Pearls & Oy-sters: Primary Pineal Melanoma With Leptomeningeal Carcinomatosis

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Pearls

- Pineal masses commonly present with Parinaud syndrome, a triad consisting of upgaze restriction, convergence-retraction nystagmus, and pupillary light-near dissociation from compression of the quadrigeminal plate.
- The differential diagnosis for pineal region tumors includes germ cell tumors, pineal parenchymal tumors, glioma, atypical teratoid rhabdoid tumor, and metastatic disease. While exceedingly uncommon, primary pineal melanoma is also a known histopathologic entity that is suspected to arise from melanocytes in the pia mater of the pineal gland.
- Primary pineal melanoma is often treated with surgical resection, radiation, and either chemotherapy or immunotherapy. Some patients have received targeted therapy (such as vemurafenib in patients with *BRAF V600E* mutation) with varying degrees of success.

Oy-sters

- CSF sampling can assist in the diagnosis of pineal tumor, specifically to test for germ cell tumor markers (α -fetoprotein, β -human chorionic gonadotropin, placental alkaline phosphatase), systemic tumor markers such as carcinoembryonic antigen, cell-free DNA, or malignant cells on cytopathology.
- Pineal tumors can result in obstructive hydrocephalus; therefore, lumbar puncture is not always a feasible option due to the risk of herniation. In patients with melanoma of the CNS, a careful survey consisting of systemic imaging and total body skin examination are warranted to exclude a separate primary melanoma lesion.
- The differential diagnosis for rapidly progressive bilateral sensorineural hearing loss includes meningitis, superficial siderosis, ototoxicity, and leptomeningeal disease. Difficulty in speech comprehension in excess of pure tone audiometry may suggest involvement or compression of the inferior colliculus.

A 62-year-old man presented with 5 months of rapidly progressive bilateral hearing loss. He was evaluated by a local provider who ascribed his symptoms to normal aging and prescribed hearing aids. The patient then developed intermittent binocular diplopia. He denied personal or family history of malignancy. Neuro-ophthalmologic examination revealed light-near dissociation with minimal retraction nystagmus on upward gaze consistent with Parinaud syndrome (eFigure 1, data available from Dryad; doi.org/10.5061/dryad.cvdncjt2w). No papilledema was seen. Audiometry showed moderate to severe high-frequency bilateral sensorineural hearing loss and absent word recognition skills. The remainder of his neurologic examination was unremarkable.

Contrast-enhanced MRI of the brain demonstrated an intrinsically T1 hyperintense contrast-enhancing mass in the pineal region with extension into the tectum, midbrain, and bilateral thalami, and protruding into the third ventricle, resulting in ventriculomegaly (Figure 1). The

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Figure 1 Non-enhanced Axial T1-Weighted MRI

(A) Hyperintense pineal region mass and numerous hyperintense foci in the subarachnoid space with enhancement after gadolinium administration (B). Sagittal view of contrast-enhanced MRI. (C) High signal intensity on T1-weighted images is attributed to the effects of free radicals in melanin and blood products.

MRI also demonstrated small nodules of T1 hyperintensity through the local ventricles and sulci in this region, concerning for leptomeningeal seeding. The vestibulocochlear nerves were not readily apparent due to imaging technique and slice thickness. Systemic imaging and physical examination showed no other sites of disease involvement. CSF sampling was deferred due to hydrocephalus and concern for herniation. MRI of the total spine with and without contrast showed no spinal cord lesions or radiographic evidence of leptomeningeal enhancement elsewhere in the neuroaxis.

The patient underwent a right frontal endoscopic biopsy of the lesion and intraoperatively black material was seen lining the ventricular surface (eFigure 2, data available from Dryad; doi.org/10.5061/dryad.cvdncjt2w). Pathology revealed a high-grade pigmented epithelioid neoplasm with strong tumor cell expression of melanoma markers HMB45, MART1, and tyrosinase as well as CD10 and MITF on differentiation marker immunophenotyping (eFigure 3, data available from Dryad; doi.org/10.5061/dryad.cvdncjt2w). Mutational testing (particularly for *BRAF V600E*, *KIT*, *NRAS*, *GNAQ*, *CDKN2A*, and *MC1R*, which are all commonly mutated in melanoma) was not performed as only minimal tissue was available.

The patient received a dose each of checkpoint inhibitors ipilimumab and nivolumab, which were complicated by transaminitis. Following this, he was diagnosed with COVID-19 pneumonia and during hospitalization was found to have progression on MRI of the brain, associated with new left ptosis and worsening intermittent diplopia. He transiently required supplemental oxygen, but was not intubated, and was treated with a 5-day course of azithromycin, hydroxychloroquine, and cefepime. He was started on dexamethasone with improvement in his neurologic symptoms. Tumor-directed therapy was held for 1 month, during which time he tapered off steroids and remained neurologically stable. Then, upon recovery from the viral pneumonia, he was dispositioned to palliative whole brain radiation therapy (WBRT) with boost to the third ventricle and concurrent temozolomide chemotherapy. Following WBRT and 3 cycles of adjuvant temozolomide, he remained clinically and

radiographically stable without appreciable change in his neurologic symptoms.

Discussion

Pineal region tumors commonly present with features of increased intracranial pressure such as headache, nausea, and vomiting due to obstructive hydrocephalus. Parinaud syndrome—a triad of upgaze restriction, convergence-retraction nystagmus, and pupillary light-near dissociation resulting from compression of the quadrigeminal plate—is also common and should raise suspicion for a pineal mass. The “setting-sun” phenomenon, in which the lower lid partially covers the lower iris in pupil, may also occasionally be seen, resulting from the upward gaze paresis.

Germ cell tumors comprise the most common pathologic entity in the pineal region, with nongerminomatous germ cell tumors (yolk sac tumor, choriocarcinoma, teratoma, and embryonal carcinoma) occurring with greater frequency than pure germinomas.¹ These are followed by pineal parenchymal tumors (pineocytoma, pineal parenchymal tumor of intermediate differentiation, and pineoblastoma).² Other pathologies are possible as well and include neuroepithelial neoplasms (ependymoma, astrocytoma, and other glioma), atypical teratoid rhabdoid tumor, or, rarely, metastatic disease from distant primary malignancies. As hydrocephalus is often observed, the risks and benefits of CSF sampling by lumbar puncture must be weighed carefully. For patients in whom lumbar puncture is safe, testing for germ cell tumor markers (α -fetoprotein, β -human chorionic gonadotropin, placental alkaline phosphatase), other tumor markers (such as carcinoembryonic antigen), or cell-free DNA (as may be indicated in the setting of systemic cancer) and cytology can be diagnostically useful.³

Primary pineal melanoma is an extraordinarily rare entity, first described in 1899, estimated to account for 3.6% of all primary CNS melanomas, which themselves only account for approximately 0.07% of intracranial neoplasms.⁴ It is thought to arise from melanocytes in the pia mater of the pineal interlobular

septa, as neural crest cells are known to migrate into the leptomeninges during development.⁵ Leptomeningeal spread appears to be common in primary pineal melanoma. The optimal treatment paradigm is unknown, but commonly these tumors are treated with surgical resection, radiation, and either chemotherapy or immunotherapy. Some patients have received targeted therapy (such as vemurafenib in patients with *BRAF* V600E mutation) with varying degrees of success.⁶ Ipilimumab and nivolumab are known to have activity in brain metastases from melanoma and nivolumab has been shown to cross the blood–brain barrier when administered systemically.⁷

Bilateral rapidly progressive sensorineural hearing loss has a limited differential diagnosis, which most notably includes ototoxicity, meningitis, superficial siderosis, autoimmune disease, vasculitis, and leptomeningeal disease. In contrast, for cases of more indolent hearing loss, other etiologies such as neurofibromatosis type 2 or normal aging can be entertained. It is estimated that up to 8% of patients with cancers may develop leptomeningeal disease, and melanoma is 1 of the 3 most common malignancies that metastasizes to the meninges.⁸ The inferior colliculus is known to be involved in speech processing as well. In our patient, compression of the quadrigeminal plate may therefore also be implicated in his poor hearing and word recognition. In patients with cancer with bilateral profound hearing loss, such as the present case, cochlear implantation remains a viable auditory rehabilitation option even in patients requiring chemotherapy or radiation therapy.⁹

As a final learning point from this case, neurology trainees and general neurologists may encounter patients with cancer who are navigating their care in the COVID-19 era. Active chemotherapy, radiation, and immunotherapy may represent risk factors for both infection and worse outcomes¹⁰ and is an area of active study. Current guidelines from the American Society of Clinical Oncology recommend that patients who are diagnosed with COVID-19 pneumonia be placed on a treatment break for either 14 days or 72 hours after symptoms abate with 2 negative nasal swabs 24 hours apart.¹¹ In this patient, COVID-19 infection coincided with progression of disease. However, his neurologic symptoms were successfully temporized with corticosteroids while awaiting resumption of treatment. At this time, the potential effects of COVID-19 and the resulting delay in cancer therapy for this patient are not yet known. Further investigation is needed to track outcomes in these patients.

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Appendix Authors

Name	Location	Contribution
Ashley E. Aaroe, MD	MD Anderson Cancer Center, Houston, TX	Conceptualized manuscript
Isabella Claudia Glitza Oliva, MD, PhD	MD Anderson Cancer Center, Houston, TX	Revised manuscript for intellectual content
Naghham Al-Zubidi, MD	MD Anderson Cancer Center, Houston, TX	Provided figure, revised manuscript for intellectual content
Marc-Elie Nader, MD	MD Anderson Cancer Center, Houston, TX	Revised manuscript for intellectual content
Diana Kaya, MD	MD Anderson Cancer Center, Houston, TX	Provided figure, revised manuscript for intellectual content
Sherise Desiree Ferguson, MD	MD Anderson Cancer Center, Houston, TX	Revised manuscript for intellectual content
Chenyang Wang, MD, PhD	MD Anderson Cancer Center, Houston, TX	Revised manuscript for intellectual content
Gregory Fuller, MD, PhD	MD Anderson Cancer Center, Houston, TX	Provided figure, revised manuscript for intellectual content
Rebecca Anne Harrison, MD	MD Anderson Cancer Center, Houston, TX	Revised manuscript for intellectual content

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