Published in final edited form as:

Neuropathol Appl Neurobiol. 2018 December ; 44(7): 743–746. doi:10.1111/nan.12481.

Non-Meningothelial Meningeal Tumours with Meningioangiomatosis-like Pattern of Spread

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Keywords

Meningioangiomatosis; Meningioma; Meninges; Solitary fibrous tumour/hemangiopericytoma; Atypical Teratoid/Rhabdoid Tumour

Meningioangiomatosis (MA) is a rare entity characterized by the perivascular spread of meningeothelial and fibroblastic cells along the Virchow-Robin spaces of small leptomeningeal and intracortical blood vessels [1,2]. Sporadic cases of MA are thought to represent benign hamartomatous proliferations that are associated with refractory seizures and plaque-like cerebral hemispheric masses, primarily involving the temporal and/or frontal lobes. A distinct subset of MA presents in association with neurofibromatosis type 2 (*NF2*), where the MA is often multifocal, non-epileptogenic, and accompanied by perilesional glial microhamartomas [3,4]. In contrast to sporadic and *NF2*-associated MA, the MA associated with an overlying meningioma shares the genetic hallmarks of the adjacent meningioma and thus represents a spread of neoplastic cells along perivascular Virchow-Robin spaces that produces an MA-like pattern. Meningiomas with MA-like spread are predominantly situated

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Conflict of interest: The authors declare that they have no competing interests related to this article.

Authors' contributions: Conception and design of study: JBI and AP. Data analysis: JBI and AP. Writing and critical review of manuscript: all authors.

in the leptomeninges and display a transition zone of perivascular meningeothelial nests that resemble those of the overlying meningioma. In the deeper cortical levels, the perivascular meningeothelial cells often transition to a more fibroblastic appearance with increased vascular hyalinization. Critically, the MA-like spread of meningiomas must be differentiated from genuine brain parenchymal invasion, a feature sufficient for a WHO grade II designation [5].

Although meningioma is the most common neoplasm associated with MA-like perivascular spread, we have also encountered a spectrum of rarer tumours with a similar growth pattern. Herein we examine three such tumours - solitary fibrous tumour/hemangiopericytoma (SFT/HPC), atypical teratoid/rhabdoid tumour (AT/RT), and rhabdomyosarcoma (RMS) - that were associated with MA-like spread along Virchow-Robin spaces. This study was performed with local Institutional Review Board approval.

The first example was a 31-year-old man who presented with a sharp headache, nausea and vomiting, and indolent personality changes. On imaging, he was found to have a lobulated extra-axial mass of the frontal pole associated with the overlying meninges and oedema. Small feeding cortical vessels were identified. Following resection, histological evaluation revealed a cellular neoplasm comprised of a jumbled architecture of cells with round-to-oval nuclei and moderate amounts of cytoplasm, tightly packed around thin-walled gaping vascular channels (figure 1a). The mitotic index was low (<5/10 hpf). There were foci of spindle cell morphology, microcystic change, and hyalinized vessels. The tumour cells exhibited immunoreactivity for STAT6 (nuclear), BCL-2, CD99 (membranous), and CD34 (patchy), and were negative for epithelial membrane antigen (EMA), consistent with a diagnosis of SFT/HPC (WHO grade II) [5]. Notably, in the abutting neocortex there was perivascular spread of STAT6-positive SFT/HPC cells and collagen deposition in an MA-like pattern (figures 1b–c).

The second example was a 4-year-old girl who presented with generalized tonic-clonic seizures and on imaging was found to have an enhancing, solid and cystic parietal mass associated with the overlying meninges and oedema. The resection specimen revealed a meningeal-based cellular neoplasm (figure 2a) composed of large epithelioid cells with vesicular nuclei, prominent nucleoli, abundant eosinophilic cytoplasm, and numerous mitotic figures. In areas, the cells were arranged in a chordoid fashion with trabecular architecture and abundant basophilic mucinous stroma. The tumour cells exhibited immunoreactivity for smooth muscle actin (SMA), CD99, vimentin, EMA (patchy), and CD34 (focal). No definite rhabdoid cells were identified, however tumour nuclei demonstrated the hallmark loss of INI1 expression, consistent with the diagnosis of AT/RT (WHO grade IV) [5]. Notably, there was extensive perivascular spread in an MA-like pattern into adjacent cortex (figure 2b), which also exhibited loss of INI1 expression (figure 2c). In foci of perivascular spread, the AT/RT cells often became more fibroblast-like and were associated with increased collagen deposition. The patient was without recurrence 2 months following resection. Of note, a potential new entity was recently reported, involving 2 adult patients with SMARCB1 (*i.e.* INI1)-deficient primary meningeal tumours containing epithelioid to rhabdoid cells. Although this could be an alternate diagnostic consideration, our case involved a child, the morphology was within the spectrum of AT/RT in general, and

the tumour was not considered purely meningeal on MRI.[6] Lastly, it should be noted that rare AT/RTs presenting in the meninges have also been documented.[7]

The third example was a 2-year-old boy who presented with intractable seizures associated with a parieto-occipital mass, of which a biopsy revealed a highly cellular neoplasm involving the leptomeninges (figure 3a). The primitive-appearing ovoid-to-spindle tumour cells displayed round-to-oval nuclei with mild nuclear pleomorphism, small quantities of eosinophilic cytoplasm, and a high mitotic index. Several psammoma bodies were present but appeared to be from entrapped native meningotheial elements. The tumour cells exhibited strong immunoreactivity for SMA, desmin, and retained nuclear INI1; they were negative for EMA, CD99, BCL-2, myogenin, GFAP, synaptophysin, and neurofilament protein. Together the morphological and immunohistochemical features were most consistent with a poorly differentiated meningeal sarcoma, showing features of rhabdomyosarcoma. Notably, the adjacent cortex demonstrated a bland perivascular spindle cell infiltrate with marked hyalinization in an MA-like pattern (figures 3b–c), which was also positive for SMA and desmin. No molecular studies were performed. Surgery was followed by chemoradiotherapy and there was no evidence of recurrence 7 years after initial diagnosis.

All three non-meningothelial meningeal tumours described herein (*i.e.* SFT/HPC, ATRT, and RMS), as well as a fourth case (not shown) of a low-grade fibroblastic mesenchymal tumour that was difficult to characterize morphologically and molecularly, presented as masses situated in the meninges and were associated with an MA-like pattern of perivascular spread into the adjacent cortex. Like meningiomas with MA-like patterns of spread, the perivascular components of these tumours morphologically and immunohistochemically resembled their primary cellular lesions, although there appeared to be a transition zone in each. The perivascular infiltrates were more cytologically bland, spindled, and collagenous, and often displayed less mitotic activity and weaker immunoreactivities than their primary cellular counterparts. Similar to meningiomas with MA-like spread, but unlike sporadic MA cases, the intervening cortical neurons were unremarkable in these cases.

A review of the literature revealed a paucity of non-meningothelial meningeal tumours with MA-like spread. Whereas simple perivascular spread occurs in many malignancies of the subarachnoid space (*e.g.*, meningeal carcinomatosis, medulloblastoma), these usually retain their malignant cytology and do not otherwise resemble MA. However, the involvement of Virchow-Robin spaces in an MA-like pattern was previously reported in a primary fibrosarcoma that had focal malignant fibrous histiocytoma-like dedifferentiation.[8] Although the solid component was negative for EMA, regions of the MA-like component interestingly displayed membranous EMA positivity with psammoma bodies, possibly suggesting that the fibrosarcomatous component arose from or overlaid an existing MA. Although a rare phenomenon, we demonstrate that a spectrum of non-meningothelial meningeal tumours can access the Virchow-Robin spaces of leptomeningeal vessels and subsequently spread along perivascular spaces of adjoining intracortical vessels in an MA-like pattern, including tumour cells assuming a cytologically benign appearing fibroblast-like cytology with marked perivascular hyalinization.

Acknowledgments

JBI is supported by an NIH NCI LRP 1L30-CA209256-01 award and an Arthur Purdy Stout award.

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The histological and immunohistochemical features of non-meningothelial meningeal tumours with an MA-like pattern of spread, including 1) a SFT with a characteristic jumbled architecture of cells tightly packed around thin-walled gaping vascular channels (1a) and STAT6-positivity, which spread into neighbouring cortex in an MA-like pattern (1b–1c); an AT/RT with solid to trabecular/chordoid architectural patterns (2a), basophilic mucinous stroma, and INI1 loss, including foci of MA-like spread (2b–2c); and 3) a poorly differentiated meningeal sarcoma showing features of rhabdomyosarcoma (3a) with MA-like spread into adjacent cortex (3b–3c).