

Case Report

Heterotopic ossification in psammomatous spinal meningioma: a diagnostic controversy

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Abstract: Heterotopic ossification (HO), a synonym for osseous metaplasia, is a pathological phenomenon, characterized by abnormal bone formation outside the skeletal system observed commonly in various neoplastic and non-neoplastic diseases. HO occurring in meningioma is exceptionally rare. We report herein an unusual case of spinal meningioma containing numerous calcified psammoma bodies and extensive HO in a 75-year-old woman, who presented with progressive worsening bilateral lower limb weakness and numbness. The presence of remarkable bone formation within a meningioma is controversial among pathologists; while some regard them as psammomatous meningioma as the primary diagnosis, others prefer osteoblastic meningioma, a form of metaplastic meningioma. There is compelling molecular data to advocate that HO is an active disease process involving metaplastic (osseous) differentiation of meningioma stroma mesenchymal stem-like cells, but not the meningotheial-derived tumor cells. Henceforth, the term “metaplastic meningioma” may not be appropriate in this context. A plausible designation as “psammomatous meningioma with osseous metaplasia” defines this entity more accurately. This paper highlights the need for a unifying nomenclature to reduce diagnostic controversy caused by conflicting terms in the literature. The possible pathogenesis of this intriguing phenomenon is discussed.

Keywords: Diagnostic dilemma, heterotopic ossification, meningioma, osseous metaplasia, psammomatous

Introduction

Heterotopic ossification (HO), a synonym for osseous metaplasia, is a diverse pathologic phenomenon well described in various neoplastic and non-neoplastic diseases. It is characterized by abnormal bone formation outside the skeletal system, and usually occurs following traumatic injuries, local or systemic insults, and surgery [1]. HO in meningioma is exceedingly rare, with approximately 30 published cases worldwide [2]. We report herein an unusual case of spinal meningioma containing numerous calcified psammoma bodies and extensive HO in a 75-year-old woman with no prior history of spinal injury.

The issue raised was whether this phenomenon represents a true tumor metaplasia. The exact histogenesis of this devastating occurrence remains elusive to date. This confusion has created a diagnostic controversy among

experienced pathologists; some regarded them as psammomatous meningioma, while others preferred osteoblastic meningioma, a form of metaplastic meningioma [2]. The most relevant key genes implicated in the osteogenesis pathways in meningiomas linked to the possible pathogenetic etiology of this intriguing phenomenon are discussed in the light of the literature.

Case presentation

A 75-year-old woman presented to us with two-year history of bilateral lower limb weakness and numbness. Her symptoms had progressively worsened two months prior to presentation. She had no other constitutional symptoms such as fever, urinary and faecal incontinence. There was no previous history of spinal injury. On examination, the motor strength of both lower extremities was reduced, with associated sensory deficit from the T2 up to S1 level. Both

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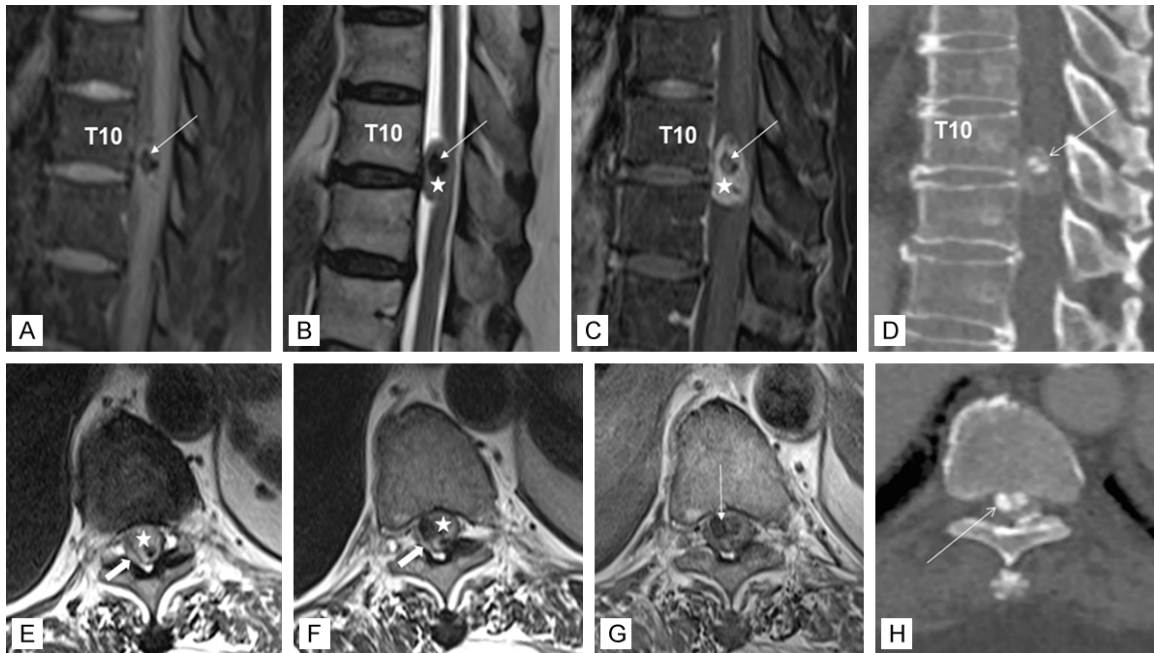


Figure 1. MR imaging of the thoracic spine in T1-weighted image with fat saturation (A), T2-weighted image (B), T1-weighted fat saturation post contrast image (C), and CT bone setting reconstruction image in sagittal plane (D) and T2-weighted image (E, F), T1-weighted post contrast image (G), and CT reconstruction image in bone setting in axial plane (H). The intradural extramedullary lesion (star) exhibits isointense signal on T1, is hyperintense on T2, and enhances homogeneously with contrast. There are hypointense foci within (arrow) that are markedly hypointense on T1 and T2 consistent with intratumoral calcification as shown in the CT images. The spinal cord is displaced and compressed right posterolaterally by the mass and returns high signal intensity on T2 indicating cord edema (block arrow).

the ankle and knee jerks were hyperreflexic. Anal tone was normal.

Magnetic resonance imaging (MRI) of the spine revealed a 16 mm well-defined intradural extramedullary lesion at T10/T11 level, compressing the adjacent spinal cord. Remarkably, noticeable hypointense signal was seen centrally on T1- and T2-weighted sequences, representing intratumoral calcification (**Figure 1**). In addition, there were multilevel extensive degenerative disc changes of the spine with protrusion of osteophyte-discal complex from C3 to C7, most severe at the C5/C6 level with associated significant spinal canal stenosis and cord compression (not shown), corresponding to the neurological impairment elicited. Computed topography (CT) examination of the spine demonstrated a highly attenuating intratumoral calcification within the spinal canal, in agreement with the MRI finding (**Figure 1**). She underwent a left T10 hemilaminectomy and excision of the intradural extramedullary mass. The tumor was removed piecemeal successfully with minimal adherence to surrounding structures. No residual disease was detected by postoperative MRI.

Gross examination of tumor showed grey brownish “hard” tissue fragments which imparted a gritty sensation on cutting. Histopathologic examination displayed morphologic features of classical psammomatous meningioma (**Figure 2A**), composed of syncytial sheets and lobules of uniform neoplastic meningothelial cells arranged in a whorled configuration. The tumor cells had round to oval nuclei with delicate chromatin and inconspicuous nucleoli. Rare pseudonuclear inclusions were identified. Numerous psammoma bodies were readily apparent (**Figure 2B**). There was no increase in mitosis or tumor necrosis detected. Interestingly, a substantial interlacing network of immature woven bony trabeculae without osteoblastic rimming representing HO (**Figure 2C**) was intermingled intimately with these lobules of neoplastic meningothelial cells. No haematopoietic marrow element was present. An area suggestive of an endochondral ossification was also observed (**Figure 2D**).

Immunohistochemically, the meningothelial tumor cells exhibited epithelial membrane antigen (EMA) (**Figure 2E**), progesterone receptor (focal) (**Figure 2F**), vimentin and S-100 immu-

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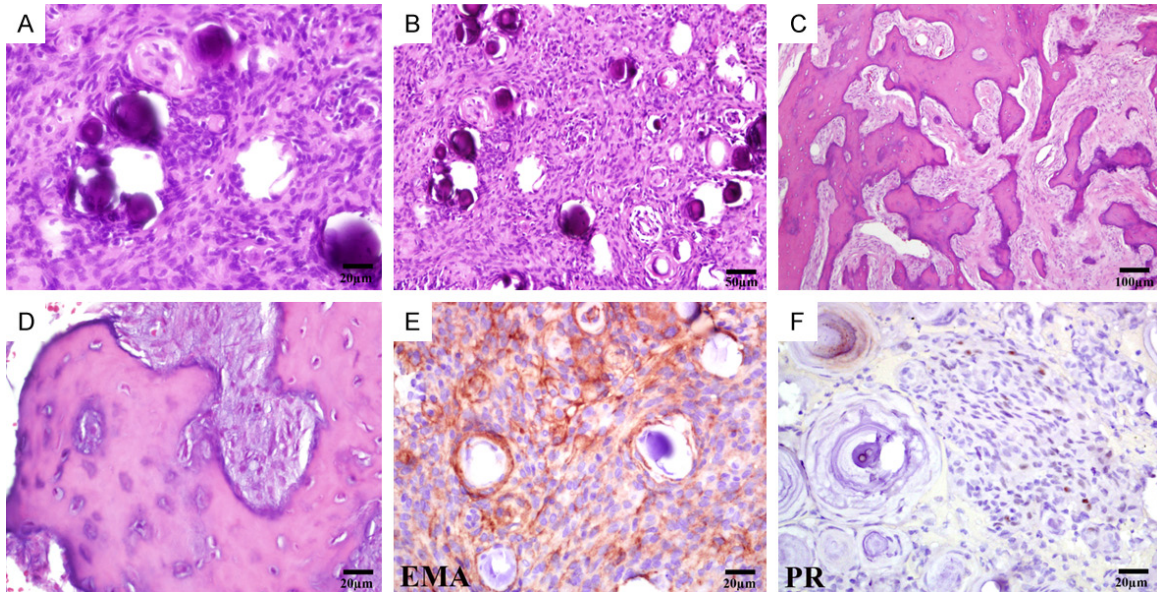


Figure 2. Microphotographs of psammomatous spinal meningioma with osseous metaplasia. (A) The tumor exhibits syncytial sheets and lobules of uniform neoplastic meningothelial cells arranged in a whorled configuration (H&E $\times 400$); (B) Numerous psammoma bodies are readily apparent, consistent with a diagnosis of psammomatous meningioma (H&E $\times 200$); (C) Intermingled closely with the tumor, there is a substantial interlacing network of immature woven bony trabeculae without osteoblastic rimming, signifying heterotopic ossification (H&E $\times 100$); (D) An area suggestive of an endochondral ossification is seen (H&E $\times 400$). Immunohistochemically, the neoplastic meningothelial cells are immunoreactive for (E) epithelial membrane antigen (EMA) ($\times 400$) and (F) progesterone receptor (PR) ($\times 400$).

noreactivity, while the osteoblastic component was stained negative. Ki-67 proliferative and p53 labelling indices were low (approximately 1% and 10% respectively). After multidisciplinary discussion following extensive literature review, a diagnosis of psammomatous meningioma with extensive osseous metaplasia, World Health Organization (WHO) grade I was rendered.

The patient was discharged a week after surgery with no immediate post-operative complications. At six months post-surgical extirpation of tumor followed up, her neurological symptoms did not show significant improvement. She was subsequently counselled for C3-T1 posterior laminectomy and instrumentation.

Discussion

Spinal meningioma is relatively less frequent than its intracranial counterpart, accounting for approximately 12% of all meningiomas and 25% of all spinal neoplasms. A wide spectrum of morphologic appearances comprising 15 distinct histologic subtypes of spinal meningioma was illustrated in the latest WHO classifica-

tion, with psammomatous, meningothelial and transitional being the commonest histologic variants [3]. Metaplastic meningioma is infrequently described in the spine. It is characterized histologically by the presence of focal or widespread osseous elements, singly or in combination with other mesenchymal differentiation including xanthomatous, cartilaginous, lipomatous, or myxoid components [4].

Ossification in meningioma was first described by Rogers [5] in 1928, and was rarely reported thereafter. A literature search from PubMed database using the search terms ((((((ossified) OR osteoblastic) OR osseous metaplasia) OR bone) OR psammomatous AND spinal) AND meningioma) retrieved 667 articles. After filtering our initial selection and excluding irrelevant articles, only 21 papers with 30 cases of ossified spinal meningioma were identified in the English literature, and five of them were psammomatous meningioma exhibiting osseous metaplasia. Clinicopathologic characteristics of these published cases [2, 6-9] are summarized in **Table 1**.

HO in meningioma should be distinguished from tumoral invasion of the overlying bone, a

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phenomenon commonly depicted in meningioma. Endochondral ossification or presence of woven (immature) bone is not a feature in the latter. In meningioma with bony invasion, the bony trabeculae usually appear thicker in parallel arrangement, commonly with osteoblastic rimming [10]. The characteristic MR imaging appearance of bony infiltration by meningioma, demonstrating gadolinium enhancement in the involved bone [11], may help in this distinction.

Another differential diagnosis worth mentioning is ossifying fibroma, especially the juvenile psammomatoid variant (JPOF). The presence of numerous psammomatoid ossicles uniformly distributed within a fibroblastic stroma admixed with small bone trabeculae with osteoblastic rim may mimic psammomatous meningioma with HO to perfection. Unlike psammomatous meningioma, which is predominantly found in the spine in older women, JPOF has a predilection for the craniofacial skeleton of the young [12]. A careful search for tumor cells showing unique meningeothelial features, such as ovoid nuclei with delicate chromatin and nuclear pseudoinclusions, provides important clues to diagnosis.

The differential between psammomatous meningioma with HO and calcifying pseudoneoplasm of the neuraxis (CAPNON), a benign non-neoplastic calcified lesion of the central nervous system can be problematic. CAPNON represents a spectrum of unusual reactive processes involving the meninges and/or adjacent bone. It is characterized histologically by nodules of chondromyxoid matrix with palisading spindle to epithelioid cells embedded within a fibrous stroma. In addition, the presence of variably calcified or even ossified basophilic amorphous to fibrillated material, frequently described as “chicken-feet calcifications” is a fairly distinctive feature [13]. The presence of rare meningeothelial hyperplasia in this entity, however, should not be mistaken for a meningioma.

The enigmatic association of meningioma with HO remains obscure to date. In the past, the process of HO was perceived as passive dystrophic mineralization of the degenerating neoplastic cells [1]. The hypothesis speculated that the presence of psammoma bodies could serve as a nidus for initial ossification was debunked. There was no clear association between bone formation and psammoma bodies, as HO did

occur in cases devoid of psammoma body formation [14].

In general, HO develops by intramembranous ossification or endochondral ossification. Intramembranous ossification involves direct differentiation of a mesenchymal template into bone; whereas in endochondral ossification, replacement of a pre-existing hyaline cartilage model with mineralized bone occurs [1]. The presence of endochondral bone in the present case might indicate that endochondral ossification had taken place, a feature seldom emphasized in the literatures.

HO in meningioma was regarded as a metaplastic process and was covered by the term “metaplastic meningiomas” in the recent WHO classification [4]. Metaplasia by definition is characterized by reversible substitution of one mature cell type for another. It was once believed that these meningeothelial-derived tumor cells retained their pluripotential aptitude to differentiate, in which they had transformed into osteoblasts, a mesenchymal derivation. Emerging literature supported our postulation that HO is indeed an active disease process encompassing metaplastic (osseous) transformation of the meningiomatous stroma mesenchymal stem-like cells (MS-MSLCs), a component in the microenvironment, but not the meningeothelial-derived tumor cells themselves [2, 15]. Henceforth, the term “metaplastic meningioma” may not be appropriate in this context. A plausible designation as “psammomatous meningioma with osseous metaplasia” defines this entity more accurately, given the abundance of intralesional psammoma bodies as well as extensive HO present within the same lesion.

The metaplastic process of MS-MSLCs requires active secretion of osteogenic factors by the meningeothelial-derived tumor cells [2, 15]. This is further substantiated by the expression of osteogenic lineage genes in the neoplastic meningeothelial cells, such as bone morphogenetic proteins (BMPs), BMP receptor type 2 (BMPR2), transforming growth factor- β 2 (TGF- β 2), and SMADs. BMPs are a heterogeneous group of proteins belonging to the larger TGF- β superfamily, together with other members including TGF- β s (1-3). To date, there are more than 30 BMPs being recognized, with BMP-2, BMP-4, and BMP-7 directly implicated in the occurrence of HO [16]. TGF- β 2, in particular, acts synergistically with BMPs in promoting het-

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Table 1. Clinicopathologic characteristics of the published cases of ossified psammomatous spinal meningiomas

Reference	No. of cases	Age/Gender	Symptoms and duration	Tumor Laterality	Tumor size (mm)	Histologic subtype/WHO grade	Recurrence
Freidberg et al. (1972) [6]	1	69/female	Progressive weakness lower limbs for 9 months, recent urinary incontinence	T1-T2, intradural extramedullary	20	Psammomatous/WHO grade I	NA
Uchida et al. (2009) [7]	1	76/female	Painful lower limb weakness & numbness for 2 years	T8, T11/T12, extramedullary	NA	Psammomatous, fibrous & metaplastic/WHO grade I	No
Chotai et al. (2013) [8]	1	61/female	Lower leg numbness & Weakness for 3 years, gait disturbances for 6 months	T4, intradural	NA	Psammomatous/WHO grade I	No
Prakash et al. (2017) [9]	1	60/female	Progressive lower limbs weakness & numbness, urinary incontinence for 1 year	T7, intradural extramedullary	15	Psammomatous/WHO grade I	NA
Wang et al. (2019) [2]	1	52/female	Chronic back pain for 5 years	T4, intradural extramedullary	12	Psammomatous/WHO grade I	No
Present case	1	75/female	Bilateral lower limb weakness and numbness for 2 years	T10/T11, intradural extramedullary	16	Psammomatous/WHO grade I	No

erotopic bone formation by TGF- β signalling (through the SMAD pathway) and non-canonical p38MAPK pathway. In addition, the overexpression of BMP2 in meningioma may facilitate BMP-2-induced osteoblastic metaplasia and calcium mineralization [16] of the MS-MSLCs.

In summary, we describe an exceedingly rare case of HO in psammomatous meningioma. This highlights a need for a unifying nomenclature to reduce diagnostic controversy caused by the variety of terms in the current literature.

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Disclosure of conflict of interest

None.

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