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Meninges Outside the Meninges: Ectopic Meningiomas and Meningothlelial Proliferations

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Abstract

Extracranial meningiomas have been reported for decades now and have been described in the head and neck; calvarial, nasal cavity, paranasal sinuses, nasopharynx, parotid gland and in various remote anatomical locations systemically. The presence of microanatomical structures for all intents and purposes resembling and having the histopathological characteristics of meninges outside of the central nervous system meninges is uncommon but well-documented. Typically, these lesions are found in the lung or part of hamartomatous/choristomatous lesions and frequently occur in the head and neck anatomical region. The lesion first described by Suster and Rosai termed "hamartoma of the scalp with ectopic meningothelial elements" is the prototypical example of lesions with meningothelial elements. We have described recently a similar hamartomatous lesion with meningothelial elements occurring in the tongue. In this chapter, we will review the clinicopathological features of ectopic meningiomas and lesions that contain meningothelial elements and their possible pathogenesis.

Keywords: ectopic, meningioma, meningothelial, hamartoma, choristoma, pathology

1. Introduction

This chapter will cover, in brief, clinical and pathological characteristics of what are known as primary ectopic meningiomas (PEM) and the presence of tissue histomorphologically and immunophenotypically consistent with meningeal tissue (meningothelial) occurring in other organs or as part of teratomas or hamartomas/choristomas. PEMs, that is, those that occur outside of the central nervous system (CNS) can occur as a result of direct extension of a primary CNS meningioma (through calvarial bone into adjacent soft tissue), as a metastatic lesion, or as a primary ectopic meningioma [1]. Cutaneous meningiomas or primary cutaneous meningiomas describe a subset of PEMs mostly found in the scalp and have a classification system delineated by whether lesions are congenital or acquired and whether they have connection to a primary intracranial meningioma. Type I are congenital and may present as midline scalp cystic lesions (rudimentary meningoceles, acoelic meningeal hamartomas). Rarely sinus tracts have been found connecting these to the CNS. Type II are soft tissue meningiomas that have predilection for the nose, mouth, eyes, and ears and have no connection to an intracranial meningioma. Type III are soft tissue extensions of a primary intracranial meningioma [2]. Meningothelial tissue (not meningioma) can be seen most

notably described in the lungs and rarely in hamartomas/choristomas (lesions composed of tissue types arranged haphazardly but indigenous to the location; hamartoma or not indigenous to location; choristoma) particularly in the head and neck location. PEM have been described in teratomas and meningothelial tissue is not an infrequent component of mature neuroglial tissues in teratomas (tumors composed of tissues derived from all three primordial germ layers). This review will focus on those some aspects of meningiomas that occur outside the CNS; the primary ectopic meningiomas and lesions where meningothelial tissue has been found with particular focus on pulmonary and gonadal (in the context of gonadal mature teratomas) meningiomas and meningothelial proliferations and separately hamartomas/choristomas particularly of the head and neck. It is these latter lesions that the author has the most familiarity from practicing in the discipline of pediatric pathology.

2. Developmental aspects of meninges pertinent to primary ectopic meningiomas and ectopic meningothelial tissue

This will be a brief section and by no means an exhaustive treatment of the embryological, morphological and molecular genetics aspects of meninges development. For a more thorough review of meninges development, the reader is directed to the excellent reviews by Dasgupta and Jeong [3] and Lopes [4]. However, here, we will attempt to highlight elements of what is known about the embryological and particularly molecular pathways involved in meninges development as it may relate to the development of meningiomas and the presence of meningothelial tissues in other anatomical locations outside of the central nervous system (CNS) proper.

In contrast to other areas of CNS development, relatively little is known about the molecular characteristics of meninges development. In a broad sense, however, the meninges increasingly are being shown to be critical to proper calvarial and underlying brain development. It is noted that the cranial meninges are derived from two cellular pools; the neural crest (ectoderm) and mesoderm. Neural crest derived cells can be found in the three layers of meninges covering the forebrain cerebral hemispheres but not in the meninges covering midbrain or hindbrain. Calvarial development closely parallels meninges development in that the frontal bones are primarily neural crest derived while the parietal bones are of mesodermal origin. Foxc1 is a key and ubiquitously expressed transcription factor in meninges development with noted early upregulation in the primary meninx. Its prominent role is demonstrated by lack of apical arachnoid and dura mater formation as well as lack of apical calvarial development in Foxc1 mutant mice. Parietal bone development appears to depend on the underlying meninges (derived from neural crest) expressing transforming growth factor beta 2 receptor (Tgfbr2) as Tgfbr2 mutant mice show severe defects in both parietal bone and underlying meninges development. The dura or outer dense layer of the meninges becomes closely apposed to the underside of the bony calvarium and is the de facto periosteal layer. The mesenchyme around the developing brain is divided into layers that include a dermal layer (dermis of scalp), skeletogenic layer (skull), and then the meningeal primordium. By extension, it can be plausible that ectopic meningiomas can arise (and indeed do) in the bones of the calvarium and scalp. It has been proposed that arachnoid cells or precursors can migrate with cranial nerves as they exit their foramina during development and be the forerunners of primary ectopic meningiomas in anatomic regions such as the orbit, ear, and neck [1]. Meninges appear to play crucial roles in brain development including providing trophic factors for neuronal survival, migration/positioning of neurons, neuronal generation from neuronal progenitors, blood vessel development, corpus callosum development, and may provide a niche for neural stem cells [5].

Again, by extension, it is not implausible to think that since much of the structures comprising the head and neck are derived from neural crest (and mesenchymal) cells, cells with multipotent capabilities, that some of these cells could be dormant and later directed down a path of meningeal differentiation in aberrant locations.

3. Primary ectopic (extracranial) meningiomas

To begin this section with an aside, the designation of ectopic meningiomas as "primary" necessarily implies that there may be other categories of meningiomas as "secondary", "tertiary" and so on. The terminology "primary ectopic meningioma" (PEM for brevity sake) then designates those meningiomas that are outside of the CNS that develop presumably from separate meningeal precursor cells; either ectopic arachnoid cells or perhaps cells that are multipotent (e.g. neural crest) as we have briefly noted. In some sense, this terminology is redundant since if the meningioma (or any lesion) is designated as "ectopic" that lesion is not indigenous to its normal anatomic location and would therefore be "primary". So called "secondary extracranial meningio-mas" are defined as those lesions that are an extension of an intracranial meningioma. The author has not seen further designations of meningiomas beyond secondary and it is difficult to conjure a scenario where the designation of "tertiary extracranial menin-gioma" would be applicable. In addition, in perusing this literature, the terminology is a bit confusing because different names have been applied descriptively to lesions that probably ultimately fall under an umbrella category (see above description of Type I cutaneous meningioma). Some have described extracranial meningothelial prolifera-tions in four categories: 1) extracranial extension of intracranial meningioma, 2) extra-cranial meningioma, 3) the aforementioned primary cutaneous meningioma, and 4) metastatic meningioma [6]. We already see that category 1 is what has been referenced as a Type III cutaneous meningioma and 3 presumably encompasses the spectrum of cutaneous meningiomas that include Type III. In this author's simplistic way of thinking and since this is a review, primary ectopic meningioma is not an unreasonable designa-tion because the terms denote a meningioma that is outside the CNS as a "stand alone" or primary tumor in that location. If the designation were only "ectopic meningioma" then extracranial extensions of intracranial meningiomas could technically be under that rubric. Additionally, and similarly, the term "meningothelial" seems to imply tissue that is by all standards meningeal but not a tumor (more later). Meningothelial tissue or proliferations would seem by definition to be primary and ectopic since intracranial meningothelial proliferations are really not a diagnostic category of CNS lesions except for the possibility of meningeal tissue as part of another tumor.

That aside, it is interesting when trying to quell cases of PEM from the searchable medical literature, the variety of names given to these lesions as hinted at, and the ensu-ing difficulty that arises in attempting to exactly define the numbers and types of PEM reported. As Gibson and Prayson aptly alert the reader in their excellent chapter on this subject [7], a variety of designations have been used when reporting these lesions including ectopic, extracranial, extraneuraxial, extradural, cutaneous, intraosseous, calvarial etc. In addition, case reports may designate one of these categories to describe the lesion, but indeed the lesion may actually represent a secondary extracranial menin-gioma, or the patient may have had a previous remote intracranial meningioma.

Combined with a previous review of 178 reported cases from the English language medical literature by Lang et al. [8], Gibson cited an additional 100 cases of PEM at the time of publication of their chapter (2009). In this author's brief survey of the entire medical literature not restricted to the English language from 1/1/2008 to the present, approximately 184 cases of PEM are noted after using search terms that Gibson identified as descriptors for PEMs such as "ectopic",

"extracranial", "extraneuraxial", "extradural", "cutaneous", "calvarial", "intraosseous" and "meningioma". By far, the most cases are reported from the head/neck anatomic location with intraosseous PEM by far exceeding any other location in the head and neck or elsewhere outside of the head and neck (**Table 1**). The most common site/location for PEM outside the head and neck was interestingly pulmonary followed by spinal/mediastinal/thoracic (**Table 2**).

It should not be terribly surprising that from a teleological perspective and given the developmental biology of meninges that the most commonly cited location of PEM is in the head and neck location and more specifically in the calvarial/skull bones. The intimate association of mesenchymal and/or neural crest cells in the development of the calvarial bones and meninges, particularly the dura which is directly apposed to the bone, makes this causative possibility very plausible. Likewise could be said for the greater number of cases of PEM found in the spinal/mediastinal/thoracic location. In children, certain tumors particularly neuroblastoma and its variants, can be found in this paraxial location along the sympathetic chain where neuroblasts are migrating during development.

PEM are quite uncommon as might be expected and the multiple reviews all cite basically the same incidence of approximately 1–2% of all meningiomas. Several

Site	N
Intraosseous (skull)	62
Intraosseous (mandible)	5
Intraosseous (maxilla)	1
Scalp	13
Lacrimal/orbital	11
Sinonasal	10
Parapharyngeal/neck	9
Middle ear	2
Soft tissue	2
Cheek	1
	N = 117

Table 1.
Approximate location and number of primary ectopic meningiomas in the head and neck from 2008 to present.

Site	N
Pulmonary	34
Spinal/mediastinal/thoracic	21
Cutaneous	5
Intraosseous (hip/pelvis)	3
Adrenal gland	1
Brachial plexus	1
Kidney (hilum)	1
Soft tissue (thigh)	1
	N = 67

Table 2.
Approximate location and number of primary ectopic meningiomas outside the head and neck from 2008 to present.

excellent reviews have been published identifying the clinical and pathological characteristics of PEM in general and in specific locations including intraosseous (calvarial) [9], ear and temporal bone [10], sinonasal tract [11], and pulmonary [12–15]. In addition, PEMs have been reported in skin, kidney, retroperitoneum, mediastinum, extremities, adrenal gland, ovary (mature cystic teratoma) [7], In general, for PEM, in contrast to CNS meningiomas, there is only a slight female predominance in incidence with the exception of perhaps those presenting in the ear and temporal bone where at least in the series by Rushing et al., the M:F ratio (1,2) more closely approximated the M:F ratio for CNS meningiomas in adults [16]. PEM arising in the ear and temporal bone are particularly troublesome for the pathologist as they can have a broad differential diagnosis in a location that is not the genesis of a comparatively large number of specimens that might traverse a general patholo-gist's microscope. This differential diagnosis includes entities such as paraganglioma, schwannoma, melanoma, middle ear adenoma or carcinoid, and carcinoma. The middle ear was the most common location for these PEMs with a relatively high association with cholesteatoma (9/36 cases). A smattering of histological subtypes were identified in these PEM and this is the case for PEM in general. The most com-mon histological subtype identified by far is meningothelial (range 47% to over 90% depending on site) followed at a significant distance by atypical or psammomatous [16]. As an aside, in searching our pathology archives for cases of meningioma, we found approximately 730 cases of meningioma over 20 years, with less than 5 PEMs found that were either intraosseous (calvarial) or middle ear (mastoid) (**Figure 1**) and no cases of extracranial soft tissue, visceral, or pulmonary PEMs.
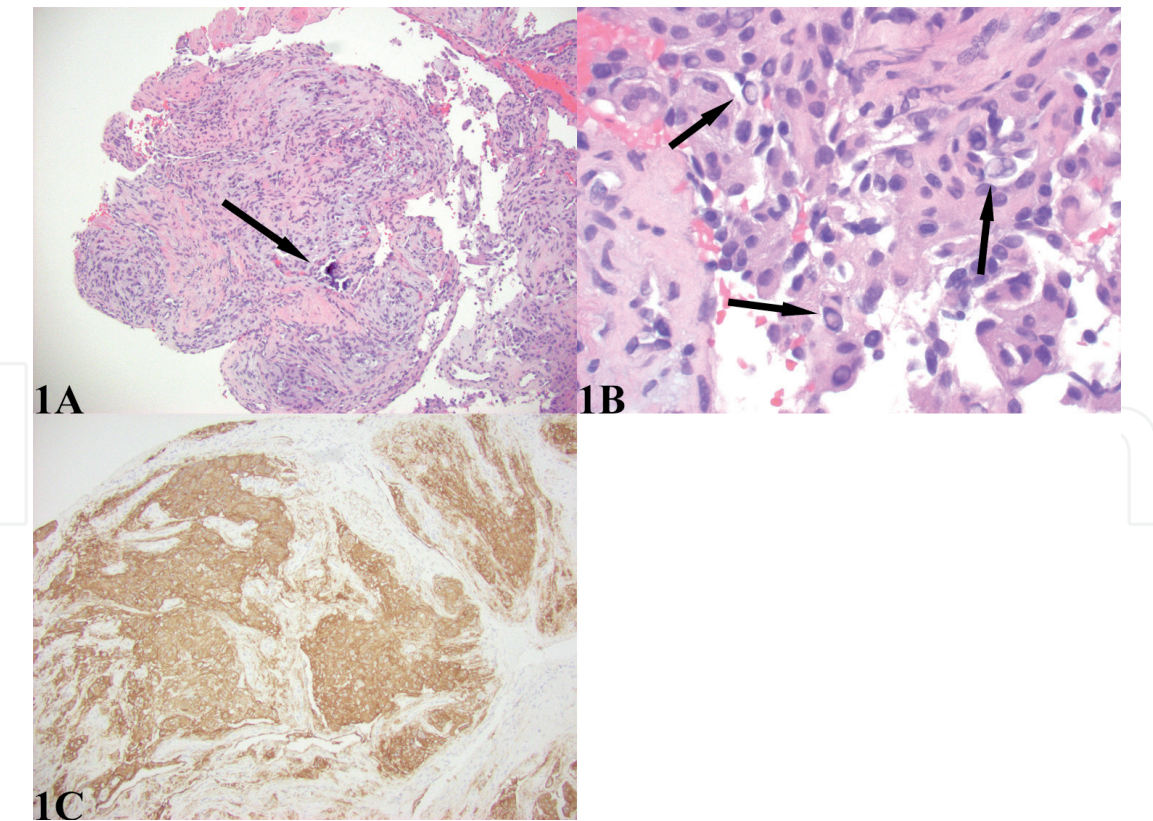

Figure 1.
Meningothelial meningioma of the mastoid presenting with tinnitus in a 46-year-old woman. No connection to the CNS was seen by imaging or intraoperatively. A: Low magnification view of meningioma composed of spindled and epitheliod cells in a whirling pattern with areas of more concentrated fibrous tissue. Scattered psammoma bodies were seen throughout the biopsy pieces (arrow, HE 40X). B: High magnification view of the relatively bland appearing nuclei with numerous pseudoinclusions, a hallmark nuclear feature of meningiomas (arrow, HE 600X). C: Diffuse staining of the meningeal lesional cells with epithelial membrane antigen (EMA 100X).

A few reviews have been published specifically addressing primary pulmonary meningiomas (PPM), that is, meningiomas that occur in the lung parenchyma as cited. Three of the four reviews included part of the time span included in the review here [12, 14, 15]. Our review provides perhaps more emphasis on the pathological phenotypes and concurrence with other tumors than other reviews.

PPMs are interesting entities for several reasons. One, their pathogenesis might not be as teleologically obvious compared to PEMs that occur say in the head and neck. Two, pulmonary meningothelial proliferations/nodules are not a terribly uncommon finding incidentally in lung resections and will be the subject of the latter part of this review as part of the spectrum of extracranial/extraneuraxial lesions of meningothelial lineage. Three, there are multiple case reports of concurrent CNS and pulmonary meningiomas [17] as well as reports of concurrent PEMs in lung and bone [18], metastases from CNS meningiomas to the lung [19] in particular, and metastases from other tumors into CNS meningiomas [20] and even metastases from PEMs to the lung [21]. Four, PPM can be mimickers of a primary lung cancer, now the second most common cancer in both men and women in the United States and therefore should be considered (albeit somewhat down the differential diagnostic list) by every pathologist who looks at lung biopsies and resections [22]. Five, pulmonary meningothelial proliferations, either sporadic or diffuse, may even be more troublesome for the pathologist. These interesting categories in the spectrum of meningiomas cannot, unfortunately, be further elucidated in this brief review.

Table 3 represents a review of the medical literature (English and non-English) searched in PubMed using the search terms "pulmonary" or "lung" and "meningioma" contained in the title/abstract from January 1, 2008 to August 16, 2021 (roughly corresponding to the last cases of PEM reported by Gibson et al. as noted). This search yielded 407 results of which 34 case reports were included reporting PPM [12–15, 18, 22–50]. One patient had two case reports approximately 10 years apart and one article published in a Spanish journal could not be obtained. The clinical characteristics (age, gender, location, size, recurrence rate) are in keeping with other reviews of PPM [12–15]. The immunohistochemical profiles were also in line with other reviews with most PPMs demonstrating staining with epithelial membrane antigen (EMA), progesterone receptor (PR), and vimentin. This review demonstrated perhaps higher numbers of both WHO grades II and III tumors (if presuming the remainder of the undesignated cases were WHO grade I which is a reasonably safe assumption).

An interesting aspect in the review of these cases and not overly emphasized in other reviews is the seemingly high number of patients with a history of other malignancies; almost one-third of the patients (10/34) with one patient having multiple (3) other tumors (osteosarcoma, fibrous dysplasia, and giant cell tumor of bone). This patient had a somatic mutation in the giant cell tumor of H3.3A and a germline mutation of BRCA2. Of course, one must be careful in drawing conclusions from a small dataset and in this case the patients with other malignancies were all in the age range where other malignancies are not uncommon (mean age 65 years, range 52–80). The malignancies in this group included buccal (1) (presumably squamous cell carcinoma), breast (2), gastric adenocarcinoma (1), papillary thyroid carcinoma (1), thymoma (1)/renal cell carcinoma (1)(same patient), rectal adenocarcinoma (1), concurrent lung adenocarcinoma (1) and teratoma (1) (immature and mature teratoma of the ovary and retroperitoneum, respectively). With the exception of the teratomas and thymoma, the other tumors are not uncommonly seen in this age group. As an aside, the PPM in the patient with teratomas does raise the remote possibility of a meningothelial/meningioma metastases from one of the teratomas particularly since one teratoma was designated as immature.

Characteristic	N = 34 cases
Age at presentation (years) (n = 34)	
Mean (SD)	57.1 (17.8)
Range	18–108
Median	60
Gender (M:F)	9:25 (1:2.8)
Symptoms at presentation	11 (23- no designation)
Follow-up (n = 17)	
Disease free/no recurrence	17
Mean (years) (SD)	3.2 (4.5)
Range	0.17–20
Patients with history of other malignancies	10/34
Multiple PPM	3/34
Site (R/L)	19:15
Size (cm) (n = 31)	
Mean (SD)	2.4 (2.6)
Range	0.45–15
Histological type (n = 29)	
Malignant	3
Atypical	1
WHO I	2
Transitional	5
Chordoid	2
Fibrous	1
Meningothelial	1
Psammomatous	1
Rhabdoid	1
Intrapulmonary metastases	1
No designation	17
WHO grade (I, II, III)	28/3/4*
Psammoma bodies	11/15
No designation	20
Epithelial membrane antigen/EMA +	30/30 (5-no designation)
Progesterone receptor (PR) +	17/18 (17-no designation)
Vimentin +	20/20 (15-no designation)
S100 +	6/14 (21-no designation)
Cytokeratins +	0/16 (19-no designation)
Ki-67 (≥ 10%)	3/14 (15-no designation)
≥ 10%	3
< 10%	13
No designation	19

*- One patient had two asynchronous tumors.

Table 3.
Review of clinical and pathological characteristics of primary pulmonary meningioma 2008–2021.

A 21-year-old female with Diamond-Blackfan anemia was included in this cohort who presented with a chordoid histology PPM [39]. Diamond-Blackfan anemia (DBA) is an inherited bone marrow failure syndrome that has approximately 20 known genetic aberrations in genes encoding small/large subunit associated ribosomal proteins (RPS and RPL genes) [51]. A cursory review shows no definitive RPS or RPL genes to be associated with any of the non-neurofibromatosis, type 2 (NF2) associated genes known to be mutated in meningiomas [52–54]. While DBA is associated with higher rates of other cancers including osteosarcoma, vaginal squamous cell carcinomas, esophageal cancer, colon adenocarcinoma, and myeloid leukemias, increased risk for meningiomas have not been seen in patients with DBA to date [51]. However, subsequent to the publication of this young patient with DBA and chordoid meningioma, she was found to have a mutation of the RSP19 gene [51].

As noted, one patient in this cohort had papillary thyroid carcinoma (PTC). An interesting epidemiological study by Sughrue et al. [55] showed that compared to the expected prevalence for a similar population, patients with meningioma had a statistically higher incidence of papillary thyroid cancer and acute leukemia. From a pathology perspective, it is also interesting that both tumors share at least one characteristic histopathological feature; psammoma bodies. Psammoma bodies can be seen characteristically in several tumors including PTC, meningiomas, serous cystadenocarcinoma of the ovary, and melanotic schwannoma (one of the tumors with high prevalence in Carney syndrome). The pathogenesis of psammoma bodies is still controversial with theories involving vascular thrombosis of papillae, followed by calcification and endothelial necrosis. More recently, osteopontin (OPN), a calcium-binding glycophosphotein has been implicated in the formation of psammoma bodies being expressed in CD68 positive macrophages along with other factors that include alkaline phosphatase, osteocalcin, metalloproteinases, bone sialoprotein, and others [56]. OPN expression has been shown to be increased in meningiomas compared to normal meninges, correlates with histological grade, and is a predictor of recurrence in WHO grade I tumors [57, 58].

The pathogenesis of PPM and PEM particularly those outside of the head and neck, of course, remains speculative as do many aspects of normal meninges development as noted earlier. Hypotheses regarding the origin of PEMs have included ectopic arachnoid cells that are present in cranial and peripheral nerve sheaths and in cranial sutures, misplacement of arachnoid cells during development, pluripotent mesenchymal cells, perineurial cells of peripheral nerves, and entrapped meninges at sites of trauma [7, 16]. Meningiomas, arachnoid cap cells (cells making up the outer layer of the arachnoid mater and villi), and spindle cells within perineurium express EMA that is detected immunohistochemically. While nearly all meningiomas and perineuriomas express EMA, only about one-third of meningiomas express glucose transporter-1 (GLUT-1) while most perineuriomas express GLUT-1. Similarly, SSTR2 and PR are expressed in a high percentage of meningiomas compared to perineuriomas while the reverse is true for claudin-1 [59]. Indirect support for pluripotent mesenchymal cells as the cell of origin for PEMs derives from the fact that meningiomas can exhibit histologically other tissue types including bone, cartilage, muscle, vascular, and other tissues. With regards to PPM specifically, two theories have arisen regarding their pathogenesis. The first is similar to what has been proposed for PEMs elsewhere; pluripotent mesenchymal cells that reside in the subpleural region or from "precursor" lesions known as minute pulmonary meningothelial nodules (MPMN, more on these later) [12]. Both PPM and MPMN share some similar phenotypes particularly the expression of similar immunohistochemical markers (EMA, PR, vimentin) but it is certainly unclear if MPMNs are truly precursors of PPM. Indeed, there seems to be some

discrepancy in incidence of MPMN and meningiomas in autopsy series leading some to conclude that MPMN cannot be a precursor lesion [12]. Some have argued that MPMN are not precursor lesions based on genotyping studies demonstrating higher frequencies of loss of heterozygosity (LOH) and LOH affecting different loci in meningiomas compared to MPMN [60]. It is interesting that a progression of increasing frequency of LOH was noted from solitary MPMN to meningotheliomatosis to meningioma. Weissferdt et al. demonstrated that MPMN do share some genotypic alterations with PPM and CNS meningioma particularly deletion of the NF2 gene and gains of chromosome 22q [61]. The distinction between the two has mostly been by somewhat arbitrary size criteria (≤ 3 mm for MPMN). PPMs also tend to form a "mass" displacing lung.

From the pathology perspective, PEMs present specific and diverse diagnostic challenges. This is largely due to the variable histomorphologies that have been described not only in CNS meningiomas but also in PEMs and the various locations that PEMs can occur which raise different differential diagnoses. The differential diagnoses for PEM in the middle ear and temporal bone has already been discussed. For all PEMs in the head and neck location, Rushing et al. found paraganglioma, schwannoma, and metastatic carcinomas to be the most frequent misdiagnoses for ear and temporal bone PEM; Carcinoma, melanoma, olfactory neuroblastoma, and aggressive psammomatoid ossifying fibroma for sinonasal tract PEM, and dermatofibroma, melanoma, fibrosarcoma, leimyosarcoma, and synovial sarcoma for soft tissue and skin PEM [16]. The differential diagnosis for PPMs brings a variety of entities that can occur in the lung and mediastinum. These include sarcomatoid mesothelioma, solitary fibrous tumor, spindle cell thymoma, spindle cell carcinomas, inflammatory myofibroblastic tumor, synovial sarcoma, epithelioid hemangioendothelioma, and of course metastases [12]. As noted, meningiomas can present with a wide range of histological features including meningothelial, fibrous, microcystic, transitional (spindle cell component) psammomatous, angiomatous, secretory, metaplastic (lipidized cells), lymphoplasmacytic rich (all WHO grade I), clear cell (mimicking clear cell renal cell carcinoma), chordoid, atypical (WHO grade II), and rhabdoid (cells with eccentric nuclei and abundant eosinophilic cytoplasm), papillary, and anaplastic (WHO grade III). There are several excellent reviews of the histopathology of meningiomas along with the criteria for atypical and anaplastic variants [52, 54, 62]. And as mentioned before, other tissue types can be seen occasionally within meningiomas (i.e. bone, cartilage/chondroid, muscle). The variety of tissue types and potential to produce other tissues speaks highly for a pluripotent cell of origin (neural crest, mesenchymal) and are reminiscent of some other tumors that have such potentially variable histological appearances (e.g. yolk sac/endodermal sinus tumor which is derived from a pluripotent cell). Suffice it to say that given these variations, the differential diagnoses become expanded and criteria for narrowing the diagnoses are critical. Most of the identified histological subtypes have been identified in PEMs. In the review by Rushing et al. of extracranial head and neck PEMs, meningothelial, psammomatous, clear cell, atypical, and anaplastic were noted [16]. In sinonasal tract meningiomas, meningothelial is the most common subtype and transitional, metaplastic, and psammomatous types have been identified [11]. In PPMs, as noted in this review and others, meningothelial, transitional, fibrous, chordoid, rhabdoid, psammomatous, atypical, and anaplastic have been reported. Transitional histology is reported as the most common histological subtype in PPMs [12]. As seen in our review and noted in many publications, the immunohistochemical trio of EMA, vimentin, and progesterone receptor is present in the majority of cases of meningioma including PPMs. A smattering of cases will show staining with CD34, S100, and CD68 but are almost always negative for cytokeratins. In cases where these stains and morphology still leave doubt,

other markers should be included in the work-up panel. A cytokeratin stain (both high and low molecular weight or pankeratin) is very important in the exclusion of entities such as metastases from carcinoma, mesothelioma, and thymoma. Neural markers (chromogranin, synaptophysin) are usually negative in meningiomas and positive in paragangliomas for instance. CD56 has been shown to mark some meningiomas (4 positive cases in our series although most cases in the series did not perform or report this marker) but is also strongly positive in most paragangliomas. Since melanoma can be a great mimicker of many tumors, markers such as HMB-45, melan-A, MART1, and MITF are helpful in this distinction since these are almost always negative in meningiomas. S100 may be useful also in the distinction of melanocytic tumors and peripheral nerve sheath tumors (schwannoma) with usual strong diffuse staining of these entities. However, as seen, 6/14 cases that reported results of S100 staining in PPMs were positive in our series. While most did not report the extent or intensity of staining for S100, in general, it is probably not to the degree seen in melanocytic or peripheral nerve sheath tumors. Vascular markers, CD31 and CD34, can be helpful since most meningiomas are negative for these markers. These vascular markers should be positive in hemangioendothelioma. CD34 is usually positive in solitary fibrous tumor along with bcl-2 and is almost always negative for EMA. Bcl-2 is also useful for distinguishing synovial sarcoma. Muscle markers (smooth muscle actin, muscle specific actin, calponin and others) can helpful in the distinction of smooth muscle neoplasms and inflammatory myofibroblastic tumors along with ALK-1.

Another marker that demonstrates very high positive and negative predictive values for meningiomas is the monoclonal antibody to SSTR2a (somatostatin receptor 2a) [63]. This receptor is highly expressed in meningiomas as are other somatostatin receptors. Somatostatin ligand analogs such as DOTATOC and DOTATATE have been linked to ^{68}Ga and used in PET imaging of meningiomas with great success. ^{68}Ga-DOTATATE uptake correlates with SSTR2 expression and has high sensitivity for detecting active tumor in untreated and recurrent meningiomas [64]. In tissue specimens, the monoclonal antibody to SSTR2a has higher sensitivity than EMA or PR and did not stain with high intensity other lesions in the differential diagnoses including peripheral nerve sheath tumors (malignant and benign) and other carcinomas, mesenchymal tumors, or melanomas [63]. A high percentage of meningiomas also express p40 which is one isoform of p63 (p53 homolog gene) and the intensity of expression correlates with histological grade and recurrence [65].

All meningiomas are not sporadic. Multiple familial syndromes associated with specific genetic aberrations have increased risk for development of meningiomas. Neurofibromatosis 2 (NF2 gene, chromosome 22q12) has the highest lifetime risk for development of meningioma at 50%. Approximately 40% of sporadic meningiomas are driven by other genetic mutations other than NF2 [54]. **Table 4** highlights the known familial syndromes associated with varying degrees of increased risk of meningioma. As somewhat of an aside, patients with Werner syndrome (Progeria, premature aging syndrome) as noted have an increased risk of meningioma. In the excellent review by Lauper et al. [66], they noted 27 meningiomas in their cohort of 189 confirmed Werner syndrome patients. Eight of these tumors occurred in patients with multiple tumors and 5/9 patients with meningiomas also had thyroid neoplasia (1 PTC, 1 thyroid carcinoma NOS, 3 adenomas). Four of 5 patients had only meningioma and thyroid neoplasia as manifestation of their multiple tumors. Gardner/Turcot syndrome (APC-associated polyposis), PTEN hamartoma syndrome (Cowden, Bannayan-Riley-Ruvalcaba, Lhermitte-Duclos syndromes), MEN1 (Wermer syndrome), and Werner syndrome are familial inherited syndromes also highly associated with thyroid neoplasia [67]. Carney complex also has a high

Familial syndrome	Gene	Chromosome location	Risk %
Neurofibromatosis 2	NF2	22q12	>50
Multiple spinal meningiomas	SMARCE1	17q21.2	
BAP1 tumor predisposition	BAP1	3p21.1	2
Familial schwannomatosis	SMARCB1	22q11.23	
Gorlin syndrome	PTCH1	9q22.3	5
Cowden disease	PTEN	10q23.31	8
Familial multiple meningiomas	SUFU	10q24.32	
Li-Fraumeni	TP53/CHEK2	17p13.1/22q12.1	
Rubinstein-Taybi	CREBBP	16p13.3	
Gardner syndrome/Turcot syndrome	APC	5q21–22	
Multiple endocrine neoplasia I	MEN	11q13	
Werner syndrome	WRN (RECQL)	8p11.1–21.2	14
Von Hippel–Lindau	VHL	3p25.3	
Ataxia telangiectasia	ATM	11q22	

Table 4.
Familial syndromes associated with increased risk of meningioma.

association of thyroid neoplasia and has as a pathognomonic lesion the melanotic schwannoma, a tumor characterized by schwannian differentiation with the feature of psammoma bodies. Carney complex is known to result from mutations in PRKAR1A (chromosome 17q22–24) and CNC2 (2p16) while WHO grades II and III meningiomas have been shown to be associated with gains and amplification of 17q [53, 54, 67]. In addition, interestingly, Gardner/Turcot syndrome, Carney complex, and Werner syndrome all have various bone tumors as part of the manifestation/ diagnostic criteria for their respective syndromes. In the review by Lauper et al. [66], 17/189 Werner syndrome patients had osteosarcoma with 7/19 osteosarcomas occurring in patients with multiple tumors and one of these patients had meningioma/thyroid adenoma/osteosarcoma as the manifestation of multiple neoplasia. Another association is the presence of neoplasia associated with derivatives of the neural crest (retinal epithelial hypertrophy, benign and malignant peripheral nerve sheath tumors, benign and malignant melanocytic lesions). Gardner/Turcot, Carney complex, PTEN hamartoma, Werner syndromes all have melanocytic lesions as part of their neoplasia spectrum.

These are very interesting associations and can and will lead us to further elucidation of unifying mechanisms of molecular and cellular origins of tumors and in this case meningiomas. It is worth noting here that there are very few reports of PEMs associated with a familial inherited syndrome. What was presented above was data for associations with primary CNS meningiomas. Very few reports of PEMs in patients with a familial syndrome can be found. One case report describes an ectopic meningioma of the right parapharyngeal space in a 14-year-old girl with NF2 [68]. A second report describes an intranodal meningothelial proliferation in a 55-year-old woman with confirmed Cowden syndrome [69]. There seems likely a true difference in familial genetic syndromes and association with PEMs since one would think that specific case reports would address this as part of the unique spectrum of individual presentations of PEM.

4. Meningothelial proliferations

I suppose a general definition of "meningothelial proliferation" would likely be in order. It was alluded to earlier in this review. I say "general" because as noted in the case of PPMs the distinction between what is a meningothelial nodule/proliferation and what is termed a meningioma may be a bit arbitrary and certainly subjective. In this review of PPM, for instance, 6/31 "meningiomas" were less than 1 cm in greatest dimension. In pathology, the distinction between what determines a proliferation and what determines a "tumor" is sometimes based on size with 1 cm being a threshold size for specific tumor designations. For instance, the distinction of papillary thyroid microcarcinoma and papillary thyroid carcinoma is based on the former being less than 1 cm in greatest dimension. In radiology, the standard threshold for detecting tumors has traditionally (although not as much now with improvements in imaging modalities) been less than or greater than 1 cm. In the practice of pathology, these distinctions are not always clear and other features in addition to size are considered in the diagnostic algorithm. An important feature is what the tumor is doing to the surrounding tissue. Is it "blending" in as in the cases, for example, of dominant hyperplastic nodules in the thyroid or nephroblastomatosis in the spectrum of Wilms tumor or it is replacing/pushing normal tissue.

With regards to meningothelial proliferations that occur outside the CNS, that is the presence of meningothelial or meningeal tissue that is not a tumor of meninges, these have been described in a few general settings (although not an exhaustive list) including heterotopic neuroglial proliferations, pulmonary meningothelial nodules (to include diffuse pulmonary meningotheliomatosis), teratomas, and rarely in choristomatous lesions particularly in the head and neck.

One of the reasons to include a review of PPM as cited above was that meningothelial proliferations are well-described in the lungs. In the older pathological literature, MPMNs were originally termed "minute pulmonary paragangliomas" or "chemodectomas" since their ontogeny was thought to be distal airway chemoreceptors [70]. However, subsequently, these have been shown not only morphologically but immunohistochemically and ultrastructurally to be meningothelial in origin. They present as a nested proliferation of spindled and epithelioid cells with bland nuclei around small veins in the lung and exhibit the characteristic EMA+, vimentin+, and PR+ immunophenotype. The incidence of MPMN is reported up to 5% in autopsy studies and in up to approximately 14% of surgical biopsy specimens and in nearly half of lobectomy specimens [70]. Interestingly, in the large series by Mukhopadhyay that included resections from patients in the pediatric age range and over 90 pediatric autopsies, no MPMN were seen in the pediatric population [71]. Radiographically, by CT, MPMN are round solid or partially solid nodules and can be multiple and have a "ground glass" appearance. They typically show low SUV (benign) values for FDG-avidity on ^{18}F-FDG PET-CT imaging [13]. Depending on the clinical scenarios (concurrent other lung lesions, history or concurrence of other tumors), metastases or synchronous tumors cannot be entirely excluded thus necessitating removal and pathological examination. Rarely, MPMN can occur in the setting of PPM; some of these cases being diagnosed as intrapulmonary metastases [14, 25].

Diffuse pulmonary meningotheliomatosis (DPM) is an interesting if not quite rare entity. These patients can present with symptoms of restrictive pulmonary disease with diffuse bilateral reticulonodular infiltrates that have the differential diagnoses including a variety of interstitial lung diseases, carcinomatosis, neuroendocrine tumorlets, metastatic meningioma, and pulmonary lymphangioleiomyomatosis (PLAM). The separation of these entities is relatively straightforward based on morphology and immunophenotyping. Metastatic meningiomas should

be distinguished by clinical grounds (presence of a CNS tumor), involvement of the bronchovascular tree as opposed to DPM which is usually found centered around small veins, and more atypical appearance. Carcinomatosis, neuroendocrine tumorlets, and PLAM are distinguished by positivity for keratins, neuroendocrine markers (typically synaptophysin and chromogranin), and actins while similarly to MPMN and PPM, DPM lesions are EMA, vimentin, and PR positive [61, 71–73]. Primary pulmonary meningothelial lesions (MPMN, DPM, and PPM) are very interesting from developmental and genetic perspectives as lung meningothelial lesions seem to predominate the epidemiological landscape of meningothelial lesions outside of the CNS and head/neck and seem to have an extremely low prevalence in the pediatric population leading some to speculate that their origins may not be pluripotent mesenchymal cells but more related to environmental and age-related factors. Although, just because they are not found in the pediatric age group, should not totally discount that they arise from resting pluripotent stem cells or other dormant embryological remnants and their recrudescence as meningo-thelial lesions is stimulated by other factors. The lungs like other organs also have a "stem cell niche" that is triggered when there is bronchial epithelial injury for the purposes of regeneration/repair [74]. As we have also discussed there seems to be a spectrum of increasing mutations in MPMN and DPM raising the possibilities for a mutational spectrum or "hit" hypotheses in their pathogenesis.

Meningothelial tissue can occur as part of other pathological lesions. In this final section we will briefly touch on the presence of meningiomas and meningothelial tissue in teratomas and meningothelial elements as part of heterotopic/choristo-matous/hamartomatous lesions. Somewhat surprisingly, very few cases of menin-gioma or meningothelial tissue in teratomas are described. A search of PubMed for "meningiomas" and "teratomas" yielded 8 results. One case was a posterior fossa tumor mimicking a meningioma and another case was teratoma and meningioma in the temporoparietal region. The remaining 6 cases were all gonadal teratomas with meningioma [75–82]. The clinical and pathological characteristics of these meningi-omas is presented in **Table 5**. Two cases were in the pediatric age range (5-year-old male and 15-year-old female and all meningiomas were seen on gross examination to be whitish or brown firm nodular areas within the broader context of the mature

Characteristic	N = 6 cases
Teratoma type (T/O*)	
MCT** (T)	2
MCT (O)	4
Gender (M:F)	2:4
Age (years) (SD)	33.8 (20.7)
Range	5–60
Size (cm) (SD)	2.7 (1.2)
Psammoma bodies	5/6
Epithelial membrane antigen/EMA +	5 (1 with no designation)
Vimentin +	2 (4 with no designation)
Progesterone receptor (PR) +	2 (5 with no designation)

*T-testis, O-ovary.
**MCT-mature cystic teratoma.

Table 5.
Clinicopathological characteristics of meningiomas arising in gonadal teratomas.

cystic teratoma (MCT). Chen et al. searched for and characterized meningothelial proliferations in 25 consecutive ovarian MCT [83]. They found that 40% of their tumor had meningothelial proliferations that resembled what has been described in hamartoma of the scalp with ectopic meningothelial elements (more on this later). The meningeal nature of the tissue was confirmed morphologically and by EMA positivity. In all cases the meningothelial tissue was in close association with skin and mature glial tissue (ectodermally derived). Eight of 10 cases had pigmented cells and 3 had psammomatous calcifications. In the author's anecdotal experience, having microscopically examined numerous teratomas from children and adults and teratomas derived from the harvested embryonic stem cells from several species, the finding of meningeal tissue seems not that uncommon, although I have not encountered a meningioma tumor. A recent case of mine illustrates this from a 13-year-old girl with MCT. The meningeal tissue is intimately associated with mature neuroglial tissue and resembles arachnoid of the meninges (**Figure 2**).

Meningothelial tissue can be part of lesions described as heterotopias, particularly of the neuroglial flavor, hamartomas, and choristomas (tissues not indigenous to the anatomic location). In 2005, we reported a temporal glioneuronal heterotopia in a 19-month-old child without underlying connection to the CNS or calvarial defect. In our review of similar cases from the medical literature to that time, 11 infants were identified ranging in age from birth to 15-months. Six of 11 cases had no connection to the CNS (true heterotopias) and 2/6 had meningothelial elements as a component histologically [84]. In another review published at approximately
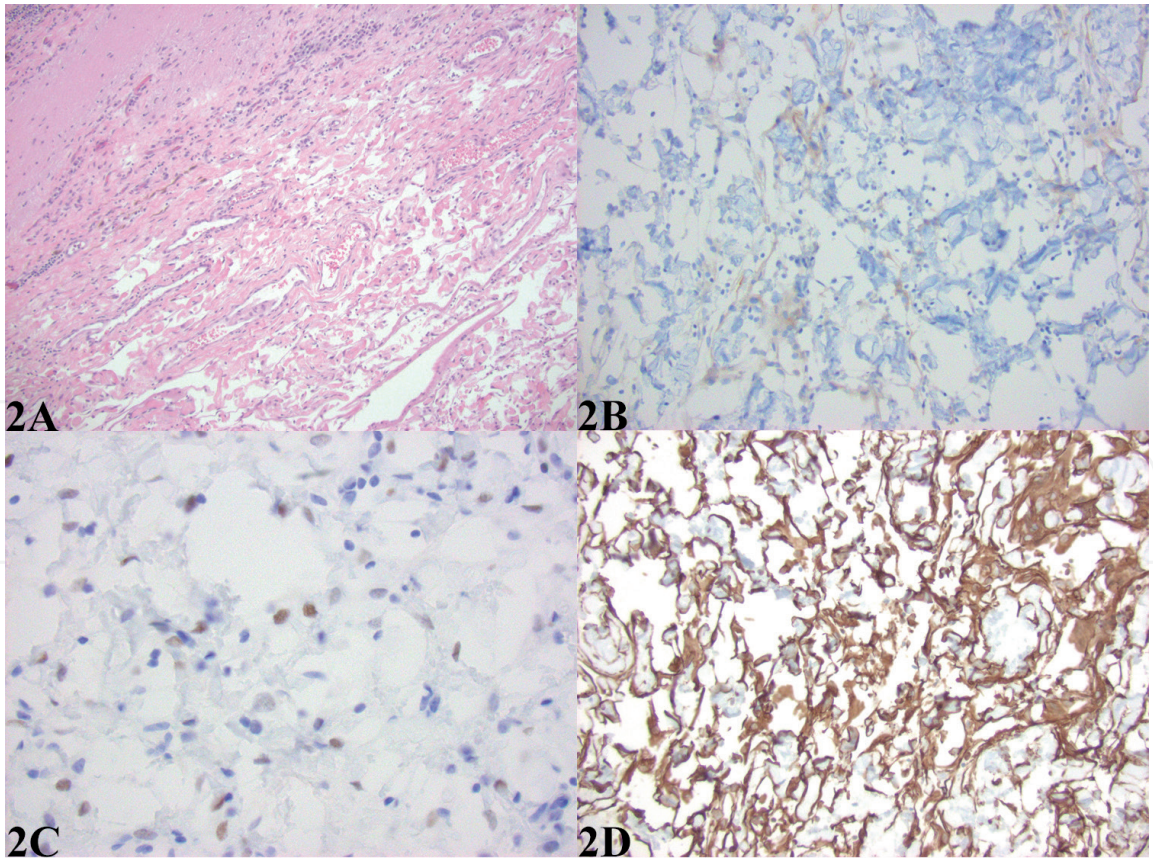

Figure 2.
Meningeal/meningothelial tissue within a mature cystic teratoma of the ovary in a 13-year-old girl.
A: Low magnification view showing mature neuroglial tissue (upper left corner) adjacent to a proliferation of rarified, wispy anastomosing cords of fibrous tissue lined by bland small indistinct nuclei. In other areas of the teratoma, this pattern was also seen adjacent to skin and adnexal structures. This segregation of the meningothelial elements near skin and mature neuroglial is common. (HE, 40X). B: Weak by definite staining of the meningeal tissue with epithelial membrane antigen (EMA, 200X). C: Variably intense staining with progesterone receptor (PR, 400X). D: Diffuse strong intensity staining with vimentin (vimentin, 200X).

the same time by Rogers et al. from Boston Children's Hospital, they reported 11 patients with 12 tumors of the scalp ranging in age from 1-month to 20-months. Seven of the 12 tumors had no connection to the CNS and 5 of those 7 tumors had meningothelial tissue as a prominent component histologically [85].

Ectopic meningothelial tissues have been described that appear to arise entirely within the skin and often present in the neonate or infant (so called Type I cutaneous meningioma; defined in the beginning of this chapter). These have been previously termed "acoelic meningeal hamartoma" "cutaneous heterotopic meningeal nodules" and "rudimentary meningocele". In the series published in 1989 by Sibley and Cooper referenced earlier, they described 5 cases of what they termed "primary cutaneous meningioma". What they describe histologically is what is expected in meninges both morphologically and immunophenotypically including collagenous bodies and psammomatous calcifications. Some areas in the superficial dermis had a more rarified and lacy appearance with meningocytes wrapping around vessels and adnexa in intimate association similar to that described shortly thereafter by Suster and Rosai [86]. Their series described 5 patients who had pseudoinfiltrative lesions of the skin and subcutis by meningothelial elements that were in intimate association with the surrounding tissue elements (vessels, fat, connective tissue). In fact, they designated that the meningothelial elements were an interspersed component between a proliferation of connective tissue elements. Their designation for these lesions was "hamartoma of the scalp with ectopic meningothelial elements" and this has become the diagnostic term for such lesions. More recent reports in some cases have shortened the nomenclature to "meningothelial hamartoma". Suster and Rosai give the poignant perspective that the designation of these hamartomatous lesions with meningothelial elements are distinguished from primary cutaneous meningiomas by the association with other poorly arranged elements constituting a hamartoma. We have encountered similar tumors in the scalp (**Figure 3A** and **B**) and have published two cases in young children of tongue lesions with meningothelial elements (**Figure 3C** and **D**). Both tongue lesions were entirely composed of the typical anastomosing slit-like channels lined by bland flat-to-cuboidal cells expressing progesterone receptor and epithelial membrane antigen. Interestingly, but not surprisingly, meningothelial elements have been described occurring in the rare "teratoid" lesion of the palate known as hairy polyp [6]. These are pedunculated growths that can be composed of a variety of tissues derived predominantly from ectodermal and mesodermal (mesenchymal) germ layers. In the reported case, the presence of meningothelial tissue was confirmed by immunohistochemistry and ultrastructural examination demonstrating the characteristic interdigitating cytoplasmic processes connected by cell junctions, desmosomes, intermediate filaments (hence positive expression of vimentin).

In summary, CNS meningiomas are the most common primary CNS tumor and meningiomas and meningothelial tissue/proliferation occur in a multitude of extra-CNS sites and present in a diverse manner from isolated non-tumor proliferations to part of hamartomatous lesions to diffuse meningotheliomatosis to meningiomas tumors arising in multiple anatomic locations. Morphologically, immunophenotypically, ultrastructurally, and perhaps genetically, the meningeal tumors and proliferations outside the CNS are very similar to their CNS counterparts suggesting a common cellular origin. Because of the possibility of arising in diverse anatomic locations, they join a long list of differential diagnostic considerations for the practicing pathologist and should be entertained as possibilities particularly when the morphology could significantly overlap other tumors. In most cases, the immunohistochemical profile of EMA, vimentin, progesterone receptor, and SSTR2a (if available) is diagnostic in the proper morphological context. This panel should be included in diagnostically challenging cases.
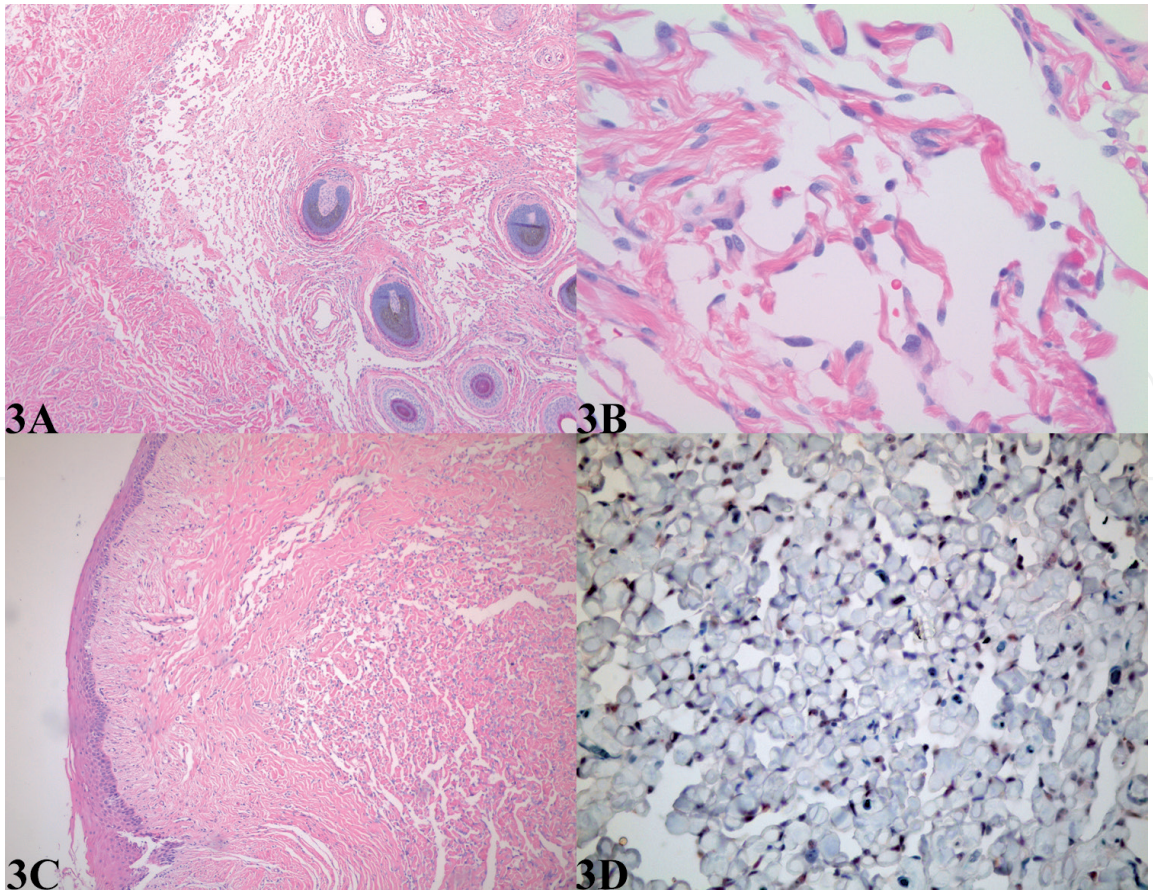
Figure 3.
Examples of ectopic meningothelial proliferations in the head and neck. A and B represent "hamartoma of the scalp with ectopic meningothelial elements" in a young child. 3A: Low magnification view of loose proliferation of anastomosing wispy fibrous cords lined by bland nuclei interdigitating around adnexal structures (HE, 40X). 3B: High magnification view of the microarchitecture of meningothelial proliferations. This pattern closely resembles vascular proliferations, particularly lymphatic malformations in children and must be excluded in the differential diagnosis (HE, 400X). C and D are from a nearly 2-year-old boy with a tongue mass. 3C: Less obvious than the previous case shown here yet the same microarchitectural pattern is appreciated below the surface epithelium of the tongue. This rarified pattern might be considered a "hemangiopericytomatous" pattern but in any case, is abnormal for the submucosa of the tongue (HE, 40X). 3D: This meningothelial proliferation show strong nuclear staining for progesterone receptor (PR, 400X).

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References

[1] Sibley, D.A. and P.H. Cooper, *Rudimentary meningocele: a variant of "primary cutaneous meningioma".* J Cutan Pathol, 1989. **16**(2): p. 72-80.

[2] Miedema, J.R. and D. Zedek, *Cutaneous meningioma.* Arch Pathol Lab Med, 2012. **136**(2): p. 208-11.

[3] Dasgupta, K. and J. Jeong, *Developmental biology of the meninges.* Genesis, 2019. **57**(5): p. e23288.

[4] Lopes, M.B.S., *Meninges: Embryology*, in *Meningiomas*, J.H. Lee, Editor. 2009, Springer London: London. p. 25-29.

[5] Decimo, I., et al., *Meninges: from protective membrane to stem cell niche.* Am J Stem Cells, 2012. **1**(2): p. 92-105.

[6] Olivares-Pakzad, B.A., et al., *Oropharyngeal hairy polyp with meningothelial elements.* Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 1995. **79**(4): p. 462-8.

[7] Gibson, S.E. and R.A. Prayson, *Primary Ectopic Meningiomas*, in *Meningiomas*, J.H. Lee, Editor. 2009, Springer London: London. p. 573-583.

[8] Lang, F.F., et al., *Primary extradural meningiomas: a report on nine cases and review of the literature from the era of computerized tomography scanning.* J Neurosurg, 2000. **93**(6): p. 940-50.

[9] Omofoye, O.A., et al., *Primary intraosseous meningioma of the calvarium: A systematic review.* Clin Neurol Neurosurg, 2020. **199**: p. 106283.

[10] Thompson, L.D., et al., *Primary ear and temporal bone meningiomas: a clinicopathologic study of 36 cases with a review of the literature.* Mod Pathol, 2003. **16**(3): p. 236-45.

[11] Thompson, L.D.R. and J.C. Fanburg-Smith, *Update on Select Benign Mesenchymal and Meningothelial Sinonasal Tract Lesions.* Head Neck Pathol, 2016. **10**(1): p. 95-108.

[12] Han, D., H. Deng, and Y. Liu, *Primary pulmonary meningiomas: report of two cases and review of the literature.* Pathol Res Pract, 2020. **216**(12): p. 153232.

[13] Incarbone, M., et al., *Primary pulmonary meningioma: report of a case and review of the literature.* Lung Cancer, 2008. **62**(3): p. 401-7.

[14] Masago, K., et al., *Is primary pulmonary meningioma a giant form of a meningothelial-like nodule? A case report and review of the literature.* Case Rep Oncol, 2012. **5**(2): p. 471-8.

[15] Ohashi-Nakatani, K., et al., *Primary pulmonary meningioma: A rare case report of aspiration cytological features and immunohistochemical assessment.* Diagn Cytopathol, 2019. **47**(4): p. 330-333.

[16] Rushing, E.J., et al., *Primary extracranial meningiomas: an analysis of 146 cases.* Head Neck Pathol, 2009. **3**(2): p. 116-30.

[17] Sathirareuangchai, S., et al., *Low grade intracranial meningioma presenting with pulmonary metastasis: Case report and literature review.* Pathol Res Pract, 2019. **215**(7): p. 152390.

[18] Tamura, H., et al., *Extracranial meningiomas concurrently found in the lung and vertebral bone: a case report.* J Med Case Rep, 2018. **12**(1): p. 279.

[19] Enomoto, T., et al., *WHO Grade I Meningioma Metastasis to the Lung 26 Years after Initial Surgery: A Case Report and Literature Review.* NMC Case Rep J, 2019. **6**(4): p. 125-129.

[20] Turner, N., A.H. Kaye, and I. Paldor, *Metastases to meningioma-review*

and meta-analysis. Acta Neurochir (Wien), 2021. **163**(3): p. 699-709.

[21] Murakami, K., et al., *A case report of resected ectopic malignant meningioma with lung metastasis.* Medicine (Baltimore), 2019. **98**(23): p. e15853.

[22] Fujikawa, R., et al., *A case of a primary pulmonary meningioma mimicking a metastasis from a papillary thyroid carcinoma due to a size reduction after radioactive iodine therapy.* Surg Case Rep, 2020. **6**(1): p. 57.

[23] Bae, S.Y., et al., *Primary Pulmonary Chordoid Meningioma.* Korean J Thorac Cardiovasc Surg, 2018. **51**(6): p. 410-414.

[24] Bercovici, D., et al., *[A rare pulmonary tumor].* Ann Pathol, 2017. **37**(5): p. 434-436.

[25] Chakrabarti, R. and D. Ghuman, *Diagnostic and Management Considerations in a Patient With Primary Pulmonary Meningioma With Associated Micro-Solid Nodules.* Cureus, 2021. **13**(6): p. e15700.

[26] Cimini, A., et al., *A Patient with a Benign and a Malignant Primary Pulmonary Meningioma: An Evaluation with 18F Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography and Computed Tomography with Iodinated Contrast.* Indian J Nucl Med, 2019. **34**(1): p. 45-47.

[27] Fidan, A., et al., *Endobronchial primary pulmonary meningioma.* Saudi Med J, 2008. **29**(10): p. 1512-3.

[28] Gurcay, N., et al., *Primary pulmonary meningioma mimicking pulmonary metastasis: A rare case report.* Turk Gogus Kalp Damar Cerrahisi Derg, 2020. **28**(4): p. 699-701.

[29] Hong, S., et al., *Computed tomography findings of primary pulmonary meningioma: A case report.* Medicine (Baltimore), 2018. **97**(2): p. e9651.

[30] Huang, S., et al., *Primary pulmonary meningioma: A case report.* Medicine (Baltimore), 2017. **96**(19): p. e6474.

[31] Izumi, N., et al., *Primary pulmonary meningioma presenting with hemoptysis on exertion.* Ann Thorac Surg, 2009. **88**(2): p. 647-8.

[32] Jiang, M., et al., *A case report of primary pulmonary meningioma masquerading as lung metastasis in a patient with rectal carcinoma: role of (18) F-FDG PET/CT.* J Cardiothorac Surg, 2021. **16**(1): p. 153.

[33] Juan, C.M., et al., *Primary Pulmonary Meningioma Simulating a Pulmonary Metastasis.* Case Rep Pulmonol, 2016. **2016**: p. 8248749.

[34] Kim, Y.Y., et al., *Primary pulmonary meningioma: an unusual cause of a nodule with strong and homogeneous enhancement.* Clin Imaging, 2016. **40**(1): p. 170-3.

[35] Lepanto, D., et al., *Atypical primary pulmonary meningioma: a report of a case suspected of being a lung metastasis.* Ecancermedicalscience, 2014. **8**: p. 414.

[36] Luo, J.Z., et al., *Primary pulmonary meningioma mimicking lung metastatic tumor: a case report.* J Cardiothorac Surg, 2018. **13**(1): p. 99.

[37] Minami, Y., et al., *Malignant primary pulmonary meningioma with bone metastasis.* Oxf Med Case Reports, 2020. **2020**(2): p. omaa005.

[38] Oide, T., et al., *Primary Pulmonary Meningioma Presenting as a Coin Lesion.* Intern Med, 2017. **56**(15): p. 2073-2074.

[39] Petscavage, J.M., et al., *Primary chordoid meningioma of the lung.* J Thorac Imaging, 2011. **26**(1): p. W14-6.

[40] Sakai, K., et al., *[Multiple Primary Pulmonary Meningiomas]*. Kyobu Geka, 2019. **72**(9): p. 677-680.

[41] Satoh, Y. and Y. Ishikawa, *Multiple primary pulmonary meningiomas: 20-year follow-up findings for a first reported case confirming a benign biological nature.* Int J Surg Case Rep, 2017. **31**: p. 58-60.

[42] Tauziede-Espariat, A., et al., *[A pulmonary tumor that racks our brains!]*. Ann Pathol, 2021.

[43] Vaideeswar, P. and J. Chaudhari, *Primary pulmonary meningioma.* Indian J Pathol Microbiol, 2019. **62**(3): p. 486-487.

[44] Walter, J., et al., *Pulmonary meningioma and neurinoma associated with multiple CNS tumours in a patient with neurofibromatosis type 2.* Clin Neurol Neurosurg, 2009. **111**(5): p. 454-9.

[45] Wang, X., et al., *Intrapulmonary metastasis from primary pulmonary meningioma presenting as multiple cystic lesions: a case report.* BMC Pulm Med, 2019. **19**(1): p. 8.

[46] Weber, C., et al., *Primary pulmonary malignant meningioma with lymph node and liver metastasis in a centenary woman, an autopsy case.* Virchows Arch, 2013. **462**(4): p. 481-5.

[47] Xu, K.K., F. Tian, and Y. Cui, *Primary pulmonary meningioma presenting as a micro solid nodule: A rare case report.* Thorac Cancer, 2018. **9**(7): p. 874-876.

[48] Zhao, P., et al., *Rhabdoid Meningioma Arising Concurrent in Pulmonary and Intracranial with a Rare Malignant Clinical Progression: Case Report and Literature Review.* World Neurosurg, 2017. **107**: p. 1046 e17-1046 e22.

[49] Zhao, Z., et al., *Multiple primary tumors: a case report and review of the literature.* BMC Musculoskelet Disord, 2020. **21**(1): p. 394.

[50] Zulpaite, R., et al., *Primary Pulmonary Meningioma With Rhabdoid Features.* Int J Surg Pathol, 2019. **27**(4): p. 457-463.

[51] Vlachos, A., et al., *Increased risk of colon cancer and osteogenic sarcoma in Diamond-Blackfan anemia.* Blood, 2018. **132**(20): p. 2205-2208.

[52] Huntoon, K., A.M.S. Toland, and S. Dahiya, *Meningioma: A Review of Clinicopathological and Molecular Aspects.* Front Oncol, 2020. **10**: p. 579599.

[53] Lee, Y.S. and Y.S. Lee, *Molecular characteristics of meningiomas.* J Pathol Transl Med, 2020. **54**(1): p. 45-63.

[54] Ogasawara, C., B.D. Philbrick, and D.C. Adamson, *Meningioma: A Review of Epidemiology, Pathology, Diagnosis, Treatment, and Future Directions.* Biomedicines, 2021. **9**(3).

[55] Sughrue, M.E., et al., *Prevalence of previous extracranial malignancies in a series of 1228 patients presenting with meningioma.* J Neurosurg, 2010. **113**(5): p. 1115-21.

[56] Ferreira, L.B., et al., *Molecular Aspects of Thyroid Calcification.* Int J Mol Sci, 2020. **21**(20).

[57] Arikok, A.T., et al., *Osteopontin expressions correlate with WHO grades and predict recurrence in meningiomas.* Brain Tumor Pathol, 2014. **31**(2): p. 94-100.

[58] Li, H.Z., et al., *The role of osteopontin and its receptor in meningioma development and progression.* J Biol Regul Homeost Agents, 2018. **32**(1): p. 69-74.

[59] Agaimy, A., et al., *Comparative study of soft tissue perineurioma and*

meningioma using a five-marker immunohistochemical panel. Histopathology, 2014. **65**(1): p. 60-70.

[60] Ionescu, D.N., et al., *Pulmonary meningothelial-like nodules: a genotypic comparison with meningiomas.* Am J Surg Pathol, 2004. **28**(2): p. 207-14.

[61] Weissferdt, A., et al., *Pleuropulmonary Meningothelial Proliferations: Evidence for a Common Histogenesis.* Am J Surg Pathol, 2015. **39**(12): p. 1673-8.

[62] Backer-Grondahl, T., B.H. Moen, and S.H. Torp, *The histopathological spectrum of human meningiomas.* Int J Clin Exp Pathol, 2012. **5**(3): p. 231-42.

[63] Menke, J.R., et al., *Somatostatin receptor 2a is a more sensitive diagnostic marker of meningioma than epithelial membrane antigen.* Acta Neuropathol, 2015. **130**(3): p. 441-3.

[64] Rachinger, W., et al., *Increased 68Ga-DOTATATE uptake in PET imaging discriminates meningioma and tumor-free tissue.* J Nucl Med, 2015. **56**(3): p. 347-53.

[65] Guadagno, E., et al., *Expression of p40 (Np63) protein in meningiomas, an unexpected finding: immunohistochemical study and evaluation of its possible prognostic role.* J Neurooncol, 2016. **129**(3): p. 405-413.

[66] Lauper, J.M., et al., *Spectrum and risk of neoplasia in Werner syndrome: a systematic review.* PLoS One, 2013. **8**(4): p. e59709.

[67] Ozolek, J.A., *Selected Topics in the Pathology of the Thyroid and Parathyroid Glands in Children and Adolescents.* Head Neck Pathol, 2021. **15**(1): p. 85-106.

[68] Su, C.Q., et al., *Ectopic meningioma in a patient with neurofibromatosis Type 2: a case report and review of the literature.* BJR Case Rep, 2018. **4**(3): p. 20180007.

[69] Olofson, A., et al., *Intranodal meningothelial proliferation in a patient with Cowden syndrome: a case report.* Hum Pathol, 2017. **66**: p. 183-187.

[70] Morresi-Hauf, A.T., et al., *[Diffuse pulmonary meningotheliomatosis].* Pneumologie, 2015. **69**(9): p. 553-9.

[71] Mukhopadhyay, S., O.A. El-Zammar, and A.L. Katzenstein, *Pulmonary meningothelial-like nodules: new insights into a common but poorly understood entity.* Am J Surg Pathol, 2009. **33**(4): p. 487-95.

[72] Lin, D., et al., *Radiological manifestations, histological features and surgical outcomes of pulmonary meningothelial proliferation: a case series and rethinking.* Transl Lung Cancer Res, 2020. **9**(4): p. 1159-1168.

[73] Suster, S. and C.A. Moran, *Diffuse pulmonary meningotheliomatosis.* Am J Surg Pathol, 2007. **31**(4): p. 624-31.

[74] Wang, Y. and N. Tang, *The diversity of adult lung epithelial stem cells and their niche in homeostasis and regeneration.* Sci China Life Sci, 2021.

[75] Adams, H., et al., *[Meningothelial meningioma in a mature cystic teratoma of the ovary].* Pathologe, 2007. **28**(4): p. 278-80.

[76] Castro Pereira, F.M., et al., *A rare component of psammomatous meningioma in a testicular teratoma.* Case Rep Pathol, 2013. **2013**: p. 645415.

[77] Coulibaly, O., et al., *Mature posterior fossa teratoma mimicking infratentorial meningioma: a case report.* Neurochirurgie, 2012. **58**(1): p. 40-3.

[78] Lanuza, M., T.P. Poon, and A. Belmonte, *Mixed teratoma and meningioma in the temporoparietal region.* Surg Neurol, 1985. **23**(4): p. 399-402.

[79] Liu, Y.Y., et al., *Meningioma in mature cystic teratoma of the ovary: clinical and computed tomography findings.* Cancer Imaging, 2020. **20**(1): p. 15.

[80] Mandal, S., et al., *Rare growth of a psammomatous meningioma in a mature ovarian teratoma: a case report.* Pathol Res Pract, 2010. **206**(5): p. 322-4.

[81] Sinha, R., et al., *Meningothelial Meningioma Component in a Prepubertal Testicular Teratoma.* Case Rep Pathol, 2020. **2020**: p. 6495321.

[82] Takeshima, Y., et al., *Meningioma in mature cystic teratoma of the ovary.* Pathol Int, 2004. **54**(7): p. 543-8.

[83] Chen, E., C.D. Fletcher, and M.R. Nucci, *Meningothelial proliferations in mature cystic teratoma of the ovary: evidence for the common presence of cranially derived tissues paralleling anterior embryonic plate development. An analysis of 25 consecutive cases.* Am J Surg Pathol, 2010. **34**(7): p. 1014-8.

[84] Ozolek, J.A., et al., *Temporal soft tissue glioneuronal heterotopia in a child with a seizure disorder: case report and review of the literature.* Pediatr Dev Pathol, 2005. **8**(6): p. 673-9.

[85] Rogers, G.F., J.B. Mulliken, and H.P. Kozakewich, *Heterotopic neural nodules of the scalp.* Plast Reconstr Surg, 2005. **115**(2): p. 376-82.

[86] Suster, S. and J. Rosai, *Hamartoma of the scalp with ectopic meningothelial elements. A distinctive benign soft tissue lesion that may simulate angiosarcoma.* Am J Surg Pathol, 1990. **14**(1): p. 1-11.