Ischemic strokes occur in 3-4% of patients with GCA[1], and the causes are multi-factorial. Inflammation of intra- and extra-cranial vasculature lead to intimal thickening, luminal irregularities, stenoses, and occlusions, which can cause borderzone hypoperfusion and infarction. *In situ* thrombosis of inflamed vessels can also result in occlusion and distal embolization.[1]

It would be ideal to treat both inflammatory and thrombotic mechanisms. High-dose corticosteroids are the mainstay of therapy in GCA, but small observational studies have explored the addition of antithrombotics. Use of low-dose aspirin was associated with lower rates of visual loss and strokes.[2] Another study looked at antithrombotics in patients with GCA and found they could be treated with baseline antiplatelet or anticoagulant agents, without an increased risk of bleeding.[3] Several case reports have described mixed success with use of anticoagulation in patients with GCA,[4] but none have documented the presence and resolution of iNOT while on anticoagulation. One study looked at iNOT on CT angiography in patients with acute ischemic events (non-arteritic) and found a non-significant trend to resolution of iNOT with dual or triple compared to single antithrombotic therapy.[5]

Our patient developed new ischemic infarcts despite high dose corticosteroids. On neuroimaging, there was evidence of luminal irregularities as well as an iNOT. We used IV steroids and a limited course of IV heparin and aspirin to target inflammation and thrombosis. We observed the interval resolution of the iNOT after several days of combination therapy, without evidence of bleed. Due to limited prospective studies on use of antithrombotics in GCA, the risks and benefits of such therapy is unknown. In our patient, the small size of her strokes and the progression of disease despite treatment prompted a more aggressive approach. Well-designed prospective studies are necessary to explore combined therapy for treatment-refractive GCA.

Disclosures

Dar Dowlatshahi has served on an Advisory Board for Bayer and has received travel reimbursement from Boeringer Ingleheim.

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To the Editor

Plaque-Type Blue Nevus with Meningeal Melanocytomas

Pigmented primary neoplasms of the central nervous system are uncommon. Differential diagnosis of such lesions is limited and includes pigmented meningioma, melanocytic schwannoma, and primary versus metastatic melanoma.

Primary melanocytic tumors of the meninges remain among some of the rarest neoplasms. Again, a variety of entities fall under such a category, including: pigmented meningioma, melanocytic schwannoma, pigmented primitive neural-ectodermal tumor, diffuse melanosis, and meningeal melanocytoma[1]. Of interest, is the entity of purely melanocytic origin that arises from the dura, that being meningeal melanocytomas (MM).

Meningeal melanocytomas are scarcely found in the literature. First ever described by Virchow in 1959, *Pigment und diffuse Melanose der Arachnoides*, these pigmented dural based neoplasms were definitively classified with the help of electron microscopy. As of 2000, only about 110 cases were present in the literature. The WHO estimates a prevalence approaching one per 10 million, in the population.

The usual MIB index of these lesions is below 5%, making them typically a benign entity. Those MM's with MIB indices in the intermediate range, 5-10%, are uncommon. In addition, melanocytic dermatological manifestations such as nevus of Ota, have been associated with ipsilateral intracranial MM[1,2], with only seven cases being described as of 2009[1]. Even rarer is the association of ispsilateral benign blue nevus and MM, with only two cases previously being described in the literature[3,4].

Here we describe a new and rare case report of a patient with a plaque-type blue nevus, ipsilateral meningeal melanocytomas, and an intermediate pathological grade (MIB index of 5-10%).

Case Report

A 25-year-old, right hand dominant, female presented to her local emergency department via ambulance with a history of first onset generalized tonic-clonic seizure, witnessed at home. She had no significant past medical history, and the only remarkable features on examination were papules with an underlying dark blue pigmented patch of skin over the right temporal region, in the area of V1 distribution of the trigeminal nerve and blue macules over the right cheek and sclera. The seizure was described as an acute loss of consciousness with generalized shaking of all four limbs, lasting approximately one minute. During the episode, she was completely unresponsive, cyanotic and postictally combative. The patient was loaded with intravenous dilantin and transferred to our hospital.

Computed tomography (CT) scan of the head demonstrated questionable hyperdensity near the right anterior clinoid process in the area of the cavernous sinus. Computed tomography angiogram including the circle of Willis demonstrated two distinct lesions. The first, a 2 cm dural-based multilobed enhancing mass near the right cavernous sinus extending into the suprasellar cistern and abutting the right M1 segment of the middle cerebral artery (MCA). The second, was a 2 cm supratentorial dural-based mass lateral to the right temporal lobe at the junction of the transverse and sigmoid sinuses. The radiologic interpretation at that time was meningiomas. The etiology of the seizure episode was attributed to the right temporal dural based lesion.

Of note, prior to the seizure episode, the lesion in the right temporal scalp was biopsied by a dermatologist to rule out malignancy. Histopathological diagnosis at that time was plaque-type blue nevus, with the possibility of a nevus of Ota. This was subsequently re-reviewed by two dermatopathologists who both agreed that this was indeed a plaque-type blue nevus.

After spending four days in hospital under observation, the patient was discharged on dilantin. She had no further seizures. Follow up magnetic resonance imaging (MRI) scan of the brain, with gadolinium, conducted three months after the initial event revealed again the two dural based lesions. They were hyperintense on T1, and slightly hypointense on T2 weight imaging. As previously the two lesions enhanced with contrast, and were thought to be meningiomas. Outpatient neurology follow up and electroencephalogram (EEG) failed to demonstrate focal epileptiform discharges, though the right temporal lesion remained the likely causal factor. Further management, including surgical removal of at least the supratentotial right temporal region mass was discussed. The patient declined and non-surgical management was arranged.

Regular repeat MRI scans initially showed no changes. However, 15 months after the initial event, a follow up MRI indicated interval growth of the right temporal lesion. It was now 3 cm and there was adjacent temporal lobe edema. With the patient being pregnant at the time, it was elected to wait until the second trimester to surgically resect the right temporal lesion. After obtaining informed consent, a Simpson grade 3 resection was achieved. A small amount of tumor remained adherent to the dura at the junction of the transverse and sigmoid sinuses. Of note, the dura had areas of black pigmentation, and a poor brain-tumor interface was found.

Gross pathology demonstrated a soft tan tissue with dark red brown hemorrhagic material. Histopathology revealed a dense spindle cell neoplasm, with prominent nucleoli, cigar-shaped nuclei. Nuclear grooves were seen. Intracellular pigment was identified, that failed to stain for hemosiderin on Perl's stain. No areas of necrosis were seen, and 1-2 mitosis per 10 high power field (hpf) was seen. The tissue was noted to be glial fibrillary acidic protein (GFAP), estrogen receptor (ER), progesterone receptor (PR), cytokeratin, chromogranin, and neurofilament negative. However, HMB-45, Mart1, and S100 were positive on tissue stains, suggesting melanocytic origin. The Ki-67 and MIB index was determined to be between 5-10%. The diagnosis of an intermediate grade melanocytic neoplasm was made by two Neuropathologists at our medical centre. The case and

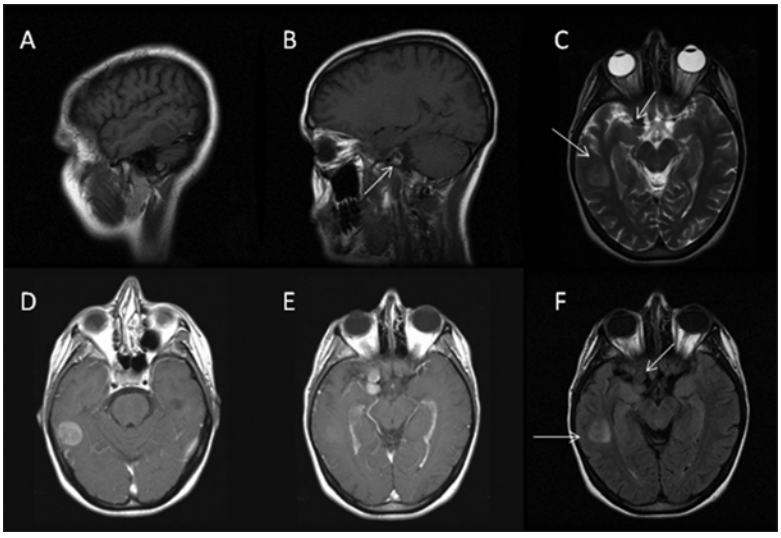

Figure: *MRI Characteristics of Patient's Meningeal Melanocytomas.*
(A) Sagittal T1WI of the right temporal lobe, showing a hypointensity surrounded by a hyperintense capsule. (B) Sagittal T1WI through right cavernous carotid demonstating a hyperdense lesion in the lateral wall of the cavernous sinus (indicated by white arrow). (C) Axial T2WI demonstrating right temporal and cavernous sinus lesions relatively hypointense with some surrounding hyperintense edema (indicated by arrows). (D) Axial T1WI with GAD showing right enchancing dural based lesion in temporal lobe close to sigmoid sinus. (E) Axial T1WI with GAD demonstrating right cavernous sinus enhancing lesion encroaching right M1 segment of the MCA. (F) Axial T1 Flair imaging indicating peri-tumor edema in the right temporal lobe and right uncinate process. WI = weighted image, GAD = gadolinium.

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histopathology was also reviewed with Anatomic Pathologists at our centre, as well as an external Neuropathologist, who all agreed with the diagnosis. The external Neuropathologist stated that the histopathological features of this lesion indicate that it may have an aggressive biology. Furthermore, a high proliferative index and invasion of the brain suggest an increased risk of disease progression without further treatment.

Given the potential for aggressive behaviour, it was recommended that the patient undergo a second operation for the right parasellar dural based lesion, due to prediction that it would also be melanocytic in origin and have the same histopathology. Thus, after obtaining a second informed consent, she underwent a pterional craniotomy with debulking of the second dural based lesion near the right cavernous sinus eight months after the first operation, post-partum. Of note, intraoperatively there was dark pigmentation of the temporalis muscle and the dura. A Simpson grade 3 resection was achieved with a small amount of adherent residual tumor left along the lateral wall of the right cavernous sinus. Neuropathology confirmed that this lesion was also of melanocytic origin, identical to the temporal tumour, and diagnosis of a second intermediate grade melanocytic neoplasm was made.

Post-operative follow up MRI scans are being done at regular intervals. None have shown evidence of residual or recurrent tumor at either site since the operations were conducted, the first three years ago. The MRI scan of the entire spine showed no evidence of tumor. She has not received an adjunctive therapy. She remains neurologically asymptomatic, seizure free on Lamictal as of last follow up.

Discussion

Meningeal melanocytomas are a rare entity in neurosurgery and neuropathology. With low incidence in the population, and less than 200 cases in the literature ever described, it makes these lesions poorly understood.

The presence of ipsilateral cutaneous lesions and MM is rare[2]. When searching for the association of cutaneous melonanytic lesions and intermediate grade MM, one finds a paucity of articles[1,3,4]. Occasional reports of MM associated with ipsilateral nevus of Ota have been described. Similarly, as mentioned above, there appears to be only two previous cases of plaque-type blue nevus and associated ipsilateral MM[3,4], with our case being the third.

Macroscopic appearance consists of focal, dural-based lesions. Upon examination, typical appearance is a soft dark brown/tan mass. In situ, the dark pigmentation is also located on the cortical surface and meninges. Thorough pathologic characteristics have been described by Navas et al[1], and others. Microscopically, as described by Brat et al[5], MM are typically well differentiated lesions, being very distinctive from the surrounding leptomeninges. Histologically they consist of heavily pigmented cells with melanophages. They usually arise from melanocytes derived from the neural crest, found in the leptomeninges throughout the CNS, typically found over the ventro-lateral surface of the medulla. They are composed of a sheet like organization of melanocytes containing the pigment melanin, with nuclear atypia possible.

Typical immunohistochemical features are negative GFAP, nucleotide specific enolase (NSE), cytokeratin, and neurofilament[5]. Perl's stain for hemosiderin is typically also negative unless malignant transformation has occurred. The HMB-45 and S100 are positive markers in both MM and malignant melanoma[1]. The two are therefore further distinguished via gross and microscopic appearance. Occasional reticulin staining is seen around nests of tumor cells. There is an absence of necrosis or CNS invasion, in contrast to malignant melanomas. The MIB-1 index is typically less than 5%. However, there are rare reports of "intermediate grade" MM have surfaced with MIB-1 indices ranging from 5-10%[1,5]. Various tumor locations have been described.

Clinical presentation varies from incidental finding, to neurological manifestations secondary to local mass effect. Radiologically these tumors are very similar in appearance to meningiomas. Computed tomography scans remain nonspecific with the presence of hyper to iso-dense lesions in contact with the dura. Infused CT typically demonstrates homogenous enhancement, though this can vary. As a result, radiographic diagnosis is still dependent upon MRI. Classical MRI appearance is a hyperintense lesion on T1WI with hypo to iso-intensity on T2WI. The T1 FLAIR sequences may demonstrate some peri-lesional edema in nearby parenchyma. Gadolinium administration shows homogeneous enhancement[2].

Currently, there is no treatment consensus with the natural history of these lesions poorly defined. Most are diagnosed by histopathology after removal. Patients with intermediate grade lesions typically have almost complete resection due to concerns surrounding their potential aggressive nature. However, no guidelines exist governing the use of radiation or stereotactic radiosurgery post-operatively, with sparse case reports in the literature. The degree of resection may be limited by location, for example cavernous sinus and along dural sinuses, as occurred in our case.

Benign ipsilateral cutaneous blue nevus associated with intermediate grade meningeal melanocytomas is scarcely found in the literature, with only two case reports found on our search of PubMed, Medline, UpToDate, and Cochrane Library[3,4]. This makes the above described case the third, to our knowledge.

Given the variability of tumor progression for a given pathological subtype of MM, we have elected the watch and wait approach in our case. With a total of 48 months of close clinical follow-up with repeat MRI, even in our case of an intermediate grade lesion, the absence of recurrence or progression demonstrates the uncertain nature of this disease process. Thus, we will continue to watch closely and treat appropriately should there be a recurrence. Whether or not this is the correct approach to MM with intermediate pathological grade is unknown, and will likely remain unknown until larger case series with longer follow up periods are published on the topic.

In conclusion, pigmented neoplasms of the central nervous system have a variable differential diagnosis. Meningeal melanocytomas are among some of the rarest primary CNS tumors described in the literature. The association of ipsilateral MM and plaque-type blue nevus is an exceedingly rare entity, with this case (to the best of our knowledge) being only the third ever described. With the presence of an intermediate grade at diagnosis, it possesses an uncertain prognosis, and according to

the literature that exists, remains uncertain. The behavior of MM and its subtypes has yet to be defined and requires extended patient follow up, with larger patient series. Our patient is being followed very carefully with regular scheduled clinical and radiological follow-up

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To the Editor

Fatal Cerebellar Hemorrhage Following Australian Brown Snake Envenomation

Venomous snakebites cause significant global morbidity and mortality, but their sequela are rarely encountered in neuropathology practice in North America. This case illustrates the potential dire consequences of a bite from one of the world's most venomous snakes, the Australian brown snake.

A 69-year-old female with a past medical history of hypertension stepped on an Australian brown snake outside of her home in Western Australia and was bitten on the instep of her foot. Appropriate pressure-immobilization first aid was initiated and the Emergency room assessment within 15 minutes of the bite revealed an INR of 0.9 and a baseline Creatinine of 191. Thirty minutes after the bite she began feeling unwell, vomited, started bleeding from her IV site, and her INR was 10. Brown snake venom was detected in her urine and she was treated with 5 Units of Brown snake anti-venom. Over the course of the next 48 hours her coagulopathy worsened (INR > 30), she was persistently hypertensive (up to 235/150 despite medical management), and she developed microangiopathic hemolytic anemia and renal failure (maximum Creatinine of 303). When her level of consciousness deteriorated a computed tomography (CT) scan showed an intraparenchymal hemorrhage in the posterior fossa (Figure 1). She died within 48 hours of being bitten.

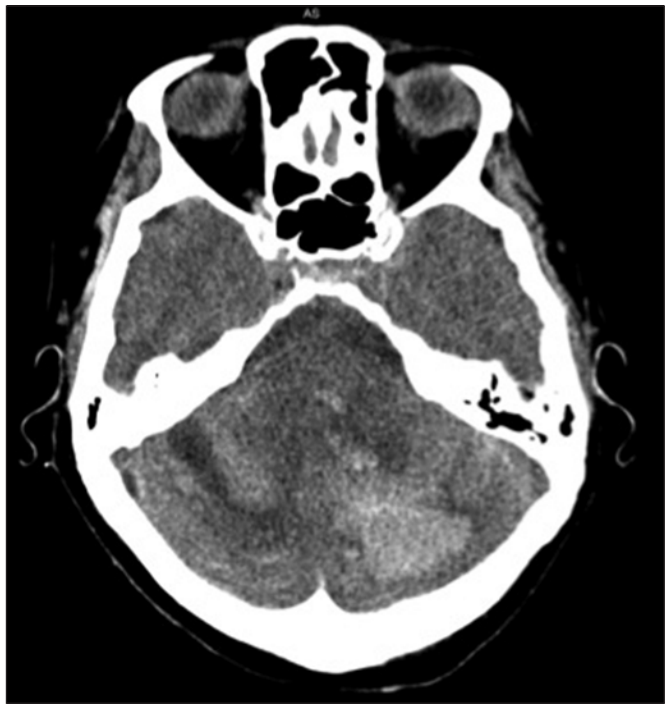

Figure 1: *Axial CT scan showing intraparenchymal hemorrhage within the cerebellum.*

At autopsy the brain was swollen with tonsillar herniation and a 50 x 25 mm V-shaped hemorrhage within the cerebellum (Figure 2). Histologic examination showed no evidence of an underlying vascular malformation, neoplasm or infarct.

Venomous snakebites are a significant global health problem, with an estimated five million cases of snake envenomation resulting in 125,000 deaths worldwide each year[1]. Many of these fatal envenomations are from *Naja* species (cobras) in Asia, or from Viperidae species in Africa[1]. In the United States there are 7000-8000 snakebites resulting in five or six deaths a year[2], mostly from Rattlesnakes. There are four species of venomous snakes in Canada but reports of significant morbidity and mortality from snakebites in Canada are few. The Australian Snake Bite Project has documented between 1000-3000 snakebites and four resulting deaths a year within Australia. All of the Australian deaths have been due to one of three snake species: Australian brown snakes (most commonly), tiger snakes

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