Diagnostic Challenges of Benign Fibro-Osseous Lesions and Psammomatous Meningiomas of the Craniofacial Region: A Comparative Review of their Clinico-pathological Features

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Abstract

Conventional ossifying fibroma (COF), juvenile psammomatoid ossifying fibroma (JPOF), juvenile trabecular ossifying fibroma (JTOF), fibrous dysplasia (FD), cemento-osseous dysplasia (COD) and psammomatous meningioma (PM) share overlapping clinico-pathologic characteristics. This can be diagnostically challenging for pathologists. Although remarkable progress has been made over the years using ancillary studies like immunohistochemistry and molecular cytogenetics to distinguish histologically similar diseases; such diagnostic aids are yet to be successfully employed within this group of lesions. The implication is that pathologists have to rely heavily on traditional H&E stained sections in differentiating these lesions. It is important to make the distinction because of differences in their clinical behavior, modes of treatment and prognosis. In this article, the clinico-pathologic features of each entity are reviewed.

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Key Words:

Fibro-osseous lesions, ossifying fibroma, fibrous dysplasia, cemento-osseous dysplasia and meningioma

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1. Introduction

Conventional ossifying fibroma (COF), juvenile psammomatoid ossifying fibroma (JPOF), juvenile trabecular ossifying fibroma (JTOF), fibrous dysplasia (FD) and cemento-osseous dysplasia (COD) all belong to the fibro-osseous group of lesions. These are conditions characterized by the replacement of bone with varying amounts of fibrous and mineralized tissues.[1] Thus, they share some common clinical and histological characteristics although they represent distinct entities with diverse origins. While some are neoplastic, others are developmental or reactive in nature.[2] JPOF, JTOF and COF are considered as true neoplastic lesions, while FD and COD are said to be developmental and reactive lesions respectively. Psammomatous meningioma (PM) is not a member of the fibro-osseous group of lesions. However, it has been included here because it shares some common features with other conditions, particularly JPOF. PM is a true neoplastic entity derived from aberrant rests of meningoepithelial cells.[3] The diagnosis of any of these entities can prove difficult and this is well documented in the literature. For example, it has been reported that the clinical and radiologic features of PM involving the paranasal sinuses can be confused with those of JPOF.[3] Similarly, Ferris and Tien (1995) noted that imaging studies such as plain x-ray films, CT scans and MRI findings are generally unreliable in distinguishing between fibro-osseous lesions.[4] Su *et al*. (1997) reviewed the pathologic features of 316 cases of CODs and COFs and concluded that differentiating between these two entities can be

problematic.[5] Likewise, Slootweg and Mofty (2005) stated that the histological picture of FD can be confused with those of COF.[6] Furthermore, Brannon and Fowler (2001) cited difficulties in differentiating COF and its subtypes, JPOF and JTOF.[2]

Unfortunately, immunohistochemical (IHC) markers are not very helpful in diagnosing these conditions. Granados *et al.* (2006) concluded that immunoprofiling cannot be relied upon in distinguishing JPOF, COF and PM.[3] They had investigated many IHC markers, including: epithelial membrane antigen (EMA), cytokeratin (CK), smooth muscle actin (SMA), desmin, vimentin, CD34, CD10, S-100 protein and glial fibrillary acidic protein (GFAP); but failed to identify any reliable distinguishing marker(s). This is in spite of the fact that the immunoprofile of meningiomas has long been established. Toyosawa *et al*. (2007) suggested osteocalcin could be used as a marker for isolating FD from COF based on their strong and weak signals respectively.[7] Other investigators however demonstrated higher osteocalcin differential staining in COF relative to another entity, the peripheral ossifying fibromas.

Table 1. Clinical And Radiological Characteristics.

	JPOF	**JTOF**	**COF**	**FD**	**COD**	**PM**
Type	Neoplastic	Neoplastic	Neoplastic	Developmental	Reactive	Neoplastic
Incidence	Rare	Rare	Common	Common	Common	Uncommon
Age range (decades)	1-2nd	2nd-3rd	3rd-4th	1st-2nd	4th-5th	4th – 6th
Gender predominance	Males (slightly)	Males (slightly)	Females	Equal; Polyostotic - Females	Females	Females
Racial predilection	unknown	unknown	Whites	Equal	Blacks	None
Site Occurrence - Gnathic - Extragnathic	 Yes Yes	 Yes Yes	 Yes Yes	 Yes Yes	 Yes No, except by direct extension from gnathic site	 Yes Yes
Site predilection	Paranasal sinuses & orbital bones	Jaws - Maxilla	Jaws - Mandible body	Long bones & craniofacial bones In Jaws - Maxilla	Jaws - Mandible anterior (root apices)	Spinal cord – thoracic region
Common Symptoms	Facial disfigurement; nasal & lacrimal discharge	Same as JPOF + painless jaw expansion	Painless, well demarcated jaw expansion	Painless, diffuse jaw swelling	Often asympto-matic	Paralysis When extracranial, same as PJOF
Biological behaviour	Aggressive; but can be slow growing	Aggressive; but can be slow growing	Slow growing	Slow growing; stabilizes post-puberty	Slow growing	Slow growing,
Main Radiological Findings	Variable - radiolucent with varying opacities; Ground glass opacification +/- well-defined borders	Same as JPOF	Variable - Radiolucent / mixed / radiopaque Well-defined borders	Variable - diffuse, fine ground glass opacification; imperceptible borders; radiolucent/radio-opaque	Variable - radiolucent / mixed / radiopaque Well to ill-defined borders; small <2cm	Bone erosions, remodelling, sclerosis; no large radiolucent lesion
Variants	None	None	None	Monostotic Polyostotic	FCOD PCOD FLCOD/FaFLCOD	None
Familial/genetic/syndromic association	No	No	Yes HPJT synd*	J-L synd* Mc-A synd* Mazabraud synd*	FaFLCOD type	Yes, in association with NF-2
Malignant potential	No	No	No	Yes Sporadic 0.4% Syndromic 4%	No	Rarely, metastases with bland cytology
Management	Excision	Excision	Enucleation/Excision	Surgical shave down	Watchful observation/ Currettage	Excision
Recurrence	Yes (30-50%)	Same as JPOF	Unusual, as it shells out easily.	Low, but can be as high as (25-50%)	No	Yes

J-L synd.–Jaffe-Lichtenstein syndrome; Mc-A synd.–McAlbright syndrome; HPJT synd.–hyperparathyroidism-jaw tumor syndrome; NF-2–neurofibromatosis type 2.

Similarly, use of molecular cytogenetic analysis in separating this group of lesions is still in the early stages[9-11] and is of no diagnostic significance today. FD is the only exception, where mutations in the α-subunit of the stimulatory G protein gene (*GNAS*) at the Arg[201] codon have been proven.[7,12] Therefore, in order to avoid diagnostic pitfalls, the pathologist must be familiar with the clinical, radiologic and histological characteristics of each of these entities and how they differ from one another. Accurate diagnoses of these lesions are critical because clinical course, management and prognosis vary among these conditions. JPOF and JTOF generally demonstrate more aggressive growth patterns and higher recurrence rates than COF.[13] COD on the other hand, has the best prognosis of the entire group and seldom needs surgical removal. When treatment is required, simple curettage is the mainstay of treatment.[5,14] Some entities have malignant potential. Approximately 0.4% of sporadic FD and up to 4% of the syndromic variants carry a risk of malignant transformation.[15] On rare occasions, metastases can occur in PM also.[16]

In the following sections, the clinico-pathologic characteristics of each of these conditions are reviewed, emphasizing key features that aid in making a definitive diagnosis.

2. Clinico-pathological Characteristics

Fibro-osseous lesions generally have a predilection for the craniofacial skeleton including the jaws.[2] Meningiomas on the other hand are more commonly found within the axial skeleton.[17] JPOF, JTOF, COF, FD and PM can occur at both extragnathic and gnathic sites, while COD is considered to be exclusively gnathic in origin.[12,14,18] Certain variants of COD may however extend to involve the maxillary sinus.[19] A summary of the clinical/radiological and histological features of these conditions is shown in **Tables I** and **II** respectively.

2.1. Conventional ossifying fibroma

COF is a benign, slow growing, painless neoplasm primarily seen in the jaws, particularly the mandible.[20] It can also occur at extragnathic locations such as the sinonasal region.[15] Patients with COF are usually in their 3rd – 4th decades of life[18] and are often Caucasian females.[2,20,21] The hyperparathyroidism-jaw tumor syndrome is linked to this condition.[14] Plain x-ray films and CT scans reveal a circumscribed lesion that may be lytic, sclerotic or mixed, often indistinguishable from any of its other variants, JPOF or JTOF.[20] When small and present in the tooth bearing region of the jaws, it can be highly suggestive of a COD.[5] A significant feature of COF is its proclivity to shell out *in toto* during surgery.[5] Histological sections reveal a well circumscribed lesion with or without encapsulation[6] (**Figure 1A**). The body of the lesion consists of islands of irregular, lamellar and woven bone or osteoid. These are embedded within a moderately cellular fibrous connective tissue stroma (**Figure 1B**), often demonstrating a storiform appearance.[5,6] Prominent osteoblastic rimming of the bone trabeculae is observed, but is not pathognomonic.[6] Cementicle-like structures with or without brush borders are frequently seen interspersed among these bone trabeculae.[14,15] COFs show variations in mineralization pattern and stromal content, with alternating regions of hypo- and hyper-cellularity.[6,13] These features are not unique to COF because they may be seen in other entities, such as COD, JPOF or JTOF.[6,15] Of all the fibro-osseous group lesions, FD lesions are the hardest to differentiate from COF.[2,6,15] One helpful distinguishing factor is that FD tends to exhibit a uniform distribution of its mineralized and stromal elements.[15] The treatment of choice of COF is excision with only rare recurrence.[2,13] When COF involves the paranasal sinus region, it can behave more aggressively.[2,15]

2.2. Juvenile psammomatoid ossifying fibroma & Juvenile trabecular ossifying fibroma

JPOF and JTOF are described together here because they are mostly considered as variants of the aggressive subclass of ossifying fibroma.[6,13,15] COF represents the other subclass of ossifying fibromas.[15] JPOF and JTOF share many similarities including their rarity of occurrence, but JTOF distinctively presents with fewer documented cases in the literature.[22] In terms of location, JTOF occurs more in the jaws, particularly the maxilla, while JPOF is more commonly seen within the sino-naso-orbital regions.[22] JPOF and JTOF can both present with symptoms such as nasal obstruction; rhinorrhea and orbital displacement.[22,23] These features may also be seen in patients with PM, COF and FD.[3,15,24,25] The term 'juvenile' is a misnomer because both JPOF and JTOF can occur in a wide age range including the elderly.[13] However, most patients with JPOF are older than those with JTOF by about a decade, but younger than COF patients by a similar margin.[6] Gender predilection is slightly skewed towards males for both JPOF and JTOF.[22] CT scans of JPOF and JPOF exhibit a mixture of radiolucent and radiodense areas with thin sclerotic rims that may be incomplete.[22] Both lesions typically lack fibrous capsules and tend to infiltrate adjacent bone, thus tissue specimens are usually submitted fragmented.[13,22]

In other situations, they can also show delineation from surrounding bone.[2] Other common histologic features of JPOF and JTOF include a highly cellular connective tissue stroma often with variations and irregular woven bone trabeculae surrounded by osteoblasts.[6,22] Additional findings are mature lamellar bone, osteoclast-like giant cells, mitotic figures and focal areas with myxoid, microcystic or aneurysmal-like features.[6,22] The predominant features of JPOF are the osteoid spherules (psammomatoid bodies), often with laminated concentric basophilic cores, with/without eosinophilic brush borders[6] (**Figure 2A** and **Figure 2B**). JTOF characteristically show irregular, highly cellular osteoid or woven bone trabeculae that blend into the supporting fibrocellular stroma[22] (**Figure 3A** and **Figure 3B**). These are referred to as "paintbrush strokes" pattern.[22] The histological picture can be confusing because JPOF and JTOF also contain varying amounts of each other's main identifying features, albeit to a lesser extent.[15] Thus psammomatoid bodies are often seen in JTOF and vice versa.

Psammomas or psammoma type bodies may also occur in a variety of other conditions including PM[17] and COF[15] respectively, further adding to the confusion. Both JPOF and JTOF tend to behave more aggressively and have much higher recurrence rates than COF.[13] The recommended treatment is complete excision when possible with close follow up.[22]

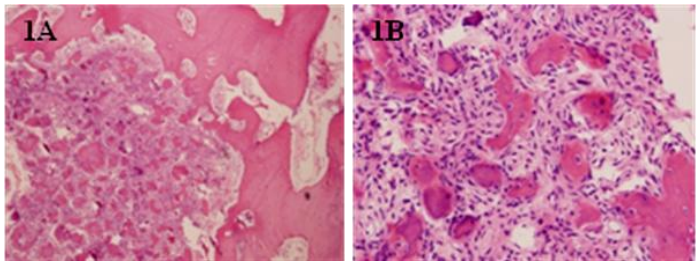

Figure 1. Conventional ossifying fibroma.
1A. Lesional tissue showing demarcation from surrounding normal bone trabeculae.
1B. Islands of irregular woven and lamellar bone showing osteoblastic activity with a moderately cellular connective tissue stroma.

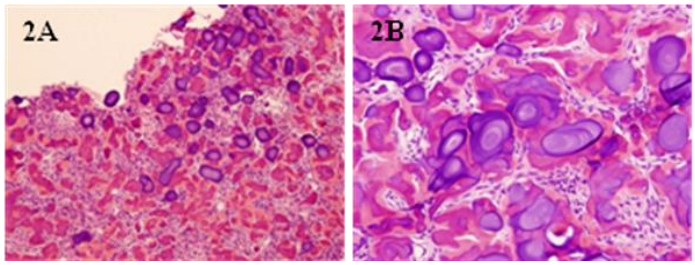

Figure 2. Juvenile psammomatoid ossifying fibroma. **2A.** Ovoid spherules of osteoid and basophilic calcifications and irregular woven bone trabeculae. **2B.** Psammomatoid bodies showing concentric basophilic laminations with eosinophilic brush borders.

2.3. Fibrous dysplasia

FD is a non-hereditary, developmental condition that occurs predominantly within the long bones and craniofacial skeleton.[12,15] The most common location within the craniofacial complex is the maxilla, where it presents as a painless, slow growing diffuse lesion in children and young adults.[12,15] When the mid-face region is involved, nasal obstruction, chronic sinusitis, proptosis and visual disturbances may be seen.[24] FD can occur as monostotic or polyostotic forms, with or without a syndromic association.[15] The monostotic type accounts for 80% of cases seen.[12] Craniofacial FD is more commonly associated with the polyostotic types.[25] There is an equal gender distribution, but polyostotic forms are more common in females.[12] The radiologic picture of an ill-defined lesion blending imperceptibly with the adjacent bone is said to be a defining characteristic of FD.[15] Nonetheless, COF can present with an ill-defined border in cases where there has been rapid growth.[21] Also, both FD and COF lesions exhibit variable densities depending on the amount of fibrous or osseous elements present.[25] Another prominent radiologic feature of FD is the presence of a fine, diffuse radiopacity referred to as "ground glass appearance".[15] While this feature is more often seen in established FD lesions,[15] it may also be occasionally seen in other conditions such as JPOF or JTOF.[22,26] Grossly, a FD specimen is normally received as small, fragmented pieces because the lesion merges with adjacent normal bone.[15] This helps to distinguish it from COF with its typical well demarcated borders, but often the tumor-normal tissue boundary is obscured.[15]

Microscopically, FD shows discrete islands of delicate, mostly woven bone trabeculae with odd shapes usually described as "Chinese-character pattern" (**Figure 4A**). These bone trabeculae characteristically have a monotonous distribution and are usually devoid of osteoblastic rimming[2,12] (**Figure 4B**). The intervening connective tissue stroma is normally unremarkable, showing moderate cellularity.[25] In long standing lesions, osteoblastic rimming and lamellar bone are often present.[12] Psammomatoid or cementicle-like calcifications, may also be seen, though in fewer numbers.[15] These latter group of features can mirror those of other fibro-osseous lesions especially COF, hindering an accurate diagnosis. A helpful pointer is that the mature bone trabeculae of FD tend to run in a parallel configuration.[12] The standard treatment of FD is surgical paring down of bone in symptomatic patients, since its growth tends to plateau after puberty.[2,12] In asymptomatic patients, surgical intervention is traditionally discouraged for the same reason,[24] though some surgeons choose to operate because growth sometimes continues unabated post-puberty.[27] Radical surgery may be indicated for extragnathic lesions of the head and neck.[27] Recurrence of FD is generally low,[25] but rates as high as 25-50% have been reported in some cases treated by surgical recontouring.[2] A significant fact is that both syndromic and non-syndromic FD can undergo malignant transformation although the risk is quite low.[15] Therefore, long-term follow-up is crucial for all patients diagnosed with FD irrespective of the particular variant.[15]

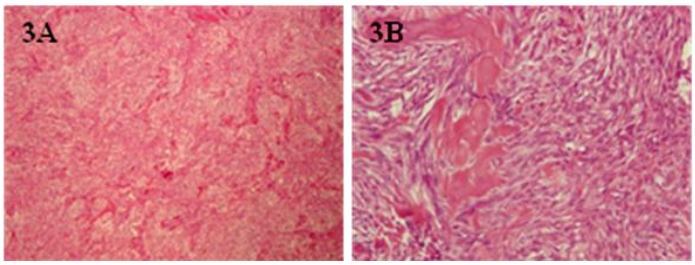

Figure 3. Juvenile trabecular ossifying fibroma. **3A & 3B.** Irregular, anastomosing strands of woven bone trabeculae blending into fibrocellular connective tissue stroma described as "paint-brush strokes pattern".

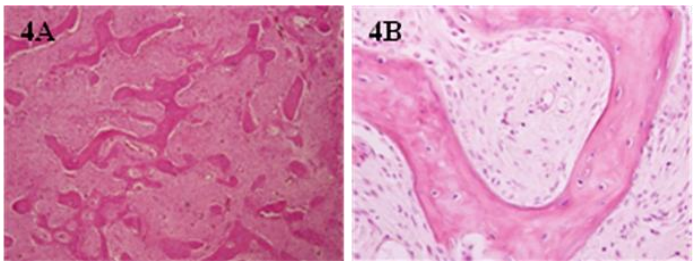

Figure 4. Fibrous dysplasia.
4A. Delicate odd shaped trabeculae of woven and lamellar bone described as "Chinese character" pattern.
4B. Bone trabeculae devoid of osteobastic rimming in bland connective tissue

2.4. Cemento-osseous dysplasia

COD is of particular significance because it is the most commonly encountered fibro-osseous lesion in clinical practice.[14,21] Historically, many CODs were misclassified as variants of COFs.[14] Today, they are still frequently misdiagnosed as other fibro-osseous lesions, COF and FD in particular, because they share certain pathological attributes.[2,14] CODs are considered reactive lesions that occur exclusively in the jaws.[21] There are 4 recognized sub-types: focal cemento-osseous dysplasia (FCOD); periapical cemento-osseous dysplasia (PCOD); florid cemento-osseous dysplasia (FLCOD) and familial florid cement-osseous dysplasia (FaFLCOD).[2] The terms "FCOD" and "PCOD" are often loosely used interchangeably in the literature. Strictly speaking however, PCODs are reserved for localized lesion(s) in intimate contact with roots of vital teeth, usually mandibular incisors.[2] The term "COD" in this article is referring only to either FCOD or PCOD. FLCOD and FaFLCOD involve multiple jaw quadrants and can easily be distinguished from other fibro-osseous lesions discussed here.[15] The typical COD patient is a middle aged, black female who presents with single or multiple, small, painless mandibular jaw lesion(s).[2] Radiologically, CODs appear as radiolucent lesions with varying degrees of opacities, bordered by ill- or well-defined margins.[15, 21] When present as a solitary, well-defined lesion in the posterior jaw region, COD can resemble COF clinically and radiographically.[21] Due to its varied radiographic presentations, it may also mimic JPOF, JTOF or FD, but COD lesions rarely attain a size greater than 2 cm.[15] This is probably why they are usually asymptomatic,[21] and often discovered as incidental findings. The gross specimen of COD appears as multiple small fragments of soft tissue and bone,[5] because the lesion blends with those of adjacent normal bone.[15] This is similar to what obtains in FD and sometimes in JPOF or JTOF. Early stages of COD consist of scattered islands of osteoid or woven bone trabeculae rimmed by osteoblasts.[15] These are interspersed within a proliferating, vascular-rich, moderately cellular fibrous connective tissue stroma, that may or may not contain cementicles.[15] Established lesions demonstrate the characteristic features CODs are known for: thick curvilinear, mostly acellular, mature bone trabeculae said to resemble ginger roots shape[5] (**Figure 5A** and **Figure 5B**). Some of these mature bone trabeculae fuse to form irregular sclerotic basophilic globules and may show prominent reversal lines, characteristic of Paget's disease.[15] This stage of COD demonstrates fewer stromal cells and loosely arranged collagen fibers.[5] An intermediate stage exists, consisting of a combination of features of both early and established lesions. This stage is more likely to be confused with COF[5] or any of its other variants. CODs usually contain foci of cavernous type vascularity, free hemorrhage, and giant cells[5] seen in other fibro-osseous lesions like JPOF or JTOF. Often CODs are left untreated but monitored by periodic recalls alone.[14] Otherwise they can be effectively managed by thorough curettage alone.[5,14]

2.5. Psammomatous meningioma

PM is an uncommon histological variant of meningiomas.[28] According to the 2007 classification scheme for meningiomas, it is classified as a WHO grade I (benign) tumor.[17] Meningiomas are tumors that typically arise in close proximity to the meninges and are often easy to diagnose.[28] Diagnostic difficulties can arise when they occur in unusual locations as extracranial tumors of the head and neck.[28] Extracranial meningiomas are often situated within the paranasal sinuses.[3] Here, they cause symptoms such as nasal obstruction[25] or proptosis[28] and can be mistaken clinically for JPOF, JTOF, COF, or FD. PMs have an affinity for the thoracic spinal region of middle-aged women,[17] but they have also been described within the craniofacial region, including the oral cavity.[18] Jones and Freedman (2001) described a case of an extracranial meningioma of the psammomatous type occurring within the mandible.[18] Of all the fibro-osseous lesions, JPOF constitutes the greatest diagnostic challenge to extracranial PM because they can have clinical, radiologic and histologic similarities.[3] CT scans of meningiomas of the sinonasal nasal region usually reveal a mass devoid of bony destruction.[28] Bone remodeling and sclerosis are the usual accompanying features,[28] but bony rarefactions, without a large osteolytic defect is not unusual.[29] Psammomatous meningiomas are typified by numerous psammoma bodies randomly distributed among whorls of cells proliferating within a connective tissue stroma.[3] These proliferating cells have meningoepithelial features, with pale cytoplasm and ovoid nuclei that contain delicate chromatin material and pseudoinclusions.[3] Sometimes these whorls of cells may be

less obvious because there is almost complete domination by psammoma bodies[17] (**Figure 6A** and **Figure 6B**). Furthermore, the usually discrete psammoma bodies become confluent, forming irregular calcified masses, even bone.[17] The histological picture in such instances can be mistaken for JPOF.[17] An important difference is that osteoid, osteoblasts and osteoclasts are absent.[28] In addition, the stroma is not as fibrotic and the meningoepithelial cells may appear infiltrating surrounding normal bone.[28] PMs are slow growing lesions treated mainly by complete excision.[28] Prognosis is very good[28] although metastases have been rarely reported.[16] The estimated 5-year survival rate for WHO Grade I meningiomas is 92.4%.[28] Meningiomas commonly arise in patients with neurofibromatosis type-2,[30] where there are other weighty co-morbidities to contend with. Multiple meningiomas can occur with/without an association with this syndrome.[30]

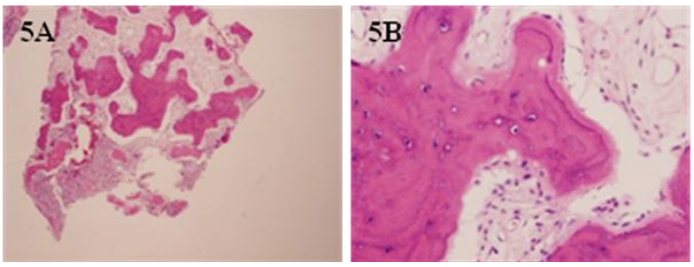

Figure 5. Cemento-osseous dysplasia.
5A. Thick, curvilinear mature bone trabeculae with "ginger roots" shape.
5B. Dense bone trabeculae showing reversal lines within a loose connective tissue stroma.

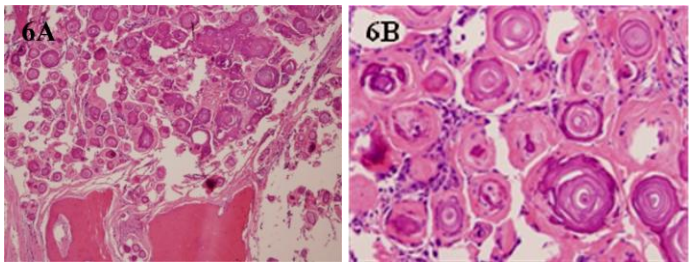

Figure 6. Psammomatous meningioma.
6A. Numerous psammoma bodies infiltrating surrounding bone.
6B. Psammoma bodies showing concentric laminations and few surrounding meningoepithelial cells.

Table 2. Histological Characteristics.

	JPOF	**JTOF**	**COF**	**FD**	**COD**	**PM**
Fibro-osseous lesion	Yes	Yes	Yes	Yes	Yes	No
Gross features	Gritty; multiple, small, fragmented pieces	Same as JPOF	Intact, often large; gritty	Gritty, fragmented; Submitted as surgical shavings	Gritty, small, fragmented pieces	Granular mass with gritty consistency; fragmented.
Histology – main distinguishing features	Numerous psammoma bodies and osteoid trabeculae in highly active stroma	"Paint-brush strokes" type trabeculae with prominent nuclei, in highly active stroma	Well circumscribed; +/-encapsulation ; variation in stromal cellularity & mineralized content	"Chinese-character" type trabeculae devoid of osteoblastic rimming in a monotonous connective tissue stroma	"Ginger-root" type acellular, trabeculae with loose fibrous stroma	Psammoma bodies + whorls of meningoepithelial cells.
Osteoblastic rimming	Yes	Yes	Yes	No, but may be seen in older lesions	Yes – usually in early lesions	No osteoid, osteoclasts/osteoblasts.
Ovoid osteoid/ cementicle-like calcifications	Yes	Yes, few	Yes, often with brush borders	Yes, few	Yes	No, but psammoma bodies can coalesce to form irregular calcifications, even bone
Giant cells	Yes	Yes	Yes	No	Maybe	No
Aneurysmal-like spaces	Yes	Yes	No	No	Yes	No
Predominant Stromal cellularity pattern	Hypercellular	Same as JPOF	Moderate	Moderate	Hypocellular – usually in later stages	Whorls of meningoepithelial cells obscure CT stroma

3. Conclusion

The histological diagnoses of many entities can be pretty straightforward, often made without much input from the clinical and radiological findings. In cases where overlapping histological characteristics create a confusing picture, IHC stains can be very helpful in reaching a definitive diagnosis. However, with COF, JPOF, JTOF, FD, COD and PM, no suitable IHC markers are currently available to distinguish them. Utilization of a combination of the clinical, radiological and histological information is the most appropriate way to obtain the correct diagnosis. It is therefore paramount that the pathologist is able to recognize the obvious and subtle differences among these lesions.

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