Discussion of case and challenge answers on page 80

A Woman With a Large Dural-Based Lesion

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Case Presentation

Clinical Presentation and Imaging

An Hispanic woman, age 52, presented with persistent dizziness and the inability to "bring out certain words." She had been having difficulty speaking for a number of months. Recently, she began to notice some clumsiness in her right hand and occasional weakness in her right leg. Her neurologic examination showed severe expressive aphasia and mild right hemiparesis. Brain MRI showed a dural-based left frontotemporal convexity lesion measuring 5.7 cm x 3.2 cm x 5.1 cm, diving into the left Sylvian fissure (Figure 1).

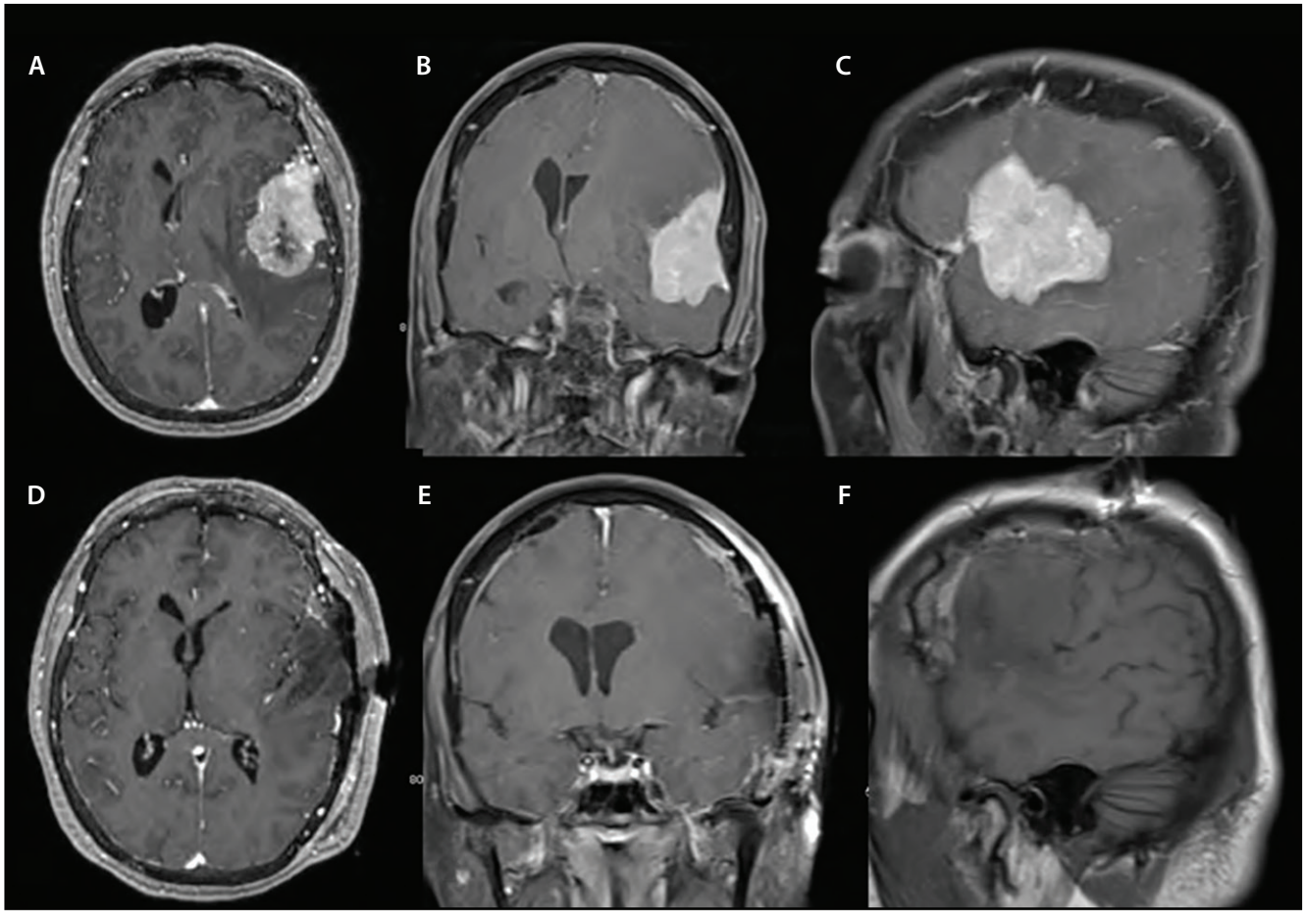

Figure 1. Representative images from preoperative and postoperative brain MRI. The top row shows a large dural based lesion, in axial (A), coronal (B), and sagittal (C) orientation that seems to be splitting the fissure between the frontal and temporal lobes. The bottom row (D-F) is the post-operative MRI that confirms gross total resection of this lesion, with preservation of adjacent brain.

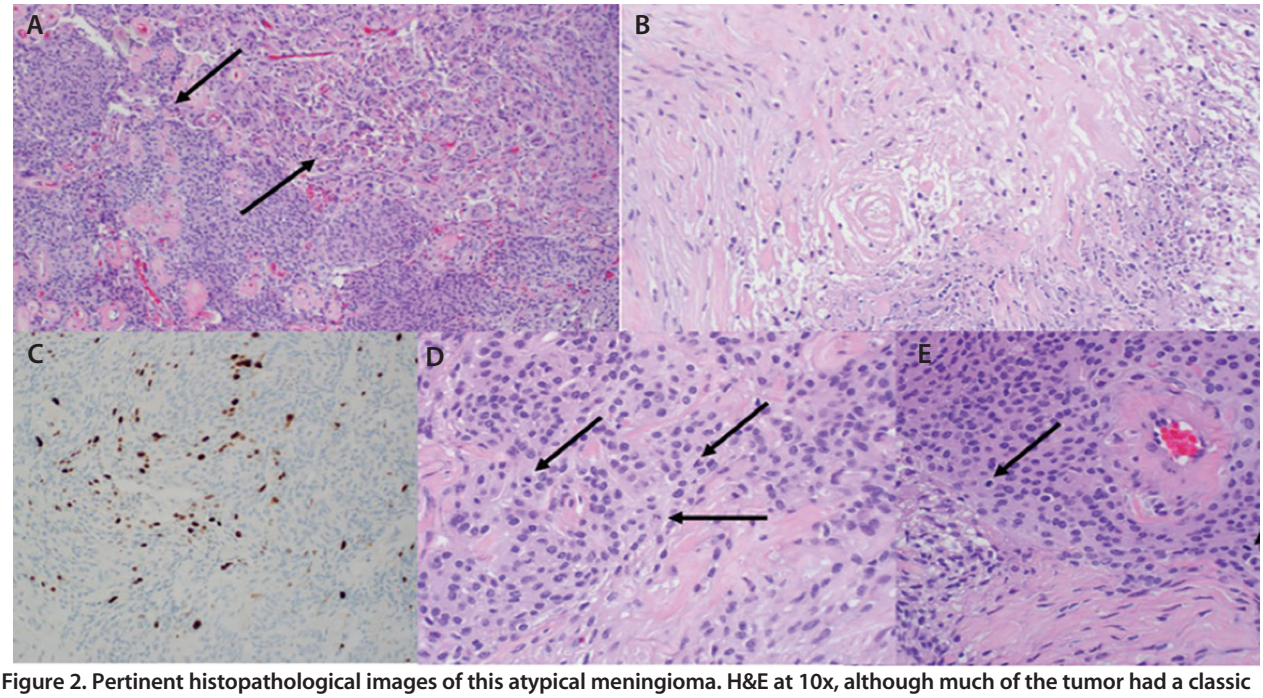

Figure 2. Pertinent histopathological images of this atypical meningioma. H&E at 10x, although much of the tumor had a classic meningothelial appearance (A upper right, arrow); there were many more patternless-appearing foci (A, lower left). H&E at 20x, occasional foci of necrosis were associated with hyalinization. Ki-67 at 20x, a proliferation index appears to exceed 4% (C). H&E at 40x, although it was uncommon to find more than 2 mitotic figures in 1 high-power field, a mitotic index exceeded 5/10 hpf focally (D). H&E at 40x, 2 mitotic figures in 1 hpf (E).

Treatment and Outcome

Our patient underwent uneventful gross total resection of the lesion, which, during surgery, was confirmed to arise from the dura and invade overlaying bone, the latter of which was removed with margins. Lesion pathology was consistent with World Health Organization (WHO) grade II atypical meningioma (Figure 2). The patient's weakness resolved and her aphasia improved. She has been referred for a clinical trial for higher-grade meningiomas and was randomized to observation. She will continue to be followed clinically and radiographically.

Challenge Questions
(See p 80 for Answers and Discussion)

1. The incidence of meningioma:
a. Increases with age and is more predominant in women
b. Increases in age and is higher in men compared to women
c. Is unaffected by a prior history of cranial radiation
d. Is lower in African Americans compared to Caucasians

2. Simpson grade 1 resection described in the case indicates:
a. A gross total resection with dura and bone
b. A gross total resection
c. A subtotal resection
d. A biopsy

3. The following defines the meningioma as at least grade 2:
a. Meningothelial whorls
b. Calcification
c. Bone invasion
d. Brain invasion

4. The following systemic therapy is approved by the FDA for the treatment of meningioma:
a. Bevacizumab
b. Sunitinib
c. Hydroxyurea
d. None of the above

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CORRECT ANSWERS

Question 1: A, The incidence of meningioma increases with age and is higher in women compared to men.

Question 2: A, The Simpson grade 1 resection described in the case indicates a gross total resection with dura and bone.

Question 3: D, Brain invasion defines the meningioma as at least a grade 2 tumor.

Question 4: D, There is no systemic therapy approved by the FDA for the treatment of meningioma.

Discussion

Epidemiology and Etiology

Meningioma incidence increases substantially with age and is the most common primary CNS tumor in patients > age 35. Menigioma is very uncommon in children (0.14/100,000 in those age 0-19 years) compared to the elderly (37.75/100,000 in those age 75-84). There is a somewhat higher incidence in African Americans compared with Caucasians.[1] Cranial radiation is a risk factor for meningioma development. Recently, a specific genetic abnormality, an NF2 gene rearrangement, was found in almost half of patients with radiation-induced meningiomas.[2]

Grading Extent of Resection

The Simpson grading system wass developed to standardize descriptions of resection extent and predict recurrence risk.[3] The Simpson grades are still used clinically and in the literature and, as originally described, include all pathologic grades; percentages below reflect this. Simpson grades 1-3 apply to macroscopic gross total resections. Grade 1 includes removal of all dural attachments and any abnormal bone (9% recurrence risk in 10 years). Grade 2 includes coagulation of dural attachments (19% risk of recurrence in 10 years). Grade 3 involves gross total removal of tumor without coagulation of dural attachments (29% risk in 10 years). Grade 4 is a subtotal resection (44% in 10 years). Grade 5 is simple decompression and biopsy. The influence of Simpson grades may be diminished in the contemporary era.[4]

Histopathology

Meningothelial whorls are a common histologic feature of meningiomas across all grades. Calcifications are quite common in meningiomas and usually reflect slower or no growth and grade 1 nature; as such, calcifications might be a favorable finding. Although bone invasion does not alter grading of meningiomas, in the most recent update to the WHO Central Nervous System Tumor Classification, brain invasion qualifies a meningioma as at least a grade 2 (Table).[5]

TABLE. WORLD HEALTH ORGANIZATION GRADING FOR MENINGIOMA.

	Grade 1	Grade 2	Grade 3
Histopathologic subtype	Meningothelial, fibrous, transitional, psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte-rich, and metaplastic	Clear cell, chordoid	Rhabdoid, papillary
Mitoses	< 4 mitoses in 10 consecutive high-power fields	≥4 mitoses in 10 consecutive high-power fields	≥ 20 mitoses in 10 consecutive high-power fields
Brain invasion	Not present	May be present	May be present
OR	**< 3 of following:**		**>3 of following:**
	Increased cellularity Small cells with high nucleus to cytoplasm ratio Prominent nucleoli Sheeting and foci of spontaneous necrosis		

Treatment

Surgery and radiation have long been the mainstays of meningioma treatment. The role of postoperative radiation for completely resected grade II meningiomas is being explored in the NRG BN003 phase 3 clinical trial.[a]

Although numerous systemic therapies have been investigated for the meningioma treatment, none has demonstrated a substantial benefit yet.[6,7] More recently, specific genetic mutations have been reported in subsets of meningiomas.[2,8] In particular, mutations of genes coding for smoothened (SMO), a G-protein coupled receptor; the Akt protein kinase; and tumor suppressor NF2, have garnered particular interest as they appear to describe mutually exclusive molecularly defined subsets of meningioma that correlate with neuroanatomic localization. Some of these and other targets are being actively investigated as potential therapeutic targets in clinical trials of systemic therapies for meningiomas.[b,c] Future systemic therapies may be incorporated into treatment algorithms for some subtypes of meningiomas.

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2. Agnihotri S, Suppiah S, Tonge PD, et al. Therapeutic radiation for childhood cancer drives structural aberrations of NF2 in meningiomas. *Nat Commun*. 2017;8(1):186.
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4. Oya S, Kawai K, Nakatomi H, Saito M. Significance of Simpson grading system in modern meningioma surgery: integration of the grade with MIB-1 labeling index as a key to predict the recurrence of WHO grade I meningiomas. J Neurosurg. 2012;117(1):121-128.
5. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System. Acta Neuropathol. 2016;131(6):803-820.
6. Shaikh N, Dixit K, Raizer J. Recent advances in managing/understanding meningioma. F1000Res. 2018;7:F1000.
7. Buerki R, Horbinski CM, Kruser T, et al. An overview of meningiomas. Future Oncol. 2018;14(21):2161-2177.
8. Brastianos PK, Horowitz PM, Santagata S, et al. Genomic sequencing of meningiomas identifies oncogenic SMO and AKT1 mutations. *Nat Genet*. 2013;45:285-289.

a Observation or radiation therapy in treating patients with newly diagnosed grade II meningioma that has been completely removed by surgery (NCT03180268)
b Vistusertib (AZD2014) for recurrent grade II-III meningiomas (NCT03071874)
c Vismodegib and FAK inhibitor GSK2256098 in treating patients with progressive meningiomas (NCT02523014)