Ear and Temporal Bone Pathology: Neural, Sclerosing and Myofibroblastic Lesions

A. N. Flaman¹ · J. K. Wasserman¹ · D. H. Gravel¹ · B. M. Purgina¹

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Abstract

Neural, sclerosing, and myofibroblastic lesions of the ear and temporal bone present diagnostic challenges for both clinicians and pathologists due to significant overlap in their clinical presentations, histologic appearances, and immunohistochemical profiles. While some of these lesions, such as schwannomas, are relatively common, others are rendered even more difficult because they are encountered very rarely in routine surgical pathology practice. This review is intended to provide an update on the pathology of some of the most commonly encountered primary diagnostic entities for the ear and temporal bone, and includes the following neural lesions: schwannoma, meningioma, and encephalocele/meningocele. Sclerosing lesions that will be discussed include spindle cell and sclerosing rhabdomyosarcoma, sclerosing epithelioid fibrosarcoma, and sclerosing paraganglioma. Finally, myofibroblastic lesions that will be reviewed are nodular fasciitis, IgG4-related disease, and solitary fibrous tumor. For each of these lesions, the differential diagnosis and useful ancillary tests will be discussed in the context of a broad range of additional primary and secondary lesions.

Keywords Temporal bone · Ear · Neurilemmoma · Meningioma · Encephalocele · Rhabdomyosarcoma · Solitary fibrous tumor · Paraganglioma · Fibrosarcoma

Neural Lesions of the Temporal Bone

Benign Peripheral Nerve Sheath Tumors (PNST)

The most common benign PNST in this location is a schwannoma (vestibular schwannoma, acoustic neuroma or neurilemmoma). It most commonly arises in the internal auditory canal from the 8th cranial nerve and represents the most common neoplasm of the temporal bone [1]. The majority of patients present with hearing loss, tinnitus and other neurologic symptoms. About 95% are unilateral and sporadic. Those that arise in young patients or are bilateral are often associated with neurofibromatosis type 2 (NF 2) [1].

Pathologic Features

Classic schwannoma are encapsulated lesions that typically exhibit hypercellular Antoni A and hypocellular Antoni B areas in varying proportions (Fig. 1a). The Antoni A areas consist of short fascicles of spindle cells with fibrillary cytoplasm, indistinct cell borders and elongated wavy or buckled nuclei with pointed ends. Nuclear palisading is common and stacked arrangements of palisaded nuclei separated by fibrillary cytoplasm are referred to as Verocay bodies. The Antoni B areas are comprised of loose matrix containing delicate spindle cells and microcystic spaces along with inflammatory cells including lymphocytes and foamy macrophages. Small- to medium-sized, typically ectatic blood vessels often demonstrate characteristic perivascular hyalinization (Fig. 1b).

Other morphologic subtypes of schwannoma include cellular schwannoma and ancient schwannoma. A cellular schwannoma is comprised exclusively of hypercellular Antoni A areas, frequently without Verocay bodies, and arranged in a fascicular pattern with long sweeping fascicles. Ancient schwannomas demonstrate extensive degenerative changes with central hemorrhage and fibrin, foamy

✉ B. M. Purgina
bpurgina@ottawahospital.on.ca

¹ Division of Anatomical Pathology, Department of Pathology and Laboratory Medicine, The Ottawa Hospital/University of Ottawa, 501 Smyth Road, Ottawa, ON K1H 8L6, Canada

Fig. 1 Spindle cell neural lesions. **a** Schwannoma: both hypercellular ▶ Antoni A area with subtle nuclear palisading (left) and hypocellular Antoni B area (right) are pictured [H&E, 50×]. **b** Cellular schwannoma: essentially the entire lesion is composed of hypercellular Antoni A areas with elongated spindle cells, wavy, tapered nuclei, and indistinct eosinophilic cytoplasm; a typical hyalinized vessel is also shown [H&E, 100×]. **c** MPNST: low power image showing “fibrosarcoma-like” architecture of an MPNST arising in a patient with NF 1 [H&E, 40×]. **d** MPNST: partial loss of H3K27me by IHC, specific for MPNST [H3K27me, 200×]

macrophages and degenerative atypia. Typically, schwannomas exhibit a low mitotic activity with <4 mitoses per 10 HPFs. Significant nuclear pleomorphism, tumor necrosis and mitotic rate >4 mitoses per 10 HPFs suggest malignancy.

Ancillary Studies

Schwannomas often exhibit diffuse and strong expression of S100 protein and SOX10, particularly in cellular schwannomas. CD34 may be positive in the hypocellular Antoni B areas. Glial fibrillary acidic protein (GFAP) and neuron-specific enolase (NSE) may be occasionally positive.

Differential Diagnosis

The differential diagnosis includes meningioma, discussed below, neurofibroma and less likely, malignant peripheral nerve sheath tumor (MPNST). Neurofibromas are rare in this anatomic site. Neurofibromas, derived from Schwann cells, perineurial cells, and intraneural fibroblasts, are unencapsulated tumors characterized by a haphazard arrangement of spindle cells set in a variable myxoid to collagenous stroma. The spindle cells have wavy/buckled nuclei and indistinct cytoplasm. The interspersed collagen bundles typically have so-called “shredded carrot” appearance. Unlike schwannomas that demonstrate strong, uniform S100 protein expression and CD34 localized to Antoni B areas, neurofibromas tend to show more variable staining with S100 and CD34.

Although 20–30% of MPNSTs occur in the head and neck, they are exceedingly rare in this anatomic site. However, they may be considered in a tumor of neural origin with an infiltrative growth pattern, nuclear pleomorphism, increased mitoses, and necrosis [2, 3]. MPNSTs either arise de novo from peripheral nerves or from malignant degeneration of benign PNST, more commonly neurofibroma than schwannoma. Rare examples of MPNST developing in a vestibular schwannoma following radiation have been reported [4]. MPNSTs are more common in adults, with sporadic cases typically presenting in the 5th decade and in the 3rd to 4th decades in neurofibromatosis type 1 (NF1) patients [5]. There are variable histologic patterns, but the most common consists of spindle cells arranged in alternating hypocellular and hypercellular areas, imparting

a marbled effect at low power, with perivascular accentuation, fascicular growth, poorly defined nuclear palisading and wavy to buckled nuclei (Fig. 1c). Hemorrhage, necrosis and mitoses, including atypical forms, are frequent. S100 protein and SOX10 typically demonstrate only limited

positivity in approximately half of cases. In contrast, the rare subtype of epithelioid MPNST, which can arise from a schwannoma, typically shows strong, diffuse staining with S100 protein and about 70% of cases demonstrate loss of nuclear staining with INI1 [6]. On occasion, MPNST may demonstrate focal staining with cytokeratin, EMA, and CD34. A recently described antibody, H3K27me, seems to be specific for MPNST [7, 8]. H3K27me is a nuclear marker; approximately 50% of MPNSTs show complete loss of staining, and a smaller fraction display partial loss (Fig. 1d) [7, 8]. This loss of expression appears to be highly specific for MPNST. Complete or partial loss is not a feature of epithelioid MPNST. Complete or partial loss of H3K27me is particularly useful to distinguish MPNST from other soft tissue sarcomas and spindle cell melanoma [7, 8]. The most common molecular alterations in MPNST include loss of *NF1* on 17q11 and *TP53* on 17q13. Inactivation of *NF1* can occur in sporadic MPNSTs [5].

Meningioma

Meningioma can occur in the ear and temporal bone either as a primary lesion or through extension of an intracranial tumor [9]. As a primary lesion, they are rare, with only about 70 cases reported in the English-language literature to date [10–12]. They are believed to be derived from arachnoid cap cells [13]. Similar to meningiomas in other locations, the sex distribution is approximately 2:1 female to male [9]. They can occur at any age, however, adults in the fifth to seventh decades are most commonly affected [9, 10]. Like other lesions at this site, the clinical presentation is usually non-specific, with hearing loss, chronic otitis, and pain being the most common symptoms [9].

Pathologic Features

As in other locations, ear and temporal bone meningiomas can have a variety of histologic patterns. The meningothelial pattern is most common (Fig. 2a), followed by psammomatous and fibroblastic patterns [13]. Transitional, secretory and atypical meningiomas have also been reported [9, 12, 14]. Histologically, meningothelial meningiomas demonstrate a lobular syncytium of epithelioid, round to polygonal, meningothelial cells with moderate amphophilic-eosinophilic cytoplasm, indistinct cell borders, and bland oval nuclei with delicate chromatin. They may also show small nucleoli, central nuclear clearing and cytoplasmic nuclear inclusions (pseudoinclusions). A whorled arrangement is possible but less common than in other subtypes [15]. The histologic appearance of psammomatous meningioma may resemble transitional meningioma (described below) with whorled architecture, however they have a striking predominance of psammoma bodies, which may become confluent.

Fig. 2 Meningothelial meningioma. **a** Small, epithelioid cells with bland ovoid nuclei arranged in a syncytial pattern [H&E, 100×]. **b** Positivity for progesterone receptor by IHC [PR, 200×]. **c** Positivity for epithelial membrane antigen by IHC [EMA, 200×]

Fibroblastic meningioma is composed of interlacing and parallel fascicles with variable amounts of intervening collagen. The cells are spindle-shaped and resemble fibroblasts with bland, wavy nuclei and indistinct chromatin [15]. Finally,

transitional meningioma has intermediate features between fibroblastic and meningothelial subtypes, and/or a distinct mix of both areas. Meningothelial whorls are common, and psammomatous calcifications are often seen [15]. All of the types listed above are grade I and benign. Grade II lesions, or atypical meningiomas, have either brain invasion or mitotic activity equal to or greater than 4 mitoses/10 HPFs. Atypical meningiomas may also be diagnosed in a meningioma that has at least three of the following features: diffuse or sheet-like growth, geographic necrosis, increased cellularity, small cells with increased nuclear to cytoplasmic ratio, or conspicuous nucleoli [15].

Ancillary Studies

Immunohistochemical evaluation is typically positive for epithelial membrane antigen (EMA), vimentin, and progesterone receptor (PR) (Fig. 2b, c). Meningiomas are typically negative for cytokeratins, S100, smooth muscle actin (SMA), CD34, STAT6, and nuclear β -catenin, although a lot of aberrant expression has been reported. For example, some authors have reported that fibroblastic meningiomas express S100 and CD34 in up to 90 and 60% of cases respectively [16]. Although PR is normally positive, estrogen receptor (ER) is usually negative, and meningiomas that express ER typically have a worse prognosis than those that express PR alone [17]. Secretory type meningiomas often show variable cytokeratin positivity and strong staining for carcinoembryonic antigen (CEA). Finally, claudin-1 is reported to be specific, but not sensitive, for meningioma [16].

Differential Diagnosis

The differential diagnosis of meningiomas depends on their morphology. The top differential diagnostic considerations for meningothelial and secretory meningiomas are meningothelial hyperplasia and primary and metastatic carcinomas. The clinical impression of a mass-forming lesion should help to differentiate between meningioma and meningothelial hyperplasia, and a panel of cytokeratin stains can be used to rule out carcinoma. For fibroblastic meningiomas, the differential diagnosis includes many of the lesions listed herein, such as schwannoma, solitary fibrous tumor (SFT), hemangiopericytoma, and less commonly, fibrosarcoma. Positive IHC for EMA and PR, and negative IHC for S100, CD34, STAT6, and SMA help to differentiate these entities, though they must be interpreted with caution and in the context of a panel due to morphologic and immunophenotypic overlap. Higher grade meningiomas may mimic carcinoma, sarcoma, and melanoma [15, 18]. Again, an IHC panel including the markers outlined above, as well as SOX10, Melan-A or HMB45, must be used to rule out a more aggressive primary or metastatic lesion.

Encephalocele

Middle ear and mastoid cavity encephalocele, meningocele and meningoencephalocele are rare lesions consisting of herniation of brain tissue, meninges, or a combination of both, through a defect in the tegmen tympani and/or the tegmen mastoideum in the middle cranial fossa of the temporal bone. The defect may be congenital, traumatic (including local trauma from a tumor or other lesion), post-surgical, post-infectious, or idiopathic in etiology [19]. Common presenting signs and symptoms include clear otorrhea, hearing loss, headache, and in some cases, infectious complications such as meningitis or intracranial abscesses. In the age of computed tomographic (CT) and magnetic resonance imaging (MRI), the lesion is usually diagnosed preoperatively. Surgical management consists of repair of the bony defect, with either reduction (one-third) or excision (two-thirds) of the herniated tissue [19, 20]. Due to these factors, it is exceptionally rare for encephaloceles to present to the pathology laboratory as undiagnosed middle ear masses.

Pathologic Features

Histologic examination of the herniated tissue demonstrates disorganized neuroglial tissue with small, uniform, round nuclei among a fibrillary eosinophilic background, accompanied by a variable meningeal component, which is usually less prominent than the neuroglial component (Fig. 3) [20]. Often, this is accompanied by granulation tissue, evidence of prior hemorrhage, and/or perivascular chronic inflammation. The bony defect may arise from erosion of a localized process through the tegmina, thus, cholesteatomas and other lesions may be seen in association.

Fig. 3 Encephalocele: reactive neuroglial white matter (left) and fibrotic arachnoid with perivascular chronic inflammation (right and lower aspects of the field) [H&E, 100 $\times$]

Ancillary Studies

In cases with a meningeal component, IHC is positive for EMA. GFAP is positive in the neuroglial tissue.

Differential Diagnosis

A similar lesion to encephalocele, in which a connection to the normal brain tissue is not demonstrated, is designated “neuroglial heterotopia” or “neuroglial choristoma”, catchall terms for benign mature ectopic brain tissue with no connection to the brain or spinal cord [21]. The exact pathogenesis of neuroglial heterotopia is unclear; some postulate that it represented a prior encephalocele, in which the connection has been resorbed [20]. The clinical presentation and pathologic features are similar to those of encephalocele and its related lesions described above. Clinical differential diagnoses include other mass-forming lesions in the middle ear, such as cholesteatomas, granulation tissue, cholesterol granulomas, paragangliomas, and peripheral nerve sheath tumors. Histologically, encephalocele may resemble other neural and neuroglial tumors, thus, middle ear involvement by other central nervous system tumors, such as gangliocytoma and ganglioglioma, must also be ruled out.

Sclerosing Lesions of the Ear and Temporal Bone

Spindle Cell/Sclerosing Rhabdomyosarcoma

Rhabdomyosarcoma (RMS), a malignant mesenchymal neoplasm that exhibits a skeletal muscle phenotype, involves the ear in 3.9% of cases [22]. Spindle cell/sclerosing RMS has a predilection for the head and neck and has been described in the region of the temporal bone [23]. In the most recent WHO classification, spindle cell/sclerosing RMS is now separated into its own category of histologic subtypes and its relationship to other RMS subtypes is currently evolving [24]. Spindle cell and sclerosing RMS have similar clinical presentations and outcomes, overlapping morphologic and molecular features and thus, are likely related tumors in a morphologic spectrum [23, 24]. Spindle cell/sclerosing RMS in adults tends to have a more aggressive clinical course and worse outcomes compared to pediatric patients [24].

Pathologic Features

Spindle cell RMS consists of elongated spindled tumor cells with vesicular nuclei, inconspicuous nucleoli, and eosinophilic cytoplasm, embedded within a variable collagenous matrix. Rare scattered spindled to polygonal

rhabdomyoblasts with occasional cross striations and hyperchromatic nuclei may be observed (Fig. 4a). Mitotic figures, including atypical forms, are usually apparent. Pleomorphic areas and myxoid stroma are not present. Spindle cell RMS may also demonstrate areas consisting of round to spindle tumor cells with scant eosinophilic cytoplasm separated into nests, cords, pseudovascular structures, and micro-alveoli by sclerotic and hyalinized stroma that mimics osteoid or chondroid matrix (Fig. 4b). These sclerotic areas may be focal or diffuse, with the latter characterizing the sclerosing variant of RMS [23–25].

Ancillary Studies

As with other RMS, spindle cell/sclerosing RMS can express various skeletal muscle antigens including desmin, muscle-specific actin (MSA), myoglobin, myogenin and MyoD1 (Fig. 4c). Spindle cell RMS most often demonstrates strong immunoreactivity with desmin and nuclear reactivity with MyoD1 and myogenin. SMA and MSA immunoreactivity is frequently seen in spindle cell RMS [23, 24]. Sclerosing RMS typically demonstrates strong immunoreactivity for MyoD1. Myogenin is variable and may be negative or only demonstrate focal staining [23, 24]. Desmin immunoreactivity in sclerosing RMS ranges from focal to diffuse, and may on occasion exhibit a dot-like positivity [26, 27]. Aberrant expression of immunohistochemical markers have been described including cytokeratins, CD99, S100, WT1 and SMA [23–25, 28].

Cytogenetic analyses of spindle cell/sclerosing RMS have shown aneuploidy and non-recurrent structural rearrangements. *PAX3*- and *PAX7-FOXO1* gene fusions are essentially absent [23, 24]. *MYOD1* mutations have been identified, some with co-existing *PIK3CA* mutations [23, 29]. Owosho et al. demonstrated a fatal outcome in head and neck spindle cell/sclerosing RMS with adult age, sclerosing morphology and the presence of *MYOD1* and *PIK3CA* mutations, and recommended molecular evaluation of the *MYOD1/PIK3CA* hot spot mutations for risk stratification [23].

Differential Diagnosis

There are a variety of spindle cell lesions that enter the differential diagnosis of spindle cell RMS, including spindle cell (sarcomatoid) carcinoma, spindle cell or desmoplastic melanoma, malignant peripheral nerve sheath tumor (MPNST) with rhabdomyoblastic differentiation (malignant Triton tumor), cellular schwannoma, desmoid-type fibromatosis, solitary fibrous tumor, monophasic (spindle) synovial sarcoma and leiomyosarcoma. Most of these can be resolved by demonstration of immunoreactivity for myogenic markers in RMS, specifically desmin, myogenin, and MyoD1.

Fig. 4 Spindle cell and sclerosing RMS. **a** Spindle cell RMS with fascicles of spindle cells that have brightly eosinophilic cytoplasm and scattered terminally differentiated rhabdomyoblasts with striations [H&E, 200×]. **b** Sclerosing RMS with tumor cells separated by eosinophilic, hyalinizing fibrous stroma that mimics osteoid [H&E, 200×]. **c** Spindle cell/sclerosing RMS with diffuse immunoreactivity for desmin (left), diffuse nuclear immunoreactivity with MyoD1 (middle) and focal nuclear immunoreactivity for myogenin (right) [all 50×]. Spindle cell and sclerosing RMS often demonstrate diffuse nuclear immunoreactivity with MyoD1 and only focal, occasionally absent, nuclear immunoreactivity with myogenin. **d** MPNST with rhabdomyoblastic differentiation (malignant Triton tumor) with scattered rhabdomyoblasts and more typical fascicles of spindle cells at the bottom of the field [H&E, 100×]. The differential diagnosis of RMS includes malignant Triton tumor

In the head and neck region, spindle cell carcinoma is the number one diagnostic consideration for any malignant spindle cell neoplasm in an older adult. It represents an uncommon variant of either cutaneous or mucosal squamous cell carcinoma (SCC). Sarcomatoid carcinomas may also develop from salivary gland malignancies. In order to diagnosis spindle cell (sarcomatoid) carcinoma, one must demonstrate epithelial differentiation either by identifying overlying squamous dysplasia/carcinoma in situ, a focus of conventional SCC, or immunoreactivity for epithelial markers, which typically require multiple cytokeratins including markers of squamous differentiation, CK5, 34βE12 (Ker903) and p40/p63, as well as other cytokeratins and EMA. Deeper levels or additional sections, particularly of an interface with overlying epithelium, are often useful in identifying a focus of conventional SCC or squamous dysplasia/carcinoma in situ. Myogenic markers are typically negative except in rare cases that exhibit heterologous rhabdomyosarcomatous differentiation [30].

Spindle cell melanoma and desmoplastic melanoma may be confused for spindle cell RMS, particularly in an older patient. Helpful features to distinguish spindle cell melanoma and desmoplastic melanoma from a spindle cell RMS include the presence of an in situ melanoma (lentigo maligna) or junctional component and intracytoplasmic melanin pigment. Ultimately, IHC is the most useful; spindle cell melanoma typically expresses S100, SOX10 or MITF, but may be negative for HMB45, and desmoplastic melanoma expresses S100 and SOX10 and is frequently negative for other melanocytic markers [31]. Myogenic markers are usually not expressed unless there is heterologous rhabdomyoblastic differentiation [30].

Cellular schwannoma (discussed above) will demonstrate strong, diffuse staining with S100 and is negative for myogenic markers. MPNST with rhabdomyoblastic differentiation may be challenging to distinguish from spindle cell RMS. The tumor demonstrates typical histologic features of MPNST (discussed above) with areas of rhabdomyoblastic differentiation present only focally (Fig. 4d).

Myogenic markers will be positive in the focal areas with rhabdomyoblastic differentiation [30]. S100 demonstrates only limited positivity in about half of cases. Complete or partial loss with H3K27me will confirm the diagnosis of MPNST [7, 8].

Desmoid-type fibromatosis is a poorly circumscribed, infiltrative tumor that consists of fascicles of bland spindle and stellate cells with vesicular nuclei, small nucleoli and fibrillary cytoplasm embedded within an abundant collagenous stroma. Mitoses may be seen but no atypical mitotic figures or significant atypia are observed. Desmoid-type fibromatosis demonstrates a fibroblastic/myofibroblastic phenotype with at least focal SMA immunoreactivity. Desmin is rarely focally positive and myogenin and MyoD1 are negative. In addition, many cases demonstrate nuclear staining with β -catenin.

SFTs are well-circumscribed, unencapsulated tumors consisting of bland, oval-to-spindled fibroblastic cells arranged in “patternless” pattern with alternating collagenized and hypercellular areas and staghorn-shaped vessels. SFTs are typically positive for STAT6 and CD34. Focal staining with SMA may be seen in rare cases but desmin, myogenin and MyoD1 are negative.

Monophasic spindle cell synovial sarcoma consists of a uniform population of mildly atypical spindle cells arranged in fascicles. Monophasic spindle cell synovial sarcomas are immunoreactive for TLE-1 (nuclear) and focally for epithelial markers, particularly EMA and low molecular weight cytokeratins CK7, CK8, CK18 and CK19. Myogenic markers are not expressed. Synovial sarcoma is characterized by t(X;18) translocation.

The differential diagnosis of sclerosing RMS includes angiosarcoma, sclerosing epithelioid fibrosarcoma, extraskeletal osteosarcoma, primary or metastatic carcinomas, and sclerosing non-Hodgkin lymphoma. As with spindle cell RMS, most of these can be resolved by demonstrating expression of myogenic markers, specifically desmin, myogenin, and/or MyoD1.

Angiosarcoma, a tumor of older adults, enters the differential when sclerosing RMS exhibits a pseudovascular pattern. Angiosarcomas are infiltrative tumors that consist of irregular, branching and anastomosing vascular channels lined by atypical spindled to epithelioid tumor cells. Angiosarcomas are immunoreactive for various vascular markers including CD34, ERG, CD31, Factor VIII related protein and FLI-1, and are negative for myogenic markers.

Sclerosing epithelioid fibrosarcoma is a rare tumor composed of cords, single-file arrays, and nests of epithelioid cells with clear-to-eosinophilic cytoplasm and round to oval nuclei, embedded within a dense collagenous stroma. Usually areas resembling low-grade fibromyxoid sarcoma (Evans tumor, LGFMS) or adult-type fibrosarcoma are found. Myogenic markers are not expressed and MUC4 is frequently positive.

Extraskeletal osteosarcoma occurs predominantly in adult patients and rarely involves the head and neck region. The lace-like osteoid of osteosarcoma can be distinguished from the hyalinizing sclerotic stroma of sclerosing RMS by the

presence of matrix mineralization/ calcification. The tumor cells of osteosarcoma are also usually larger and more pleomorphic than those of sclerosing RMS. IHC for myogenic markers are typically negative in osteosarcoma.

Primary or metastatic carcinomas can be distinguished from sclerosing RMS by the demonstration of immunoreactivity for epithelial markers and lack of expression of myogenic markers. Sclerosing non-Hodgkin lymphomas are immunoreactive for CD45 as well as various B- and T-cell markers depending on the lymphoma subtype; myogenic markers are not expressed.

Sclerosing Epithelioid Fibrosarcoma

Sclerosing epithelioid fibrosarcoma (SEF) is an exceedingly rare variant of fibrosarcoma that is morphologically low grade but demonstrates an aggressive clinical course. Although the literature contains small series and reviews with variable follow-up, the local recurrence rate, metastatic rate and mortality rate are in the ranges of 36–50, 83–86 and 34–57% respectively [32, 33]. Only a few cases have been reported in the area of the temporal bone [33–35].

Pathologic Features

SEF is a well-defined but focally infiltrative, multinodular, hypocellular tumor separated by fibrous septae. The epithelioid tumor cells have clear-to-eosinophilic cytoplasm and are arranged in single-file arrays, nests, cords, and occasionally acini separated by dense collagenous stroma (Fig. 5a). Areas resembling LGFMS are often seen and these examples are referred to as hybrid LGFMS-SEF (Fig. 5b). Necrosis may occasionally be seen and mitoses are inconspicuous.

Ancillary Studies

SEF has a fibroblastic or occasionally myofibroblastic phenotype and thus, a non-specific immunoprofile with staining for vimentin and sometimes SMA. About 50% of cases may demonstrate immunoreactivity with EMA but negativity for cytokeratins. IHC expression of MUC4, which is a consistent finding in LGFMS, has been described in more than 70% of SEF and in all hybrid tumors (Fig. 5c) [36, 37]. Because of the morphologic and immunohistochemical overlap, a potential relationship between LGFMS and SEF has been suggested. Many LGFMSs and some SEFs have been shown to contain *FUS* rearrangements. Less common, *EWSR1* rearrangements have been described [36–38].

Differential Diagnosis

The differential diagnosis of SEF includes sclerosing RMS, extraskeletal osteosarcoma, and primary and metastatic

Fig. 5 Sclerosing epithelioid fibrosarcoma and low-grade fibromyxoid sarcoma. **a** SEF with single-file arrays of small epithelioid cells among dense collagenous stroma [H&E, 40 $\times$]. **b** LGFMS (Evans tumor) with alternating collagenous and myxoid areas at the top of the field, imparting a “tiger stripe” appearance [H&E, 40 $\times$]. **c** LGFMS is diffusely and strongly positive for MUC4 on immunohistochemistry [MUC4, 200 $\times$]. Sclerosing epithelioid fibrosarcoma often has areas that resemble LGFMS (hybrid SEF-LGFMS), and 70% of SEF and all hybrid SEF-LGFMS are MUC4 positive

sclerosing carcinoma. In terms of mesenchymal neoplasms, MUC4 is highly specific for SEF, and strong diffuse positivity has only been described in the glandular component of biphasic synovial sarcoma. Thus, MUC4 positivity will

exclude extraskeletal osteosarcoma and sclerosing RMS. In addition, SEF is negative for myogenic markers. However, many carcinomas are also immunoreactive for MUC4, therefore negative staining with cytokeratins would be helpful to exclude a primary or metastatic sclerosing carcinoma.

Sclerosing Paraganglioma

Middle ear paragangliomas (PGLs) arise from the paraganglia of the jugular bulb or middle ear medial promontory wall and account for about 30% of head and neck PGLs [39]. They may be sporadic or familial. Sporadic PGLs are more common in females whereas familial PGLs are more common in males. There are five autosomal dominant PGL syndromes (PGL1-PGL5) characterized by different germline activating mutations in the succinate-ubiquinone oxidoreductase gene (*SDH*) family of genes and associated with other tumors including gastrointestinal stromal tumors, renal tumors and pituitary adenomas [39]. For PGL1-3, the head and neck region is the most common site for development of a PGL, with a significant portion of those associated with PGL4 occurring in this anatomic location as well. In addition, PGLs resulting from at least three of these syndromes have been reported in the middle ear specifically (PGL1, PGL2, and PGL4). Familial PGLs account for approximately 40% of head and neck PGLs and are often bilateral and multifocal, highlighting the importance of correct diagnosis and additional testing for *SDH* mutations in all cases (discussed below) [39]. Other syndromes that may have PGLs include NF1, Von Hippel-Lindau, and multiple endocrine neoplasia 2. The most common symptoms include pulsatile tinnitus, hearing loss and pain. Clinical examination reveals a vascular mass posterior to the tympanic membrane. PGLs, including middle ear PGLs, are no longer considered to be benign tumors and are now considered to be tumors of indeterminate behavior. The metastatic rate in middle ear PGLs is approximately 2–5% [39, 40].

Pathologic Features

Middle ear PGLs are unencapsulated, usually infiltrative, moderately cellular tumors that consist of tumor cells arranged in the characteristic zellballen or clustered architecture embedded within a richly vascular stroma. Surrounding these nests are sustentacular cells that may be difficult to appreciate on routine hematoxylin and eosin (H&E) stains. The tumor cells are small to intermediate in size with variable cytoplasm that may be granular, clear, basophilic, or fibrillary. In general, the nuclei are uniform in appearance with delicate chromatin (Fig. 6a). Isolated marked nuclear atypia may be seen. Mitoses are rare and occasionally, multinucleated cells are present.

Fig. 6 Paraganglioma. **a** Paraganglioma with classic features: zellballen architecture, small ovoid nuclei, clumped chromatin, amphophilic to granular cytoplasm, and delicate vasculature [H&E, 200×]. **b** Sclerosing paraganglioma with similar features to (a), with the addition of irregular thick bands of dense collagen [H&E, 100×]. **c** Sclerosing paraganglioma with diffuse immunoreactivity for synaptophysin [Synaptophysin, 100×]. **d** Paraganglioma with immunoreactivity for S100 protein in the sustentacular cells, highlighting the zellballen architecture [S100, 100×]. **e** SDHB-deficient paraganglioma, note the internal positive control, consisting of endothelial and mesenchymal-stromal cells, which show cytoplasmic granular staining, whereas the paraganglioma tumor cells show global loss of cytoplasmic granular reactivity [SDHB, 200×]

Degenerative changes are common after embolization procedures. Importantly, glandular structures and mucin are absent.

Sclerosing PGL is an important morphologic variant to recognize as it is often initially mistaken for carcinoma. In this variant, the nests of tumor cells are separated by irregular bands of hyalinized fibrous tissue that separate the tumor cells into irregular nests and cords (Fig. 6b) [41]. At the periphery of the lesion, the areas of sclerosis impart an infiltrative growth appearance [41].

At present, there are no reliable histologic features to determine malignancy in PGL [39, 40]. The presence of infiltration, mitoses, necrosis, vascular invasion or nuclear atypia is not sufficient to determine metastatic risk.

Ancillary Studies

In the majority of cases, the tumor cells of paraganglioma are immunoreactive for neuroendocrine markers including synaptophysin, chromogranin, CD56, and NSE (Fig. 6c). S100 and GFAP highlight the supporting sustentacular cells (Fig. 6d). Most importantly, cytokeratins are negative.

Familial or hereditary PGLs demonstrate germline inactivating mutations in any of the genes of the *SDH* family, including *SDHA*, *SDHB*, *SDHC* and *SDHD*. The *SDH* family of proteins bind together to form the mitochondrial complex II. SDHB antibody is sensitive to alterations in this mitochondrial complex and loss of staining with SDHB indicates mutation in any of the four *SDH* genes; therefore, IHC for SDHB is a useful marker to screen for familial syndromes and is recommended for testing in all cases (Fig. 6e) [39].

Differential Diagnosis

The main differential diagnosis of PGL in the middle ear includes schwannoma, meningioma, middle ear adenoma, and primary or metastatic carcinoma, particularly in the case of sclerosing PGL. Schwannoma is strongly and diffusely positive for S100, whereas only the sustentacular cells of PGL are immunoreactive for S100. Unlike PGLs, meningiomas are negative for synaptophysin and chromogranin

and are usually positive for EMA. PGLs are negative for cytokeratins, which is the most reliable marker to distinguish it from a middle ear adenoma and carcinoma.

Fig. 6 (continued)

Other entities, in addition to carcinoma, that may enter the differential in the case of sclerosing PGL including SEF, which is distinguished by the lack of staining with neuroendocrine markers and frequent immunoreactivity with MUC4, and sclerosing RMS, which is distinguished from sclerosing PGL by immunoreactivity for myogenic markers.

Myofibroblastic Lesions of the Ear and Temporal Bone

Nodular Fasciitis

Nodular fasciitis is considered to be a benign, self-limited proliferation of myofibroblasts that presents as a superficial solitary mass. In some instances, there is a prior history of trauma in the region. The head and neck is a common location for nodular fasciitis, especially in children and young adults, and it has been described in the literature both in the region of the ear and in the ear itself [42, 43].

Pathologic Features

Nodular fasciitis is usually superficially located, most often centered within the fascia. It consists of plump, spindled fibroblasts and myofibroblasts with tapering fibrillary cytoplasmic processes resembling tissue culture fibroblasts, arranged in a loose storiform pattern with microcysts and extravasated red blood cells in a myxoid background (Fig. 7a, b). Mitoses are common, but atypical mitoses are absent, and there is no significant nuclear atypia. Chronic inflammation and multinucleated giant cells may be seen. Over time, the stroma becomes more collagenized with deposition of keloidal collagen.

Fig. 7 Nodular fasciitis and differential diagnosis, LGFMS. **a** Nodular fasciitis, low power: spindle cells with low to moderate cellularity and a fibromyxoid background [H&E 40×]. **b** Nodular fasciitis, high power: spindled and stellate “tissue culture” fibroblasts in a fibromyxoid background [H&E, 200×]. **c** LGFMS: despite its bland, low-grade appearance pictured here, LGFMS must be differentiated from nodular fasciitis because it follows a more aggressive clinical course [H&E, 200×]

Ancillary Studies

In classic nodular fasciitis with loose myxoid stroma, immunohistochemical stains are typically not necessary. The lesional cells demonstrate a myofibroblastic phenotype with positive staining for SMA and calponin, and negative staining for S100 and cytokeratins. Desmin may occasionally be

focally positive. Nearly all nodular fasciitis demonstrate a *MYH9-USP6* gene fusion [44], which is helpful to distinguish nodular fasciitis from its mimics including fibromatosis, fibrosarcoma, and LGFMS.

Differential Diagnosis

The differential diagnosis for nodular fasciitis varies depending on the amount of stromal collagen and includes LGFMS, fibromatosis, and inflammatory myofibroblastic tumor (IMT). LGFMS is rare in the head and neck with about 20 reported cases [45], and unlike nodular fasciitis that tends to be superficial, LGFMS are typically deep. LGFMS consist of bland spindle cells with alternating myxoid and fibrous areas imparting a “tiger stripe” appearance, and prominent arching vessels. Despite its low-grade morphology, as with SEF (discussed above), it has an aggressive clinical course. LGFMS may be EMA, bcl-2 and SMA positive, and is negative for S100, cytokeratins and nuclear β -catenin [45]. LGFMS demonstrates strong, diffuse staining with MUC4, which is the most useful immunohistochemical marker to distinguish LGFMS from its histologic mimics including fibromatosis, perineurioma and nodular fasciitis [38, 45]. Most often LGFMS demonstrate *FUS* rearrangements [38]. In cases that lack *FUS* rearrangements, *EWSR1* rearrangements have been identified [46].

Fibromatosis may occur in the head and neck, especially in younger patients. It is a poorly circumscribed hypocellular tumor consisting of elongated fascicles of bland, spindle cells with vesicular nuclei and small, punctate nucleoli, set in an abundant collagenous stroma. Mitoses may be seen in more cellular lesions but no atypical mitotic figures or cytological atypia are observed. The spindle cells demonstrate a fibroblastic/myofibroblastic phenotype with at least focal staining for SMA and most cases demonstrating nuclear immunoreactivity with β -catenin. Fibromatosis and nodular fasciitis with more abundant stromal collagen and focal infiltration into skeletal muscle may have similar appearances, especially on biopsy. However, fibromatosis is often larger and more infiltrative. The presence of nuclear β -catenin in fibromatosis and *MYH9-USP6* gene fusion in nodular fasciitis distinguishes the two entities.

IMT has been reported in the head and neck and is more commonly encountered in children and young adults [47]. IMT consists of spindle to stellate myofibroblastic cells that can be loosely dispersed within an edematous/myxoid stroma containing abundant blood vessels or arranged in fascicles within a variably collagenized stroma with prominent mixed inflammatory infiltrate, consisting of lymphocytes, polyclonal plasma cells, neutrophils and eosinophils. Occasionally, larger “ganglion-like” cells are seen. The tumor cells are immunoreactive for SMA, calponin, and desmin, and some cases demonstrate cytokeratin positivity. About

50% of cases are anaplastic lymphoma kinase (ALK)-1 positive, mainly in the visceral examples arising in childhood, often with corresponding *ALK* gene rearrangements [47]. In contrast to nodular fasciitis, IMTs tend to be less cellular with a more prominent heterogeneous inflammatory cell component that includes neutrophils. In addition, the spindle cells of IMTs are more diffusely positive for SMA and IMTs lack the *MYH9-USP6* gene fusion.

IgG4-Related Disease

IgG4 related diseases (IgG4-RD) are fibrosing and inflammatory lesions that can affect one or multiple organs. The entity was first described in the pancreas in 2001. In the head and neck, possible sites of involvement include salivary glands, lacrimal glands and periocular tissue, thyroid gland, upper aerodigestive tract, lymph nodes, soft tissue, and skin [48, 49]. Cases described in the past as Mikulicz’s syndrome (bilateral enlargement of salivary and/or lacrimal glands), Kuttner tumor (chronic sclerosing sialadenitis), Riedel’s thyroiditis, and even some cases of Hashimoto thyroiditis were in fact part of the spectrum of IgG4-RD [48–50].

Pathologic Features

IgG4-RD share three common histologic findings: fibrosis, chronic lymphoplasmacytic inflammatory infiltrate, and sclerosing phlebitis (Fig. 8a). The fibrosis is composed of spindle cells within a collagenous background. The spindle cells are focally seen radiating perpendicular to a central point giving the lesion a storiform architecture composed of fibroblasts and myofibroblasts. The fibrosis may appear hypercellular, but the hypercellularity is mainly caused by an elevated number of inflammatory cells. The inflammatory infiltrate includes lymphocytes with possible germinal centers, and a high number of plasma cells. Eosinophils can be present but are not usually prominent. The sclerosing phlebitis affects small- and medium-sized veins with a dense lymphoplasmacytic infiltrate within the vascular wall, possibly obstructing the lumen.

Ancillary Studies

In addition to the histologic findings, the diagnosis of IgG4-RD relies on IHC studies and clinical correlation [51]. IHC helps to identify IgG4-secreting plasma cells (Fig. 8b); their absolute number per HPFs and their relative ratio to total IgG-secreting plasma cells help to qualify the biopsy findings into a three tier classification system that was described in the 2012 consensus statement: highly suggestive of IgG4-RD, probable histological features of IgG4-RD, and insufficient histological findings to suggest IgG4-RD [52]. Of note, the absolute number of

Fig. 8 IgG4-related disease and IMT. **a** IgG4-related disease: sclerosis and mixed inflammatory infiltrate with lymphocytes, plasma cells, and eosinophils (note: this is a representative case, which is from the submandibular gland) [H&E, 200×]. **b** IgG4-related disease: IHC staining for IgG4 (left) shows both an absolute increase in IgG4 as well as a relative increase in comparison to all IgG-stained plasma cells (right) [200×]. **c** IMT: mixed spindle and inflammatory cells in a collagenized and mildly edematous background [H&E, 100×]. **d** IMT: a few plump spindle cells, sclerotic collagen, and a dense mixed inflammatory infiltrate consisting of lymphocytes, plasma cells, and eosinophils [H&E, 200×]

IgG4-secreting plasma cells criterion varies between different organs. Additional clinical, serological, and radiological findings are however still necessary for a definite diagnosis of IgG4-RD.

Differential Diagnosis

Any chronic inflammatory process can be associated with a lymphoplasmacytic infiltrate and reactive fibrosis, but should not be associated with a proportional significant increase of IgG4-secreting plasma cells. Granulomas and/or neutrophilic infiltrate usually exclude the diagnosis of IgG4-RD. In addition, IgG4-secreting plasma cells can be found adjacent to malignant tumors including lymphoma, and may cause difficulty in small biopsy samples that may not be representative of the overall lesion.

The most likely tumoral lesion to be confused with IgG4-RD is IMT, which is also associated with a lymphoplasmacytic cellular infiltrate (Fig. 8c, d). IMTs are usually mass-forming and well-circumscribed [47, 53]. They are most commonly present in the lungs, but may occur rarely in the head and neck region. They have a 25% risk of local recurrence, and rarely, cases of distant metastases have been described. IMTs have been reported in the maxillary sinus, ethmoid sinus, sphenoid sinus, masticator space, infratemporal fossa, nasal cavity, parotid gland, orbit, and larynx [47, 54]. They are predominantly composed of myofibroblasts, which have more eosinophilic cytoplasm, vesicular nuclei with distinct nucleoli, and epithelioid appearance that can resemble ganglion-like cells, in addition to spindle and stellate cells. The tumor cells are found within a myxoid background that may degenerate into a more hyalinized, fibrous background. Nuclear atypia can be significant, and the lesion is more likely to be confused with malignancy. Immunohistochemical studies are useful to confirm the myofibroblastic phenotype. Overexpression of ALK-1 and/or *ALK-1* rearrangement is seen in the lesions of the larynx and approximately half of most other organ sites [55]. However, *ALK-1* does not seem implicated in most adult sinonasal IMTs [56].

Solitary Fibrous Tumor

SFT is a rare spindle cell neoplasm that usually occurs in adults. SFT of the head and neck most commonly involve the orbit, oral cavity and meninges, but has been described in the external ear and auditory canal [57–60]. SFTs are typically benign but malignant variants exist and have been reported in the head and neck [61]. Features that suggest malignancy include patient age > 55 years, large tumors (> 15 cm) with necrosis, nuclear pleomorphism, and increased mitoses [60]. In the head and neck, recurrence is related to incomplete resection.

Pathologic Features

SFTs are usually well-circumscribed, unencapsulated tumors of variable cellularity, consisting of bland, ovoid-to-spindled fibroblastic cells in a “patternless” pattern with alternating collagenized and hypercellular areas (Fig. 9a). Typically, there is a hemangiopericytoma-like vascular pattern with ectatic, branching vessels that occasionally demonstrate perivascular hyalinization. In some cases, there are thick bands of hyalinized, keloidal collagen between the tumor cells. A particularly helpful diagnostic clue, especially on biopsy, is the characteristic “cracking” between the collagen bundles and the tumor cells (Fig. 9b). On occasion, SFTs may demonstrate a myxoid stroma, which can be extensive. A subset of SFTs may contain variable amounts of mature adipose tissue and if the adipocytic component is prominent, these may be referred to as fat-forming SFTs. Microscopic features that are worrisome for malignancy include more than 4 mitoses per 10 HPFs, tumor necrosis, increased cellularity, nuclear pleomorphism, and high nuclear-to-cytoplasmic ratios [60].

Ancillary Studies

SFTs commonly express strong, diffuse staining with CD34, CD99, and bcl-2. SMA may be seen in a small proportion of cases but desmin, keratins, S100, and nuclear β -catenin are usually negative. Strong nuclear immunoreactivity with STAT6 is considered to be sensitive and specific for SFT (Fig. 9c) [62, 63]. Low levels of cytoplasmic and/or nuclear expression have been identified in other mesenchymal neoplasms and are of uncertain significance [64]. A recurrent *NAB2-STAT6* gene fusion has been identified in SFT and is implicated in almost all SFTs, both benign and malignant.

Differential Diagnosis

The differential diagnosis of SFT includes schwannoma, neurofibroma, benign fibrous histiocytoma, fibromatosis, spindle cell RMS, monophasic spindle synovial sarcoma

Fig. 9 Solitary fibrous tumor. **a** SFT with “patternless” pattern of short spindle cells, fibrous background and hyalinization seen around the vessel in the upper central aspect of the field [H&E, 40 $\times$]. **b** SFT with characteristic “cracking” artifact between the hyalinized collagen bundles and spindle cells [H&E, 200 $\times$]. **c** SFT with diffuse nuclear immunoreactivity for STAT-6 [STAT-6, 100 $\times$]. STAT-6 is a very specific marker for SFT

and spindle cell (sarcomatoid) carcinoma. In general, the histologic features including pattern of growth, cellular features and stromal characteristics, along with

immunoreactivity with STAT6 (nuclear) and CD34 and molecular alterations will distinguish SFT from its histologic mimics.

Compliance with Ethical Standards

Conflict of interest The authors have no conflicts of interest to disclose.

Ethical Approval This article does not contain any studies with human participants performed by any of the authors.

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