Pathology of the Extracranial Carotid and Vertebral Arteries

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Abbreviations

AIT	Adaptive intimal thickening
ACA	Anterior Cerebral Artery
BA	Basilar artery
CCA	Common carotid artery
CMD	Cystic medial degeneration
COPD	Chronic obstructive pulmonary disease
ECA	External carotid artery
ECCA	Extracranial carotid artery
ECVA	Extracranial vertebral artery
EEL	External elastic lamina
FMD	Fibromuscular dysplasia
FS	Fatty streak
GCA	Giant cell arteritis
ICA	Internal carotid artery
IEL	Internal elastic lamina
LDL	Low-density lipoprotein
PIT	Pathologic intimal thickening
SDHL	Succinate dehydrogenase
TA	Takayasu's arteritis
TIA	Transient ischemic attack
VA	Vertebral artery
VCAM-1	Vascular cell adhesion molecule-1

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Anatomy and Histology of the Extracranial Carotid and Vertebral Arteries

Understanding the pathogenesis and symptomatology behind diseases involving the extracranial carotid arteries (ECCAs) and extracranial vertebral arteries (ECVAs) requires a basic understanding of the anatomy and histology of these vessels.

Although variations in anatomy exist, the right common carotid artery (CCA) typically originates from the brachiocephalic trunk, and the left CCA originates from the aortic arch [1]. The CCAs divide into two branches (the internal carotid artery (ICA) and external carotid artery (ECA)) at the superior border of the thyroid cartilage. The paired ICAs provide blood to the anterior portion of the brain (anterior cerebral circulation) and meninges. The proximal portion of the ICA has a slight dilation termed the carotid sinus where baroreceptors are present in the vessel wall. These baroreceptors are stretch receptors which are important for blood pressure monitoring. The cervical segment of the ICA is freely mobile and extends through the neck to enter the skull through the carotid canals in the petrous portion of the temporal bone at the skull base. The ICAs give off no branches in the neck. The terminal intracranial branches of the ICAs are the anterior and middle cerebral arteries. The ECAs provide blood supply to the neck, face, and base of the skull and course under the submandibular gland and into the

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parotid gland. They give off six branches including the superior thyroid artery, lingual artery, facial artery, ascending pharyngeal artery, occipital artery, and posterior auricular artery and terminate in two branches (the maxillary artery and superficial temporal artery).

Although variations in anatomy exist, the vertebral arteries (VAs) typically branch from the subclavian vessels and can be divided into four distinct segments [1]:

- Cervical (V1) segment: Portion of the VA between its origin from the subclavian artery and its entrance into the transverse foramina of the C6 vertebra.
- Vertebral (V2) segment: Portion of the VA that passes vertically through the bony canal of the transverse foramina from the C6 to the C2 vertebra.
- Suboccipital (V3) segment: Portion of the VA that exits the transverse foramina of C2 and ends as the vessel passes through the foramen magnum/posterior atlanto-occipital ligament.
- Cranial (V4) segment: Intracranial portion of the VA. The V4 segments fuse to form the basilar artery (BA) at the inferior border of the pons. The paired vertebral arteries (VAs) via the basilar artery (BA) provide blood to the posterior brain and brainstem (posterior cerebral circulation) and meninges.

Occlusive lesions of the ECVAs only rarely cause a significant decrease in blood flow to the posterior cerebral circulation [2]. As the VAs are paired vessels that join to form a single BA, if one is compromised, the other can typically compensate. Also, even when there is bilateral occlusive disease of the ECVAs, patients typically do not develop posterior circulation stroke. As opposed to the ICAs, the ECVAs give rise to numerous branches in the neck which provide conduits for collateral circulation. For example, the costocervical and thyrocervical branches of the Subclavian Artery can develop collateral circulation between the external carotid and subclavian arteries.

The most common variations of VA anatomy include origin of the left VA from the aortic arch (~5% of people) and entrance of the V1 segment into a vertebral foramen more superior than C6 level. The VAs are often of unequal caliber (only ~25% of people have similar caliber vessels), and the left is commonly larger than the right [3]. One of the two is atretic (<2 mm in diameter) in approximately 15% of the population. The vertebral arteries can also be duplicated or fenestrated.

The circle of Willis connects the anterior and posterior cerebral circulation and is formed by the posterior cerebral arteries (which are the terminal branches of the BA), the posterior communicating arteries (which connect the posterior cerebral arteries to the ICAs), the ICAs, the anterior cerebral arteries (ACAs), and the anterior communicating arteries (which connect the two ACAs). Only ~20% of the population has a complete circle of Willis, with most of the variation attributed to vascular hypoplasias or aplasias [4]. It should be noted that the carotid arteries provide ~80% of the cerebral blood flow while the vertebral arteries supply ~20% [5]. Given the presence of collateral circulation through the circle of Willis, chronic occlusive disease of the extracranial cerebral vasculature is better tolerated than in other vascular beds such as the coronary circulation. Development of symptomatic cerebrovascular ischemia typically requires significant occlusive pathology often involving multiple vessels in both the carotid and vertebrobasilar pathways to overcome this collateral compensation [2, 6].

Arteries in general are composed of three layers (or tunics) histologically [7]:

- Tunica intima: Innermost layer composed of a monolayer of endothelial cells with underlying basement membrane and loose subendothelial connective tissue containing fibroblasts, smooth muscle cells, collagen and elastic fibers, and proteoglycan ground substance.
- Tunica media: Middle layer composed predominantly of varying numbers of smooth muscle and elastic fibers and some collagen fibers.
- Tunica adventitia: Outermost layer composed mainly of connective tissue, nerves, and the vasa vasorum which supplies blood to the vessel wall.

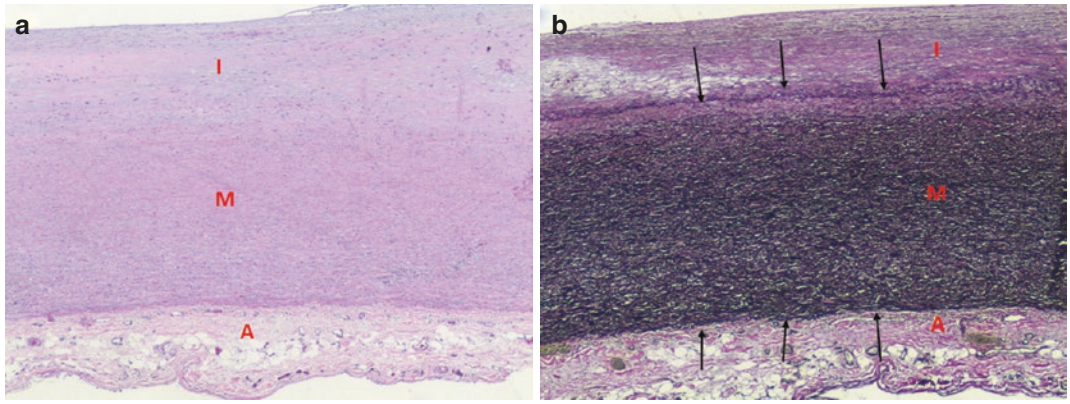

Fig. 3.1 Elastic artery. (**a**) Longitudinal section of the aorta which is an elastic vessel. The vessel intima (I) is the innermost layer and is mildly thickened in this example secondary to atherosclerotic change. The vessel media (M) is thick and composed of numerous concentric elastic fibers. The vessel adventitia (A) is the outermost layer (hematoxylin and eosin, 40×). (**b**) The thick elastic layer (arrows) in the media is best highlighted with an elastic stain (Verhoeff-van Gieson elastic stain, 40×). The vessel intima (I), media (M) and adventitia (A) are also labeled

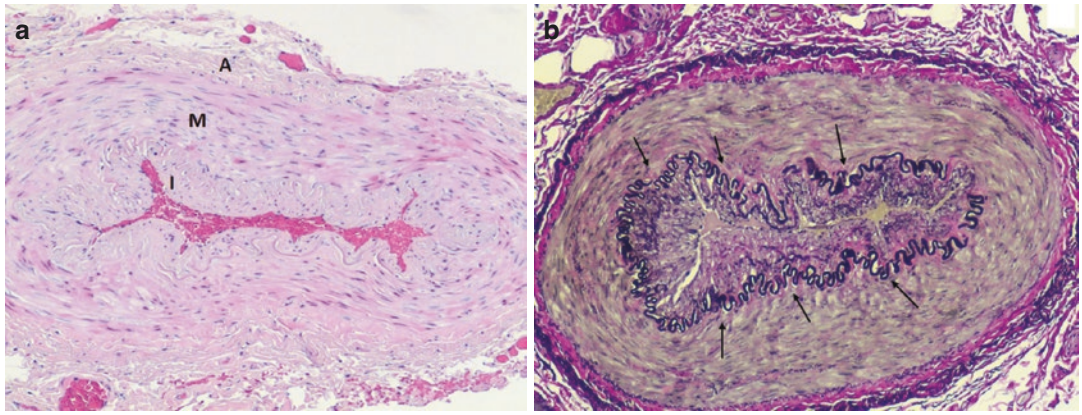

Fig. 3.2 Muscular artery. (**a**) Cross section of the temporal artery which is a muscular vessel. The vessel intima (I) is the innermost layer and is lined by endothelium. The vessel media (M) is composed predominantly of concentric smooth muscle fibers, and the vessel adventitia (A) is the outermost layer which blends into the surrounding connective tissue (hematoxylin and eosin, 40×). (**b**) The internal elastic lamina (arrows) is a layer of concentric elastic fibers which separates the vessel intima from the vessel media and is best highlighted by an elastic stain (Verhoeff-van Gieson elastic stain, 40×)

The internal elastic lamina (IEL) is a thick concentric layer of interwoven elastic fibers, which separates the tunica intima from the tunica media [8]. The external elastic lamina (EEL) is a thinner concentric layer of interwoven elastic fibers which separates the tunica media from the tunica adventitia. The IEL is not well defined universally and may be absent in areas of vessel bifurcation or branching. Fragmentation, duplication, and calcification of the IEL are common changes that occur with aging [9].

Arteries can be subdivided into two major histologic subtypes, elastic (also known as conducting) and muscular (also known as distributing) depending on vessel size and predominant fiber type (elastic or muscular) in the vessel media. Elastic arteries are larger vessels that have a broad tunica media with a higher percentage of concentrically organized elastic fibers (Fig. 3.1). The tunica intima of elastic vessels is often thicker than that of muscular vessels. Muscular arteries are typically medium or small sized ves-

sels which have a higher percentage of concentrically oriented smooth muscle cells within the vessel media (Fig. 3.2). The IEL and EEL are better defined in muscular than they are in elastic vessels. The aorta and its major branches including the CCAs and subclavian arteries with vertebral artery branches are considered elastic arteries [9]. The majority of the remaining grossly identifiable and named arteries are considered muscular vessels. The CAs are considered muscular vessels by some [10] or of "mixed type" by others [9] as they are in a transitional regions between elastic and muscular composition.

Atherosclerotic Disease of the Extracranial Carotid and Vertebral Arteries

The most common pathologic disorder to affect the ECCAs and ECVAs is atherosclerosis [11]. Atherosclerosis is characterized by pathologic thickening of arteries secondary to fibrofatty plaque formation. Atherosclerosis is derived from the Greek "athero" meaning gruel (corresponding to the necrotic core of the plaque) and "sclerosis" meaning hardening (corresponding to the plaque's fibrous cap) [12]. The most detrimental complications of extracranial large vessel atherosclerotic disease include TIA and stroke. Approximately 87% of all strokes are of ischemic etiology, and ECCA and ECVA atherosclerosis accounts for up to 20% of cases of ischemic stroke [13, 14]. Risk factors for ischemic stroke secondary to atherosclerosis of these vessels include advanced age, male gender, race (blacks and Hispanics have higher risk than whites), hypertension, hypercholesterolemia, diabetes mellitus, tobacco smoking, physical inactivity, obesity, prior TIA or stroke, family history of TIA or stroke, or history of significant coronary atherosclerotic disease, among others [13].

The ECCAs are more commonly affected by significant atherosclerotic disease than the ECVAs [2]. In fact, the carotid artery is the fourth most common vessel impacted by atherosclerosis behind the abdominal aorta, coronary, and popliteal artery [15]. In a study of patients aged 60–79 years, 10.5% of men and 5.5% of women had stenosis of their ICA by carotid duplex ultrasound [16]. Around 20% of ischemic strokes involve the posterior circulation, and around 20% of posterior circulation stroke can be attributed to ECVA atherosclerosis [3, 17, 18]. The most common location of extracranial large vessel atherosclerotic disease is at the carotid bifurcation (often with involvement of the proximal portion of the ICA), and the second most common location is in the V1 segment of the vertebral artery (at its origin from the subclavian artery) [2, 18]. It is well known that atherosclerosis is more common at arterial bifurcations and branch points. Studies have shown that disturbed blood flow/blood stagnation and low or oscillatory shear stress on the vessel wall in these regions alters endothelial function by enhancing inflammatory cell activation [19] and release of nitric oxide [20] contributing to development of atherosclerosis.

Atherosclerosis has been most extensively studied in the coronary circulation, which provides insight into other disease loci including the ECCA and ECVA. Elucidation of the pathogenesis of atherosclerosis has relied on gross and microscopic examination of pathologic specimens and clinical and experimental studies (including study of animal models), and multiple theories have developed over time. It is known to be a complex multifactorial process and a chronic inflammatory disease with pathogenesis initiating at formation of a fibrous lipid-rich plaque (known as a fibroatheroma or fibroinflammatory lipid plaque). The components of the plaque include fibrous tissue, smooth muscle cells, lipid, and inflammatory cells in varying proportions. The process of atherosclerosis has traditionally been thought to follow an orderly linear progression [12, 21]; however more recently it has been considered a more variable or dynamic process [22].

Histologic studies have identified precursor lesions which may predispose a region of an artery to develop an atherosclerotic plaque. These precursor lesions include the fatty streak (FS), known by some as the intimal xanthoma and adaptive intimal thickening (AIT). Both develop in childhood and are clinically quiescent as they do not cause significant vessel obstruction. The FS is grossly identifiable as a flat or slightly raised yellow-colored intimal spot, patch, or

streak [21]. The FS is present secondary to foam cell (lipid-laden macrophage) accumulation in the subendothelial space. Accumulation of smooth muscle cells and extracellular matrix in the intima leads to AIT [22]. AIT can involve a vessel in a circumferential or eccentric manner. The eccentric form is thought to predispose to atherosclerotic plaque formation [21]. It is common at vessel branch points and has been described in various vessels including the coronary and CAs [8].

The most widely accepted mechanism of atherosclerotic pathogenesis begins when proatherosclerotic conditions (including disturbed blood flow and hyperlipidemia) lead to endothelial dysfunction and stimulate endothelial cells to overexpress adhesion molecules including vascular cell adhesion molecule-1 (VCAM-1) on their surfaces. VCAM-1 participates in the recruitment of monocytes and other inflammatory cells (e.g., T lymphocytes) to the region [23, 24]. LDL particles become entrapped in the intima by proteoglycans and are oxidized by oxygen free radicals that are produced by macrophages and other cells [25]. Monocytes enter the intima via diapedesis having been induced into the subendothelial space by chemoattractants, mature into macrophages and engulf oxidized low-density lipoprotein (LDL) particles via scavenger receptors. Oxidized LDL is degraded in lysosomes in the macrophage, and excess free cholesterol is transferred to the endoplasmic reticulum where it is esterified into cholesterol esters and packaged into cytoplasmic lipid droplets creating the foam cell [26]. Foam cells produce cytokines and reactive oxygen species which further oxidize LDL and recruit modified smooth muscle cells (myointimal cells) and T cells into the intima by chemotaxis. Eventually, the pathways to metabolize excess lipoproteins are overwhelmed, and toxic excess free cholesterol builds up leading to cell death. Myointimal cells proliferate and undergo apoptosis, leading to further inflammatory signaling. As foam cells and myointimal cells undergo apoptosis, necrotic debris and crystalline cholesterol accumulate in small pools (preatheroma) which coalesce to form larger lipid cores (atheroma) typically leading to plaque expansion from the fourth decade of life. Concurrently, myointimal cells secrete extracellular matrix including proteoglycans which further entrap LDL particles and secrete collagen at the endothelial barrier leading to formation of a fibrous cap (fibroatheroma). Decreased diffusion of oxygen and nutrients from the vessel lumen through the thickened fibrous cap likely contributes to necrosis in the core of the fibroatheroma. Fibroatheroma can involve a vessel in a focal, patchy, or diffuse manner and can be either eccentric or concentric (eccentric growth is more common at vessel branch points). The fibrous cap in a fibroatheroma can be thick or thin [22]. Another poorly defined pathway of plaque formation occurs in areas of pathologic intimal thickening (PIT) and consists of abnormal accumulation of smooth muscle cells and proteoglycan-rich matrix in the vessel intima with very little inflammation or lipid content [22].

Atherosclerosis can lead to end organ ischemia via chronic progressive plaque growth which can lead to narrowing of the vessel lumen over time or a wide range of plaque complications [27]. In the North American Symptomatic Carotid Endarterectomy Trial, there was a correlation between the degree of carotid artery stenosis and risk of stroke in symptomatic patients. Risk of stroke in patients with 70–79% stenosis was 19%, 80–89% stenosis was 28%, 90–99% stenosis was 28%, and 90–99% stenosis was 33% after 18 months of medical therapy without a revascularization procedure [28]. Plaque complications include intraplaque hemorrhage, plaque rupture, plaque erosion, mural thrombosis with or without embolization, plaque calcification, and aneurysm formation. Intraplaque hemorrhage occurs when rupture or leak of thin-walled neovasculature (arising from the vasa vasorum) causes blood pooling/thrombosis within the plaque, plaque expansion, and further luminal obstruction. Rupture of the fibrous cap of a plaque uncovers thrombogenic plaque components which form a nidus for intraluminal thrombosis (which can be occlusive or subocclusive). Intuitively, thin plaque fibroatheroma are more prone to rupture than thick plaque fibroatheroma. The surface of the plaque (including endothelial lining) can erode which can also form a nidus for luminal thrombosis. Plaques that form secondary

to PIT are prone to erosion which can form a nidus for intraluminal thrombosis. Repeated plaque rupture or erosion with healing can lead to further luminal narrowing. Portions of luminal thrombus or atherosclerotic debris can break off and travel downstream leading to artery-to-artery thrombo- or atheroembolization. Calcification of atherosclerotic plaques is common, and calcified plaques, also known as fibrocalcific plaques, typically have smaller lipid cores. It is believed that plaque calcification occurs in the process of plaque healing after intraplaque hemorrhage, plaque rupture, or erosion. Large calcium nodules (calcified nodules) can form in some cases which can predispose to cap rupture or erosion and thrombosis [22]. Some plaques undergo osseous metaplasia. Occasionally, atherosclerotic plaque formation can weaken the vessel wall and lead to vascular dilatation or aneurysm formation. This process is more common in larger elastic arteries, including the aorta, than smaller muscular arteries (see section on aneurysm). Morphologic features that contribute to carotid plaque instability include a thin fibrous cap, decreased number of smooth muscle cells, high lipid content, increased numbers of macrophages, increased vascularity, surface irregularity, and presence of plaque erosion [29–32]. Vulnerable carotid plaques have a mean fibrous cap thickness (72 ± 24 μm) thicker than that of vulnerable coronary artery plaques (which have a mean cap thickness of 65 μm or less) [33].

Although the pathophysiology behind formation of an atherosclerotic plaque is similar in the coronary and extracranial cerebral circulation, the mechanism by which acute plaque change leads to ischemic symptomatology typically differs between them [33]. It is well known that atherosclerotic plaque rupture with occlusive thrombosis is the most common cause of acute myocardial infarction. Thrombotic occlusion usually only occurs in the background of severe luminal narrowing in the extracranial cerebral vasculature given the normally high blood flow rate in these vessels [34]. Also given the high flow rate, if acute thrombosis of the ECCA does occur, it often propagates distally [35]. The most common cause of TIA or stroke in patients with atherosclerosis of the extracranial cerebral vasculature is artery-to-artery embolization. Embolus material (consisting of either atherosclerotic or thrombotic debris) can travel distally to occlude smaller intracranial arteries or arterial branches. Patients with embolization from the ECCA present most commonly with middle cerebral artery territory ischemic symptoms [2, 36]. Embolization from the ECVA typically occludes the V2 segment of the vertebral artery and the intracranial portion of the vertebral or basilar artery and/or its branches and leads to stroke involving the cerebellum, temporal, or occipital lobes.

Endarterectomy is an open surgical procedure which consists of removal of an intimal plaque. As carotid endarterectomy is the most frequently performed surgical intervention to prevent stroke, carotid artery plaques are commonly examined pathologically [33]. It should be noted that not all institutions routinely process endarterectomy specimens histologically. Some may only provide a gross examination of the specimens. Vertebral artery plaques are only rarely examined pathologically as vertebral artery endarterectomy is a rare procedure and specimens are usually not obtained from bypass procedures [3]. Grossly, the carotid endarterectomy specimen consists of a variably fragmented tubular segment of intimal plaque. If performed at the area of carotid bifurcation, the specimen will be bifurcated. A longitudinal surgical excision is typically identified (Fig. 3.3a). When cut in cross section, a noncomplicated intimal plaque appears white to yellow in color (depending on the proportion of fibrous tissue and lipid) and typically has a smooth surface. Plaques with abundant extracellular lipid will have bright yellow cores. Microscopically the intimal plaque has a fibrous cap of varying thickness. The fibrous cap consists predominantly of fibrous tissue with numerous collagen and some elastic fibers. Extracellular matrix, myointimal cells, and inflammatory cells including macrophages, foam cells, and lymphocytes can also be present. The necrotic core is highly variable in size and consists of extracellular lipid, cholesterol clefts, necrotic debris, and various numbers of inflammatory cells including foam cells and T cells. Cholesterol clefts are needle-shaped spaces formed when cholesterol crystals

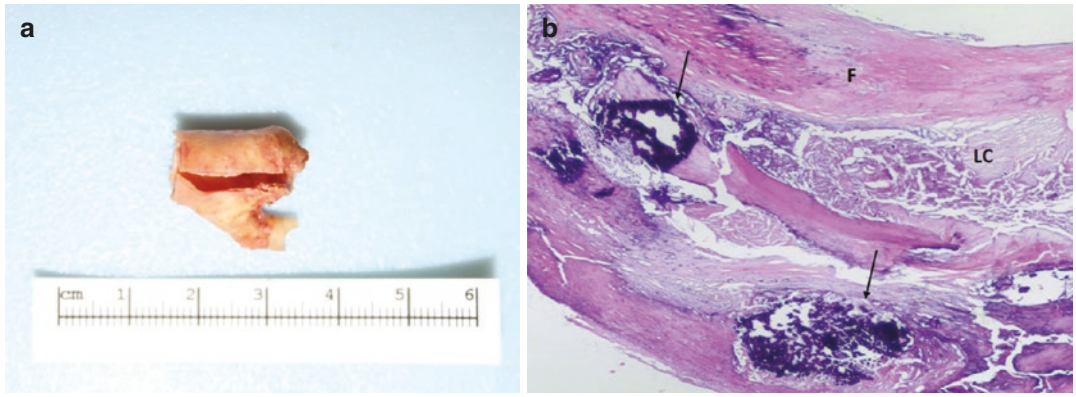

Fig. 3.3 Carotid endarterectomy specimen. (**a**) Gross photograph of a bifurcated intimal atherosclerotic plaque which is white to focally yellow in color and has a longitudinal surgical incision. (**b**) Histologic cross section of the endarterectomy specimen reveals an intimal fibroatheroma with a fibrous cap (F) and lipid core (LC) containing cholesterol clefts (cleft-like spaces). Calcification is also seen (arrows) which is relatively common in atherosclerotic plaques of the carotid artery (hematoxylin and eosin, 20×)

are dissolved by the alcohol used in specimen processing/staining (Fig. 3.3b).

Some endarterectomy specimens have plaque complications that can be identified either grossly or microscopically. Calcification is a common finding in an intimal plaque and can be of variable degree. Plaques that are highly calcified must be decalcified before sectioning. Some plaques are ossified. Fibrous cap rupture and erosion with or without luminal thrombus can be seen in some cases. Plaques with intraplaque hemorrhage will appear red-yellow and variegated in color grossly. Hemosiderin-laden macrophages identified within a plaque histologically are evidence of previous intraplaque hemorrhage or healed plaque rupture. Plaque complications that are more common in the extracranial cerebral circulation than the coronary circulation include surface erosion, intraplaque hemorrhage, and calcified nodules [34].

Dissection of the Extracranial Carotid and Vertebral Arteries

Isolated dissection of the ECCA or ECVA is not uncommon and can occur spontaneously, secondary to trauma, or iatrogenically. For example, incidental canalization of the carotid artery during central line placement has been described to cause dissection [37]. These vessels can also be secondarily involved via extension from a thoracic aortic dissection. This section will focus on spontaneous and traumatic dissection.

Spontaneous dissection is the second most common pathology to affect the ECCA or ECVA behind atherosclerosis [38] and accounts for approximately 2% of ischemic strokes overall [39] but 10–25% of ischemic strokes in young and middle-aged patients [40]. Spontaneous dissection of the ECCA occurs more often than the ECVA, and the ICA is most commonly involved. The incidence of spontaneous carotid artery dissection is approximately 2.5–3 per 100,000, and vertebral artery dissection is approximately 1–1.5 per 100,000 [40]. Spontaneous dissection of these vessels can occur at all ages, but there is a distinct peak in the fifth decade [39, 40]. In up to 16% of cases, multiple vessels can be involved [41]. Common traumatic causes of dissection include motor vehicle accidents, assaults, falls, hangings, or sports injuries. Traumatic dissection of the ECCA or ECVA occurs in 1–2% of patients admitted to the hospital with blunt trauma, and 10–20% of these patients develop stroke [42].

The ICA and ECVA are especially sensitive to dissection, even more so than their intracranial portions or other arteries of similar size. This can be attributed to their unique mobility during neck movement and their surrounding

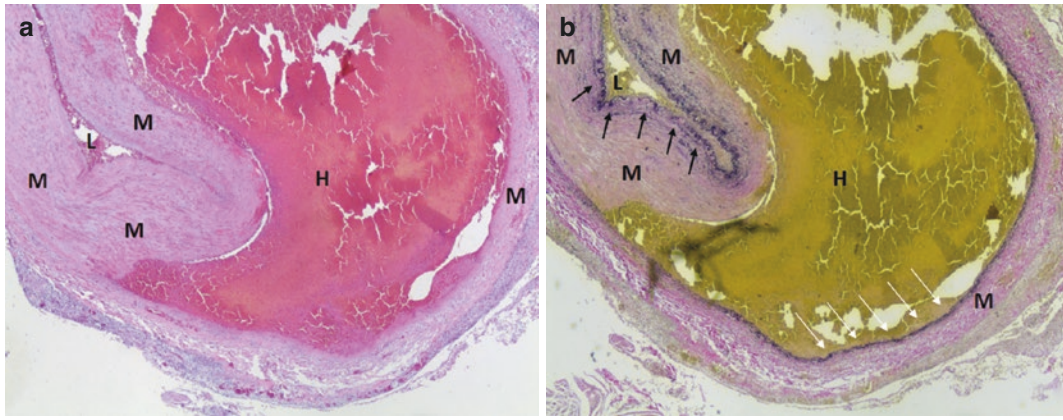

Fig. 3.4 Spontaneous internal carotid artery dissection in a middle-aged man who presented with headache and neck pain. (**a**) Histologic cross section of the internal carotid artery in area of dissection revealing hemorrhage (H) in the outer portion of the vessel media (M). The compressed lumen (L) of the vessel can also be identified (hematoxylin and eosin, 20×). (**b**) An elastic stained cross section of the internal carotid artery in area of dissection highlights the internal (black arrows) and external elastic lamina (white arrows). The vessel lumen (L) and area of dissection/intramural hemorrhage (H) in the outer portion of the vascular media (M) are also labeled (Verhoeff-van Gieson elastic stain, 20×)

skeletal anatomy. The entire extracranial ICA and V1 and V3 segments of the ECVA are mobile and prone to stretch injury. The ICA and ECVA are also prone to injury by contact with adjacent bony structures including the cervical vertebrae, styloid process of the temporal bone, and the angle of the mandible [40]. Fracture of a cervical vertebra can lead to ECVA dissection in the V2 segment given the intimate relationship of the vessel with the cervical vertebra including the transverse foramen in this region [42].

Classic clinical symptoms of carotid artery dissection include unilateral pain in the neck, unilateral headache, partial Horner's syndrome (including meiosis and ptosis), cranial nerve palsies and later-onset anterior cerebrovascular ischemic symptoms including TIA or stroke, or, rarely, retinal ischemic symptoms including transient monocular blindness [40]. Classic clinical symptoms of vertebral artery dissection include pain at the back of the neck or occipital headache followed by posterior cerebrovascular ischemic symptoms including TIA or stroke. Clinical diagnosis is typically difficult given the diverse and nonspecific symptomatology and is supported by imaging studies.

As dissection of the ECCA or ECVA is typically treated medically or via minimally invasive surgical techniques, pathologic examination can often only be performed at postmortem examination. Historically, knowledge of the histopathologic features of dissection has helped to elucidate the mechanism of the disorder. Dissection occurs when there is vessel injury leading to intramural hemorrhage into a false lumen between the vessel wall layers (Fig. 3.4). In some cases, blood can dissect back from this false lumen into the true vessel lumen leading to a double channel of blood flow through the vessel (called a double lumen vessel). Dissection typically results from 1 of 2 mechanisms: (1) an intimal tear or (2) rupture of the vasa vasorum [41]. Rarely, the area of intimal disruption that initiated the dissection can be identified histologically. Hemorrhage inward between the vessel intima and media can lead to stenosis or even complete occlusion of the true vascular lumen, while hemorrhage outward between the vessel media and adventitia with associated disruption of the elastic lamina can result in aneurysmal vascular dilatation [40]. Dissection can sometimes extend intracranially which is more common in cases of ECVA than ICA dissection [40]. Dissection which extends intracranially (especially cases with associated

aneurysmal vascular dilatation) is more prone to rupture and can result in subarachnoid hemorrhage [38]. The wall of the intracranial portion of the ICA and VA is weaker than the extracranial portion as there is loss of elastic fibers including the external elastic lamina intracranially, and the media and adventitia are thinner [43, 44].

Spontaneous cervical artery dissection is likely a multifactorial disease resulting from a combination of an environmental trigger (such as minor precipitating trauma) superimposed on an underlying vascular abnormality (such as weakness in the vessel wall secondary to an underlying connective tissue disorder) [40, 41, 45, 46]. Patients with spontaneous dissection typically have a history of a minor precipitating event such as a coughing fit, rapid neck rotation, or hyperextension. Other environmental triggers including infection has been suggested [41, 47–49]. Some patients with spontaneous dissection likely have a clinically unapparent undiscovered connective tissue disorder that may be genetic in etiology. A study of dermal connective tissue in patients with spontaneous cervical artery dissection found that 36 of 65 (55%) had ultrastructural connective tissue abnormalities in collagen and elastin, and many of these patients had no other clinical manifestations of connective tissue disease [46]. Up to 20% of patients have a clinically apparent yet unnamed connective tissue disorder. Up to 5% of patients have a known connective tissue disorder (mainly Ehlers-Danlos syndrome type), and an additional 5% of patients have a family history of spontaneous artery dissection in the absence of known connective tissue disease [40]. Histologic findings of cystic medial degeneration (CMD) also called cystic medial necrosis is common in cases of spontaneous carotid artery dissection. CMD is a nonspecific histologic finding that can be seen in dissections or aneurysms from many causes including atherosclerotic disease; however finding significant CMD in a dissection specimen in a younger patient can suggest the possibility of an underlying connective tissue disorder [50]. Microscopically, CMD is characterized by disruption of the elastic lamina in the vessel media (best seen in elastic stained sections) and increased basophilic ground substance. There may or may not be associated necrosis. Another structural abnormality that may predispose to spontaneous dissection is fibromuscular dysplasia (FMD) [40]. FMD has been reported as the etiology of spontaneous carotid or vertebral artery dissection in ~15–20% of cases [51]. Atherosclerosis as a cause of ICA or ECVA dissection is uncommon.

The intimal injury that results in dissection can form a nidus for luminal thrombosis which can be occlusive or can embolize distally. ICA or ECVA dissection typically result in ischemic stroke by one of two mechanisms: (1) artery-to-artery embolization of intraluminal thrombus from the site of injury downstream or (2) luminal stenosis or obstruction leading to downstream ischemia [38–40, 42]. Ischemic stroke secondary to artery-to-artery embolization is more common and is thought to be the mechanism of stroke in greater than 90% of these cases.

The prognosis of cervical artery dissection is based on many factors including location and severity of the dissection, the number of vessels involved, and the presence or absence of collateral blood flow. Most dissections will heal spontaneously, and the reported death rate is less than 5% [40].

Aneurysm of the Extracranial Carotid and Vertebral Arteries

ECCA or ECVA aneurysms are relatively uncommon [52]. ECCA aneurysms comprise less than 1% of all peripheral aneurysms [53] and represent only 0.1–2% of all carotid artery surgical procedures [54]. Vertebral artery aneurysms comprise ~1% of all vertebral artery lesions. Involvement of the ECVA is very rare as the majority of aneurysms affect the intracranial portion of the vessel [55] (Fig. 3.5).

An aneurysm can be broadly defined as a localized abnormal dilatation of a blood vessel secondary to a congenital or acquired weakness in the vessel wall. To be categorized as an aneurysm, the diameter in the area of vascular dilatation must be at least 50% greater than the normal vessel diameter [56]. As there is normal dilata-

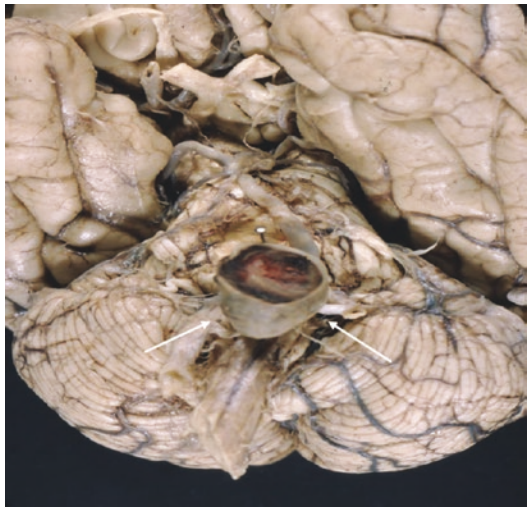

Fig. 3.5 Fusiform aneurysm of intracranial portion of the left vertebral artery with thrombosis (arrows)

tion at the carotid bulb, there has been debate as to what constitutes an aneurysm in this region. The two main subtypes of aneurysms are true aneurysms and false aneurysms (or pseudoaneurysms) [15]. True aneurysms are outpouching that involve all three layers of a vessel wall. A false aneurysm is created when a transmural disruption in a vessel wall leads to formation of an extravascular hematoma which maintains connection with the vessel lumen and is contained by adventitial or extravascular soft tissue. False aneurysms occur most commonly secondary to trauma, in the setting of dissection or iatrogenically (e.g., in areas of suture line disruption). True aneurysms can be subdivided by shape into fusiform or saccular types. Fusiform forms are circumferential outpouchings of the vessel wall (Fig. 3.6a), while saccular aneurysms are localized outpouchings that affect only a portion of the vessel circumference (Fig. 3.6b). Saccular aneurysms are typically more prone to enlarge, rupture and lead to ischemic symptomatology than fusiform types [42].

Aneurysms in general have a wide range of etiologies, many of which are discussed elsewhere in this chapter. Causes of aneurysm include atherosclerosis, trauma, infection, vasculitis, FMD, radiation therapy, and connective tissue disease. They can develop iatrogenically or be congenital in origin. Aneurysm can develop in the setting of dissection (see previous section) if there is disruption of the elastic lamina and hemorrhage toward the vessel adventitia [42]. The most common cause of ECCA aneurysm is atherosclerosis. Atherosclerotic aneurysms are typically fusiform in shape and most commonly involve the carotid bifurcation or proximal ICA [57]. Histologically, the vessel wall in the region of an atherosclerotic aneurysm will typically have severe atherosclerotic disease with destruction of the internal elastic lamina and thinning of the tunica media. Other common etiologies of ECCA aneurysm include trauma or dissection [58]. Iatrogenic aneurysms of the ECCA are relatively rare but can occur as a complication of carotid endarterectomy. The most common cause of ECVA aneurysm is trauma, and the most common location is the V3 segment [55]. Infection only rarely causes ECCA or ECVA aneurysms and is most commonly bacterial in origin (mycotic aneurysm). Mycotic aneurysms can develop secondary to septic embolization from an infected heart valve or contiguous infection from surrounding structures (such as meningitis or cervical lymphadenitis). Secondary infection can occur after surgical manipulation. Acute inflammation and destruction of the vessel wall predisposes to aneurysm formation in these cases.

Aneurysms can result in significant morbidity, the main complications of which include local symptomatology secondary to compression, thromboembolic events, or rupture [59].

Fibromuscular Dysplasia of the Extracranial Carotid and Vertebral Arteries

Fibromuscular dysplasia (FMD) is a group of nonatherosclerotic, noninflammatory disorders of medium-sized arteries [60]. FMD is characterized by structural abnormalities in the vessel wall which can lead to luminal stenosis/occlusion, dissection, and/or aneurysm formation with or without associated vascular thrombosis or embolization [61, 62]. Clinical manifestations vary

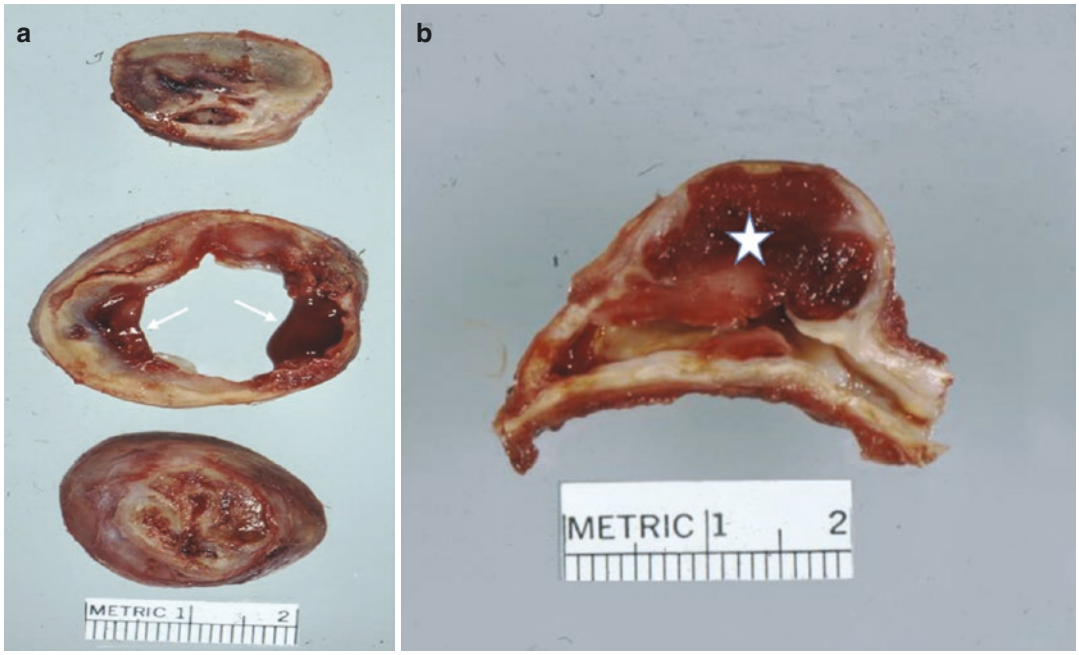

Fig. 3.6 Major subtypes of true aneurysms. (**a**) Fusiform atherosclerotic aneurysm of the right femoral artery cut in cross section revealing circumferential dilatation (middle cross section) and partially occlusive adherent thrombus (arrows). (**b**) Longitudinal section of a saccular atherosclerotic aneurysm of the right popliteal artery revealing a localized outpouching filled with organized thrombus (star)

widely and depend on the vascular bed affected, the histologic type of FMD, and degree of disease, and some patients are asymptomatic. Its prevalence in the general population is unknown and, although historically thought of as a rare disease, may be underdiagnosed [63].

It has been described in nearly every arterial bed but most commonly affects the renal arteries, ICAs and ECVAs [64]. It less commonly affects the ECA and its branches or intracranial vessels [51]. In the US FMD registry, imaging studies demonstrated renal artery involvement in ~80% of patients, carotid artery involvement in ~75% of patients, and ECVA involvement in ~35% of patients [65]. The disease often affects multiple vascular beds. Involvement of the renal artery can result in flank pain and renovascular hypertension. Involvement of the ECCA and ECVA can lead to headache, dizziness, pulsatile tinnitus, neck pain, TIA, or stroke [60]. In the US FMD Registry, ~13% of patients with FMD had a history of TIA, and ~10% of patients had a history of stroke [61]. In FMD, the mid- to distal portion of a vessel is more commonly affected than the proximal portion. The cervical segment (C1–C2) is the most common location of ICA involvement, and the V2 segment is the most common location of vertebral artery involvement [62].

Although FMD can affect people of all ages, it is most common in the middle-aged and is more common in females than males. In the US FMD registry, the median age at diagnosis was 52 years, and ~90% of patients were females [61]. The etiology of FMD is unknown; however genetic factors or tobacco smoking may play a role [51].

In 1971, Harrison and McCormack developed a detailed histologic classification for FMD in patients with renal artery involvement which can be used to classify lesions in other vascular beds [66]. In this classification system, the disorder is separated into three categories based on the vascular wall layer with the most severe pathology: intimal fibroplasia, medial dysplasia, or adventitial (periarterial) fibroplasia. Intimal fibroplasia is characterized by segmental luminal vascular narrowing secondary to accumulation of collagen in

the intima. It can involve a vessel either circumferentially or eccentrically and may cause fragmentation or reduplication of the internal elastic lamina. It is often difficult to distinguish the intimal fibroplasia in FMD histologically from other forms of intimal thickening. The intimal fibroplasia in FMD is noted to lack a lipid or inflammatory component. Although the early study by Harrison and McCormack suggested that intimal fibroplasia was relatively infrequent (1–2% of cases) [66], it is thought to be the second most common subtype today comprising less than 10% of cases overall [67]. Medial dysplasia can be divided into three subcategories: medial fibroplasia, perimedial fibroplasia, or medial hyperplasia. Medial fibroplasia is the most common pattern of FMD and comprises greater than 90% of cases. In medial fibroplasia, involved vessels have alternating areas of luminal stenosis (due to thickened fibroproliferative ridges or webs) and aneurysmal outpouching (secondary to medial thinning and defects in the internal elastic lamina) forming a grossly and radiographically identifiable "string of beads" appearance. In areas with fibromuscular ridges, the smooth muscle of the vessel wall is partly or completely replaced by loose collagenous tissue. Medial hyperplasia is characterized by luminal narrowing secondary to smooth muscle hyperplasia without fibrosis. The internal elastic lamina is unaffected in these cases. Although this early study suggested that medial hyperplasia occurred in 5–15% of cases [66], today it is thought to occur in <1% of cases [51]. Perimedial fibroplasia is characterized by increased collagen deposition in the outer half of the media leading to irregular medial thickening. The external elastic lamina is often replaced by collagen in these cases. Although the early study by Harrison and McCormack suggested it occurred in 15–25% of cases [66], today it is thought to occur in <1% of adult cases [51]. It is the predominant form in children. Adventitial fibroplasia (<1% of cases) is characterized by circumferential adventitial fibrosis, sometimes extending into the periadventitial tissue. The other layers of the artery as well as the elastic laminae remain intact. A mild inflammatory infiltrate (predominantly lymphocytes and plasma cells) may be present in the adventitia.

Diagnosis of FMD used to rely on histologic classification; however pathologic findings can be nonspecific, and the disorder is almost exclusively diagnosed by radiographic methods today. As the disorder is often treated medically or by endovascular procedures which are less invasive, pathologic specimens are only rarely obtained.

Vasculitides of the Extracranial Carotid and Vertebral Arteries

The vasculitides are a heterogenous group of disorders which are characterized by inflammation and damage to blood vessel walls. Vasculitis is considered primary (or idiopathic) when the underlying etiology is unknown and secondary when the etiology is known (e.g., infection or underlying connective tissue disease) [68]. The two primary vasculitides that predominantly affect large vessels and can affect the ECCA and ECVA are giant cell arteritis (GCA) and Takayasu's arteritis (TA). These entities have indistinguishable histologic features and occur predominantly in females. They differ in demographics such as age of onset, ethnic distribution, and vascular predilection [69].

Giant Cell Arteritis

Giant cell arteritis (GCA) is the most common primary systemic vasculitis seen in older adults. It typically affects patients over 50 years of age, and the risk of disease is highest among those 75–85 years of age [70]. It is most common in patients of Scandinavian descent [71, 72] and is 2–4 times more common in women than men [73, 74].

The underlying mechanism regulating GCA pathogenesis has not been fully elucidated; a mixture of genetic and environmental factors appears to be at play. Studies attempting to link GCA to an infectious origin have thus far failed to reach consensus. The most prominent genetic risk factor is HLA-DR4 [75], which has been implicated in various autoimmune syndromes [76]; however co-occurrence of GCA with other autoimmune

diseases is rare, indicating pathogenesis may involve unique genetic or environmental triggers. Additional immune-associated genes have been implicated at the genetic and/or epigenetic level [77]. The current understanding of pathogenesis involves progressive immune activation in situ (reviewed in [77]). Dendritic cells (DC) become activated in the adventitia and present tissue-specific antigen to CD4 T cells, recruited by an assortment of chemokines, which in turn break tolerance and become erroneously activated against self-antigen. These autoreactive CD4 T cells are polarized by pro-inflammatory cytokines, including IL-6, toward Th1, Th17, and Th21 in the microenvironment, driving production of IFNγ, IL-17, and IL-21, respectively. These signaling molecules trigger the recruitment of CD8 T cells and monocytes, the latter of which differentiate into macrophages as progenitors of giant cells. This immune infiltrate milieu leads to tissue remodeling in part via PDGF and VEGF production, and cytokines produced by these immune cells contribute to disease symptoms.

GCA typically affects large- and medium-sized arteries in the head and neck (including the aorta and its major branches) and most commonly affects the extracranial branches of the carotid artery [68]. Given its unique predilection for the temporal artery, it is commonly referred to as temporal arteritis. GCA occasionally involves the ECVA or ECCA [78]. Vertebral artery involvement is more common than carotid artery involvement [79, 80]. The disease typically spares intracranial vessels (likely due to lack of the elastic lamina intracranially) [44, 78, 80].

A wide array of symptomatology can be seen in patients with GCA including general manifestations of inflammation such as fever, myalgia, fatigue, malaise, or weight loss [81]. Elevated acute phase reactants are present in over 90% of patients [81]. Ischemic symptoms are dependent on the distribution of arterial involvement and typically result from vessel wall inflammation leading to intimal hyperplasia and associated luminal stenosis/occlusion and/or thrombosis. The classic symptoms of headache, scalp tenderness, and jaw claudication are secondary to involvement of the temporal artery. Involvement of the ECCA or ECVA can result in cerebrovascular ischemic manifestations or pain (carotidynia). Of patients with active GCA, 4% will experience TIA or stroke during their illness [82]. Ophthalmic involvement ranges between 14% and 40% in different studies [83] and can lead to vision loss in as many as 20% of patients [84, 85]. Given the risks of blindness or cerebral infarction, prompt diagnosis and urgent corticosteroid treatment in cases of active disease are required.

The American College of Rheumatology published criteria for distinguishing GCA from other forms of vasculitis in 1990 [86]. Patients who have three of the five following criteria can be classified with GCA with a sensitivity of 93.5% and specificity of 91.2%: (1) age ≥50 at disease onset, (2) new onset of localized headache, (3) temporal artery tenderness or decreased temporal artery pulse, (4) elevated erythrocyte sedimentation rate ≥50 mm/h, and (5) positive temporal artery biopsy. Although the criteria are used by some clinicians to aid in the diagnosis of GCA, they were never intended to differentiate between the presence and absence of vasculitis in any given patient [87].

Given a multitude of factors including high rate of involvement, ease of accessibility, and low complication rate, the superficial temporal artery biopsy remains the gold standard for diagnosis of GCA [88]. A positive temporal artery biopsy has a high specificity for diagnosis (approaching 100%) [7]. Sensitivity of the procedure cannot be formally calculated and widely ranges in the literature. One study calculated the sensitivity of unilateral temporal artery biopsy to be around 87% [89]. Biopsy of the bilateral temporal artery has been shown in some studies to improve the diagnostic yield as much as 5% [90, 91]. It may be beneficial in cases where a unilateral temporal artery biopsy is either negative or has unclear or atypical histologic findings, and there is still a clinical suspicion of GCA. A negative temporal artery biopsy does not rule out the possibility of GCA, and the results must be taken in context of all the available clinical and laboratory findings.

The false negative rate of temporal artery biopsy can be partially contributed to the notori-

ously focal or patchy nature of the inflammatory process in GCA. Segmental inflammation, also known as skip lesions, has been reported to occur in up to 28% of cases [92]. The length of the temporal artery biopsy is therefore important for diagnostic yield; however the optimal length is still a controversial issue. Many studies recommend an in vivo length of at least 1 or 2 cm [91, 93, 94] with one study reporting minimum length of at least 0.5 cm [95]. The longer the biopsy the better chance of diagnostic sampling and the optimal in vivo length that is typically recommended is 2–3 cm or 3–5 cm [95]. Given the patchy nature of the inflammatory process, it is also routine for most surgical pathology laboratories to examine the vessel histologically at multiple levels. It is our practice to section the segment of artery at 2–3 mm intervals, embed the whole specimen for histologic examination and serially section each tissue block.

Gross findings in GCA include nodular thickening of the vessel wall with areas of luminal stenosis or occlusion which can be patchy (skip lesions), focal, or diffuse. A spectrum of histologic features can be seen in GCA. Classically, a transmural inflammatory infiltrate consisting predominantly of CD4-positive T cells, histiocytes, and dendritic cells is described (Fig. 3.7). In

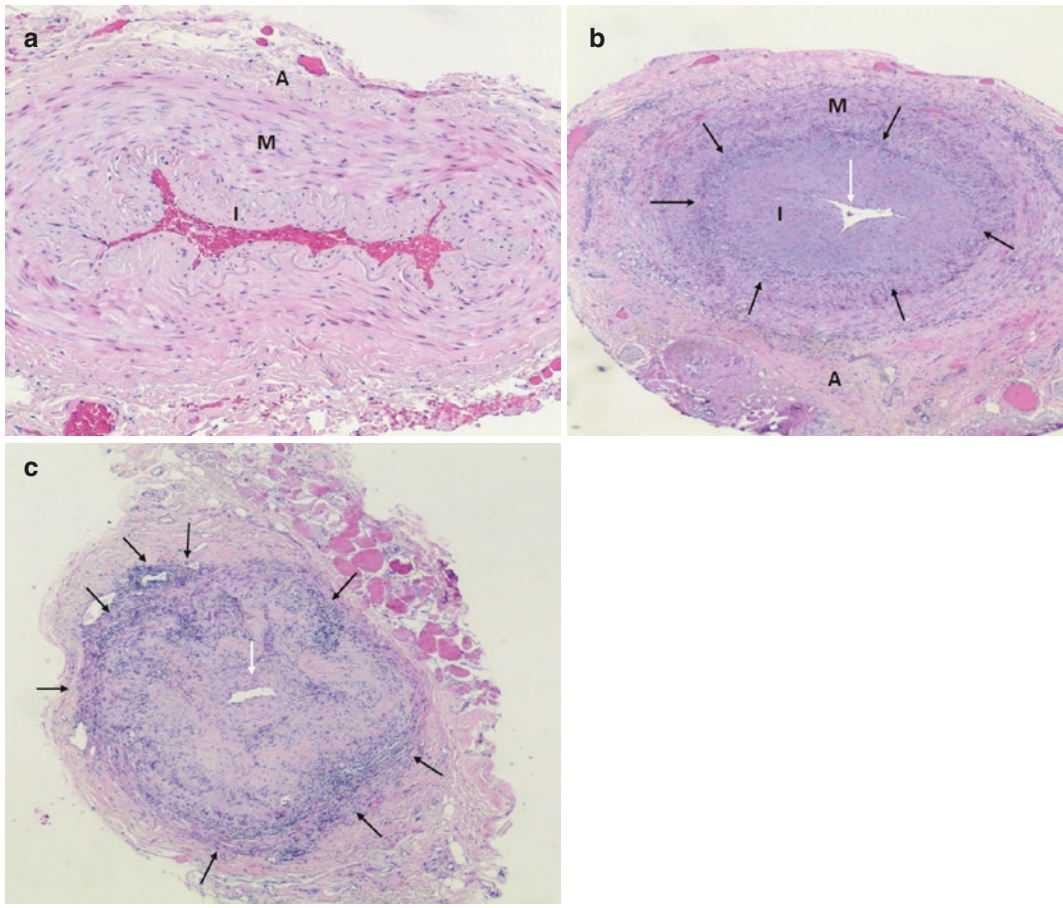

Fig. 3.7 Temporal artery biopsy. (**a**) A temporal artery without arteritis lacks an inflammatory infiltrate. The vessel intima (I), media (M), and adventitia (A) are labeled (hematoxylin and eosin, 4×). (**b**) Temporal artery with giant cell arteritis revealing a markedly thickened intima (I) with a small residual lumen (white arrow). There is a chronic inflammatory infiltrate involving the vessel media (M) and adventitia (A) with prominent involvement of the internal elastic lamina (arrows). The adventitia (A) is also thickened and fibrotic in this case (hematoxylin and eosin, 4×). (**c**) Another example of giant cell arteritis in a temporal artery revealing a marked inflammatory mural infiltrate (black arrows) and small residual vessel lumen (white arrow) (hematoxylin and eosin, 4×)

some cases, eosinophils or neutrophils can be seen. The inflammatory infiltrate is typically most pronounced along the vessel media and internal elastic lamina (IEL). Multinucleated giant cells can be identified among the inflammatory infiltrate (Fig. 3.8). Although a helpful histologic feature, their presence is not required for diagnosis of GCA. One study reported absence of giant cell in around 25% of cases [96]. The inflammatory infiltrate often causes destruction of the elastic fibers of the IEL which can be better visualized using an elastic stain (Fig. 3.9); however an elastic stain is not required for routine diagnosis [97]. Giant cells can be visualized engulfing elastic fiber debris and in some cases overt granulomatous inflammation has been described. The presence of necrosis is a relatively rare finding. Continued inflammation results in varying degrees of luminal obstruction, medial scarring, and adventitial fibrosis. Intimal thickening is common. Luminal thrombi can form which can be occlusive. Over time, a completely occluded vessel can recanalize.

Although it is optimal to perform a temporal artery biopsy before initiation of therapy, treatment should not be delayed in patients with a

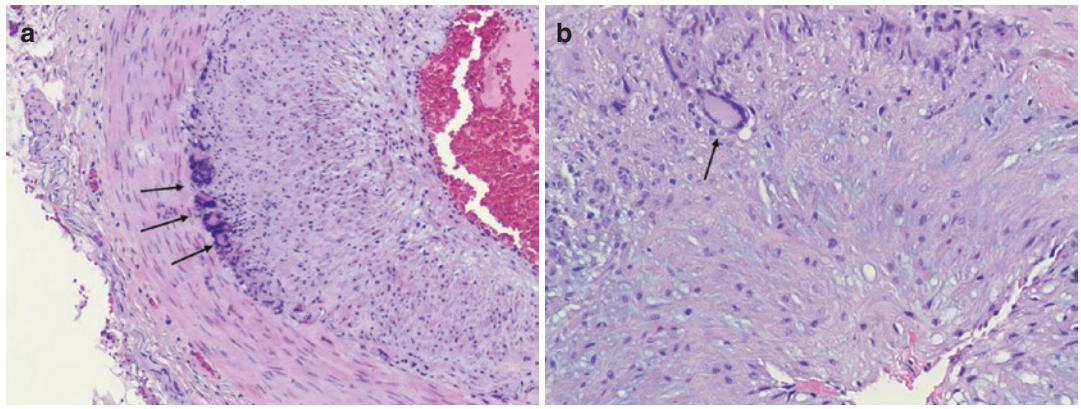

Fig. 3.8 (**a**) When present, giant cells (arrows) in giant cell arteritis are often concentrated along the internal elastic lamina (hematoxylin and eosin, 10×). (**b**) High power view of a multinucleated giant cell (arrow) in the region of the outer intima/internal elastic lamina (hematoxylin and eosin, 40×)

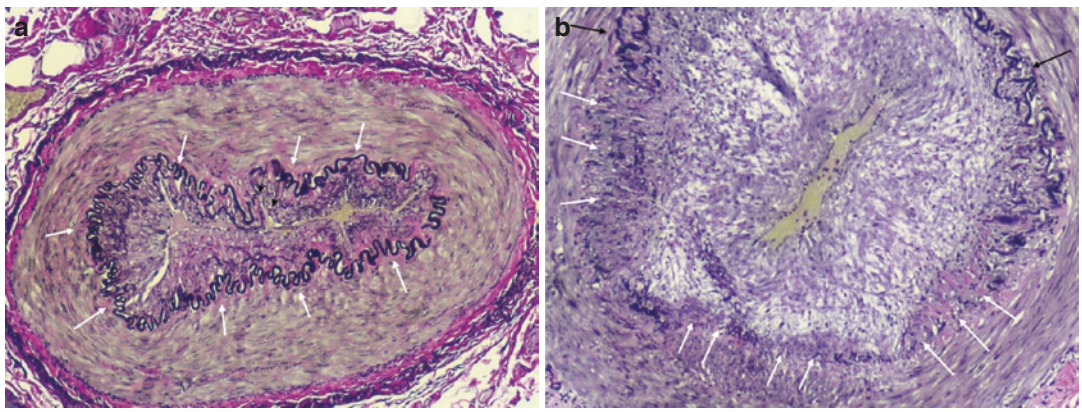

Fig. 3.9 (**a**) Elastic stain of a temporal artery without arteritis revealing a relatively preserved internal elastic lamina (arrows). The focal areas of internal elastic lamina disruption and reduplication seen can be attributed to age-related changes (Verhoeff-van Gieson elastic stain, 4×). (**b**) Temporal artery with arteritis revealing a duplicated (black arrows) and markedly disrupted (white arrows) internal elastic lamina (Verhoeff-van Gieson elastic stain, 10×)

high clinical suspicion for disease given risk of serious complications including blindness. Traditionally it is suggested that temporal artery biopsy be performed within a week of steroid therapy initiation [98]. Although some studies report a drop-off in yield after continued treatment [99], others have reported that the temporal artery biopsy can remain diagnostic at least a month after the start of treatment in some patients [100]. Given more subtle histologic findings in treated cases, the diagnosis is not always straightforward [101]. Intimal thickening, areas of mural fibrosis, and disruption of the internal elastic lamina can often be identified in treated cases, although the inflammatory infiltrate is often milder. Defects in the IEL are typically substantial involving approximately 40–50% of the vessel circumference [98].

Whether lesser forms of inflammation such as inflammation limited to small periadventitial vessels, vasa vasorum, or adventitia are diagnostic of GCA is a controversial area [96]. Some consider these borderline changes. The concept of "healed" arteritis is also controversial as there are no reliable histologic criteria to diagnose it. Although some regard histologic findings such as IEL disruption and mural scarring as evidence of healed arteritis [102]; others report that in the absence of inflammation, cases with vessel damage secondary to GCA cannot be reliably distinguished from those secondary to arteriosclerosis [103].

Diagnosis of GCA of the ECCA and ECVA typically relies on a combination of clinical findings and imaging studies. Specimens from these arteries are only rarely examined by pathologists.

Takayasu's Arteritis

Takayasu's arteritis (TA) is a relatively rare chronic progressive systemic inflammatory vasculitis syndrome of unknown origin. It typically affects patients younger than 40 years of age [86], with peak incidence occurring during the second or third decade of life [104]. Around 5% of patients are children or adolescents [105]. The reported worldwide incidence is 1–2 per million [104]. It is thought to be more prevalent in Asian countries [104]. There is a striking predominance of the disease in females, and the female to male ratio is 8:1 [106].

TA primarily affects the aorta and its major branches. Given the predilection for the aortic arch, it is also referred to as aortic arch syndrome. Although any of its branches can be involved, the most commonly affected are the subclavian and common carotid arteries [107]. Involvement of the pulmonary or renal arteries is also common. Involvement of the vertebral arteries [108] or intracranial vessels are relatively rare [109]. Vessels can be involved focally, in a patchy manner (skip lesions) or diffusely.

The pathogenesis of TA is uncertain, though multiple factors seem to be involved, namely, genetics and autoimmunity. Specific autoantigens have yet to be elucidated; however a leading hypothesis involves molecular mimicry following prior infection, where mycobacterial heat-shock proteins remain the strongest causative candidates [110, 111]. TA is associated with dendritic cell and T cell infiltration into the adventitia, and the HLA locus has been implicated as a genetic determinant in TA onset [112]. One mechanism of immune activation and tissue destruction is the involvement of cytotoxic, perforin-producing NK and γδ T cells, which may directly induce apoptosis of arterial vascular cells via 4-1BB, Fas, and/or NKG2D signaling pathways [113].

The clinical signs and symptoms of TA are nonspecific and vary from patient to patient. The rarity of the disease and its widely variable symptomatology leads to delayed diagnosis and treatment. The degree of activity tends to wax and wane over time with episodic acute flare-ups. Constitutional symptoms that can occur early in disease include low-grade fever, malaise, arthralgias, and myalgias; however, up to 50% of patients will lack these symptoms [107]. Carotidynia is observed in up to 30% of patients at time of presentation. Laboratory findings early on can include elevation in acute phase reactants [114]. Weeks to months later, patients present with a wide variety of signs and symptoms depending on

the vessels affected. Classic signs and symptoms include discrepant blood pressure between the upper extremities (>10 mmHg), absent or weak peripheral pulses (most common at the level of the radial arteries and often asymmetric), limb claudication, and arterial bruits. The term pulseless disease was proposed by Shimizu and Sano in 1951 given the finding of impalpable radial pulse [105]. Hypertension is common (typically secondary to renal artery involvement). Involvement of the aortic root or ascending aorta can lead to aortic valve insufficiency secondary to dilation or aneurysm. Involvement of the pulmonary arteries can result in pulmonary hypertension or thromboembolism. TIA or stroke can occur in up to 20% of patients and is typically due to occlusion of the carotid arteries as the vertebral arteries are only rarely involved [108].

The American College of Rheumatology published diagnostic criteria to distinguish TA from other forms of vasculitis in 1990 [115]. Patients who have three of the six following criteria can be classified with TA with a sensitivity of 92.1% and specificity of 97%: (1) age at onset of disease ≤40 years, (2) claudication of an extremity, (3) decreased brachial artery pulse, (4) difference in systolic blood pressure between arms, (5) a bruit over the subclavian arteries or aorta, and (6) arteriographic evidence of narrowing or occlusion of the entire aorta. Although the criteria are used by some clinicians to aid in the diagnosis of TA, they were never intended to differentiate between the presence and absence of vasculitis in any given patient. As accurate diagnostic criteria are not yet published and a diagnostic laboratory test is not available, clinicians usually rely on a combination of clinical and imaging findings to make a diagnosis of TA. Steroid (glucocorticoid) therapy remains the mainstay of treatment.

Pathologists only rarely encounter TA specimens as the disorder mainly affects large vessels and segments are not typically excised surgically. Therefore, much that is known about the histopathology of the disorder has been elucidated from postmortem examination [105]. The histologic features of TA are often widely variable and nonspecific and can overlap with those seen in GCA. The disease has three phases: active, chronic, and healed. During the active phase, inflammation extends from the adventitia and is most concentrated at the junction between the media and adventitia. It can progress transmurally, and there is often inflammation of the vasa vasorum. The mononuclear infiltrate consists primarily of lymphocytes, plasma cells, histiocytes, and dendritic cells. Giant cells or even granulomatous reaction can be present. The inflammatory infiltrate causes fragmentation and destruction of elastic fibers, and giant cells can be seen engulfing the elastic fibers. In some cases, patchy necrosis of the vessel wall can be seen. In cases with severe inflammation, destruction of elastic fibers and medial smooth muscle cells can lead to weakening of the vessel wall with resulting dilatation or aneurysm formation. Fibroblasts and smooth muscle cells invade the intima and produce excess mucopolysaccharides which contribute to intimal thickening [112]. On gross examination, intimal thickening has a plaque-like appearance [107]. Luminal thrombi can develop which can be occlusive in some cases. In the chronic phase of disease, inflammation (if present) is sparse, and plasma cells are common. Scarring of the vessel wall including the media, adventitia and periadventitial soft tissue can occur and lead to vascular wall thickening. The intimal thickening and mural scar causes stenosis or occlusion of the vascular lumen and thus ischemic symptomatology.

Carotid Body Tumor (Paraganglioma)

Extra-adrenal paragangliomas arise from paraganglia located along the paravertebral sympathetic and parasympathetic chains. Paragangliomas in the head and neck region are neoplasms of uncertain malignant potential of the oxygen-sensing chemoreceptive carotid body and are of neural crest origin [116–118]. The carotid body is the most common site of extra-adrenal paraganglioma, and paragangliomas in this region are also referred to as carotid body tumors. Carotid body tumors comprise as many as 60% of cases of head and neck paragangliomas.

Patients with carotid body tumors often present with a slow-growing, painless, palpable neck mass. The tumors are typically located at the carotid bifurcation, sometimes encasing the ICA or ECA and are nonfunctioning. Surgical resection is the treatment of choice. Upon gross examination, the tumors are typically well circumscribed, round to oval, and solid and rubbery in consistency and may have a surrounding pseudocapsule. The cut surface is often light tan to brown red in color depending on the amount of background vasculature (Fig. 3.10a). Tumor size varies widely, averaging around 4 cm; however some have been described up to 10 cm in greatest dimension. Histologically, the tumor is made up of chief cells (type I cells) which are neuroectodermal in origin and are typically arranged in either a nested "zellballen" or trabecular growth pattern, and there is often prominent background vasculature (Fig. 3.10b). Chief cells are variable in size and have abundant granular cytoplasm that can be eosinophilic, basophilic, or clear. The nuclei vary from round to oval with a dispersed chromatin pattern to large and vesicular. Some cases show nuclear atypia or pleomorphism

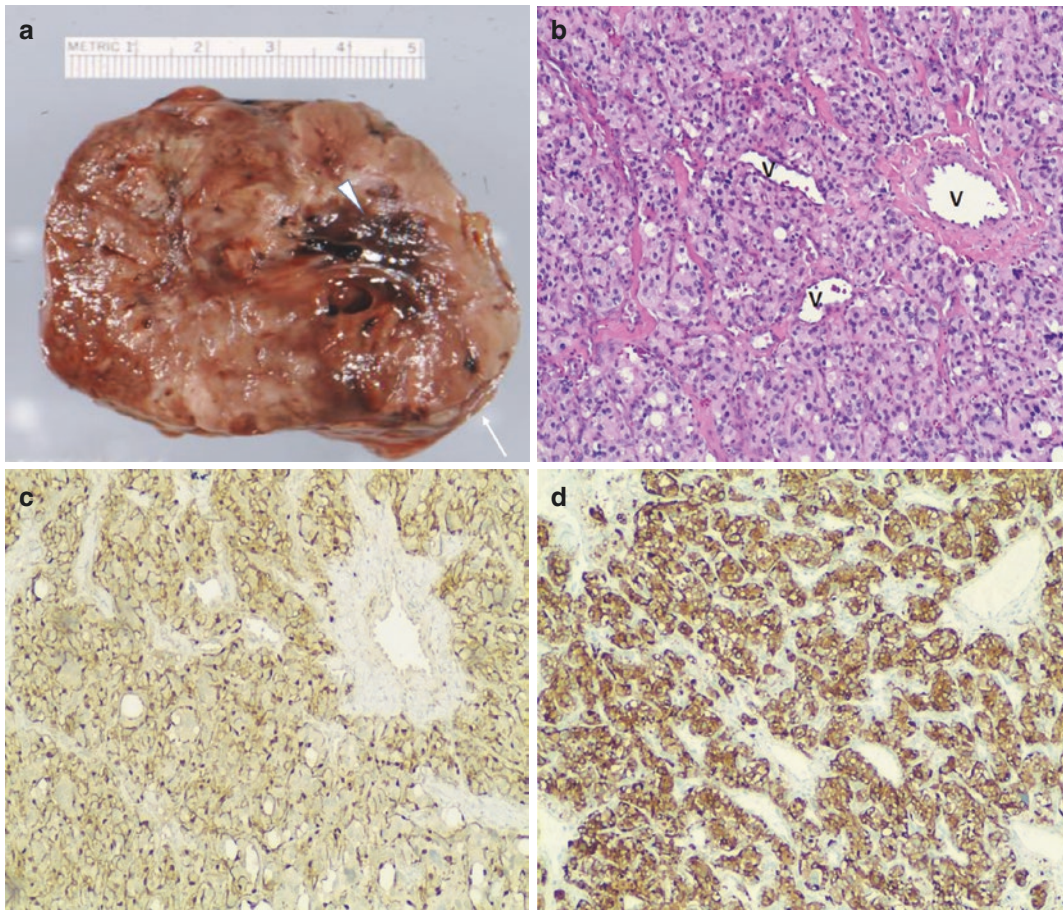

Fig. 3.10 Carotid body tumor (Paraganglioma). (**a**) Cut surface of a carotid body tumor revealing a well-circumscribed ovoid mass with pseudocapsule (arrow) and brown red to tan cut surface with focal hemorrhage (arrowhead). (**b**) Histologic section of a carotid body tumor revealing chief cells arranged in a trabecular and nested growth pattern separated by fibrous septae. Some of the background vessel lumens are labeled (V) (hematoxylin and eosin, 100×). (**c**) Supporting sustentacular cells wrap around the chief cell nests and can be highlighted by an immunohistochemical stain for S100 (S100 immunohistochemical stain, 100×). (**d**) Chief cells can be highlighted immunohistochemically for neuroendocrine markers including synaptophysin (Synaptophysin immunohistochemical stain, 100×)

which is not indicative of malignant potential. Supporting sustentacular (type II) cells wrap around the chief cell nests. Sustentacular cells are typically not morphologically apparent but can be highlighted by immunohistochemical staining for S100 protein (Fig. 3.10c). Immunohistochemically, the chief cells are positive for neuroendocrine markers including synaptophysin and chromogranin and are negative for cytokeratins (Fig. 3.10d).

Worrisome histologic features including necrosis, vascular invasion, increased mitotic rate, or infiltration into surrounding soft tissue do not adequately indicate malignant potential in these tumors. In fact, there is currently no validated histopathologic grading system that can be used to predict malignant behavior in paragangliomas. Malignant potential can only be diagnosed in the presence of local or distant metastasis which occurs in around 4% of cases of carotid body tumors. Patients diagnosed with a paraganglioma require lifetime clinical follow-up to rule out the possibility of recurrence or metastasis.

Carotid body tumors can be sporadic, familial, or hyperplastic (developing in patients with chronic hypoxia such as those with COPD or those living at high altitudes) [119]. As many as 40% of head and neck paragangliomas are familial and commonly have germline mutations in genes that encode subunits of the succinate dehydrogenase (SDH) enzyme complex. The genes SDHD and SDHB are most commonly affected. Patients with Carney triad can also develop head and neck paragangliomas that have mutations in these genes. Other tumors associated with germline mutations of SDH include gastrointestinal stromal tumors, renal cell carcinomas, and pituitary adenomas. The Endocrine Society now recommends that all patients diagnosed with paraganglioma be considered for genetic testing [120]. Loss of immunohistochemical staining for SDHB in paraganglioma can be used to screen patients for mutation in any of the SDH family of genes (SDHA, SDHB, SDHC, or SDHD).

Review Questions

1. What is the most common cause of stroke in patients with atherosclerosis of the extracerebral carotid artery?
   A. Plaque rupture with occlusive thrombosis
   B. Artery-to-artery embolization
   C. Plaque ulceration with occlusive thrombosis
   D. Intraplaque hemorrhage
   E. Ruptured atherosclerotic aneurysm

Answer: B

While all the above answers can be causes of stroke, artery-to-artery embolization of thrombotic or atherosclerotic material is the most common cause of stroke in patients with atherosclerosis of the extracerebral carotid or vertebral arteries. Plaque rupture with occlusive thrombosis of a coronary artery is the most common cause of myocardial infarction.

2. Which of the following is the most common cause of extracerebral carotid artery aneurysm?
   A. Connective tissue disease
   B. Trauma
   C. Atherosclerosis
   D. Radiation therapy
   E. Vasculitis

Answer: C

While all of the above answers are known causes of aneurysm, atherosclerosis is the most common cause of extracerebral carotid artery aneurysm. Trauma is the most common cause of extracerebral vertebral artery aneurysm.

3. Which of the following is the most common histologic pattern of fibromuscular dysplasia?
   A. Medial fibroplasia
   B. Intimal fibroplasia
   C. Adventitial fibroplasia

D. Medial hyperplasia
E. Perimedial fibroplasia

Answer: A

While all the above answers are histologic patterns of fibromuscular dysplasia, medial fibroplasia is the most common. In medial fibroplasia, involved vessels have alternating areas of luminal stenosis and aneurysmal outpouching forming a grossly identifiable "beads on a string" appearance.

4. What is the gold standard for diagnosis of giant cell (temporal) arteritis?
   A. Elevated erythrocyte sedimentation rate
   B. Physical exam findings of nodularity and thickening of the temporal artery
   C. Temporal artery tenderness
   D. Imaging studies
   E. Temporal artery biopsy

Answer: E

Temporal artery biopsy remains the gold standard for diagnosis of giant cell (temporal) arteritis. Diagnosis of giant cell arteritis of the extracerebral carotid or vertebral arteries typically relies on a combination of clinical and imaging studies.

5. Which of the following is indicative of malignant potential in carotid body tumors?

A. High mitotic rate
B. Necrosis
C. Infiltration into surrounding tissue
D. Metastasis
E. Vascular invasion

Answer: D

Although high mitotic rate, necrosis, and infiltration into surrounding tissue, metastasis, and vascular invasion are all worrisome histologic features, malignant potential of a carotid body tumor can only be diagnosed in the presence of local or distant metastasis.

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