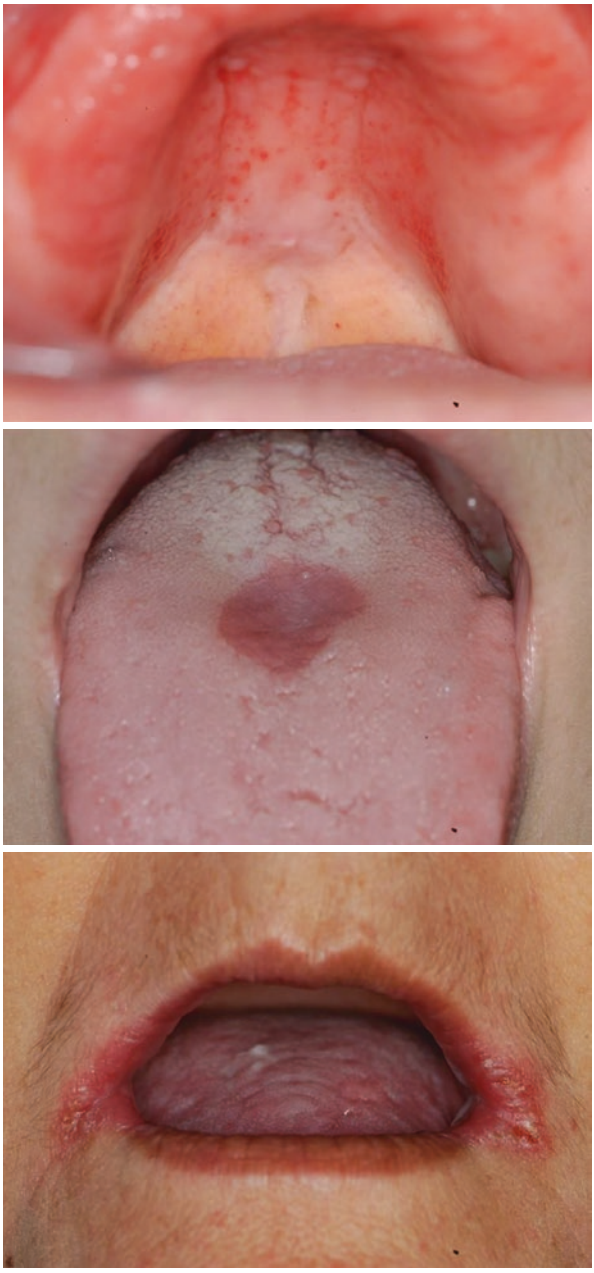

Fig. 3 Examples of erythematous candidiasis: chronic atrophic candidiasis, rhomboid median glossitis, and angular cheilitis

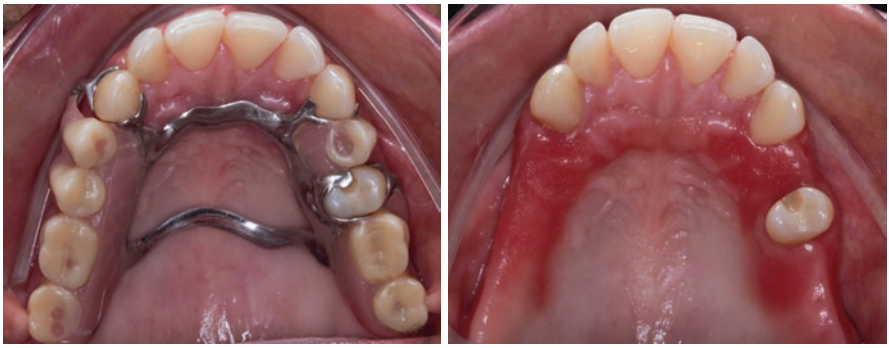

Fig. 4 Chronic atrophic candidiasis associated with prosthesis: chronic erythema accompanied by petechial hemorrhage. Courtesy of Dr. Diego Tetzner Fernandes

1.2.3 Rhomboid Median Glossitis

- A chronic symmetrical area on the tongue (Fig. 3).
- Anterior to the circumvallate papillae.
- Consisting of atrophic filiform papillae.
- Often associated with smoking and the use of inhaled steroids.

1.2.4 Angular Cheilitis

- Erythematous fissure in one or both labial commissures (Fig. 3).
- Usually, associated with an intraoral *Candida* infection.
- Facial wrinkling, especially in elderly individuals with loss of vertical dimension, can lead to a constantly humid environment that predisposes the lesion to installation.

1.3 Chronic Hyperplastic Candidiasis

- Known as Candidal leukoplakia.
- Two types:
  - *Homogeneous:* smooth white lesions.
  - *Heterogeneous:* areas of erythema resulting in a speckled nodular appearance.
- Frequent in the lip commissure and dorsum of the tongue.
- Related to smoking habits.

1.4 Mucocutaneous Candidiasis

- Rare condition.
- Immune component present.
- The degree of infection correlates with the severity of the immune defect.
- Various clinical forms are seen on mucous membranes, skin, and nails (Fig. 5).

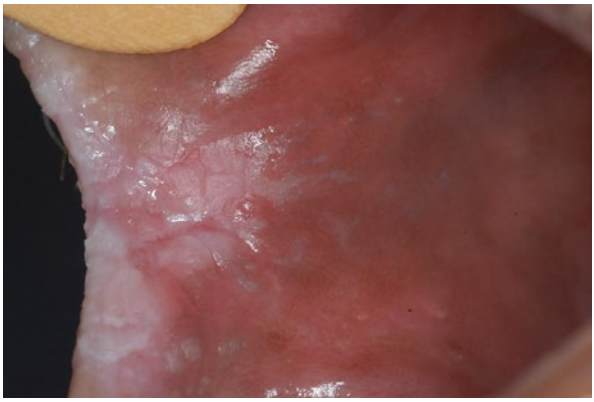

Fig. 5 Chronic hyperplastic candidiasis: lesion on the anterior buccal mucosa clinically similar to leukoplakia

2 Diagnosis

- Clinical features are the primary means of reaching a diagnosis.
- Perform cytology or incisional biopsy in cases of nondetachable white plaques.

3 Treatment

3.1 First Line of Treatment

- In all cases of oral candidiasis, reinforce maintenance of oral hygiene and/or dentures in cases of denture stomatitis.
- In cases of denture stomatitis, guide patients to sleep without the denture. In cases of old prostheses (4–5 years or more), guide the patient to replace.
- Correction of underlying conditions (HIV, diabetes, hyposalivation, etc.).
- Cases of disseminated or nonresponsive candidiasis: investigate anemia, diabetes, or immunosuppression.

3.2 Second Line of Treatment

Before systemic administration, topical treatment should be employed.

- *Nystatin:* Oral suspension (100,000 IU), 4 times a day for 7–14 days. Nystatin is presented in vials of 50 mL. Calculate how many vials the patient will need for the desired time of treatment. Usually, it is recommended to rinse the oral cavity with 10 mL four times a day, which results in 40 mL per day.
- *Miconazole:* Oral gel (20 mg/mL), used from 5 (1 teaspoon) to 10 mL at a time, 4 times a day for a period of 7–14 days. In case of chronic atrophic candidiasis on the palate, apply at the base of the prosthesis (when a patient uses prosthesis). This way, we guarantee prolonged contact of the drug with the oral mucosa.

Directions for nystatin swabbing

Note 1: Instruct dentures to be removed before rinsing.
Note 2: Remind the patient who, more important than "rinsing" the solution, is to leave it in contact with the lesion area for a long time because this potentiates the medication effect. Considering that the treatment is topical, the patient should not eat or drink for 30 minutes after using the medication.
Note 3: If candidiasis extends to the oropharynx, the patient should swallow the nystatin. It is not absorbed. However, because its composition contains sugar, it should be used with caution or avoided in *diabetic* patients.

3.2.1 Third Line of Treatment

Systemic administration should be used for cases that do not respond to topical treatment. In some cases, laboratory tests should be performed for systemic evaluation of the patient (complete blood count, fasting glycemia, platelet count, serum iron, folic acid, vitamin B2, and anti-HIV):

- *Ketoconazole***:** 200–400 mg daily for 7–14 days. Ketoconazole should be administered during one of the daily meals for maximum absorption. Presentation – Ketoconazole 200 mg tablet in a pack containing 10 and 30 tablets. Contraindications—It should not be administered to patients with acute or chronic liver pathology or to patients with known hypersensitivity to the drug.
- *Fluconazole***:** For oropharyngeal candidiasis, the usual dose is 50 mg–100 mg as a single dose daily for 7–14 days. When necessary, treatment can be continued for longer periods in patients with severely compromised immune function.

Disinfection of total or partial removable prostheses

Prosthesis without metal component: Place the prosthesis immersed in a glass of water with a tablespoon of sodium hypochlorite overnight. In the morning, wash the prosthesis with plenty of tap water before use.
Prosthesis with metal component: Place the prosthesis immersed in a glass with 0.2% chlorhexidine digluconate solution overnight. In the morning, wash the prosthesis with plenty of tap water before use.
Note: The solution of chlorhexidine digluconate is more concentrated than that used for chemical biofilm control because *Candida* penetrates the acrylic. Because of this, this solution must be manipulated.

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Oral Herpes

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Human herpes simplex virus (HSV) infection is a common condition that is typically acquired in childhood and shows an increase in prevalence with age. Although the infection is traditionally caused by HSV-1, the epidemiology of this lesion has shown a change in recent years, with an increase in the number of cases of labial and oropharyngeal herpes being caused by HSV-2, typically related to genital infections. Clinically, labial lesions progress rapidly after symptom onset, increase of lesion size, and pain being most evident within the first 24h.

Reactivation episodes of the virus can be triggered by ultraviolet radiation, fever, psychological stress, and menstrual periods. Most lesions progress from the vesicles stage to ulcers in 48 h, with appearance of crusts after 2 or 3 days. Of patients who seek treatment for recurrence, approximately 80% cite pain or discomfort, and 60% cite social stigmas as their main complaint. Difficulty with eating, fluid intake, and shame of social interaction can create significant psychosocial stress for affected patients. Although HSV-1 infection cannot be cured, it can be treated episodically once lesions begin to decrease the duration and symptoms.

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1 Clinical Characteristics

1.1 Primary Herpetic Gingivostomatitis

- Symptomatic, primary manifestation of HSV infection.
- Self-limiting clinical course.
- Prodromic signs:
  - High fever and malaise.
  - Localized adenopathy.
  - Pharyngeal erythema.
  - Headache.
  - Irritability.
  - Loss of appetite.
- After 3 or 4 days:
  - Painful generalized gingivitis (reddened and swollen gums).
  - Multiple vesicles on the oral mucosa are usually not seen.
  - Painful, superficial erosions resembling recurrent aphthous stomatitis (Figs. 1 and 2).
  - Resolution in 10–14 days without scarring.

1.2 Recurrent Herpes

- Lip vermilion (90%), palate (5%) (Figs. 3 and 4), and others (5%).
- Prodromic signs:
  - Burning.
  - Itchy.
  - Paresthesia.

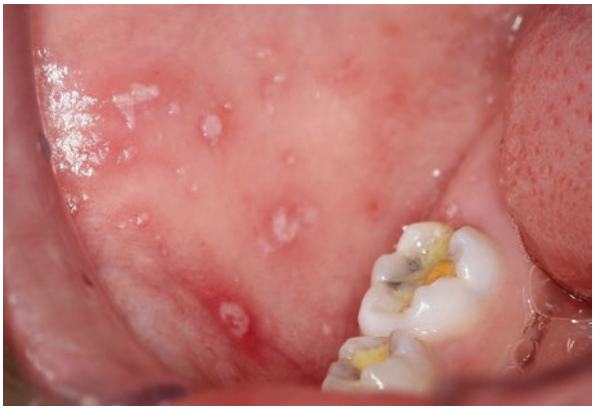

Fig. 1 Primary herpetic gingivostomatitis in a pediatric patient. Numerous irregular ulcerations on the buccal mucosa

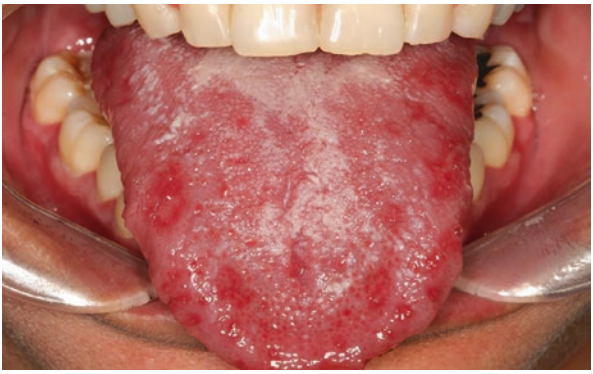

Fig. 2 Primary herpetic gingivostomatitis in a 38-year-old woman. Numerous irregular ulcerations on the tongue

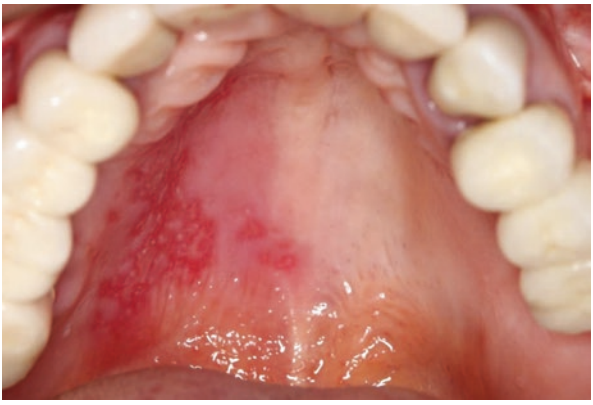

Fig. 3 Recurrent intraoral herpetic infection. Multiple ulcerations on the hard palate

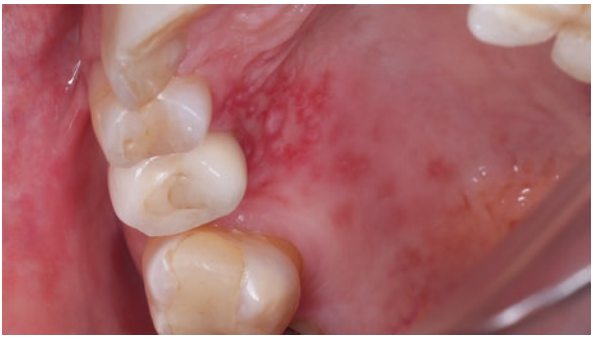

Fig. 4 Recurrent intraoral herpetic infection. Multiple ulcerations on the hard palate. Courtesy of Dr. Diego Tetzner Fernandes

- Clinical signs and symptoms:
  - Macular lesion.
  - Multiple vesicular lesions.
  - Pustule.
  - Ulceration.
  - Crust.
  - Resolution in 8–15 days, without scarring.

- Viral load peak 24 h after lesion onset (vesicular stage).
- Classic progression of recurrent herpes labialis: Prodromal signs and symptoms, erythema papule, vesicle, ulcer or softened crust, hardened crust, residual abnormalities (residual swelling or mild erythema), reepithelialization, and healing (Figs. 5 and 6).

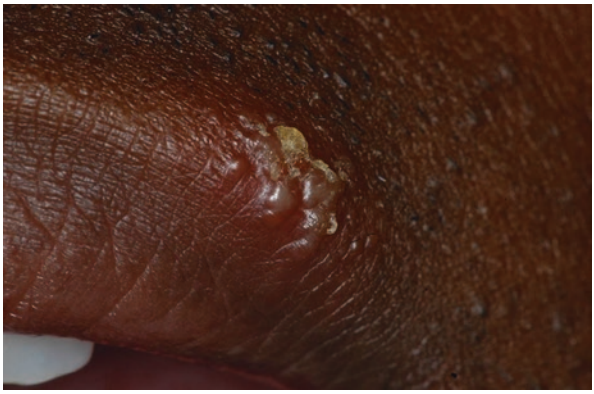

Fig. 5 Recurrent herpes labialis. A lesion in different stages of progression

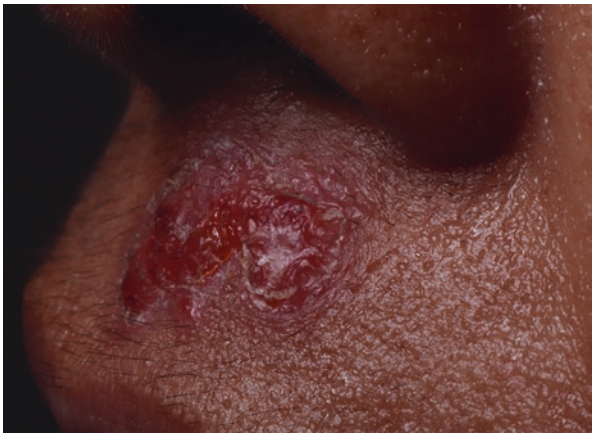

Fig. 6 Recurrent herpes labialis. A lesion in the final stage of progression. Courtesy of Dr. Diego Tetzner Fernandes

2 Diagnosis

- Clinical evaluation.
- Exfoliative cytology.
- Serological dosage of viral load.

3 Treatment

The objective of antiviral treatment is to block virus replication to decrease the duration of symptoms and accelerate the resolution of lesions. To obtain the greatest therapeutic benefits, it is recommended to start antiviral intervention as soon as possible. However, in most cases, treatment consists only of diagnostic guidance and patient education and clinical follow-up due to the self-limiting evolution of the lesion.

- In cases of herpetic gingivostomatitis:
  - Photobiomodulation.
  - Adequate hydration.
  - Symptomatic treatment with topical anesthetics (lidocaine 2%).
  - Adequate oral hygiene.
  - Acyclovir, five doses of 200 mg per day, as long as they have lesions.
  - In seropositive patients: oral acyclovir 2000–4000 mg per day while lesions are present or intravenous administration of 8 mg/kg/8 h.
- In cases with frequent or severe recurrences:
  Topical Use
  - Acyclovir cream 5%, application, five times a day for 5 days.
  - Penciclovir cream 1%, application, 2/2 h for 4 days.
  - AHC cream (acyclovir 5% + hydrocortisone 1%) application, five times a day for 5 days.
  Oral Use
  - Acyclovir, five doses of 200–400 mg daily for 5 days.
  - Valacyclovir, two doses of 2 g every 12 h for 1 day.
  - Famciclovir, a single dose of 1500 mg at the time of onset of the first sign/symptom of recurrent labial herpes.
  Photobiomodulation
  - One session/day in the early stages (macula phase), before the eruption of vesicles. The wavelengths ranged from 632.5–870 nm, with fluence of 4 J/cm^2 and power of 5 W, with irradiation of 40 s/per spot.

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Part IV

Salivary Gland Diseases and Tumors

Xerostomia (Dry Mouth)

Luiz Alcino Monteiro Gueiros, Felipe Paiva Fonseca,
João Figueira Scarini,
and Lara Maria Alencar Ramos Innocentini

Xerostomia is the subjective sensation of dry mouth, not necessarily associated with hyposalivation, that is present in the questioning of approximately 30% of the adult population, and its most common cause is the use of certain medications and polypharmacy. This complaint is more common in females (33% of women) in the 41–60 and 81–90 age groups. Other causes include high doses of radiation and inflammatory diseases such as Sjögren's syndrome (SS). In patients irradiated in the head and neck region, hyposalivation (followed by xerostomia) starts in the first days of radiotherapy and is more evident after doses of 20 Gy. In these cases, saliva initially becomes thicker and has a reduced glandular excretion rate.

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1 Clinical Characteristics

- Objective clinical features are based on diagnostic methods of hyposalivation.
- Foamy saliva (Fig. 1).
- The dry, opaque appearance of the entire mucosa and lingual fissures.
- Oral ulcers resulting from trauma to the mucosa.
- Oral infections (mainly candidiasis) with high recurrence.
- Increased volume of the parotid gland (more frequent in primary SS).
- Dysphagia, dysgeusia, and speech difficulties.

2 Diagnosis

- Measurement of stimulated and resting salivary flow rates (Table 1).
- The Xerostomia Inventory is a questionnaire that evaluates the severity of hyposalivation and its impacts on the individual's routine. The reduced version is composed of five questions, being of easy application and quite useful to evaluate both the initial condition and the response to treatment.
- In female patients over 50 years of age complaining of eye discomfort or burning and dryness of the genital region, search for SS following the classification criteria proposed by the American College of Rheumatology and European League Against Rheumatism (ACR/EULAR) (Table 2).
- Glandular function can also be evaluated by salivary gland scintigraphy, which points out changes in the pattern of uptake and excretion of the glands even before marked changes are observed in the sialometry technique.

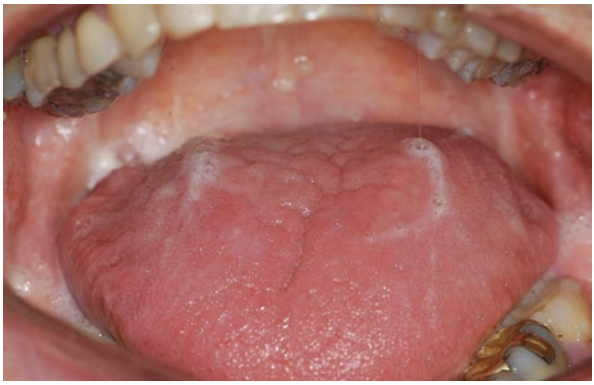

Fig. 1 Opaque mucosal appearance with thick, frothy saliva

Table 1 Reference values for salivary flow measurement

	Normal salivary flow	Hyposalivation
Stimulated	1.5–2.0 mL/min	≤0.5–0.7 mL/min
Resting	0.3–0.4 mL/min	≤0.1 mL/min

Table 2 Classification criteria for SS ACR/EULAR, 2016. After checking the exclusion criteria, scores ≥4 lead to the classification of primary SS

Item	Weight/ score
Labial salivary gland with focal lymphocytic sialadenitis and focus score ≥ 1 focus/4 mm^2	3
Anti-Ro/SSA positive	3
Ocular staining score ≥ 5 (or Bijsterveld score ≥ 4) in at least one eye	1
Schirmer's test ≤5/5 min in at least one eye	1
Total unstimulated salivary flow	1

- Salivary gland ultrasonography has a close association with the results of the sialometry technique and biopsy of minor salivary glands and is useful in the evaluation of patients with suspected Sjögren's syndrome.
- Exclusion criteria for SS:
  - History of head and neck radiotherapy.
  - Active hepatitis C infection (PCR confirmation).
  - AIDS.
  - Sarcoidosis.
  - Amyloidosis.
  - Graft versus host disease.
  - IgG4-related disease.

3 Treatment

- Control of diet (avoid sugar).
- Drink water frequently.
- Daily use of fluoride toothpaste.
- Sugar-free chewing gums based on sorbitol or xylitol.
- Oral moisturizing pH balancing gels, oral rinses, sprays and saliva substitutes (Pharmakin® Kin Care, KinHidrat®, BioXtra®) to provide lubricating comfort.
- Cholinergic agents such as pilocarpine and cevimeline are also used and show good results in glandular stimulation. A better response is expected when the stimulated salivary flow is preserved or slightly reduced.
- Electrostimulation devices (Salipen® Saliwell) are useful in cases of intense hyposalivation.
- Sialoendoscopy has been recently described as a possible alternative for the management of severe cases of salivary gland hypofunction.
- Patients with intense hyposalivation are at high risk of caries and should receive intensive oral care strategies. Fluoride gel in trays, prophylactic use of antifungal agents, and regular dental visits are useful alternatives and are commonly needed, along with the other precautions listed above.
- In cases of suspicion of SS, shared patient education and follow-up with rheumatology and ophthalmology are necessary.

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Mucus Extravasation and Retention Phenomena

Ricardo Alves Mesquita, Felipe Paiva Fonseca, João Figueira Scarini, José Alcides Almeida de Arruda, and Lara Maria Alencar Ramos Innocentini

Mucocele is a common benign lesion of the oral mucosa that develops due to extravasation (extravasation phenomena) or retention (retention phenomena) of saliva from salivary glands, especially smaller glands. However, in any location where there is a salivary gland, the lesion can develop.

Mucocele affects children, adolescents, and young adults with no sex predilection. In pediatric patients (0–10 years), it is the most common lesion among reactive/inflammatory lesions, comprising 64%. Its incidence is 2.5 lesions per 1000 patients. A history of trauma at the site has been reported in approximately 72% of cases, as well as parafunctional habits. Mucocele can also develop when there is some aggression to the minor salivary glands in individuals who use orthodontic appliances or during surgical manipulation of oral mucosa soft tissues.

A mucocele located on the floor of the mouth is called a ranula. The ranula commonly originates from the body of the sublingual gland and occasionally from Ravini's or Wharton's duct. It derives from the Latin word *rana* (meaning "frog") because the lesion is believed to resemble the belly of these amphibians.

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1 Clinical Characteristics

1.1 Mucocele

- Mucocele mainly affects the mucosa of the lower lip (81.9%), followed by the floor of the mouth (5.8%), the center of the tongue (5.0%), buccal mucosa (4.8%) (Figs. 1 and 2), palate (1.3%), and retromolar region (0.5%).
- The mucus extravasation phenomenon is more common and usually found in the lower lip of pediatric/young patients, while the mucus retention phenomenon is more frequently located in the upper lip of adult/older adult patients.
- Mucocele can vary from bluish, purple, or gray lesions (29.2%), normal mucosa coloring or pink (24.8%), whitish (12.1%), erythematous (5.3%), or yellowish

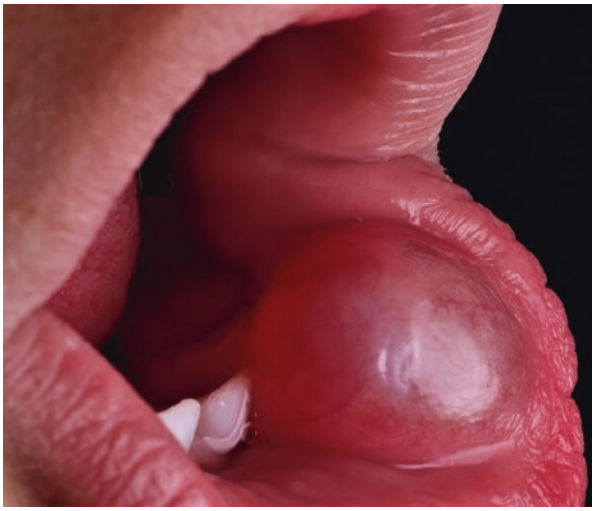

Fig. 1 Mucocele in the lower lip mucosa. Courtesy of Dr. Diego Tetzner Fernandes

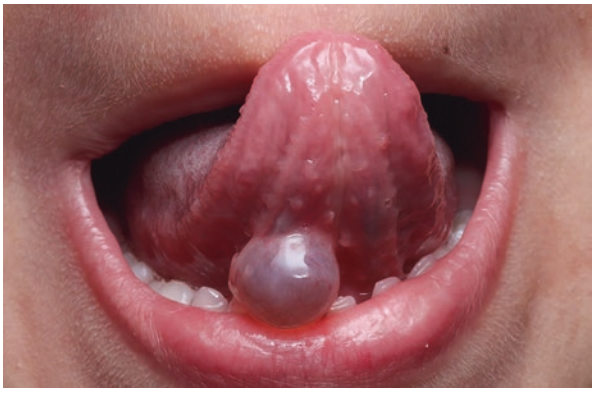

Fig. 2 Mucocele in the center of the tongue. Courtesy of Dr. Diego Tetzner Fernandes

(2.6%). It is a small lesion approximately 0.8 cm in size, varying in soft or firm consistency.

- Approximately 83.4% of the lesions with the clinical appearance of mucocele had concordance in the histopathological diagnosis. However, some lesions, such as fibrous hyperplasia, papilloma, pyogenic granuloma, lipoma, amelanotic nevus, lymphoepithelial cyst, lymphangioma, and sialolithiasis, can also be included in the differential diagnosis of mucocele.

1.2 Ranula

- Clinical features are the main data used for the diagnosis of ranulas, and they are classified as oral or dipping, depending on the location.
- The ranula presents as a normal or bluish-colored, floating, dome-shaped swelling on the floor of the mouth. Usually, the bulla is located laterally to the midline (Fig. 3).
- Palpation and inspection help in the differential diagnosis between deep ranula and fibrous hyperplasia, dermoid cyst, mesenchymal lesions, and salivary gland neoplasms. The mucoepidermoid carcinoma, for example, may mimic the ranula when well circumscribed and in the absence of pain. However, it is important to note that mucoepidermoid carcinoma is fibrous to palpation.

1.3 Mucocele and Ranulas Related to Systemic Disorders

- The emergence of mucocele and ranula associated with HIV infection may be considered in the context of HIV-related salivary gland diseases. Furthermore, the occurrence of multiple superficial mucoceles in individuals with autoimmune diseases, mainly oral lichen planus and graft-versus-host disease, has also been reported.

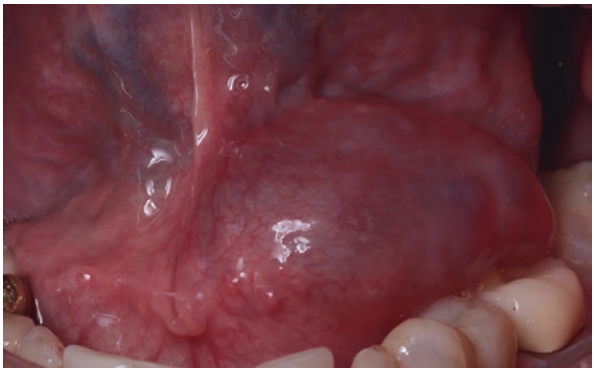

Fig. 3 Ranula located on the floor of the mouth, lateral to the midline. Courtesy of Dr. Diego Tetzner Fernandes

1.4 Lesions Similar to a Ranula

- *Retention cysts of the Ravinus or Warthon ducts*: These are small (0.5–1.5 cm), superficial, and are located posteriorly along the course of the ducts of the sublingual glands (Warthon or Ravinus ducts). These lesions have partial or complete obstruction of these excretory ducts, which causes retention of saliva and duct dilation. Swelling, pain on palpation, and purulent secretion can be observed. Because of the anatomical location, a differential diagnosis with sialolithiasis is necessary. For example, occlusal radiography is a fundamental complementary method for the diagnosis of sialoliths on the floor of the mouth.
- *Incisal gland mucocele*: The incisal glands are a small group of mucous glands found on the floor of the mouth in the lingual region of the lower incisors. The ranula in this region has mucous or whitish coloration. They are small lesions measuring less than 0.5 cm with a regular shape that are well circumscribed and present as a discrete asymptomatic swelling.

2 Treatment

2.1 Mucocele/Ranula

- The forms of treatment for these lesions are complete excision with a scalpel or high-power laser, macro- or micromarsupialization, cryosurgery, or injection of OK-432. Superficial mucoceles often rupture and have spontaneous clinical resolution;
- Surgical treatment is performed by elliptical incision with a scalpel to the deep layers, followed by complete removal of the lesion and minor salivary glands near the lesion (Figs. 4 and 5). However, the patient's age, size, and anatomical location should be considered for choice of treatment. For example, in children or aesthetic locations—more superior labial mucosa—to avoid trauma (anesthesia in children) or possible scarring in an aesthetic location.
- Another surgical technique is to make a linear incision in the central portion of the lesion, and the covering tissue is divulsed for complete removal of the lesion. In this technique, all salivary glands close to the lesion should also be removed before suturing. The removal of the salivary glands close to the lesion aims to reduce the incidence or prevent recurrence.
- The micromarsupialization technique is an effective and efficient alternative often indicated for ranulas. It is a simple, low-trauma, minimally invasive technique performed under local anesthesia. A transfixion of a silk suture thread (3.0) is performed along the axis of the lesion, followed by suturing (Fig. 6).

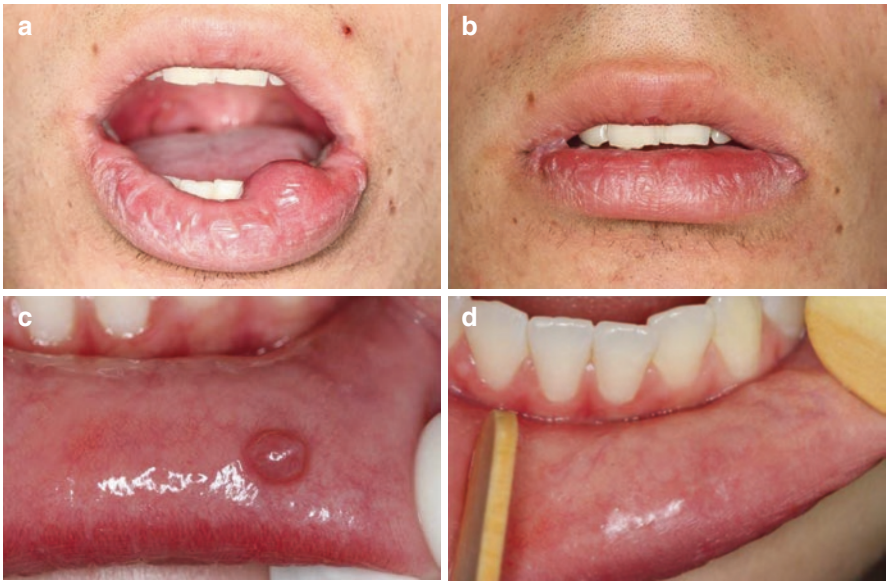

Fig. 4 Preoperative (**a** and **c**) and complete resolution (**b** and **d**) of lower lip mucoceles in pediatric/young patients treated by surgery removal with scalpel

Fig. 5 Mucocele removed completely. Note the superficial vascularization and translucency of the lesion. Courtesy of Dr. Lara Eunice Cândido Soares

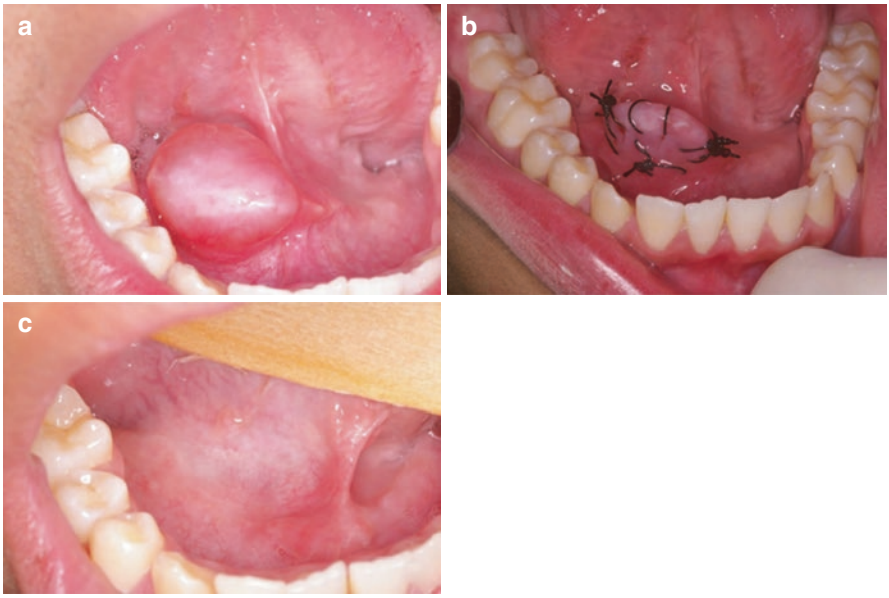

Fig. 6 **(a)** Ranula is a blister, well-delimited, smooth, and shiny surface, similar in color to the mucosa and measuring approximately 2.5 cm. **(b)** Presence of eight sutures along the largest diameter of the lesion. **(c)** Follow-up of the patient after three months and absence of clinical signs of recurrence

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Minor Salivary Gland Tumors

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Regardless of the location, salivary gland tumors represent a group of lesions with complex morphology and challenging diagnosis. The parotid glands are the preferred location of these tumors, and the involvement of minor salivary glands is less common.

Salivary gland tumors may be benign or malignant. Considering all locations, benign tumors are more common and account for 75–85% of these neoplasms, but when we analyze only the minor salivary glands, the frequency of benign tumors is similar to that of malignant tumors. The latest classification of salivary gland tumors

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of the World Health Organization (WHO) reviewed and reclassified some entities and, based on the topography of minor salivary glands, highlights, among the benign tumors, the pleomorphic adenoma and canalicular adenoma and, among the malignant ones, the mucoepidermoid carcinoma, adenoid cystic carcinoma, and polymorphous adenocarcinoma.

1 Clinical Characteristics

Salivary gland tumors are generally well-circumscribed nodular masses that are slow-growing and asymptomatic and affect more women, with peak incidence occurring in the fifth and seventh decades of life. In general, patients who develop malignant tumors are older than those who develop benign tumors. Malignant tumors are rarely observed in children and adolescents.

1.1 Pleomorphic Adenoma

- It is the most common salivary gland tumor in any location.
- It is the most common benign tumor of the minor salivary glands in young patients.
- In the minor salivary glands, it mainly affects the palate (Fig. 1), followed by the buccal mucosa and the upper lip.
- In rare cases, it may undergo malignant transformation to carcinoma and pleomorphic adenoma.

1.2 Canalicular Adenoma

- It is a relatively uncommon benign tumor.
- They generally do not exceed 1–2 cm in diameter.
- Approximately 9% of tumors are multifocal.

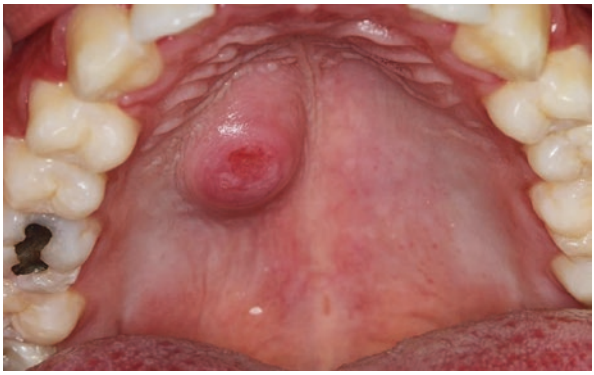

Fig. 1 Pleomorphic adenoma. Mass of firm consistency on the hard palate, lateral to the midline

- It occurs preferentially in the upper lip, although the buccal mucosa and palate can be affected.

1.3 Mucoepidermoid Carcinoma

- Second most common tumor of the minor salivary glands.
- Among the malignancies, it is the most frequent neoplasm.
- It is the most common malignant salivary gland tumor in young patients.
- The nodule may fluctuate; the presence of cystic areas is common.
- When in the minor salivary glands, it mainly affects the palate (Fig. 2); it can also affect the buccal mucosa, retromolar area, lips, and tongue; it is the most common intraosseous salivary gland tumor.
- They are generally low-grade malignant tumors.

1.4 Adenoid Cystic Carcinoma

- Second malignant salivary gland tumor in frequency, aggressive.
- Generally, it is associated with multiple local recurrences and metastases.
- Most often symptomatic; pain is a frequent finding.
- Usually, an infiltrative lesion with neural involvement and invasion of the underlying bone.
- Most common malignant salivary gland tumor of the paranasal sinuses.
- It is most common on the palate (Fig. 3) but can affect other regions, such as the buccal mucosa, floor of the mouth, and lips.

1.5 Polymorphous Adenocarcinoma

- Uncommon, almost exclusive to minor salivary glands.
- Generally, of hard consistency, without areas of necrosis and hemorrhage (Fig. 4).

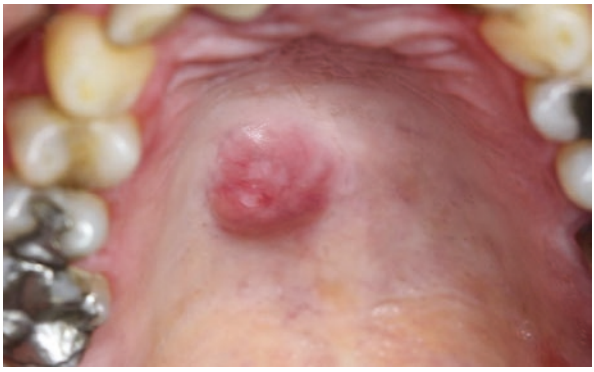

Fig. 2 Mucoepidermoid carcinoma. Well-circumscribed hard palate swelling presenting superficial telangiectasia

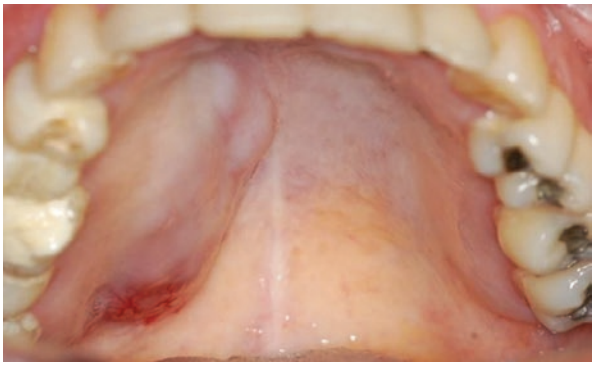

Fig. 3 Adenoid cystic carcinoma. Mass on the hard/soft palate exhibiting evident superficial telangiectasia

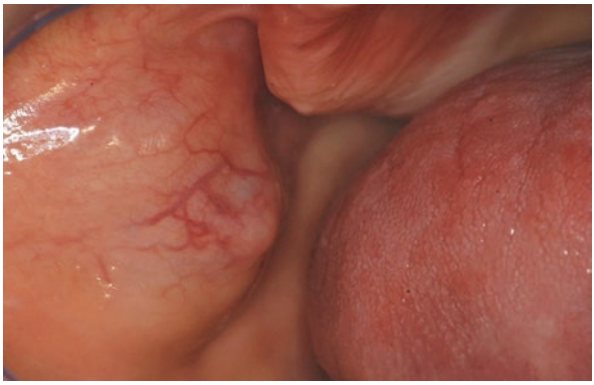

Fig. 4 Polymorphous adenocarcinoma. Tumefaction in the buccal mucosa associated with telangiectasia

- Occasional pain and ulceration may occur.
- Most often, it affects the palate, although the buccal mucosa and upper lip may be involved.

2 Diagnosis

- *Clinical diagnosis:* Signs such as tumor attachment, pain, irregular surface, bluish/purple coloration, ulceration, and telangiectasia are indicative of malignancy. For further help in trying to define the nature (benign or malignant), professionals can use fine needle aspiration or incisional biopsy. Imaging exams (especially to evaluate adjacent and deep structures, sinuses, and bone invasion), such as computerized tomography scans, can provide important information and help in diagnosis and surgical planning.
- *Anatomopathological diagnosis:* The diagnosis can be obtained after analysis of the material obtained in incisional biopsy or fine-needle aspiration (FNA) for major salivary gland tumors. It is worth remembering that several salivary gland tumors may show cystic components, and it is essential to confirm its tumor

nature to define the most appropriate treatment. In the confirmation of a salivary gland neoplasm, the patient must be referred to a head and neck surgeon. In any case, the definitive diagnosis will be determined only after anatomopathological examination of the surgical specimen.

3 Treatment

For benign tumors, the main treatment modality is surgical removal. Considering the potential for recurrence and malignant transformation of pleomorphic adenoma, long-term follow-up of affected patients is recommended.

For malignant tumors, complete surgical resection with a safety margin (which may include bone tissue in cases of tumors on the palate) is the first line of treatment. In some cases, depending on the histological grade of the tumor, involvement of surgical margins, positive lymph nodes for neoplastic cells, neoplastic emboli, and neural invasion, adjuvant radiotherapy combined with surgical treatment may be indicated. In any case, a multidisciplinary education and follow-up of these patients become necessary.

The prognosis of patients depends mainly on the location (less favorable in the sublingual gland or minor salivary glands), histological type (high-grade tumors tend to have a worse prognosis), clinical stage of the tumor, and treatment performed.

Acknowledgments The São Paulo State Research Foundation (FAPESP, São Paulo, Brazil, grant numbers FVM 15/07304-0 and JFS 19/09419-0) and the Coordination of Training of Higher Education Graduate Foundation (CAPES, Brasilia, Brazil, finance code 001).

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Part V

Vascular Diseases

Vascular Anomalies of the Oral Mucosa

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Vascular anomalies are changes that affect capillaries, veins, arteries, or lymphatic vessels. The nomenclature and classification of these lesions are sometimes confusing and divergent, but currently, two distinct groups are known by the International Society for the Study of Vascular Anomalies (ISSVA, 2018): tumors and vascular malformations (Fig. 1).

Hemangiomas are congenital vascular tumors composed of endothelial cells with a high proliferation rate that affect approximately 10% of the population and are considered the most frequent tumors of childhood. Unlike vascular malformations, hemangiomas tend to regress, presenting a proliferation phase in the first 9–12 months, followed by an involuting stage.

Vascular malformations are lesions that compromise the structure of vessels during embryonic development. Usually, these vascular anomalies are present at birth and increase in size according to the development of the individual. Capillaries,

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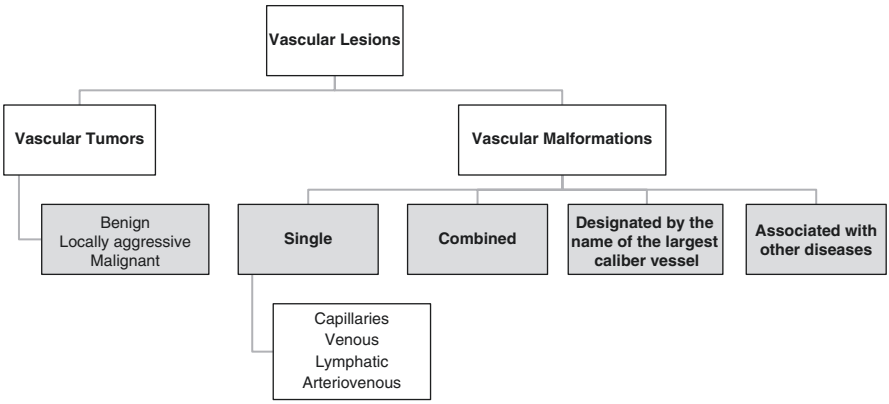

Fig. 1 Vascular anomalies according to the ISSVA 2018

veins, arteries, and lymphatic vessels can be affected. Venous malformations are the most common kind, with 80% present in the head and neck region. Lymphangiomas are rare malformations of lymphatic vessels, occurring most frequently in the oral cavity and cervicofacial (cystic hygroma) regions. It is usually present at birth and can cause major complications due to the risk of airway obstruction and functional and surgical complications.

Another vascular anomaly, however, not classified by ISSVA 2018 but frequent in the oral mucosa are varices (varicose veins). These alterations are acquired anomalies in which the veins of the dermis or submucosa become extremely dilated. Elderly individuals are the most affected, mainly due to the loss of elasticity of the blood vessel.

1 Clinical Characteristics

1.1 Hemangiomas

- Eighty percent present from the first 3 months of life.
- Seventy percent of cases showed complete regression after 7 years, and 90% showed complete regression after 9 years.
- Features: nodular, solitary lesion, well-defined limits, reddish, or purplish coloration.
- Most common site: lips, tongue, and buccal mucosa.

1.2 Vascular Malformation

- Already present at birth, does not regress, and the growth accompanies the development of the individual.
- It can present high or low blood flow; low flow (venous) is the most common in the oral mucosa.
- Features: Nodular, purplish-colored lesions with ill-defined borders (Fig. 2).
- Most common site: any region of the body, including the oral mucosa.

1.3 Arteriovenous Malformation

- Intraoral arteriovenous malformation (AVM) is a rare vascular anomaly that can be life-threatening due to potential massive hemorrhage (Fig. 3).
- Serious complications have been reported during dental extraction with undiagnosed AVM cases.

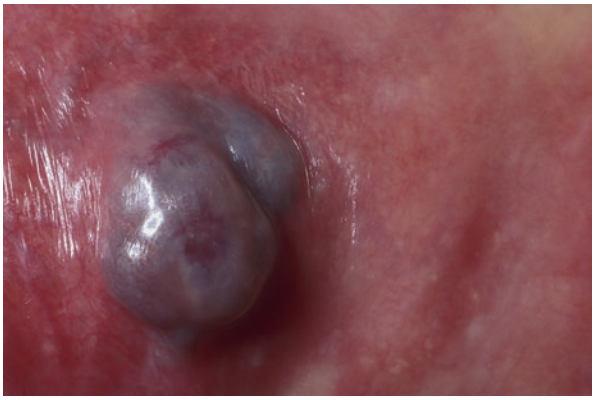

Fig. 2 Vascular malformation in the buccal mucosa. Courtesy of Dr. Lara Eunice Cândido Soares

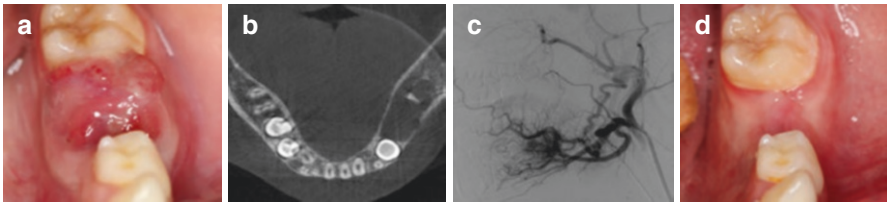

Fig. 3 A 9-year-old boy was referred for evaluation of swelling at the left mandibular gingiva associated with progressive mobility of the first permanent molar. (**a**) The swelling presented a predominant erythematous color with small hemorrhagic foci distributed on a thin overlying mucosa. **(b)** On palpation, it was soft in consistency and easily compressible, with a prominent pulsatile component. Cone-beam tomography showed an intraosseous destructive lesion through a hypodense image in the left posterior mandible. **(c)** Angiography demonstrated a large, high-flow AVM. **(d)** Impressively, the AVM spontaneously regressed after angiography without embolization. The patient is on a 24-month follow-up with no signs of recurrence

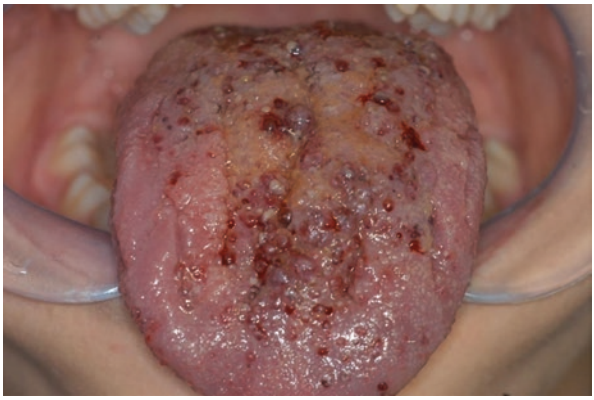

Fig. 4 Lymphatic malformation (oral lymphangioma). Reddish-white, irregular, sessile vesicle-like nodules located on the dorsum of the tongue

1.4 Lymphatic Malformation (Oral Lymphangioma)

- Fifty percent of the cases present at birth (congenital) and 80–90% appear after 2 years of age.
- Features: Multiple masses or nodules, variable in size, smooth, and translucent surface (Fig. 4).
- Clinically, they are classified as microcystic, macrocystic, or mixed.
- Most common site: orsum of the tongue and may cause macroglossia.
- They are usually asymptomatic but may present with overlapping infection or spontaneous bleeding, leading to pain or rapid expansion.
- They may regress spontaneously.

1.5 Varices (Varicose Veins)

- Commonly occur in the elderly, especially in the lower lip.
- Features: single or multiple, purplish, asymptomatic, well-defined, papule, or nodule and can range from 5 to 15 mm.
- Varices (varicose veins) present in ventral surfaces of the tongue and floor of the mouth or sublingual varices are considered developmental anomalies and no treatment is required.

2 Diagnosis

- Clinical evaluation of the lesion.
- *Diascopy:* In this clinical examination, the lesion is pressed with the fingers or a glass slide (diascopy by vitropression), temporarily expelling blood by emptying the vessels from the pressed area (blanchability). It allows differentiation, for example, between a lesion of vascular origin, which will totally or partially disappear, and a pigmented lesion, which will not disappear (Fig. 5).

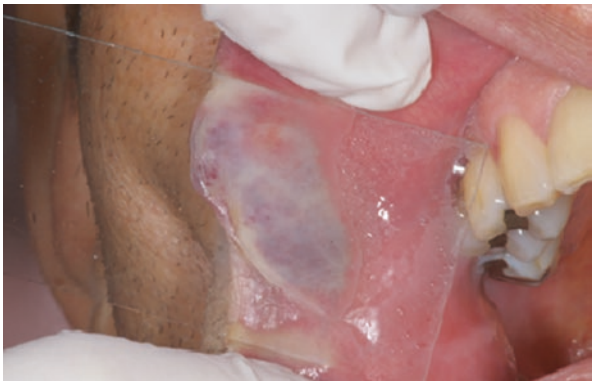

Fig. 5 Diascopy by vitropression maneuver in oral vascular malformation

- *Head lowering with abdominal compression maneuver:* The patient is seated in a chair in the 90° position. The swelling of the lesion was assessed, and the patient was asked to lower the head, bring the trunk toward the legs, and compress the abdomen for 1 min. The lesion is inspected again; if there is an increase in the swelling of change in the intensity of the lesion coloration, the maneuver is positive for vascular anomalies.
- *Imaging exams:* Ultrasound and magnetic resonance imaging allow to observe the location, size, blood flow (high and low flow), depth of the lesion, and relationship with adjacent anatomical structures.

3 Treatment

The treatment of vascular anomalies may vary according to the patient's age, lesion size, blood flow, location, and depth. Risk of trauma, bleeding, and aesthetic or functional factors are the main indications for treatment. The use of oral or systemic medications, immunomodulators, sclerotherapy, cryotherapy, surgery, laser therapy, and embolization are treatment modalities used in vascular anomalies.

3.1 Hemangioma

- Patient education and clinical follow-up mainly to pediatric patients.
- *Propranolol:* Before treatment, perform a careful cardiologic evaluation with electrocardiogram, echocardiogram, heart rate, and blood pressure measurements. During therapy, serum glucose should be monitored due to the possibility of hypoglycemia. Use 1 mg/kg/12 h or 2 mg/kg/day for 12 weeks. Side effects are drowsiness and reflux, which are contraindicated for patients with heart disease.
- *Oral corticosteroids*: Prednisone 3.0–5.0 mg/kg, early in the morning, every other day, for 8 weeks (total dose <50 mg). Dosage decreases in the following 2–3 weeks: 1.5–2.5 mg/kg at week 9, 10 mg at week 10, and 5 mg at week 11,

and it stops at week 12. Side effects are irritability, agitation, "cushingoid" appearance, loss of appetite, gastrointestinal disturbances, osteoporosis, and predisposition to infections.

3.2 Vascular Malformations, Hemangioma, and Varices (Varicose Veins)

Sclerotherapy is the most widely used treatment for vascular anomalies of the oral cavity. It is a conservative, safe, and effective procedure in which the vessel wall is irritated by a sclerosing agent, generating inflammation, with subsequent fibrosis and vessel obliteration. Several sclerosing agents can be used, such as ethanolamine oleate, sodium morrhuate, polidocanol, sodium tetradecyl sulfate, and absolute ethanol. In Brazil, one of the most used sclerosing agents is ethanolamine oleate.

- *Sclerotherapy for lesions smaller than 2.0 cm:* Intralesional injection of pure 5% Ethamolin®, 0.01 mL for each 3 mm of the lesion, that may be repeated after 14 days if there is no complete remission of the lesion. Side effects are local burning, pain and swelling lasting 2–72 h after application, and possible ulceration and bleeding (Fig. 6).
- *Foam sclerotherapy for lesions above 2.0 cm:* Foam preparation according to the Tessari technique: 2.0 mL of pure 5% Ethamolin® and 8.0 mL of air in 10 mL two syringes connected by a three-way stopcock. To create the foam, 20 cycles of transferring the contents from one syringe to the other are performed. The procedure must be agile and fast for formation of foam. An anesthetic without a vasoconstrictor is applied after puncturing the center of the lesion with a 25G needle. Observe the blood return to ensure the correct position inside the lesion and apply the foam with the same 25G needle used for anesthesia. A volume of 0.5 mL of foam per 1 cm of the lesion in a single puncture is recommended. Side effects are edema, pain, local burning, and possible ulceration and bleeding.
- *Transmucosal photocoagulation with a high-power laser:* Recommended for superficial vascular anomalies, up to 10 mm deep, in which the laser

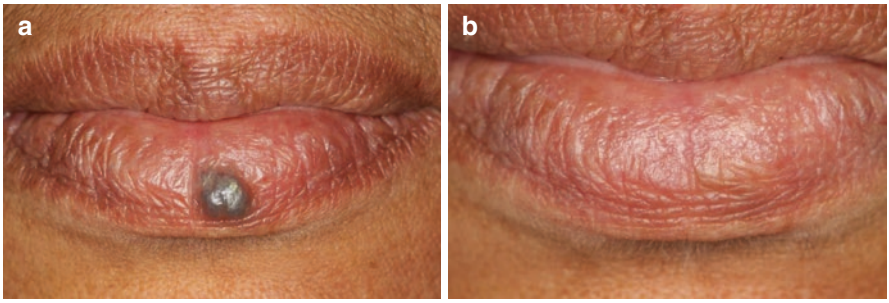

Fig. 6 Vascular malformation smaller than 2 cm in the lower lip. Initial photograph (**a**) and 3 months after sclerotherapy with 5% Ethamolin® in a single session (**b**)

energy is highly absorbed by hemoglobin. High-power laser (carbon dioxide, diode, neodymium-YAG laser) in continuous mode, power of 1000–2500 mW, putting the tip fiber approximately 2 mm from the lesion, applied by scanning for the time necessary for the "whitening" of the lesion to occur. Local infiltrative anesthesia is recommended before treatment depending on the depth of the lesion. Side effects are burning, blisters, edema, hyperemia, and fibrosis. The high-power laser can also be used for the excision of vascular anomalies, reducing the possibility of bleeding, but side effects such as necrosis, tissue atrophy, and hyperpigmentation can be observed.

- *Surgery:* Surgical removal with scalpel is indicated for lesions smaller than 2 cm. Side effects are trans- and postsurgical bleeding, scarring, and undesirable cosmetic effects. Lesions larger than 2 cm and infiltrative can also be treated by surgical removal with scalpel but must be addressed in a hospital environment and by a multidisciplinary team.
- *Combination treatments:* Combination treatments of sclerotherapy or photocoagulation followed by surgical removal with scalpel are recommended for large lesions, commonly lesions larger than 2 cm.

3.3 Lymphatic Malformation (Oral Lymphangioma)

- Patient education and clinical follow-up mainly to pediatric and asymptomatic patients.
- *Sclerotherapy:* Bleomycin 2 mg/mL intralesional injection (8 mg of bleomycin dissolved in 5 mL of saline plus 2 mL of 2% lidocaine and 1 mL of 5 mg dexamethasone). A volume of 1 mL/cm^2 of the lesion is recommended. Applications may range from 3–5 sessions, with an interval of 3 weeks. Do not exceed 8 mg in adults and 4 mg in children in a single injection. Side effects are swelling and pain lasting 3–5 days after application, fever on the day of application, ulceration, and skin eruptions. Intralesional injection of OK-432 or picibanil (*Streptococcus pyogenes* group A + benzylpenicillin): 0.1 mg/10 mL of saline solution (0.9%). The cystic spaces are aspirated, and subsequently, intracystic injection of up to 0.2 mg/session is performed. An interval of 3–6 weeks is recommended, with a maximum of four sessions. Side effects are erythema, increased swelling, pain, fever, and allergic reaction.
- *Surgery:* It is not the first choice of treatment because lymphatic malformation is poorly delimited; there is high risk of infection, resulting aesthetic and functional damage. However, surgical removal with scalpel can be indicated for superficial and well-delimited lesions or after sclerotherapy of moderate-sized lesions. The impact on the regional lymphatic systems should be noted. The high-power laser can also be used in the excision of small lymphangiomas or the localized ablation of nonexcisable lymphangiomas. The ablation area should be 2–3 m^2 per session to avoid discomfort to the patient. Antibiotics and mouthwash should be prescribed for 3–7 days postoperatively.

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Part VI

Mucocutaneous Diseases

Oral Lichen Planus

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Lichen planus is a common disorder of the stratified squamous epithelium and is accepted as a chronic mucocutaneous disease of an autoimmune, T-cell-mediated nature. The disease affects approximately 1–2% of the general adult population and has a slight predilection for female patients (1.4:1.0) over the age of 40 years.

Clinically, it presents in a very varied manner, either through whitish streaks or papules, erythema, and erosion or even through blisters that rupture easily, usually with multifocal and symmetrical manifestations. Intraoral involvement occurs more frequently in the buccal mucosa, tongue, and gingiva. In some cases, simultaneous cutaneous manifestations may be observed, typically presenting as flattened polygonal, violaceous, pruritic papules, preferentially located on the wrists, ankles, and lumbar region. Nail involvement may be noted as the first manifestation of the disease with the formation of longitudinal grooves or ridges, pitting, darkening, and/or ungual dystrophy.

Although several hypotheses have been suggested, the etiology of lichen planus remains unknown, and there are several controversies regarding the pathogenesis of

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this disease. However, a wide range of evidence points to an important role played by immune system dysregulation, and thus, different mechanisms have been considered, including (1) cellular immune response to specific antigens, (2) nonspecific mechanisms, (3) autoimmune response, and (4) humoral immunity.

1 Clinical Characteristics

- Usually, adults over 40 years of age.
- The predominance in the female gender.
- Buccal mucosa, tongue, and gingiva are the most affected sites.
- Variable clinical presentation, with six distinct patterns, described below.

1.1 Reticular

- Presence of whitish reticulate striations (Wickham's striations) (Figs. 1 and 2).
- Minimal symptomatology in most cases.

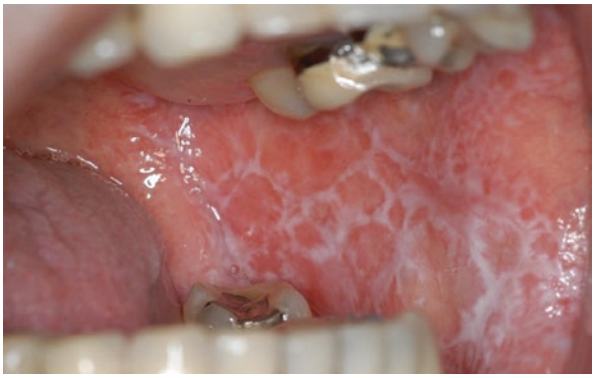

Fig. 1 Reticular white lines (Wickham's striae) involving the buccal mucosa

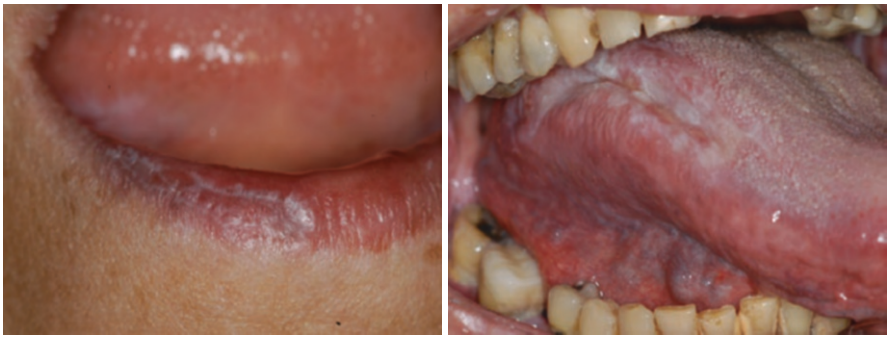

Fig. 2 Reticular lichen planus involving the vermilion of the lower lip and the lateral surface of the tongue

1.2 Papular

- Rare and often neglected variant.
- Small (0.5–1 mm) elevated white papules with fine white streaks at the periphery of the lesion.
- It usually coexists with another variant.

1.3 Plaque-Like

- Homogeneous white plaques resembling leukoplakia.
- Presence of white striae on the surface.
- It generally affects the dorsum of the tongue and oral mucosa.
- Lesions may appear multifocal.

1.4 Erosive

- Ulcerated central area.
- Presence of a fibrin network or pseudomembrane over the ulcer.
- Pain when chewing or swallowing.

1.5 Atrophic

- Erythematous areas with very fine white streaks on the surface.
- Burning, burning sensation, and sensitivity.

1.6 Bullous

- Rare variant.
- Presence of blisters a few millimeters to centimeters.
- The blisters break rapidly, causing painful erosions or ulcers.
- The buccal mucosa is the most affected in this variant.

2 Diagnosis

2.1 Clinical Evaluation

- Investigate the presence of dental materials near lesions.
- Check for recent or current use of medication (non-steroidal anti-inflammatory drugs, antihypertensives, hypoglycemic agents, or antimalarials).
- Search for other underlying diseases (graft versus host disease, liver disease, or HIV).

2.2 Incisional Biopsy

- Histopathological findings are unspecific, however, essential for a proper clinicopathological correlation and include hyperkeratosis, irregular "sawtooth" appearance suggestive of acanthosis, basal layer liquefaction, and lymphocytic banded infiltrate (lichenoid pattern).

3 Treatment

- *Asymptomatic lesions:* Patient education and clinical follow-up.
- *Lesions associated with an underlying cause:* management of the systemic condition.
- *Symptomatic lesions:*
  - Clobetasol propionate 0.05%, topical, two times a day, during the symptomatic period of the lesion, or for a maximum of 2 months (See Chap. 8) (Fig. 3). Apply on dry mucosa and do not ingest drinks or food for 30 min.
  - Triamcinolone acetate 0.1%, topical, three times daily for up to 3 months, two times daily in the fourth month, one time daily in the fifth month, and applications on alternate days in the sixth month.
  - Cyclosporin A 1.5%, topical in hydroxyethyl cellulose gel, two times daily, for up to 2 months.
  - Prednisone 0.5–1.0 mg/kg per day in the morning. Prolonged treatments require progressive reduction of the daily dose according to clinical response, suggesting medical follow-up.
  - Antifungal prophylaxis with topical miconazole, 1 time daily for 14 days, or chlorhexidine 0.12% (alcohol-free); oral rinses 3 times daily for 7 days.

Side effects of prolonged use of systemic corticotherapy
1. Cushingoid appearance 2. Hypertension 3. Tachycardia 4. Fluid retention 5. Hyperglycemia 6. Dyslipidemia 7. Opportunistic fungal infections 8. Corticosteroid induced myopathy 9. Osteopenia and osteoporosis 10. Thromboembolic complications During treatment, assess the following: • Weight gain or loss • Blood pressure • Fasting blood glucose • Serum electrolytes • Serum urea and creatinine • Liver function

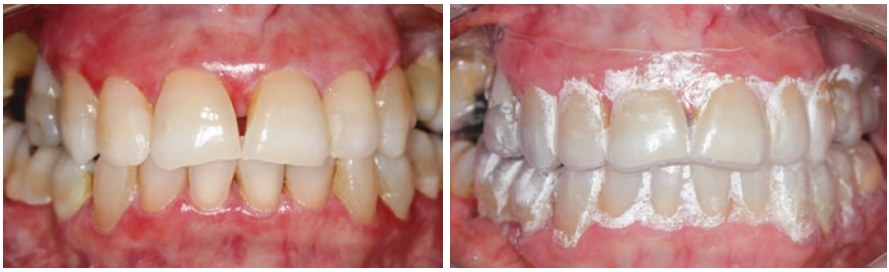

Fig. 3 Use of individual trays with clobetasol

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Pemphigus and Mucous Membrane Pemphigoid

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Pemphigus vulgaris is one of the most common autoimmune vesiculobullous disorders that, if left untreated, is life-threatening. It is estimated that the disease affects 0.1–0.5 patients/100,000 individuals/year. The clinical presentation predominantly affecting the mucous membranes (with minimal cutaneous involvement) is the most common pattern of this disease. In approximately 75% of cases, the oral cavity mucosa is the first to be affected, remaining restricted to this location for months before presenting dissemination to extraoral tissues. The blisters that characterize this disease occur due to abnormal production of autoantibodies directed against epidermal cell surface glycoproteins (desmoglein-3 and desmoglein-1), structural components of the desmosomes. As a consequence, there is impaired cell adhesion and formation of an intraepithelial cleft, which culminates in the appearance of a blister.

Mucous membrane pemphigoid, previously referred to as cicatricial pemphigoid, represents a debilitating, heterogeneous, autoimmune, vesiculobullous

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disorder that primarily affects the mucous membranes, with the oral mucosa being affected in approximately 85% of cases. It can also exhibit manifestations in the mucosa of the eyes, nose, larynx, esophagus, rectum, penis, and vagina. This disease belongs to the family of subepithelial vesiculobullous lesions due to the binding of autoantibodies to structural proteins of the basement membrane (integrins, type VII collagen, and laminins 5 and 6, among others), which induces the appearance of subepithelial clefts and the consequent appearance of blisters.

Despite the advances in understanding the etiopathogenesis of vesiculobullous lesions that have occurred in recent years, there is still a great scarcity of standardized therapeutic protocols for the treatment of patients suffering from these diseases. Currently, the main objective of the therapy of these lesions is focused on the control and maintenance of clinical remission, which would represent the inhibition of blister formation and healing of mucocutaneous erosions. Although corticotherapy has reduced the mortality rate from a vesiculobullous disease from 75% to less than 10%, the higher morbidity and mortality rates related to such diseases are due to the deleterious effects caused by the immunosuppressive therapy employed.

1 Clinical Characteristics

1.1 Pemphigus Vulgaris

- Adults of both sexes, with a mean age of 50 years.
- More prevalent in the Mediterranean population and those of Jewish descent.
- Oral manifestation in the early stages of the disease.
- Intraoral blisters and vesicles are rarely observed, as they rupture easily, forming erosions and ulcers (Fig. 1).
- Involvement of the jugal mucosa, palate, lingual belly, and lips.
- Desquamative gingivitis with edema and erythema.
- Intense pain, causing dysphagia.

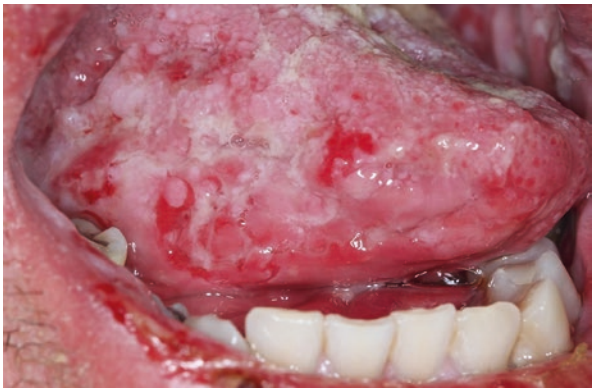

Fig. 1 Pemphigus vulgaris. Erosions and ulcers after rupturing of blisters

- Skin lesions such as flaccid, painful, or pruritic blisters rupture easily, giving rise to eroded, moist, bleeding areas with no tendency to heal.
- Positive Nikolsky sign: semitechnical maneuver consisting of the formation of a blister on the perilesional skin by firm lateral pressure. It indicates active disease.

1.2 Pemphigoid of the Mucous Membranes

- Adults 50–60 years of age.
- Predilection for women.
- Oral cavity affected in 83–100% of cases.
- Vesicles and blisters occasionally identified clinically.
- The appearance of erosions and painful superficial ulcers (Fig. 2).
- Ocular (Fig. 3) and genital involvement may be associated.
- Tendency to scar formation and synechiae.

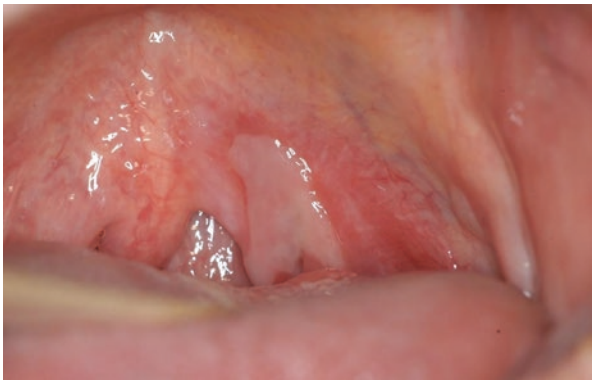

Fig. 2 Pemphigoid of the mucous membranes. Extensive, irregular ulceration after initial blister rupture

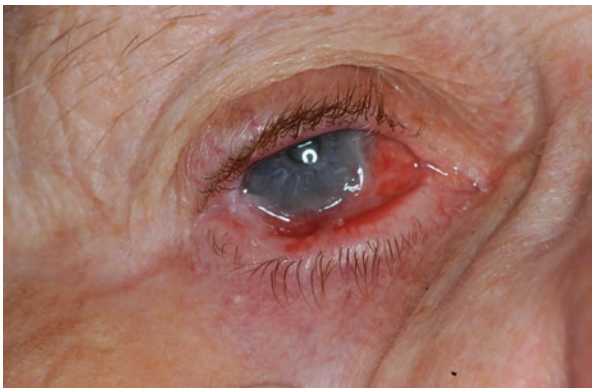

Fig. 3 Inversion of the eyelid inward in a patient with pemphigoid of the mucous membranes

2 Diagnosis

- Incisional biopsy of perilesional tissue:
  - Histopathological analysis.
  - Intraepithelial cleavage with acantholytic cells (pemphigus vulgaris).
- Subepithelial cleavage (pemphigoid of mucous membranes).
- Analysis by immunofluorescence (direct or indirect with the salt split technique).

3 Treatment

Both entities may be difficult to manage, and treatment should be performed by different specialists, such as dermatologists, otorhinolaryngologists, gynecologists, and Oral Medicine specialists. Usually, aggressive topical and systemic treatments are employed, such as high-potency topical corticosteroids (e.g., clobetasol propionate), systemic corticosteroids, and immunosuppressants (e.g., azathioprine, cyclophosphamide, methotrexate, cyclosporine, mycophenolate mofetil, sodium mycophenolate, IV immunoglobulin, plasmapheresis, anti-CD20 immunoglobulin (rituximab).

3.1 Pemphigus Vulgaris

3.1.1 Lesions Restricted to the Oral Mucosa

- Topical application of clobetasol propionate 0.05%, three times a day.
- Prednisolone 15–60 mg daily (60–100 mg daily in more severe cases), after remission and maintenance of clinical picture, reduced dosage by 5–10 mg/week. After reaching 20 mg, it decreased more slowly.

3.1.2 Lesions Disseminated to Extraoral Sites

- Referral to ophthalmologist/otorrhea specialist/dermatologist.

3.2 Mucous Membrane Pemphigoid

3.2.1 Lesions Restricted to the Oral Mucosa

- Topical application of clobetasol propionate 0.05%, three times a day.
- Prednisone 0.5–1.0 mg/kg daily in the morning.
- Prednisolone 0.5–0.75 mg/kg in the morning.

3.2.2 Lesions Disseminated to Extraoral Sites

- Referral to ophthalmologist/otorrhea specialist/dermatologist.
- Adjuvant systemic drugs:
  - Azathioprine: 50–100 mg per day.
  - Mycophenolate mofetil: 2–3 g daily.
  - Cyclophosphamide: 50–100 mg per day.

- Cyclosporine: 3–5 mg per day.
- Dapsone: 25–75 mg per day.

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Part VII

Oral Potentially Malignant Disorders and Cancer

Actinic Cheilitis

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Actinic cheilitis is a potentially malignant disorder of the lip semi-mucosa, particularly of the lower lip, closely related to chronic and excessive exposure to ultraviolet radiation. For this reason, it mainly affects the lower lip of people with light skin

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color and aged over 40 years, with a history of prolonged sun exposure, usually occupational, such as rural workers, truck drivers, and fishermen. Countries with tropical climates and a population of light-skinned immigrants, of European descent, like many countries on the Pan-American continent, present a higher number of cases.

Similar to other oral potentially malignant lesions, one or several biopsies are essential to define the degree of dysplasia and possible areas of incipient squamous cell carcinoma. In any case, it is estimated that approximately 10–20% of cases of actinic cheilitis develop into squamous cell carcinoma, in which they almost always present areas of associated actinic cheilitis.

Clinically, actinic cheilitis may range from white plaques affecting part or a large extent of the lip to erythematous areas. It also leads to the loss of sharpness of the lip (semi-mucosa) and skin border. Management implies strict follow-up. Laser resection of the vermilion of the lip or surgical resection may be indicated in cases with exuberant and recalcitrant disease.

1 Clinical Characteristics

- Actinic cheilitis is characterized by a heterogeneous clinical presentation, which may present mainly loss of delimitation between the skin and lip semi-mucosa (i.e., loss of sharpness of the lip and skin borders); atrophy; dryness; white plaques affecting part or great extension of the lip, erythematous areas, hyperpigmented and hypopigmented areas; and edema (Figs. 1, 2, 3, 4 and 5).
- They can be localized or diffuse.
- Hyperpigmented areas, crusts, fissures, and ulcers may be associated.
- It is relevant that most squamous cell carcinomas in the vermilion of the lip appear to favor the side where patients keep their cigarets while smoking (generating a synergistic effect on photo-carcinogenesis).

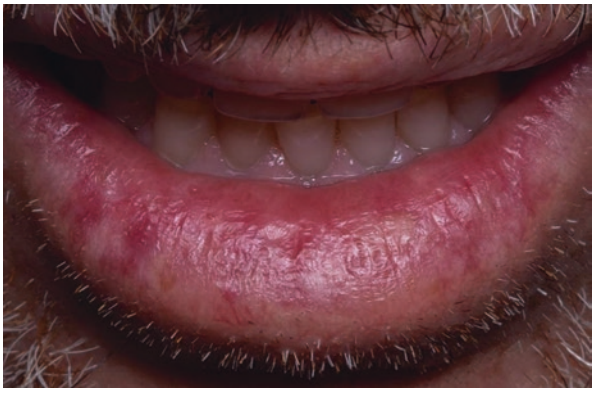

Fig. 1 Patient with actinic cheilitis presenting an undefined margin between the vermilion of the lip and the skin

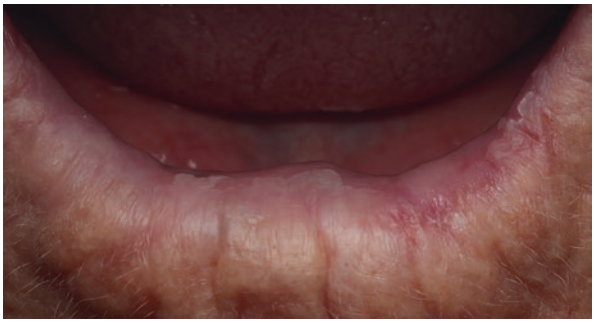

Fig. 2 Diffuse irregular white plaque in the vermilion of the lower lip

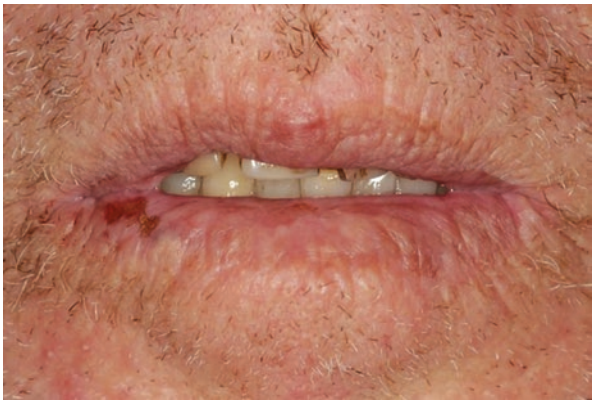

Fig. 3 Ulcerated lesion in a patient presenting actinic cheilitis

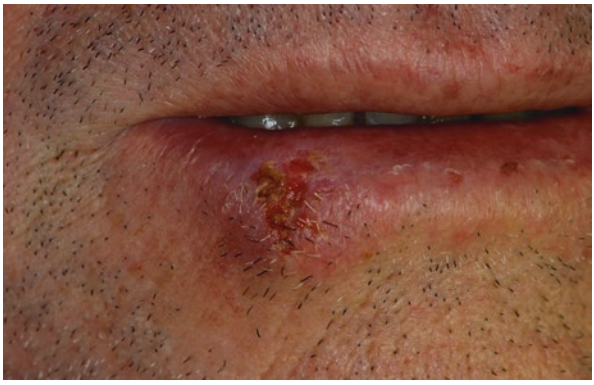

Fig. 4 Actinic cheilitis causing edema of the vermilion border of the lower lip, presenting crusts and ulcerated areas. The histopathological examination showed squamous cell carcinoma

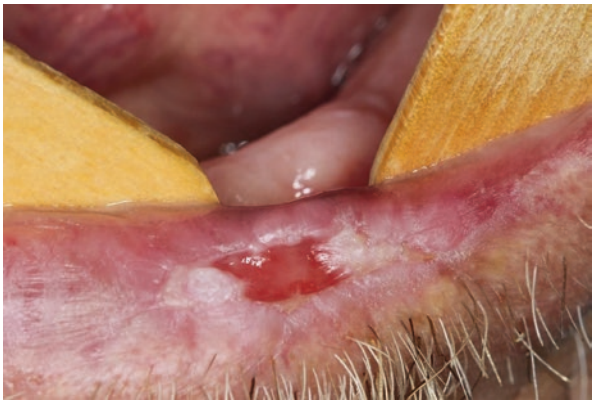

Fig. 5 Actinic cheilitis with erosion on the lower lip. Histopathological examination showed squamous cell carcinoma

2 Diagnosis

- The diagnosis is based on the association of clinical-demographic characteristics.
- Areas of recurrent ulceration, erosions, white plaques, and induration are signs that may indicate epithelial dysplasia or malignant transformation, and biopsy is indicated in these cases.
- The heterogeneity of the clinical presentation of actinic cheilitis can make it difficult to choose the region to be biopsied. In some cases, it may be necessary to choose more than one region.
- The utilization of alternative noninvasive diagnostic methods, such as the observation of tissue autofluorescence, seems to aid in the identification of regions with a higher probability of presenting tissue alterations with malignant potential.

3 Treatment

- Orientation regarding protection from the sun's rays, such as the use of a hat with a brim and continuous use of lip sun protection factor (SPF) 30.
- Surgical excision of areas with clinical features indicative of epithelial dysplasia.
- Photodynamic therapy.
- Laser resection of the vermilion of the lip or surgical resection may be indicated in cases with exuberant lesions.
- The patient with actinic cheilitis should be referred to a dermatologist due to the risk of developing skin lesions also resulting from sun exposure.
- For night hydration, indicate the vitamin B5 formula (dexpanthenol), lanolin and almond oil manipulated, or commercial as Bepantol ointment (50 mg/g tube with 30 g).
- Management implies strict follow-up, with periodic patient education, and clinical follow-up for a better prognosis of the case.

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Oral Leukoplakia and Erythroplakia

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Oral leukoplakia is defined as a white plaque that is not removable by scraping and can affect any region of the oral mucosa. This term should be used to recognize white plaques of questionable malignancy risk, considering that during the diagnostic process, other known diseases or disorders with similar clinical features have been excluded. Similar to oral leukoplakia, oral erythroplakia is also a diagnosis given by exclusion, although its clinical presentation is different—characterized by a red lesion that is reflective of atrophy of the oral mucosa epithelium.

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If not properly diagnosed and treated, both lesions in a small and significant proportion of cases, respectively, will turn into cancer. Most lesions are asymptomatic, and the main objective of treatment is to prevent their malignant transformation.

Although oral leukoplakia is found more frequently among smokers than nonsmokers, often no etiological factors related to its appearance can be observed (idiopathic appearance). It can affect any region of the oral mucosa, being more frequently observed on the floor of the mouth, lateral border of the tongue, ventral tongue, and soft palate. Recent studies indicate that the risk of malignant transformation is higher when leukoplakia is located on the tongue and/or floor of the mouth.

In any case, the most important predictive risk factor associated with the transformation of both lesions is the presence and degree of dysplasia found in the lesion epithelium through a clinicopathological correlation. Dysplastic lesions classified histopathologically as moderate and severe grade are associated with an increased risk of malignant transformation (high risk) when compared to lesions with mild dysplasia (low risk). Oral erythroplakia frequently presents moderate to intense dysplasia, and the finding of carcinoma in situ is not rare.

1 Clinical Characteristics

- Leukoplakia is a predominately white plaque clinically classified as homogeneous (thin, thick, corrugated, and granular) or non-homogeneous leukoplakia (verrucous, nodular—speckled, ulcerated, or erythroleukoplastic) (Fig. 1).
- Thus, generally non-homogeneous leukoplakias exhibit moderate and intense dysplasia at histopathological examination, while homogeneous ones present mild dysplasia.
- A different form of high-risk oral potentially malignant disorder is known as proliferative verrucous leukoplakia (PVL) (Fig. 2), which is initially characterized by homogeneous, flat plaques that grow slowly and continuously but soon become multifocal and tend to develop exophytic verrucous areas progressing to squamous cell carcinoma when not treated. The gingiva is often involved, although other sites may also be affected.

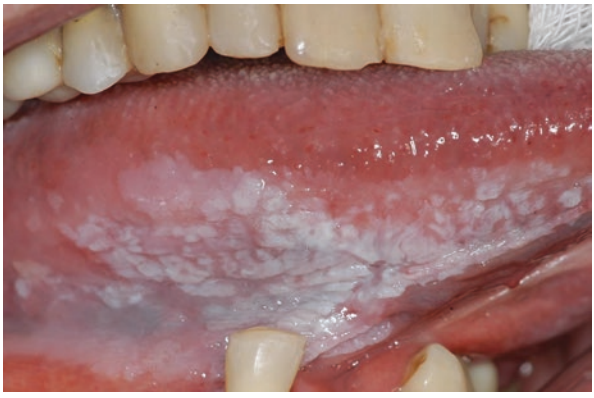

Fig. 1 Leukoplakia. Extensive white lesion on the belly of the tongue

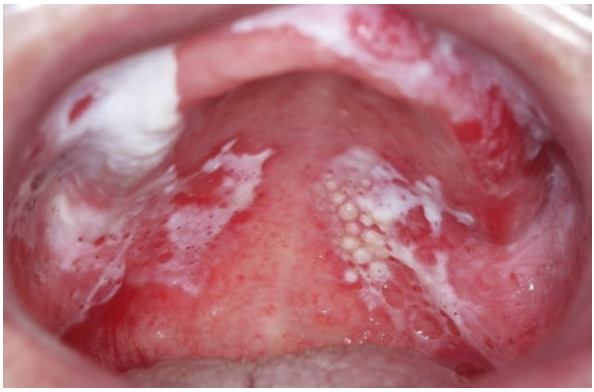

Fig. 2 Slow-growing multifocal homogeneous plaques characterizing PVL

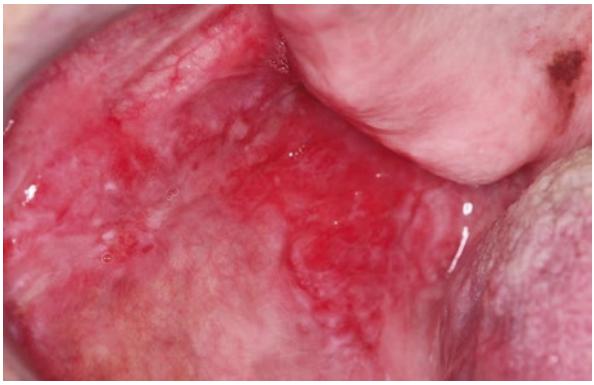

Fig. 3 Area of erythroplakia associated with white areas (erythroleukoplakia) in the buccal mucosa

Proliferative verrucous leukoplakia (PVL)
Non-smoking and non-drinking females
Over the age of 60 (over the fifth decade of life)
Associated with a high rate of malignant transformation
High recurrence rate after treatment

- Because of the red color, clinical detection and propor diagnosis of erythroleukoplakia is more challenging (Fig. 3).

2 Diagnosis

- The current reference for the diagnosis of these conditions is the correlation between clinical features and histopathological analysis from a biopsy of the lesion.

3 Treatment

- To date, there is no evidence of an effective treatment to prevent malignant transformation of leukoplakia. However, surgical treatment can be effective in resolving the lesion, and it is important to consider that recurrences may occur; therefore, patient education and clinical follow-up should be rigorous in cases of moderate and severe dysplasia and biannually in cases of non-dysplastic disease (low-risk leukoplakia) (Fig. 4).
- Recent studies point out that surgical excision is the most appropiate treatment in cases of lesions already diagnosed by biopsy as high-risk oral leukoplakia (dysplastic lesions) for a better evaluation of the specimen as a whole, excluding other potential areas of dysplasia or even carcinoma in situ.
- PVL clinical monitoring should be frequent, and biopsies should be performed whenever there are clinical signs of malignancy. The prognosis of this disease is generally limited, considering the large number of carcinomas that these patients present during the postdiagnostic period.
- The recommended treatment for erythroleukoplakia is surgical resection with scapel or laser ablation. However, sequencial biopsies are essential to characterize the presence and degree of dysplasia during follow-up or even possible malignant areas.

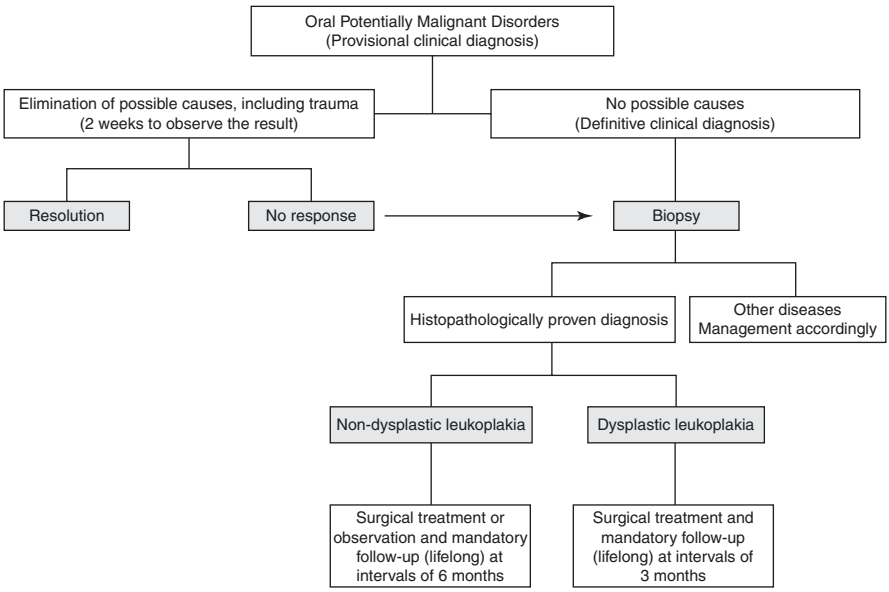

Fig. 4 Algorithm for the management of oral potentially malignant disorders. Adapted from van der Waal I (2009)

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Oral Cavity Squamous Cell Carcinoma

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In 2020, according to GLOBOCAN data, 264,211 new cases of cancers of the tongue and oral cavity in men and 113,502 in women were estimated. Oral cancer represents a considerable global health problem with a reported overall survival rate of 54%, with squamous cell carcinoma (SCC) originating in the lining epithelium of the lips and oral cavity, accounting for approximately 90% of malignant lesions in this region.

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1 General Aspects

1.1 Squamous Cell Carcinoma of the Lip

- Chronic exposure to sunlight is the most important etiologic factor, and some studies point to an association of smoking with sunlight as a relevant aspect for the development of cancer in this anatomic region.
- It is more common in individuals who live in rural areas and are involved in outdoor occupations.
- Most prevalent in Caucasian (white-skin) populations living near the Equator. Rare in dark-skinned people.
- The lower lip is involved in 85–98% of cases, with male predominance.
- The male-to-female ratio varies considerably in different case series (from 2:1 to 45:1).
- The age range is between the fifth and eighth decades of life, with an average age between 60.5 and 70 years.

1.2 Oral Squamous Cell Carcinoma

- It mainly affects elderly lifetime smokers, and the risks increase with alcohol synergism.
- Recent studies suggest that young non-smoking and non-drinking patients with oral cavity squamous cell carcinoma represent a distinct clinical entity. The high incidence of abnormalities in DNA ploidy suggests that these patients have genomic instability and indicates a genetic difference between young and old patients with oral SCC. Another emerging group of young head and neck cancer patients has non-keratinizing squamous cell carcinomas of the oropharynx (palatine and lingual tonsils) associated with oncogenic high-risk human papillomavirus (HPV) infection acquired through the practice of oral sex.

2 Clinical Characteristics

2.1 Squamous Cell Carcinoma of the Lip

- It typically occurs in the vermilion of the lower lip at an intermediate point between the midline and the labial commissure.
- Clinical presentations can vary considerably, as initial lesions may be focal, with thickened white plaque and spots of mixed white and erythematous coloration, or areas of erythema and crusting with fissures that do not regress (Fig. 1).
- More advanced lesions may be exophytic, infiltrating the underlying tissues and presenting as an ulcer with surrounding hardened areas.

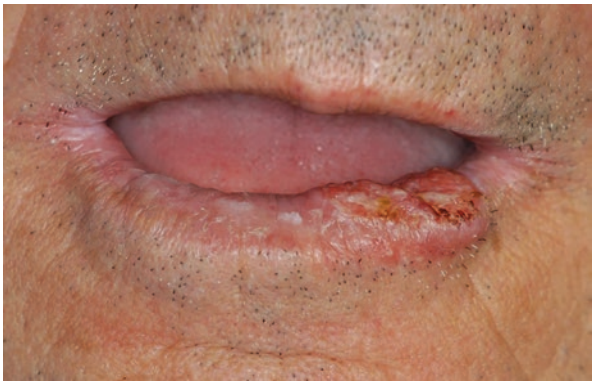

Fig. 1 Squamous cell carcinoma of the lip. Ulcerated volume increase in the vermilion of the lower lip

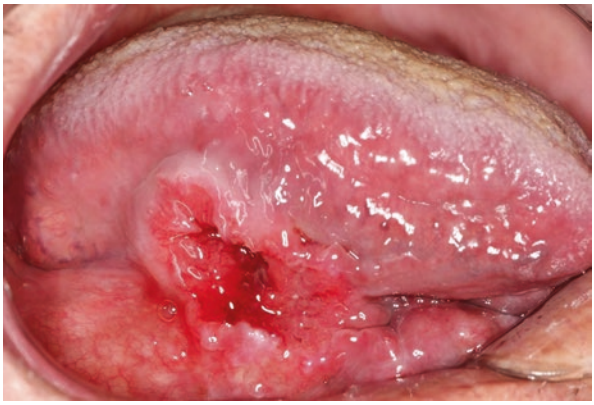

Fig. 2 Squamous cell carcinoma on the lateral border of the tongue. A deep ulcerated lesion with raised borders on the lateral border of the tongue

2.2 Oral Squamous Cell Carcinoma

- Patients with small oral SCC lesions are often asymptomatic or have only vague symptoms and minimal physical findings. Therefore, a high index of clinical suspicion is necessary, especially in patients who use tobacco products and alcoholic beverages.
- White plaques (leukoplakia) with red areas (erythroplakia) are also seen adjacent to early-stage carcinomas.
- The most common clinical appearance is an asymptomatic ulcer with elevated, hardened edges that lasts for more than 15 days (Fig. 2).
- In patients with locally advanced disease, clinical features may vary according to the affected site. In these cases, the presence of pain, halitosis, difficulty in speaking and chewing, trismus, odynophagia, dysphagia, bleeding, weight loss, and nodules in the neck is common.

3 Diagnosis

- The clinical aspects, as well as the time of evolution, are important for diagnosis.
- It is important that at the moment of the consultation, in addition to visual inspection, bimanual palpation of all structures of the oral cavity and neck be performed. Palpation is important because there are commonly hardened areas around the lesion, which can be used as an important diagnostic resource in all forms of tumors.
- Incisional biopsy must be performed in areas of greater suspicion, and it is important to avoid areas of necrosis.

4 Treatment

- The patient should be referred to the head and neck surgeon, and the appropriate treatment will be defined by cancer staging through imaging exams that complement the clinical examination requested by these professionals. The treatment may consist of surgery (primary tumor and regional neck metastasis), radiotherapy (primary treatment and regional neck drainage), and chemotherapy, isolated or associated.
- The treatment of the disease is performed by physicians, and biannual patient education and clinical follow-up should be performed by both the Oral Medicinist and the physician. This is essential for the initial detection of recurrences and second primary tumors that can occur in 10–35% of cases (because of cancerization in the field).

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Part VIII

Oral Management Strategies for Patients with Special Needs

Oral Management of Cancer Patients After Multimodality Therapy

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No currently available anticancer treatment, whether radiotherapy (RDT) or chemotherapy (CT) can destroy neoplastic cells without destroying non-neoplastic cells. In this context, the oral mucosa epithelium, a tissue with rapid cell renewal, becomes much more susceptible to acute (observed in the first weeks of treatment) and chronic toxicities (arising from 3 months after the end of therapy) of antineoplastic treatment, namely, gustatory alterations (dysgeusia), mucositis, hemorrhage, hyposalivation/xerostomia, pseudomembranous candidiasis, caries (mainly related to radiation), trismus, and osteoradionecrosis.

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Acute toxicities
Mucositis
Hemorrhage
Hyposalivation and/or xerostomia
Pseudomembranous candidiasis
Alteration in taste (dysgeusia)
Chronic toxicities
Trismus
Hyposalivation and/or xerostomia
Osteoradionecrosis
Radiation-related caries

1 Clinical Characteristics of the Toxicities of Antineoplastic Therapy

1.1 Trismus

- Limitation of mouth opening, which causes a direct influence on the quality of hygiene and speech of the patient, impairs the examination of the oral cavity and dental treatment (Fig. 1)
- Patients with tumors in the pharynx, retromolar areas, and posterior regions of the palate are the most affected.

1.2 Mucositis

- Erythema and/or ulcers on the buccal mucosa (Fig. 2)
- RDT and CT-related oral mucositis often involves nonkeratinized surfaces.
- RDT-induced mucositis involves areas primarily included in the field of radiation.

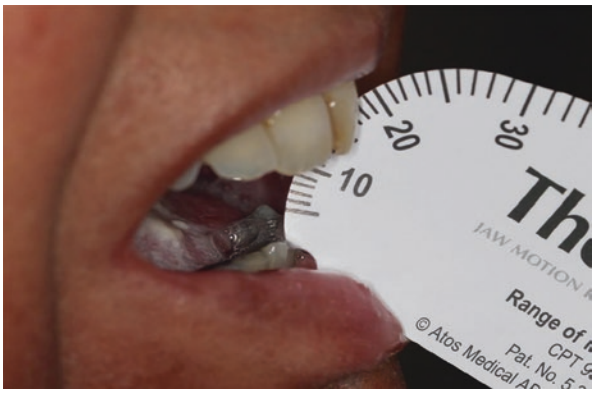

Fig. 1 Trismus in a patient undergoing antineoplastic therapy. Marked limitation of mouth opening, impaired feeding, and examination of the oral cavity

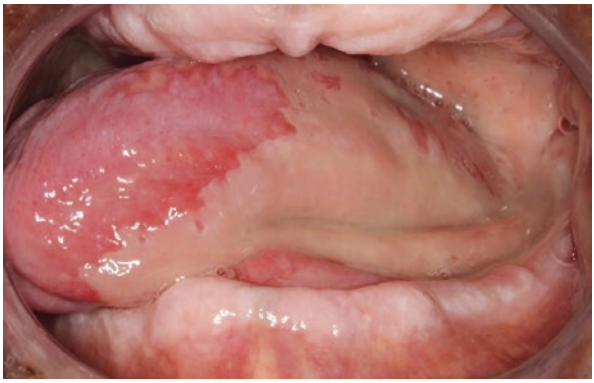

Fig. 2 Oral Mucositis in a patient undergoing antineoplastic therapy. Marked diffuse and painfull mucosa ulceration and necrosis impairing feeding

1.3 Hemorrhage

- Petechiae and ecchymoses secondary to the slightest trauma in any region of the oral mucosa.
- Bleeding may occur spontaneously or by traumatic brushing.
- It may be secondary to CT-induced thrombocytopenia liver damage.

1.4 Candidiasis

- Pseudomembranes candidiasis expose an underlying erythematous mucosa when scraped.

1.5 Alteration in Taste (Dysgeusia)

- Realized in the very first weeks of RDT.
- Progressive taste change can lead to complete loss of taste perception.

1.6 Hyposalivation/Xerostomia

- Transient during CT, permanent following head and neck RDT.
- Parotid glands are irreversibly affected by RDT, while mucous glands may partially recover after several months.

1.7 Osteoradionecrosis

- Exposure of a nonvital (necrotic) bone following RDT that persists for more than 3 months (Figs. 3 and 4).

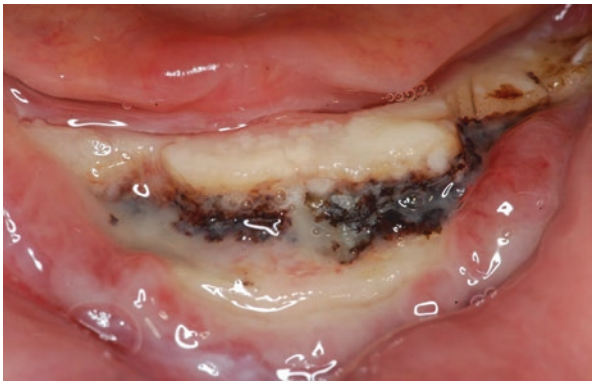

Fig. 3 Marked exposure and sequestration of the alveolar bone in the mandible region of a patient with osteoradionecrosis

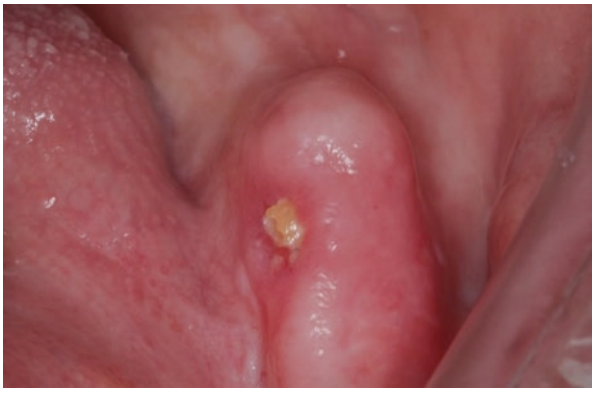

Fig. 4 Localized exposure and sequestration of the alveolar bone in the mandible region

- It can cause cortical perforation, fistula, ulceration, and jaw bones pathological fracture.
- Secondary to local trauma or tooth extraction.
- The risk of osteoradionecrosis is permanent and persists for the rest of the patients' lives.
- Mandible is more frequently affected than maxilla.

1.8 Caries

- A myriad of secondary factors (difficulty in oral hygiene, trismus, hyposalivation) may lead to increased caries risk.
- Radiation-related caries (Fig. 5)
- Brown stains on smooth enamel and dentin surfaces.
- On cervical and incisal surfaces of teeth.
- Aggressive onset and rapidly progressing.

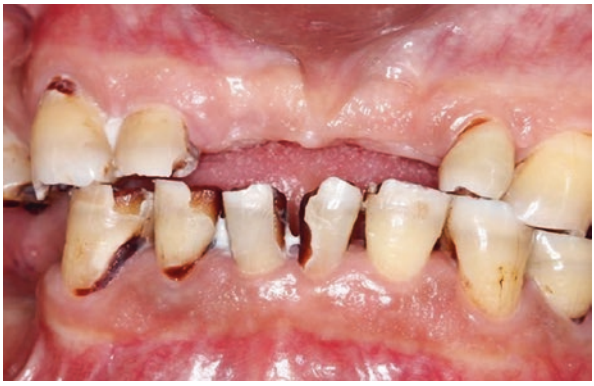

Fig. 5 Extensive cervical caries on the remaining teeth. Note incisal involvement

2 Dental Treatment in Patients Submitted to RDT

2.1 General Principles and Philosophy of Treatment

- Oral comprehensive examination and dental care prior to the start of cancer treatment is the standard of care in many cancer center. Patients who concluded RDT in the head and neck should be evaluated every 6 months by a specialized dental team. Factors such as patient prognosis, medical and oral hygiene conditions, general dental status, and radiation field (whether or not it includes maxilla/mandible, teeth, and major salivary glands) will guide dental treatment.
- In the hospital dental environment auxiliary intraoral devices should be used to minimize the adverse effects of the treatment and maximize the effect of radiation on the tumor. Tissues will be protected from undesirable doses of radiation and, consequently, from tissue reactions caused by the treatment. In addition, these devices will maintain the anatomical structures in a constant position, which highlights the oral stents and the bolus for head and neck RDT.
- A bolus is a flexible plate that adapts to the patient's skin/mucosa surface, which in clinical practice is used for the following:
  - *Dose increase at the entrance surface of a field:* It is known that the maximum dose deposited is not at the surface of the radiation field but a few millimeters below—inside the patient's body. Therefore, in an attempt to superficialize the treatment, when placing the bolus, the skin surface moves to a certain depth below the bolus, and a sufficiently required dose can be applied there.
  - *Positioning:* A confection of thermoplastic mask that guarantees the immobilization of the patient and ensures the reproducibility of the radiotherapeutic procedure, ensuring the removal of healthy tissues away from the radiation treatment field.
  - *Compensation for lack of tissue:* The purpose of this device is to fill large defects, usually maxillary, which helps in the uniform distribution of radiation through the irregular contours left by maxillectomy, for example.

2.2 Oral Conditioning Protocols

- All patients should undergo dental treatment before the beginning of RDT for head and neck cancer.
- The first step is to educate the patient about oral complications of RDT and to perform oral hygiene rigorously.
- It should treat any focus of infection installed and eliminate foci that have the potential to generate oral complications during or after RDT. Perform oral rinses three times a day with 0.12% chlorhexidine solution (alcohol-free) during all RDT protocol.

2.3 Trismus

- Exercises of the masticatory muscles using dynamic mouth openers.
- Cyclobenzaprine 10 mg, 8/8 h for 7 days for pain relief.

2.4 Oral Mucositis

- Oral hygiene should be performed with ultrasoft toothbrushes.
- Benzydamine hydrochloride (alcohol-free) administered orally for 3 min, four times a day during RDT.
- Photobiomodulation with energy between 3 and 10 J/cm^2 in concomitance with RDT. Daily prophylactic protocol, applied in at least 30 points of the oral mucosa.

2.5 Candidiasis

- According to the protocol established in Chap. 11 of this book.

2.6 Alteration in taste (Dysgeusia)

- Preventive supplementation of zinc and copper throughout RDT, with maintenance after completion of treatment.

2.7 Hyposalivation

- According to the protocol established in Chap. 13 of this book.

2.8 Osteoradionecrosis

- *Conservative treatment:* in cases of minor bone exposure, maintain strict oral hygiene associated with local and daily cleaning of the wound with chlorhexidine 0.12% solution (alcohol-free) and, in cases where bone exposure is associated with local infection, prescription of antibiotics (association of amoxicillin, clavulanate, and metronidazole for 10 days). The portion of the bone that becomes detached from healthy bone during the necrosis process should be removed atraumatically.
- *Surgical treatment:* Debridement and complete resection of the necrotic area should be performed in an atraumatic manner whenever possible. Sharp edges that may traumatize soft tissue should be removed, and primary closure of the surgical wound should be performed.
- *Pharmacological treatment (PENTOCLO)*: Therapy with pentoxifylline (vasodilator), tocopherol (antioxidant), and clodronate (bisphosphonate) minimizes the existing fibrosis process, reduces bone destruction, and promotes healing of the necrotic area. First, amoxicillin with clavulanic acid combined with prednisone 20 mg/day for 1 month should be administered to control active infections, minimize osteitis, and obtain a greater healing effect, enabling greater penetration of the drugs. After this period, the patient received a daily combination of 800 mg pentoxifylline (2 doses of 400 mg), 1000 IU tocopherol (vitamin E in 2 doses of 500 IU) and a dose of 1600 mg clodronate (when possible*), 5 times/week (Monday through Friday) and 20 mg prednisone and 1000 mg ciprofloxacin on weekends, according to the original protocol. The duration of treatment should be based on observation of progressive regression of osteoradionecrosis and the effects of pentoxifylline use.

One may have difficulty in administering clodronate because it is poorly available in the Latin-American market and has a high cost. We also do not indicate ciprofloxacin on weekends. This form of administration does not seem to be well founded, and we opted for antibiotic therapy in phases of worsening of the infectious process.

2.9 Caries

- A diet low in sugar and carbohydrates, strict maintenance of oral hygiene, frequent dental visits for cleaning and restorations, daily mouth rinses with 0.05% sodium fluoride, weekly topical applications of fluoride gel (0.2%), and mouth rinses three times a day with 0.12% chlorhexidine mouth rinse (alcohol-free) are highly encouraged for prevention radiation caries.
- Hyposalivation management.
- Restorations can be performed with conventional adhesive and composite resin, and glass ionomer should be avoided.

2.10 Exodontia

- They should be performed in the average period of 2 weeks before the start of RDT as part of the oral conditioning regimen.
- Indicated when it is an advanced and nonrestorable caries lesion, biological space invasion, advanced or symptomatic periodontal disease (with advanced bone loss), accentuated mobility or furcation involvement, residual roots not fully covered by alveolar bone or showing adjacent radiolucency, or yet symptomatic impacted teeth or partially erupted and not fully covered by the alveolar bone.
- When there is an indication for extraction post-RDT, traumatic maneuvers should be avoided, and care should be taken to maintain the contour of the alveolar bone.
- Prophylactic therapy with hyperbaric oxygenation does not seem to reduce the risk of osteoradionecrosis. Antibiotic therapy can be used at clinical discretion (1g of amoxicillin 1h before extraction and can be maintained for up to 7 days postextraction at 500mg every 8h).

3 Dental Treatment in Patients Undergoing CT

3.1 General Principles and Philosophy of Treatment

- Prevention is the best form of dental treatment for patients who will be treated by CT, and dental conditioning regimen with constant maintenance of oral health before, during, and after CT in the head and neck region are the main preventive strategies for oral complications.
- There are several types of drugs used during CT and not all can generate oral complications. Most protocols can generate anemia, neutropenia, thrombocytopenia, mucositis, and other complications that have serious repercussions for the patient's oral cavity and general health. Therefore, all patients who will start CT should be evaluated by a specialized dental team.
- Factors that will guide dental treatment before CT include patient prognosis, medical and oral hygiene conditions, general dental status, and the drug or combination of drugs that will be used during CT.
- Normally, myelosuppression due to CT results in the interruption of the bone marrow cell division process, which leads to a marked decrease in platelet and white blood cell counts in the blood. This period, known as the *nadir* period, represents the "lowest point" of circulation of these cells in the blood and occurs over a period between 7 and 14 days from initial conditioning. Marrow recovery occurs between 15 and 21 days after the end of the CT cycle and can be attested to by normalization of the values in the complete blood count (CBC). Many conditions (such as oral mucositis) can occur concomitantly with the nadir period.

3.2 Oral Conditioning Protocols

- The first step is to educate the patient about the possible oral complications of CT and to perform oral hygiene rigorously.
- It should treat any infection focus installed and eliminate foci that have the potential to generate oral complications during or after. The patient was orally rinsed three times a day with 0.12% chlorhexidine solution (alcohol-free) during CT.
- The guideline is not to perform any surgical intervention in the nadir period. An interpretation of the CBC and assessment of the timing of surgical intervention according to the CT cycle interval is mandatory.

3.3 Mucositis

- Oral hygiene should be performed with ultrasoft toothbrushes.
- Photobiomodulation with energy ranging from 3 to 10 J/cm^2 can be effective in preventing the appearance of chemo-induced mucositis if administered in a daily protocol aimed at least 30 points of the oral mucosa.

3.4 Hemorrhage

- Adequate oral hygiene to control gingival bleeding, exacerbated by thrombocytopenia.

3.5 Candidiasis

- According to the protocol established in Chap. 11 of this book.

3.6 Hyposalivation

- According to the protocol established in Chap. 13 of this book.

3.7 Invasive Dental Procedures

- Dental treatments such as dental extraction, endodontics, periodontal surgery, bone grafts, and bone-placed implants, among others, should be performed before the beginning of CT in time to allow healing and adequate bone repair.

- In general, tooth extraction is indicated before the start of CT when it is an advanced and nonrestorable caries lesion, invasion of biological space, advanced or symptomatic periodontal disease (with advanced bone loss), marked mobility or furcation involvement, residual roots not fully covered by the alveolar bone or showing adjacent radiolucency, or symptomatic impacted teeth or partially erupted and not fully covered by the alveolar bone.
- When there is an acute focus of oral infection during CT, it is more prudent to control the focus of infection with antibiotics to wait for the completion of CT and the reestablishment of the patient's systemic conditions. If dental extraction or oral surgery is the only alternative, the procedure should be performed while avoiding traumatic maneuvers and taking care to maintain the adjacent bone contour.

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Management of Patients at Risk of Medication-Related Osteonecrosis of the Jaw

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Medication-related osteonecrosis of the jaw (MRONJ) is a condition diagnosed when a patient presents with exposed bone in the maxillofacial region that does not heal in at least 8 weeks and is associated with the use of an antiresorptive agent or an angiogenic inhibiting agent, without a history of radiation in the head and neck region or metastatic disease in the jaws. Other drugs have been associated with this process but less frequently. The condition may develop on the mandible or the maxilla.

1 The Drugs Involved with MRONJ

The drugs most frequently associated with MRONJ include bisphosphonates and denosumab, key components of both the treatment of cancer patients who have skeletal metastases and for some treatment modalities of osteoporosis.

Once in the serum, most of the bisphosphonates are rapidly eliminated by the kidneys, and the rest incorporates in the bones. In the bone, osteocytes do not retain the medication, and osteoclasts, although they have eight times higher affinity for the drugs, release them within a few weeks. Osteoblasts, which have an affinity four

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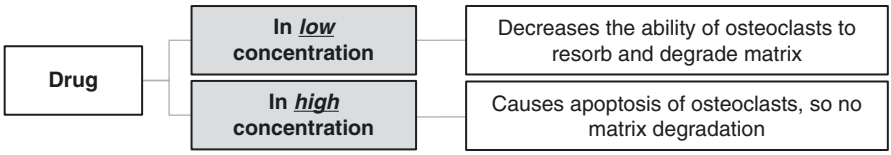

Fig. 1 Effect of the drug according to concentration

times lower than osteoclasts, not only incorporate the drug into the bone matrix but also keep them for decades.

Denosumab is not deposited in the bone and has a short half-life, so it is eliminated within a few months. In any case, the effect of the medication on the bone varies according to the concentration of the drug.

The use of these drugs and the possibility of inducing MRONJ formation depend on the ability to alter the bone resorption and neoformation system, the route of drug administration, and the time of drug use (Fig. 1).

In normal situations, when traumatic events affecting the jaw bones occur (such as those involving minor oral surgeries), the initial clot is replaced by granulation tissue and sometimes the lamellar bone, with a period of bone remodeling (lamellar bone → mature bone) of approximately 4 months. Remodeling occurs by synergism between osteoclasts, osteoblasts, and the local vascular supply. If there is functional impairment or inhibition of osteoclasts by these drugs (e.g., major targets of bisphosphonates), there will be changes in both resorption and deposition of the new lamellar bone and establishment of angiogenesis. Thus, these effects will hinder bone vascularization, which can lead to bone necrosis.

Statistical data available in the literature indicate that the use of these drugs orally (bisphosphonates), injected every 6 months (denosumab) or infused annually (bisphosphonates), can cause MRONJ in less than 1% of the people medicated, mainly in the treatment of osteoporosis. Infusion every 4 weeks (bisphosphonate) and injection every 4 weeks (denosumab) at higher doses in the treatment of patients with cancer and bone metastasis have an increased risk of MRONJ by approximately 2–3%.

2 Antiresorptive Agents

- The most common medications in association with osteonecrosis of the jaw bones include the following:
  - Aminobisphosphonates: Most cases occur in patients treated with intravenous formulations (pamidronate and zoledronic acid) and in patients with multiple myeloma. Osteonecrosis related to the use of amino bisphosphonates for osteoporosis (such as alendronate sodium) is uncommon.
  - Denosumab.
- Antiresorptive medications used for the following:
  - Multiple myeloma.
  - Breast cancer with bone metastasis.

- Prostate cancer with bone metastasis.
- Giant cell tumors of the bone.
- Paget's disease.
- Osteogenesis imperfecta.
- Arthritis.
- Osteoporosis.

3 Angiogenic Inhibiting Agents

- They are prescribed for a wide variety of neoplasms and include the following:
  - Tyrosine kinase inhibitors.
  - Monoclonal antibodies directed against vascular endothelial growth factor.

These agents in simple use can cause the formation of MRONJ, but the frequency is very low. However, in cases of renal tumors, they are associated with bisphosphonates. This increases the risk of MRONJ by almost 10%.

4 Additional Risk Factors

In addition to the use of medications, other risk factors have been considered in the literature:

- Advanced age.
- Deleterious habits: smoking and/or alcoholism.
- Use of corticosteroid and chemotherapeutic drugs.
- Diabetes.
- Poor oral hygiene and infection of dental origin.
- A poorly fitting prosthesis.

5 Clinical Features: What Is the Procedure to Diagnose MRONJ?

- The patient must be taking one of the medications associated with MRONJ.
- There should be localized bone necrosis in the jaw bones, which can be clinically visualized (Figs. 2 and 3) or probed through a fistula. These areas of necrosis may be vary in size, which may lead to extensive bone involvement, cutaneous fistula formation (Fig. 4), and pathological fracture. These areas of necrosis may be associated with recent trauma (after a tooth extraction or minor surgical procedure) or spontaneous development. These areas do not respond to routine procedures and remain exposed for 8 weeks or progress. They may be associated with infection and purulent discharge or even paresthesia of the area. A foul odor is present.

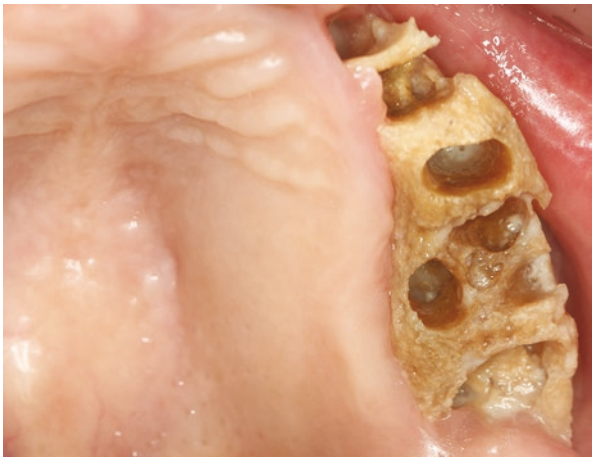

Fig. 2 Extensive and diffuse irregular area of bone sequestration with exposed alveoli in the maxilla

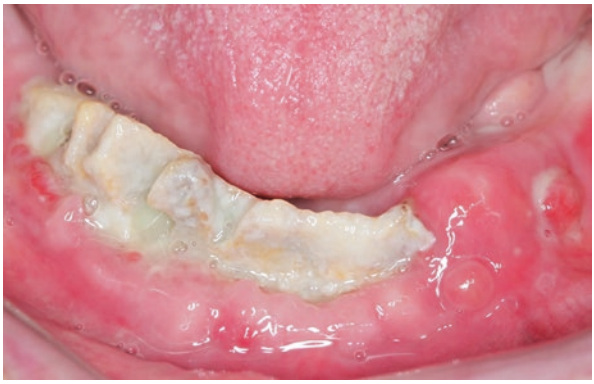

Fig. 3 Extensive and diffuse irregular area of alveolar bone exposure and sequestration in the mandible

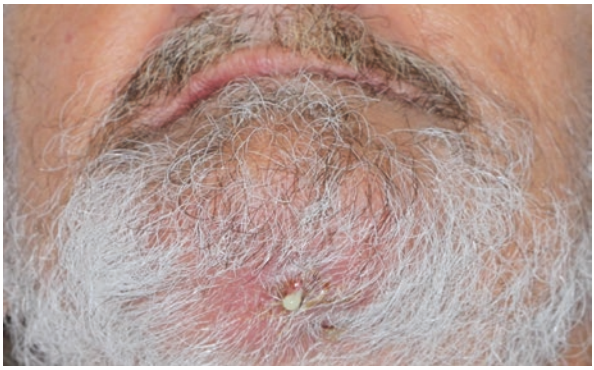

Fig. 4 Cutaneous fistula area of the patient with MRONJ shown in Fig. 3

- On panoramic radiographs, the presence of radiopacity (sclerosis) is observed in the alveolar ridge portions (areas of intense bone remodeling) and appearance closer to normal parameters in the bone distant from the areas where teeth are present. Periosteal hyperplasia is not uncommon. In more severe cases, an

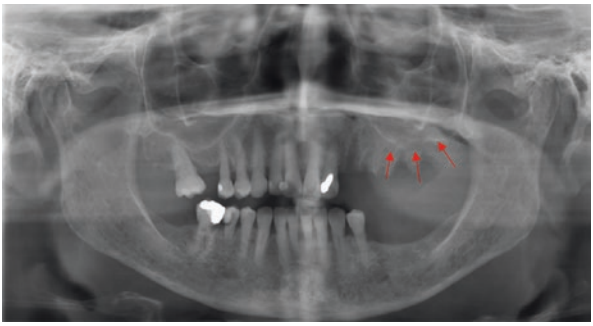

Fig. 5 Panoramic radiograph of the patient with MRONJ shown in Fig. 2. Red arrows point to the necrotic area

ill-defined radiolucent image with a moth-eaten appearance, with or without central radiopaque bone sequestrum, can be seen (Fig. 5).

Bone at imminent risk of osteonecrosis demonstrates increased radiopacity (osteosclerosis) before clinical evidence of necrosis.

6 Clinical Management to Prevent MRONJ

- The best approach is prevention, with the identification of patients at risk for MRONJ.
- Before the initiation of drug therapy associated with MRONJ, the goal is to improve dental and gingival health and prevent future procedures that may require surgical intervention on the bone (which includes an effective dental, periodontal, and radiographic examination).
- Based on the patient's assessment, a treatment plan should be developed and implemented by the health-care team (which includes the dental surgeon and the medical oncologist) to ensure that medically necessary dental procedures are performed before the initiation of drug therapy. This is the ideal plan. However, especially in cancer patients, the initiation of oncological treatment cannot be delayed. Therefore, dental treatment should be performed as soon as possible, even if the patient has already started taking drugs.
- The patient's education and clinical follow-up by the dental surgeon should be performed at least every 6 months after the initiation of antiresorptive or antiangiogenic therapy or sooner if any complaints develop in the oral cavity.
- Dentoalveolar surgical procedures are not indicated during active therapy with these drugs. Exceptions can be considered, but the benefits and risks of the proposed invasive procedure with the patient and the oncology team should be carefully evaluated. In these cases, patients should be evaluated by an experienced dental surgeon, who should propose frequent consultations until there is total coverage of the mucosa of the surgical site. It is important to consider that it is more important to treat the patient, even with the risk of MRONJ, than to decline treatment and leave the patient with active oral disease. We must remember that most patients who use these drugs do not develop MRONJ.

7 Clinical Management to Treat MRONJ

- *Initial conservative treatment:* The dental surgeon may choose antimicrobial mouth rinses (such as chlorhexidine), effective oral hygiene instruction, antibiotic therapy, and smoothing of the exposed bone (such as surface bone spicules and bone sequestrum).
- *Drug treatment (PENTO therapy):* The combination of pentoxifylline and tocopherol has been shown to be effective in reducing symptoms and reducing the area of bone exposure in patients with MRONJ. The protocol includes performing minimally invasive surgical procedures, antibiotic prophylaxis, and therapy with pentoxifylline 400 mg and tocopherol 500 IU, both 12/12 h for at least 2 months. However, it can take longer than a year for healing results to be observed.
- *Aggressive surgical intervention:* The dental surgeon may opt for mucosal flap elevation, en bloc resection of the necrotic bone, or soft tissue closure in cases where MRONJ results in persistent symptoms or affects function despite initial conservative treatment. Aggressive surgical intervention is not recommended for asymptomatic bone exposure.

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Oral Management of the Organ and Tissue Transplant Patient

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Organ and tissue transplantation (OTT) is currently considered a safe and effective therapeutic alternative for the treatment of several diseases and terminal insufficiencies of some organs and tissues. The improvement of surgical techniques, development of immunosuppressive agents, and in-depth immunological understanding of the compatibility and rejection process have provided transplanted patients with a significant improvement in their quality of life and life expectancy over the last few years.

There is an understanding among transplant teams that the main causes of loss of transplanted organs and tissues are infectious processes, responsible in many cases for the death of recipients, and a substantial increase in assistance costs. It is in this context that the insertion of the dental surgeon in the multiprofessional teams involved in the care of transplanted patients has been justified by the dental profession over the last few years.

The scarcity of precise protocols based on randomized clinical trials for the dental care of transplanted patients requires the dental surgeon to apply different strategies of pre-, trans-, and posttransplant evaluation. This evaluation should include a thorough search for active foci of infection and their respective treatments, in

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addition to the management of acute and late oral complications resulting from OTT and systemic immunosuppressive therapy, which is essential in this group of patients.

Acute post-hematopoietic stem cell transplantation complications	
Complication	**Dental management**
Oral mucositis	Photobiomodulation Mouth rinses with benzydamine hydrochloride Symptomatic pain management
Opportunistic infections	Constant monitoring in consultations Treatment according to the etiological agent (antiviral, antifungal, or antibacterial)
Xerostomia	Symptomatic treatment with hydration and salivary substitutes
The pain of neurotoxic origin	Discard odontogenic focus Symptomatic pain management
Bleeding	Local compression with gauze Topical use of antifibrinolytic agents (e.g., macerated tranexamic acid) Failure of local measures: consider platelet transfusion with the responsible hematologist
Acute GVHD	Systemic immunosuppressive therapy Topical use of corticosteroids (e.g., dexamethasone elixir 0.5 mg/5 mL, 05–10 mL, 2–4 times daily

Late complications post-hematopoietic stem cell transplantation	
Complication	**Dental management**
Chronic GVHD (graft-versus-host disease)	Surveillance for the early diagnosis of chronic GVHD Topical use of corticosteroids (e.g., dexamethasone elixir 0.5 mg/5 mL, 05–10 mL, 2–4 times daily
Salivary dysfunction	Symptomatic treatment with hydration and salivary substitutes
Caries related to hyposalivation	Reinforcement of oral hygiene instructions Regular topical application of fluorides
Sensory alterations in taste	Zinc supplementation
Opportunistic infections	Constant monitoring in consultations Treatment according to the etiological agent (antiviral, antifungal, or antibacterial)
Malignant tumors	Screening through thorough physical examination in consultations Biopsy of suspicious lesions

1 Clinical Considerations in Transplant Patients

All patients who will undergo hematopoietic stem cell transplantation (HSCT) have severe terminal diseases in specific organs. This means that without the OTT, most of these patients would probably not survive, as is the case for HSCT candidate patients. In other situations, these patients would have their quality of life extremely impaired without the transplant, as is the case of patients with terminal chronic kidney disease (CKD) who require hemodialysis.

There are clinical particularities common to this group of patients, who may present deficient cell counts and/or alterations in routine hematological exams according to the affected organ. This may be reflected in an increased tendency to spontaneous or surgical bleeding and infections (e.g., dental treatment), in addition to a reduced capacity for metabolization and excretion of drugs (e.g., liver cirrhosis and CKD, respectively).

The use of immunosuppressive agents for prolonged periods is another common characteristic in transplant patients. The main purpose of their use is to avoid graft-to-host rejection in solid organ transplantation or to minimize the complex immune reaction called graft-versus-host disease (GVHD) present in most patients submitted to allogeneic HSCT and recently recognized as an oral potentially malignant disorder.[1] Among the main immunosuppressive agents used are cyclosporine, azathioprine, mycophenolate mofetil, prednisone, tacrolimus, sirolimus, everolimus, and methotrexate.

Several adverse side effects of prolonged use of immunosuppressive agents have been reported, from opportunistic infections to delayed wound healing, in addition to the higher prevalence of malignant neoplasms known to be associated with immunosuppression (e.g., lymphomas, Kaposi's sarcoma, and squamous cell carcinoma). Cyclosporine is one of the most prescribed immunosuppressive agents and has been known to be associated with drug-induced gingival hyperplasia. In addition, patients with chronic use of corticoids may present with cushingoid reactions, osteoporosis, systemic arterial hypertension, and metabolic alterations, such as diabetes mellitus and Addisonian reactions.

2 Dental Evaluation

2.1 Pretransplant

The first point to be observed by the dental surgeon during the evaluation of a patient candidate for a OTT is that his/her terminal disease will require modifications of the dental treatment plan according to the potential clinical complications related to the affected organ. That is, a candidate for heart transplantation will certainly present severe cardiomyopathy and/or coronary disease, which should be properly managed for safe dental treatment in this period:

- The main task here is to diagnose and treat pre-existing dental problems, directing actions to remove infectious foci to avoid further short-term interventions.
- The greatest challenge is to perform the adequacy of the oral environment in time for transplantation, and the collaboration of the entire multiprofessional transplant team is essential in the early referral of this patient to the dental team.
- Instructing and educating patients and their families about the possible oral complications after transplantation is also a responsibility of the dental surgeon.

[1] It is the one in which the hematopoietic progenitor cells (HPC) or stem cells, come from another individual (donor), according to the level of compatibility between them.

2.2 Posttransplant

In solid organ transplantation, this period can be divided into three distinct phases according to the clinical particularities inherent to each: (1) immediate posttransplantation, (2) period of graft stability, and (3) period of chronic rejection.

The immediate posttransplantation period is the most critical period of the OTT and usually lasts 3 months. In this phase, the patient will be severely immunocompromised to avoid graft rejection and, therefore, susceptible to infectious processes and other acute complications. Any action should be previously discussed with the transplanting medical team due to the potential risk of morbidity and disastrous consequences of unplanned interventions.

The period of graft stability usually occurs after the first 3 months after transplantation. The graft is expected to be healed and close to normal functioning. The rate of acute complications is lower than its predecessor phase and possibly associated with exacerbated immunosuppression or the onset of rejection of the transplanted organ.

The period of chronic rejection manifests itself through clinical signs of rejection of the transplanted organ, which can be confirmed through histopathological analysis of fragments obtained by biopsies. Unfortunately, the process of rejection of a solid organ is not reversible and may lead to the need for a new transplant or even the death of the recipient.

3 Dental Treatment in Solid Organ Transplant Recipients

3.1 Pretransplant Dental Treatment Guidelines and Philosophy

- To interact with the multiprofessional transplant team before transplantation to obtain relevant clinical information about the current health status of the patient.
- Reinforce oral hygiene guidelines and encourage a reduction in the consumption of foods rich in sugar.
- To instruct and educate patients and their families about acute and late posttransplant oral complications.
- Topical application of fluorides.
- Seal active cavities from caries.
- Prioritize the removal of infectious foci (extraction of residual roots, teeth with advanced periodontal disease, and/or deep caries with pulpal involvement without the possibility of endodontic treatment in time for transplantation).
- Partially erupted third molars and/or those with a history of pericoronitis should be removed.
- Postponing complex procedures (fixed prostheses, rehabilitation with dental implants).

- Adjust and/or reline poorly fitting prosthesis.
- Consider the need and individual indication of antibiotic prophylaxis before surgical procedures to prevent local and distant infections.
- Considering the patient's motivation and level of education in making decisions about keeping teeth with doubtful prognosis is fundamental.

3.2 Posttransplantation Dental Treatment Guidelines and Philosophy

3.2.1 Immediate Posttransplant Period

- To interact with the multiprofessional transplant team before new interventions to obtain data on the current clinical condition of the patient.
- Mouth rinses with 0.12% chlorhexidine alcohol free daily.
- Emergency care for infectious processes only.

3.2.2 Period of Graft Stability

- To interact with the multiprofessional transplant team before new interventions to obtain data on the current clinical condition of the patient.
- Elective procedures are cleared.
- Special attention should be given to the periodontal control of patients, especially those taking cyclosporine, due to the increased risk for drug-induced gingival hyperplasia.
- Maintain regular consultations every 3–6 months.
- Consider potential drug interactions when prescribing antibiotics, anti-inflammatory drugs, and analgesics by the dental surgeons.
- Avoid nonsteroidal anti-inflammatory drugs (NSAIDs). Preferably use single-dose corticosteroids in front of surgical procedures with the expectation of edema (e.g., dexamethasone 04–08 mg single dose).
- Consider the need and individual indication of antibiotic prophylaxis before surgical procedures for the prevention of local and distant infections.
- Consider the need for supplementation of the corticosteroid dose in the perioperative period in patients treated for long periods with these drugs due to the risk of acute adrenal crisis.
- Screening for malignant neoplasms in the head and neck region.

3.2.3 Period of Chronic Rejection

- To interact with the multiprofessional transplant team before new interventions to obtain data on the current clinical condition of the patient.
- Emergency care for infectious processes only.
- Consider palliative dental treatment in cases with unfavorable prognosis.

4 Dental Treatment in Patients Submitted to Hematopoietic Stem Cell Transplantation (HSCT)

Previously known as bone marrow transplantation (BMT), HSCT is considered a widely used therapeutic modality for the cure of hematological diseases, or of other tissues, bone marrow insufficiencies, and congenital disorders of hematopoiesis. HSCT is based on the replacement of the diseased or deficient bone marrow with the new, healthy bone marrow through the infusion of hematopoietic progenitor cells (HPC).

HSCT can be classified according to the type of donor (allogeneic, syngeneic, autologous), the degree of kinship (related or unrelated), the degree of human histocompatibility (HLA – *human leukocyte antigen*), the source of the HPC (bone marrow, peripheral blood, or umbilical cord), and the chemotherapy conditioning regimen used (myeloablative or reduced intensity).

The oral cavity is a site highly susceptible to direct and/or indirect adverse effects related to HSCT. Approximately 80% of patients submitted to this procedure may present oral complications. These can be classified into acute and late according to the moment they manifest after HSCT and the type of sequelae generated. Among the acute oral complications, oral mucositis is the most common. Among the late oral complications, GVHD represents the most clinically relevant due to the broad spectrum of tissue sequelae (Fig. 1), affecting the oral mucosa, salivary glands, teeth, and musculoskeletal and nervous tissues.

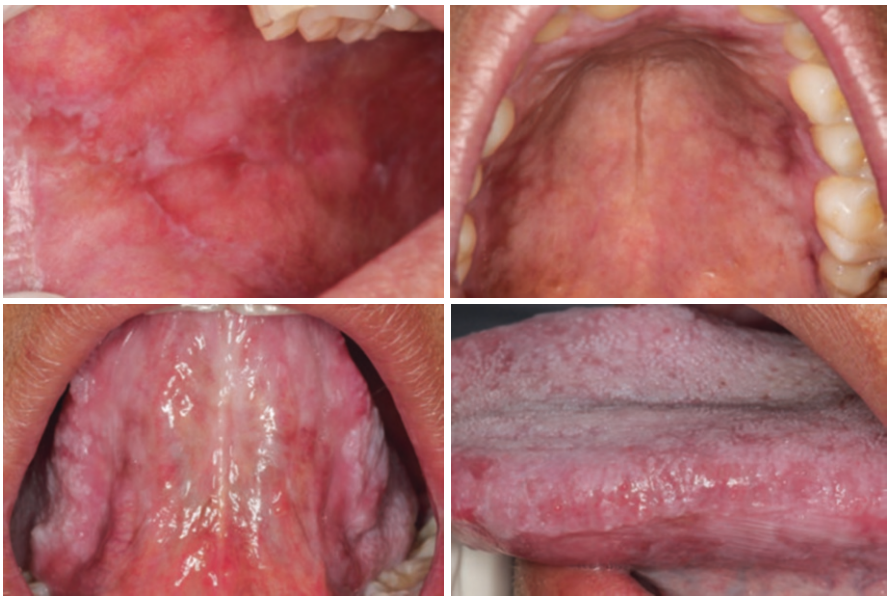

Fig. 1 Patient with chronic GVHD after allogeneic HSCT

Specialized dental support in the context of HSCT is not only able to increase transplant success rates but also substantially improve the quality of life of the patients.

5 Treatment Guidelines and Philosophy

5.1 Pre-HSCT

- To use the same criteria of oral care previously addressed for patients submitted to solid organ transplantation.
- Aggressively eliminate possible oral infectious foci.
- Diagnose malignant infiltrations of hematopoietic origin and/or relapses of the underlying disease in the oral cavity and/or maxillofacial region.
- To instruct patients and their families on oral hygiene care and possible acute and late oral complications after HSCT.
- Encourage the patient to maintain a regular pattern of oral hygiene.

5.2 During HSCT

- Maintain regular oral hygiene with the use of soft or ultrasoft brushes.
- Mouth rinses with 0.12% chlorhexidine alcohol free, two times a day during hospitalization.
- Diagnose and manage opportunistic infections in the oral cavity with the multiprofessional team (e.g., reactivation of herpes simplex virus and deep fungal infections).
- Adjust pattern of paste/liquid diet with the nutrition team according to the risk for the development of oral mucositis.
- Adequate management of oral mucositis, preferably through photobiomodulation (gold standard).
- Properly manage xerostomia through the use of salivary substitutes and perioral lubrication (e.g., regular application of lanolin to the lips).
- Encourage the patient to maintain a regular pattern of oral hygiene.

5.3 Post-HSCT

- Early diagnosis and treatment of opportunistic oral infections.
- Diagnosis and treatment of early oral changes consistent with chronic GVHD and report to the medical team.
- Early diagnosis of malignant neoplasms secondary to chronic immunosuppression and/or local recurrence of the underlying disease.
- Diagnosis and treatment of oral symptoms of dry mouth early.
- Regular topical fluoride application for caries prevention related to hyposalivation.

- Maintain regular monitoring appointments (3–6 months).
- Stimulate the reduction of the consumption of foods rich in sugar together with the nutrition team.
- Encourage the patient to maintain a regular pattern of oral hygiene.

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Oral Management of Patients Undergoing Antithrombotic Therapy

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Antithrombotic therapy (AT) is considered one of the most prevalent treatment in contemporary medicine. Its objective is to reduce the risk of thromboembolism in patients with cardiovascular diseases and/or other disorders related to hypercoagulable states in the body.

Several dental specialties, especially surgical specialties, were impacted by the need to treat patients with AT. This has occurred more frequently today due to the increased life expectancy of patients with chronic noncommunicable diseases in the population that began to demand oral care.

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Main health conditions that require the use of AT
– Atherosclerosis
– Angina pectoris
– Atrial fibrillation (AF)
– Coronary artery disease (CAD)
– Cerebrovascular accident (CVA)
– Acute myocardial infarction (AMI)
– Deep vein thrombosis (DVT)
– Pulmonary thromboembolism (PTE)
– Presence of a coronary stent
– Presence of mechanical heart valve (MHV)
– Presence of joint prosthesis
– Prophylaxis and treatment of thromboembolic events

The arrival of these patients to dentistry services has led to a series of controversies among specialists, whether physicians or dentists, about the need for maintenance and suspension of AT before the performance of surgical procedures. This debate intensified with the progressive launch of new antithrombotic agents (AA) in the market.

1 Antithrombotic Agents

AA comprises two classes of drugs: antiplatelet agents and anticoagulants. The potency and duration of their antithrombotic therapeutic effects vary according to their mechanism of action, the pathway of inhibited hemostasis, plasma peak, half-life, reversibility, and factors related to the individual, such as the drug metabolization and excretion capacity.

Depending on the thrombotic risk[1] of the individual, AA can be employed individually (monotherapy or single therapy) or combined (dual or triple therapy).

2 Antiplatelet Agents

They include drugs with different inhibitory effects on platelet activation and aggregation (Table 1). The most common is acetylsalicylic acid (ASA), which has inhibitory effects on platelet aggregation related to thromboxane A2 suppression and secondary inhibition of cyclooxygenase-1 (COX-1) at low doses (up to 100 mg/day) and cyclooxygenase-2 (COX-2) at high doses (300 mg/day). Interestingly, the most effective antithrombotic effects related to long-term ASA use are present in low-dose therapy.

[1] Thrombotic risk: degree of individual susceptibility to the occurrence of new thromboembolic events.

Table 1 Main antiplatelet agents

Medicines	Mechanism of action	Reversibility	Commercial name	Duration of effect
Acetylsalicylic acid (ASA)	Inhibition of cyclooxygenase enzyme	Irreversible	Aspirin	5–10 days
Clopidogrel	Inhibition of the P2Y12 receptor	Irreversible	Plavix®	3–10 days
Prasugrel	Inhibition of the P2Y12 receptor	Irreversible	Efficient	7–10 days
Ticlopidine	Inhibition of the P2Y12 receptor	Irreversible	Ticlid®	7–10 days
Ticagrelor	Inhibition of the P2Y12 receptor	Reversible	Brilinta®	3–5 days
Tirofiban	Gp IIb/IIIa receptor antagonism	Reversible	Agrastat® Agrastat	4–8 h
Cilostazol	Inhibition of phosphodiesterase III	Reversible	Cebralat®	2 days (?)
Dipyridamole	Inhibition of phosphodiesterase III	Reversible	Persantin®	2 days (?)

3 Anticoagulants

3.1 Oral Anticoagulants

They have inhibitory effects on different blood coagulation factors, directly or indirectly impacting the generation of thrombin. Among the anticoagulants administered orally, the most prescribed worldwide is warfarin sodium, a vitamin K antagonist (VKA), which has come under competition in the last decade after the commercialization of direct-acting oral anticoagulants (DAOA) (Table 2).

3.2 Heparins

Heparins and their derivatives have been widely used for decades as anticoagulants for the treatment and primary or secondary prophylaxis of thromboembolic diseases. Heparins are composed of a mixture of sulfated glycosaminoglycans of different sizes and molecular weights and are subcategorized into unfractionated heparins (UFHs) and low molecular weight heparins (LMWHs) (Table 3).

LMWHs are currently being used more frequently due to their practical application (subcutaneously) and the need for less frequent doses. Its use is common in the "bridging therapy" used in patients with high and moderate thrombotic risk who will be submitted to surgical procedures with high hemorrhagic risk.

Table 2 Main oral anticoagulant agents

Medication	Class	Mechanism of action	Commercial name	Half-life
Warfarin sodium	VKA	Inhibition of factors II, VII, IX, X, and proteins C and S	Marevan®, Coumadin®, Varfine®	20–60 h
Dabigatran etexilate	DAOA	Direct inhibition of thrombin (factor IIa)	Pradaxa®	12–17 h
Rivaroxaban	DAOA	Inhibition of factor Xa	Xarelto®	7–13 h
Apixabana	DAOA	Inhibition of factor Xa	Eliquis®	8–13 h
Edoxaban	DAOA	Inhibition of factor Xa	Lixiana®	10–14 h

Table 3 Main heparins and their derivatives

Medication	Mechanism of action	Route of administration	Commercial name	Half-life
UFH	Inhibition of thrombin and factor Xa	Intravenous or subcutaneous	Hemapax-S® and Liquemine®	1–1.5 h
LMWH	Direct inhibition of factor Xa	Subcutaneous	Clexane®	3–6 h

4 Perioperative Management of Patients with AT

4.1 Evidence on the Suspension and Maintenance of AT

- In dental practice, it is common that the risk for hemorrhagic events is overestimated compared to the risk for new thromboembolic events in the perioperative period.
- The clinical consequences of the inadvertent suspension of AT for long periods, or with high frequency, are severe and are demonstrably associated with the manifestation of thromboembolic events, with risk of serious sequelae or death.
- The use of the "anticoagulation bridge" was associated with higher rates of bleeding events after invasive dental procedures than maintenance of the use of oral anticoagulants.
- Systematic review studies point to statistically similar rates of bleeding events among patients who had the AT maintained and suspended or modified in the face of minor surgical dental procedures when local hemostatic measures were employed.
- Hemorrhagic events in the oral cavity can be easily visualized and managed with the use of local hemostatic measures.

4.2 Perioperative Recommendations

4.2.1 Clinical Evaluation

- Take into consideration the type of AT in use (Table 4), the patient's thrombotic risk, and the bleeding risk associated with the patient and the planned surgical procedure.

Table 4 Perioperative care related to the different types of AA

Antithrombotic agent	Laboratory monitoring	Perioperative care
Antiplatelet agents	Platelet activity tests can be performed, although not required	– *Low-risk procedures:* May be performed during the use of monotherapy or dual therapy – *High-risk procedures:* Consider suspension respecting the reversibility term of antiplatelet agents (under medical supervision)
Warfarin sodium	Coagulogram (INR)	– *Low-risk procedures:* May be performed during the use of the medication – Ideally, measure INR on the day of surgery or up to 72 hours before – Act in the therapeutic INR range (2.0–3.5); use local hemostatic measures – Pay attention to possible drug interactions (NSAIDs and antibiotics)—Potentiate the anticoagulant effect – *High-risk procedures:* Consider "bridge anticoagulation" with heparins in agreement with the medical team Obs1: Abrupt discontinuation of warfarin is contraindicated and may induce a state of rebound hypercoagulability
DAAA	They do not require clinical monitoring INR value is not able to predict the level of anticoagulation	– *Low-risk procedures:* May be performed during the use of the drug in patients free of active bleeding or without a recent history of bleeding Obs1: Ideally intervene outside the peak of drug action, 6–8 h after the last dose for Dabigatran and Apixaban and 10–12 h after the last dose for Rivaroxaban and Edoxaban. Use local hemostatic measures – *High-risk procedures:* Consider suspending 1–2 half-lives of the drug (consider patient's renal function). Resume anticoagulation regimen 4–6 h after surgery Obs1: "Bridge anticoagulation" with heparins is contraindicated
UFH	Coagulogram (TTPa)	– Wait 4–6 h after the infusion of the last dose of the drug to perform the surgical procedure – Resume anticoagulation regimen 4–6 h after surgery Obs1: Dialysis patients should perform invasive procedures preferably on the day after hemodialysis Obs2: Beware of heparin-induced thrombocytopenia—Request platelet count
LMWH	Anti-factor Xa dosage	– *Low-risk procedures:* Delay or suspend morning dose (8–12 h interval after last-dose infusion) on the day of the procedure – *High-risk procedures:* Wait 24 h after the infusion of the last dose. Resume anticoagulation regimen 4–6 h after surgery Obs1: Attention to heparin-induced thrombocytopenia—Request platelet count

- Request information from the attending physicians about the patient's thrombotic risk, which will be graded according to the following factors:
  - A clinical condition that required the use of AT, heart failure, systemic arterial hypertension, diabetes mellitus, history of stroke, high age (>65 years), female sex, and other conditions of hypercoagulability present.
- Assess the patient's bleeding risk, which will be graded on the presence of the following factors:
  - Chronic renal failure, hepatic dysfunction, low weight (<50 kg), concomitant use of NSAIDs and/or antiplatelet agents, positive history of hemorrhagic events, and idiopathic or drug-induced thrombocytopenia.
- To evaluate the bleeding risk of the planned surgical procedure (low-risk and high-risk). The vast majority of dental procedures fall into the low-risk category,[2] and there are recommendations with a good level of evidence for their performance in the presence of AT.
- High bleeding risk procedures may require modification/suspension of AT. In these cases, the approach should be previously agreed upon with the attending medical team.
- The decision to maintain, modify, or suspend the AT should prioritize an individualized assessment of the patient's thrombotic risk to the detriment of the hemorrhagic risk of the proposed procedure.

4.3 Dental Treatment

- Prioritize the adequacy of the oral environment and stimulate aggressive control of oral biofilms before surgical procedures to minimize the local inflammatory response.
- Fractionate the treatment into several sessions with the intention of not changing the AT regimen.
- Avoid repeated anesthetic punctures and perform slow infusion of the local anesthetic.
- Use minimally invasive technique, avoiding extensive surgical flaps and prioritizing osteotomies.
- Recommend cryotherapy immediately after dental intervention.
- Schedule returns every 48–72 h for reevaluation of local hemostasis.
- Persistent bleeding for more than 8–12 h should be managed with the aid of local hemostatic measures.
- Malformed blood clots should be removed to identify and control the bleeding focus.

[2] Low-risk dental surgical procedures: Extraction of up to three teeth in the same session, avoiding extensive gingival flaps.

4.4 Local Hemostatic Plan (LHP)

The use of local hemostatic measures seems to be unanimous among the authors who suggested the maintenance of AT before invasive dental procedures and for the treatment of postsurgical bleeding events.

- Adequate a preventive LHP, which is feasible and effective for the proposed surgical procedure.
- The use and combination of local hemostatic measures favor the achievement of hemostasis both in the transoperative period and in the immediate and late postoperative periods.
- Use obliterative sutures, preferably inducing primary closure of the surgical wound.
- Avoid absorbable suture threads of animal origin, such as catgut, due to low resistance to tension and induction of greater local inflammatory reaction. Other absorbable threads of synthetic origin can be used, such as polyglactin 910 or polyglycolic acid.
- Local hemostatic measures suggested the following:
  - Local tamponade with gauze.
  - Gelatin sponges (Hemospon®, Surgifoam®, Gelfoam®).
  - Conical-shaped collagen sponges (Straummann® collacone).
  - Oxidized cellulose weft (Surgicel®).
  - Glues and adhesives for synthetic (Epiglu®, Liquiband®) and biological (Beriplast®) fabrics.
  - Topical use of antifibrinolytic agents (Hemoblock®, Transamin®).
  - Fibrin-rich plasma.

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Management of Oral Lesions in HIV-Positive Patients

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The progression of HIV infection is strongly related to the appearance of oral lesions, such as candidiasis (present in more than 70% of cases), oral hairy leukoplakia, Kaposi's sarcoma, non-Hodgkin's lymphoma, and periodontal disease (mainly linear gingival erythema, necrotizing gingivitis (NG), and necrotizing periodontitis (NP)). These conditions are closely associated with decreased CD4+ cell counts. Parotid gland enlargement, lesions of viral origin (herpetic or related to human papillomavirus), and oral mucosa ulceration may also be related to HIV infection.

Pseudomembranous candidiasis and oral hairy leukoplakia, when present, usually reflect severe immunosuppression (CD4+ cell count less than 200 cells/mm^3),

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as well as high viral load. In the treatment setting, the advent of antiretroviral therapy strongly interfered with the prevalence of these lesions. Candidiasis, oral hairy leukoplakia, infection with herpes simplex virus (HSV), Kaposi's sarcoma, and necrotizing periodontal diseases decreased their prevalence, while related lymphomas remained unchanged. Human papillomavirus (HPV)-associated lesions, HIV-associated salivary gland disease, chronic periodontal disease, and oral hyperpigmentation, on the other hand, increased significantly.

Being one of the first signs of advanced immunosuppression, the appearance of these conditions suggests not only disease progression and inadequate therapeutic response but also the awareness of HIV serological status, many times unknown by the patient.

1 Oral Lesions Associated with HIV

1.1 Candidiasis

- Three main presentations (see more details in Chap. 11):
  - *Pseudomembranous:* multiple white superficial plaques, milky in appearance, which after removal reveal erythematous base, located anywhere in the oral mucosa, and may spread to the oropharynx.
  - *Erythematous (atrophic):* multiple red areas on the tongue and/or palate.
  - *Angular cheilitis:* erythema and fissures in the labial commissure, usually accompanied by clinical signs of intraoral candidiasis.
- Presence of oral discomfort, pain, and dysgeusia.
- There may be dissemination to the esophagus (invasive esophageal candidiasis).
- 95% of HIV patients will develop the lesion at some point during their disease.
- Generally, the erythematous pattern begins when the CD4+ lymphocyte count is less than 400 cells/mm^3 and the pseudomembranous pattern begins when the count is less than 200 cells/mm^3.

1.2 Oral Hairy Leukoplakia

- White corrugated plaques that cannot be removed by scraping.
- Usually, on the lateral border of the tongue (Fig. 1).
- Strongly associated with HIV infection, but other immunosuppressive conditions may induce the appearance of the lesion.
- Epstein–Barr virus (EBV) infection.
- The reference standard is EBV detection by in situ hybridization.
- Cytological examination and biopsy can be used in the search for characteristic morphological findings such as hyperkeratosis, acanthosis, and ballooning degeneration.

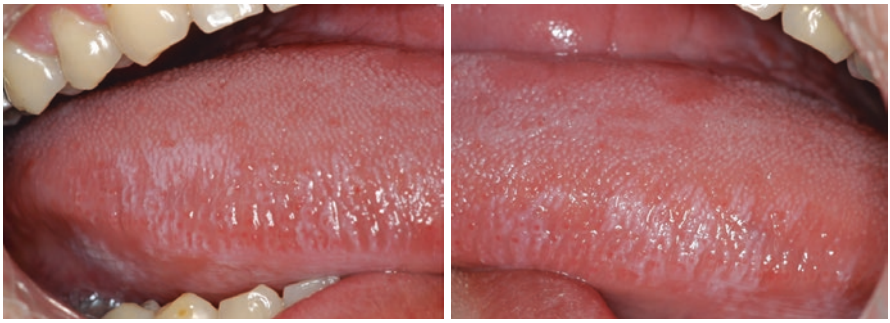

Fig. 1 Oral hairy leukoplakia. Vertical folds of keratin along the lateral border of the tongue with bilateral involvement pattern

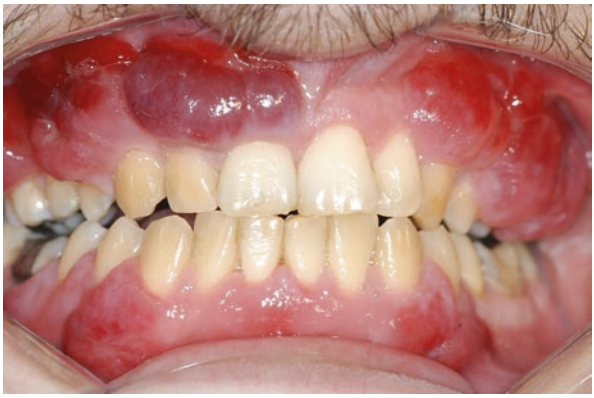

Fig. 2 Kaposi's sarcoma. Dark red, elevated volume increase in upper and lower gingiva

1.3 Kaposi's Sarcoma

- It presents as single or multiple macules and/or nodules.
- Slightly bluish or violet coloring (Fig. 2).
- Ulcerations may be present.
- Preferably on palate and gums.
- The histological aspect of the antiproliferative lesion confirms the diagnosis.

1.4 Non-Hodgkin Lymphoma

- Nodule firm and elastic.
- It can be reddish or purplish.
- Ulcerations may or may not be present.
- The gingiva, palatal mucosa, and throat are predominantly affected (Fig. 3).
- The histological appearance of lymphoproliferative lesions confirms the diagnosis, often supported by immunohistochemical and biomolecular techniques.

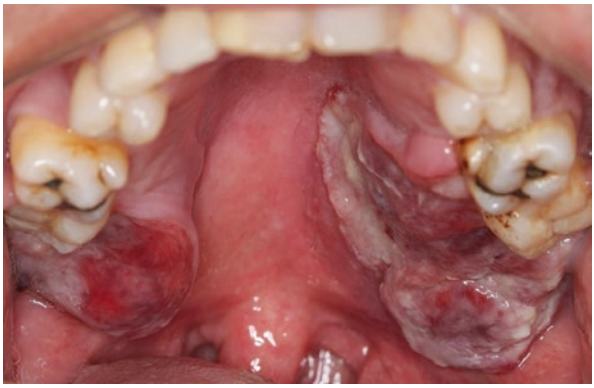

Fig. 3 Plasmablastic non-Hodgkin's lymphoma. Ulcerated and erythematous soft tissue bulges in the upper alveolar ridge. Note that on the left side, the lesion extends into the adjacent soft palate

1.5 Periodontal Diseases

There are three forms of periodontal diseases strongly associated with immunosuppression caused by HIV: gingival candidiasis (previously described as linear gingival erythema), NG, and NP. Chronic periodontal diseases, especially periodontitis, are more severe in HIV-infected individuals. All of them are determined by clinical findings:

- Linear gingival erythema:
  - Erythematous band of 2–3 mm along the marginal gingiva.
  - Not related to the presence of plaque.
  - Often associated with petechiae.
  - Amount of erythema disproportionate to the amount of plaque present on the teeth.
  - Unlike gingivitis, it persists after simple dental prophylaxis.
- NG:
  - Necrosis and ulceration of one or more interdental papillae.
  - Bleeding, pain, and fetid halitosis may be present.
- NP:
  - Rapid and extensive loss of periodontal tissues, resulting from necrosis.
  - Periodontal attachment loss and bone destruction or sequestration.
  - Mobility and tooth loss may be observed in cases with previous severe periodontitis.
  - Periodontal pockets may not be observed due to simultaneous loss of hard and soft tissue.
  - CD4+ lymphocyte count usually less than 200 cells/mm^3.
- Periodontitis:
  - Exuberance of gingival inflammation.
  - Exacerbation of preexisting periodontitis.
  - Increased probing depth, clinical attachment loss, and tooth mobility.
  - Periodontal pockets, gingival recession, and alveolar bone loss are directly related to reduced CD4+ T lymphocyte counts.

1.6 Oral Hyperpigmentation

- Associated with the chronic use of antifungal and antiretroviral medications.
- Multiple asymmetrical dark brown or blackish oral pigmentations, usually larger than 1 cm.
- They may be present in any region of the oral mucosa, with the jugal mucosa being the main affected anatomical site.
- They should be differentiated from other conditions that cause diffuse pigmentation of the oral mucosa, such as Addison's disease, McCune-Albright syndrome, Peutz–Jeghers syndrome, neurofibromatosis, and tobacco melanosis.
- Diagnosis is usually determined by clinical findings.

2 Treatment

2.1 Candidiasis

- According to the protocol established in Chap. 11 of this manual.

2.2 Oral Hairy Leukoplakia

Some reviews state that there are no strong evidence-based recommendations and that reconstitution of the immune system is sufficient for regression of lesions. However, there are reports of other treatments described:

- Topical agents:
  - Podophyllin 25%, 1–2 applications on the affected areas, at intervals of 1 week.
  - Retinoic acid (tretin).
- Surgical excision.

2.3 Kaposi's Sarcoma

- Medical referral for treatment of the lesions, since there is the possibility of local surgery, systemic chemotherapy, or radiotherapy treatment.

2.4 Non-Hodgkin Lymphoma

- Medical referral for treatment that is based primarily on chemotherapy associated with combined antiretroviral therapy.

2.5 Periodontal Diseases

- Linear gingival erythema:
  - Rinse with 0.12% chlorhexidine (no alcohol).
- NG and NP.
  - Local measures:
    Debridement of the affected areas.
    Irrigation with povidone-iodine.
    Rinse with 0.12% chlorhexidine (no alcohol).
  - Systemic measures when malaise, fever, and lymphadenopathy are present:
    Metronidazole (250 mg tablet) 8/8 h or (500 mg tablet) 12/12 h for 7–10 days.
    Clindamycin (150 mg tablet) every 6/6 h or (300 mg tablet) every 8/8 h for 7 days.
    Amoxicillin (250 mg tablet) 12/12 h for 7 days.
- Periodontitis:
  Basic periodontal therapy, initially with nonsurgical periodontal treatment, surgical treatment (access surgery), depending on the case.
  Supportive periodontal therapy in quarterly control or shorter depending on the clinical picture.

2.6 Oral Hyperpigmentation

- No therapy is necessary.

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Management of Patients with Burning Mouth Syndrome

Alan Roger Santos-Silva, Ana Gabriela Costa Normando, César Rivera, Felipe Paiva Fonseca, João Figueira Scarini, and Lara Maria Alencar Ramos Innocentini

Burning mouth syndrome (BMS) is defined as an oral burning sensation or a dysesthesia sensation, recurrent daily for more than two hours a day for more than three months, without clinically or laboratorial evident oral lesions. According to its concept, this condition becomes a diagnosis of exclusion and is applied only for cases of burning in the absence of a diagnostic alternative.

The exact etiology of this condition remains unknown, although there is consistent evidence that most patients with BMS have neuropathic alterations. Thus, today, the condition is classified into two types: peripheral and central. The peripheral BMS would be caused by subclinical trigeminal neuropathies, trigeminal trunk lesions, or small fiber neuropathy of the oral mucosa. The central BMS would be due to low brain dopamine tone accompanied by psychiatric comorbidity.

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1 Clinical Characteristics

- Male to female ratio of 1:7.
- Peri- or postmenopausal patients.
- Absence of visible changes in the oral mucosa.
- Burning sensation:
  - Duration for more than three months, daily with more than two hours a day.
  - The most frequently affected area is the tongue, mainly the tip and the anterior two-thirds. The tongue is the only area affected in approximately half of the patients, followed by the hard palate, anterior gingiva, lower lip, and pharynx.
  - In typical cases, symptoms are bilateral and symmetrical.
- Xerostomia or dysgeusia (change in taste) may be associated.
- May change in intensity during the day (less intense in the morning).
- The pain is usually spontaneous but can be triggered by certain foods (particularly spicy or acidic foods) and anxiety.

1.1 Diagnosis

- Recurrent oral pain was recorded daily for more than 2 h/day for at least 3 months.
- The pain is characterized as superficial burning.
- The pain is poorly localized and does not follow the distribution of a peripheral nerve.
- A dental cause was excluded.
- Any alteration in the systemic or local health of the patient was ruled out.
- If the burning mouth has a known cause, the diagnosis does not correspond to a true BMS.

1.2 Diagnostic Tests

They are (Fig. 1):

- Prosthetic evaluation:
  - Contact allergy.
  - Local trauma.
  - Parafunctional habits.
- Local infection:
  - Subclinical candidiasis.
- Sialometry/biochemistry:
  - Salivary flow and quality.
- Nutritional assessment:
  - Vitamins B6, B9, and B12.
  - Vitamin C.
  - Vitamin E.

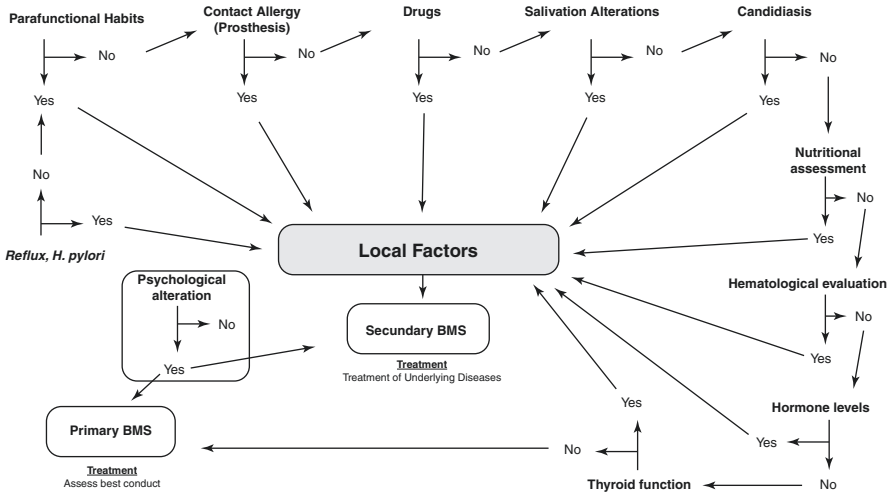

Fig. 1 Steps for the diagnosis of BMS

  - Ferritin.
  - Iron.
  - Zinc.
- Hematological evaluation:
  - Complete blood count (CBC).
  - Blood sugar.
- Gastrointestinal evaluation:
  - Gastroesophageal reflux.
- Assessment of hormone levels:
  - Dehydroepiandrosterone (DHEA).
  - Follicle-stimulating hormone (FSH).
  - Estrogen.
  - Progesterone.
- Evaluation of thyroid function:
  - T3 clear.
  - T4 clear.
  - HRT.
- Assessment of psychological conditions and patient stress:
  - Adrenocorticotropic (ACTH).
  - Cortisol.
  - The patient reports a state of unhappiness.
  - Psychiatric or psychological therapy.
- For all normal systemic parameters:
  - Anesthetize (block) the lingual nerve.
  - If the patient shows relief, a mainly peripheral BMS is suggested; if it shows no relief or worsens, it is possibly a central subtype.

2 Treatment

- Therapies aim to relieve symptoms and improve quality of life. Evidence of the effectiveness of any treatment is still weak.
- When the burning mouth has a known cause, the discomfort is often treated and cured according to its specific etiology after careful diagnosis.
- The central type does not respond to local treatments and is frequently associated with psychiatric comorbidity (depression or anxiety), whereas the peripheral type responds to peripheral lidocaine lingual nerve blocks and topical clonazepam.
- The most effective combination treatment for the peripheral BMS type is topical clonazepam 3×1 mg/day (chew tablet at the site of burning for 3 min and then spit out) and cognitive–behavioral therapy.
- If treatment does not relieve discomfort and a peripheral BMS type is suspected, topical capsaicin (0.025% oral, two times daily for 30 days) can be used in a xylocaine gel (2%), plus saliva substitute or inducer.
- Treatment with topical capsaicin may intensify the burning sensation for up to 20 min after application in one-third of patients.
- If treatment does not relieve discomfort and a central BMS type is suspected, the need for systemic clonazepam (0.5 mg/day), amitriptyline (10–25 mg/day), or gabapentin (300–900 mg/day) should be evaluated.
- Photobiomodulation has also been shown to be effective in reducing pain both alone and in association with other therapies: infrared light, with power between 300 mW and 1 W, beam area of 0.28 cm^2 in continuous frequency, and applied for approximately 10 s/point in ten sessions (twice a week for 5 weeks) can be satisfactory in reducing the burning sensation.

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Management of Oral Lesions in COVID-19 Patients

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In December 2019, an outbreak characterized by fever, dry cough, fatigue, and gastrointestinal symptoms began in China and quickly spread to all continents, with millions of cases reported worldwide and mortality rates ranging from 3% to 12%. The pathogen has been identified as a novel beta-coronavirus, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is spread primarily through droplets of saliva or nasal secretion when an infected person coughs or sneezes. Most people infected with SARS-CoV-2 develop the disease called coronavirus disease 2019 (COVID-19) and recover without the need for specialized treatment. Elderly people and those with chronic diseases, such as those with cardiovascular disorders, diabetes, respiratory diseases, and cancer, are more likely to develop the severe form of the disease.

Research shows that coronavirus invades human cells through the angiotensin-converting enzyme 2 (ACE2) receptor, and some organs are more vulnerable to infection, such as the lung. Therefore, cells with higher

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expression of the ACE2 receptor can become host cells for the virus and cause an inflammatory response in related organs and tissues, such as the mucosa of the tongue and salivary glands. In the oral medicine context, the saliva, may be a means of virus transmission even in asymptomatic individuals. In COVID-19 patients, the infection may lead to taste disturbances, xerostomia, halitosis, parotitis, and oral lesions. Usually, the lesions are symptomatic and have no sex predilection. Patients with older age and greater severity of the disease present disseminated and severe lesions. Poor oral hygiene, opportunistic infections, stress, immunosuppression, vasculitis, and secondary hyperinflammatory response are predisposing factors.

1 Salivary and Taste Disorders

Taste disturbance and xerostomia are among the most prevalent oral symptoms in patients with COVID-19. These changes are usually associated with the tropism of the virus by the peripheral and central nervous system, the oral epithelium (which includes the taste buds), and the structures that make up the salivary gland. Dysgeusia (associated or not with anosmia) seems to occur early in the course of SARS-CoV-2 infection and therefore should be considered a disease alert by dental surgeons who work directly with patients in the dental routine. Taste disorders were associated with COVID-19, with the association between taste disorders being more commonly the mild or moderate form of COVID-19 and female patients.

Data from 1017 patients with COVID-19 showed a prevalence of xerostomia of 43%. Xerostomia seemed to appear before the onset of other general symptoms of COVID-19, and the mean duration was poorly reported, being persistent in only a few cases. The discussion about xerostomia in these patients raises the question that its origin may be the result of cellular injury of the glandular parenchyma by the virus and a reflection of the use of medications, nasal congestion, mouth breathing, nutritional deficiency, diabetes, anxiety, and distress related to social isolation and/or prolonged hospitalization. In any case, the effects of SARS-CoV-2 on the salivary glands can result in decreased salivary flow, leading to distortion of the sense of taste, xerostomia, and even if less common halitosis. In addition, the involvement of the parotid gland by the viral infection may lead to parotitis, which usually occurs during the clinical course of the infection.

2 Oral Mucosal Lesions

By early 2021, 36 case reports or case series describing oral mucosal lesions in at least 308 hospitalized and nonhospitalized patients were published. Also, five cross-sectional studies show data from 2491 patients with COVID-19, of whom 512 (20.5%) had manifestations in the oral cavity. Although oral lesions may appear

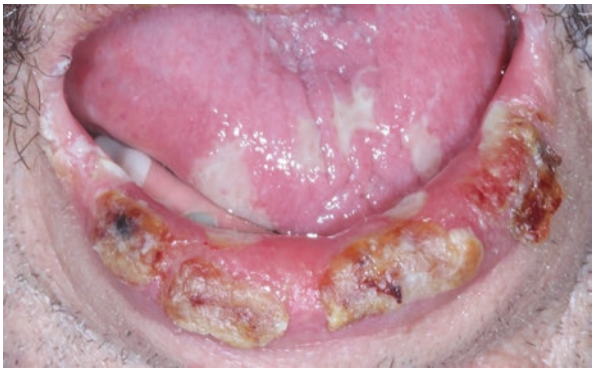

Fig. 1 On vermilion of the lip, note clustering of ulcers covered by crust. On dorsum of the tongue, numerous ulcerative lesions with superficial necrosis can be observed

earlier, their appearance is usually after the onset of COVID-19 symptoms, and the healing process occurs parallel to the resolution of the infection. Usually, the tongue is the most common anatomical location for the appearance of these lesions, but the palate, lips, and labial commissure may also be affected. Nonspecific aphthous ulcers are the most frequently reported oral lesions. The ulcers (commonly in an aphthous pattern) may be single or multiple, hemorrhagic, or not. They are usually painful, vary in diameter, and have a marked erythematous halo. They may be covered by crusts or by a fibrinopurulent membrane (Fig. 1).

Focal and shallow ulcerative areas of necrosis and erythema/petechiae areas (especially on the anterior hard palate) have been reported. Herpetic lesions, fungal infections (such as candidiasis), and a lesion popularly known as "COVID tongue," characterized by a glossitis/desquamation/geographic tongue, have also been reported.

Due to the recent knowledge of persistent oral symptoms and long-term complications known as the post-acute syndrome of COVID-19, awareness of oral tissue compromise in patients who had COVID-19 should be increased. The knowledge of the triad of xerostomia, taste dysfunction, and oral mucosal lesions as common signs and symptoms in patients with COVID-19 are important for clinical practice. In addition, the dental surgeon should be aware of persistent symptoms and long-term complications of patients with COVID-19.

3 Clinical Management of Patients with COVID-19 Presenting with Oral Lesions

- When identified, these lesions should be treated in an attempt to control pain and offer a better quality of life for the patients.
- The treatment must be individualized and the necessary conducts for the control of oral lesions have already been explored in this book.

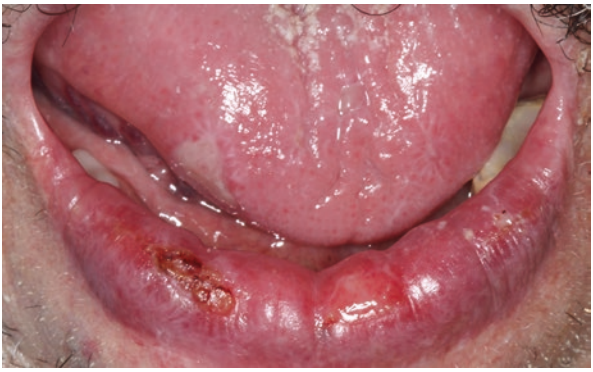

Fig. 2 Clinical appearance of the patient in Fig. 1 after PBMT

- Usually, treatment of the geographic tongue is not necessary. To alleviate the pain and burning sensation caused by lingual papillation, patients should avoid hot, spicy, and/or spicy foods and/or drinks.
- As an adjunctive measure to control pain associated with oral ulcers, the use of daily photobiomodulation therapy (PBMT) for ten consecutive days is recommended. The PBMT device should be positioned perpendicular to the surface of the oral ulcers. Symptom relief is expected after 2 days of PBMT and complete resolution of lesions after 10 days (Fig. 2).

Parameters for PMBT in COVID-19-positive patients with oral ulcers	
Time	10 s per location
Wavelength	660 nm
Average power	40 mW
Beam area	0.04 cm^2
Irradiance	1 W/cm^2
Energy	0.4 J
Fluency	10 J/cm^2

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Correction to: Clinical Decision-Making in Oral Medicine

Alan Roger Santos-Silva, Márcio Ajudarte Lopes, João Figueira Scarini, Pablo Agustin Vargas, and Oslei Paes de Almeida

Chapters 19 and 20 in : A. R. Santos-Silva et al. (eds.), *Clinical Decision-Making in Oral Medicine*, https://doi.org/10.1007/978-3-031-14945-0_19 https://doi.org/10.1007/978-3-031-14945-0_20

The original version of Chapters 19 and 20 was inadvertently published with the errors listed below and the same have been corrected in the revised publication.

On page 136, Chapter 19 "Actinic Cheilitis", line 11 "It also **prevents** the loss of sharpness of the lip (semi-mucosa) and skin border" has been corrected to "It also **leads** to the loss of sharpness of the lip (semi-mucosa) and skin border".

On page 143, Chapter 20, "**Nonsmoking and nonethnic women**" has been replaced with "**Non-smoking and non-drinking females**".

On page 144, the term **scalp** has been corrected to "**scapel**".

The updated versions of the chapters can be found at
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