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Cranial and spinal leptomeningeal dissemination in esthesioneuroblastoma: Two reports of distant central nervous system metastasis and rationale for treatment

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Abstract

Background: Esthesioneuroblastoma is a locally aggressive cancer of the nasal cavity. While systemic metastasis can occur in 10-30% of patients, there are only six reported cases of distal metastasis from leptomeningeal dissemination.

Case Description: The authors report two cases of esthesioneuroblastoma treated previously with multimodal therapy in which distal metastatic recurrence was found and describe their treatment protocol, which has resulted in long-term success.

Conclusion: Understanding the drivers of leptomeningeal dissemination in more prevalent primary neuroectodermal tumors may hold the key to developing successful treatment algorithms for this disease.

Key Words: Carcinomatosis, chemotherapy, esthesioneuroblastoma, leptomeningeal dissemination, olfactory neuroblastoma, primary neuroectodermal tumor, radiation, surgery

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INTRODUCTION

Esthesioneuroblastoma, or olfactory neuroblastoma, is a locally aggressive cancer of the nasal cavity.[4,10,23] First described in 1924,[4] its estimated incidence is 0.4/million.[15,22] The tumor originates from the olfactory epithelial cells and tends to invade the paranasal sinuses, bony orbits, cribriform plate, and anterior cranial fossa.[1,7,13] Patients typically present with unilateral nasal obstruction and/or epistaxis.[10] While there is variability in the treatment modality chosen for patients, it typically involves surgery and radiotherapy, with or without chemotherapy.[10] Histopathologically, there are typically sheets of round blue cells with uniform round nuclei. There can be either true or pseudorosette formation.[10]

Systemic metastases occur in 10–30% of patients, usually by hematogenous and lymphatic spread,[2,12,20] but distal central nervous system (CNS) metastasis from leptomeningeal dissemination is an extremely rare sequela with a grave prognosis.[21] We describe our treatment protocol for two cases of esthesioneuroblastoma treated previously with multimodal therapy in which the patients experienced distal leptomeningeal metastatic recurrence; in one patient, impressive progression-free and long-term survival were achieved.

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CASE REPORTS

Patient 1

A 48-year-old man was referred to our clinic for evaluation of a new dural-based lesion 6 years after excision, skin flap repair, and bone graft placement for a skull-base esthesioneuroblastoma followed by adjuvant radiation. His posttreatment course was complicated by externalization of the bone flap requiring a second skull-base bone flap resection. After 5 years of no radiographic evidence of residual disease, a routine follow-up magnetic resonance imaging (MRI) scan at 6 years revealed an enhancing dural lesion over the right frontal lobes [Figure 1].

The patient underwent a right frontotemporal craniotomy for resection of the enhancing dura and tumor, which was found to be partially invading the brain parenchyma. Pathological analysis indicated the lesion was consistent with recurrent metastatic esthesioneuroblastoma. The patient received adjuvant stereotactic radiosurgery. His follow-up MRIs approximately every 6 months remained negative until additional dural-based lesions along the frontal sinus, right temporal lobe, and right sphenoid wing were observed at 3 years [Figure 2]. Follow-up imaging 5 months later revealed progressive interval growth of the dural-based lesions. Treatment with cisplatin and etoposide was stopped after one cycle because of intractable nausea and vomiting. Approximately 1 year later, the patient restarted treatment with sunitinib, but the tumor showed clear progression 12 months later and the drug was discontinued. The patient succumbed to the disease 6 months later, 11 years after his initial diagnosis.

Patient 2

A 48-year-old woman presented with a large sinonasal mass with extensive intracranial extension through the cribriform plate into the anterior cranial fossa [Figure 3]. Tumor was noted in the right orbit and maxillary and sphenoid sinuses and there was lymphatic spread to a retropharyngeal lymph node. She underwent radical resection of the Kadish stage D esthesioneuroblastoma with a right orbital exenteration and upper neck dissection followed by adjuvant radiation therapy. Yearly surveillance imaging was stable until a 6-year follow-up MRI revealed 1 cm of patchy enhancement in the right frontal lobe and the dura overlying the resection cavity. Follow-up imaging 6 months later showed mildly increased dural enhancement and interval development of a new dural-based lesion in the posterior fossa.

Spinal imaging revealed multiple dural-based enhancing lesions in the cervical, thoracic, and lumbar spine with possible osseous involvement, consistent with drop metastasis [Figure 4]. The patient underwent a suboccipital craniectomy for resection of the posterior fossa lesion. Intraoperatively, the neoplasm was deep to the dura but above the arachnoid membrane; it was carefully dissected and removed *en bloc*. Two days later, the patient underwent T8–T10 laminectomies, left T9 costotransversectomy, and ligation of the nerve root for resection of a large dural-based mass displacing the thoracic cord and effacing the neural foramen. Pathological analysis of both lesions affirmed a diagnosis of recurrent esthesioneuroblastoma with leptomeningeal spread [Figure 5].

The patient initially began a course of systemic carboplatin, vincristine, and lomustine, as well as

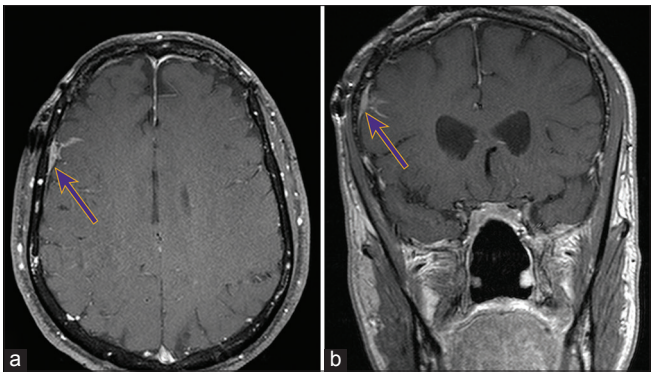

Figure 1: Axial (a) and coronal (b) T1-weighted magnetic resonance imaging showing contrast-enhancing dural-based lesion with parenchymal invasion along the right frontal lobe (arrow)

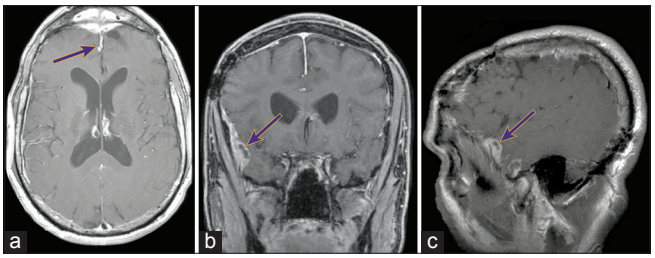

Figure 2: Axial (a), coronal (b), and sagittal (c) T1-weighted magnetic resonance imaging showing contrast-enhancing dural-based lesions through the frontal sinus and along the falx cerebri (a), right temporal lobe (b), and right sphenoid wing (c) (arrows)

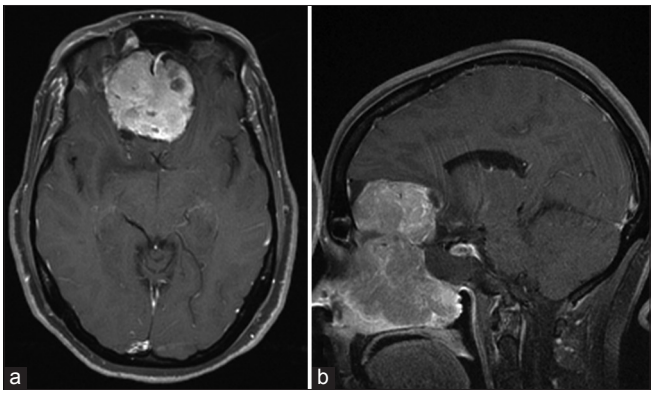

Figure 3: Axial (a) and sagittal (b) T1-weighted magnetic resonance imaging showing a contrast-enhancing sinonasal mass with intracranial extension through the cribriform plate into the anterior cranial fossa, maxillary, and sphenoid sinuses

intrathecal methotrexate. She ultimately completed the intrathecal methotrexate with carboplatin, etoposide, and cyclophosphamide. Follow-up imaging 16 months after the initiation of chemotherapy revealed resolution of the metastatic lesions and no radiographic appearance of residual disease, 9 years after her original diagnosis. She continues to receive surveillance for the recurrent disease by evaluation of her cerebrospinal fluid (CSF) every 3 months.

DISCUSSION

Even with aggressive therapy, esthesioneuroblastomas exhibit a propensity for both local and distant recurrence. They can disseminate via direct invasion into the brain parenchyma and metastasize through lymphatic, hematogenous, or leptomeningeal spread. Local recurrence and metastatic disease are seen in 50–60% and 10–62% of patients, respectively.[6] Once esthesioneuroblastoma invades the cribriform plate, the tumor can infiltrate the anterior skull-base and extend locally into the brain parenchyma or distally through the leptomeninges.[1] The cervical lymph nodes are the most common site of metastasis. Other reported locations include the breast, lung, prostate, spine, bone, parotid, viscera, and abdomen.[1,16,21] While CNS metastasis is seen in 20–30% of patients, leptomeningeal dissemination remains extremely rare, with 2 and 5 reported cases of cranial and spinal metastases, respectively.[17,19,21,23] One case of distant intracranial, leptomeningeal spread of esthesioneuroepithelioma, a rare variant, has been reported.[5] Leptomeningeal spread is an indicator of a poor prognosis with an expected survival of <2 years.[20] The most recent version of the Kadish staging system accounts for diffuse disease with tumor metastasis [Table 1],[11] as seen in our patients.

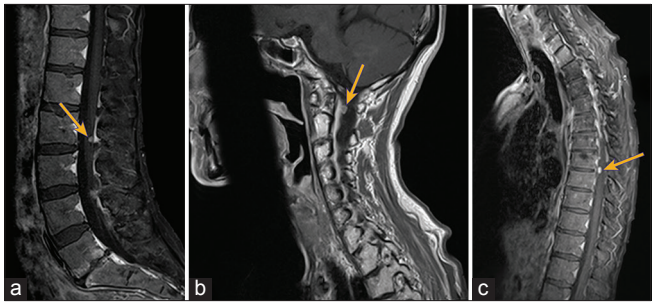

Figure 4: Sagittal T1-weighted magnetic resonance imaging showing contrast-enhancing dural-based lesions posterior to C2 vertebral body (a), posterior to T9–T10 disc space (b), and along the posterolateral dura at the L3–L4 level (c) (arrows)

The rarity of leptomeningeal dissemination in esthesioneuroblastoma has made it challenging to generate appropriate prospective studies to establish treatment protocols. Neuro-oncologists rely on case reports and retrospective studies to understand the natural course of the disease, as well as the response to treatments. Packer *et al.*[18] described a modified systemic chemotherapy regimen for medulloblastoma in addition to intrathecal chemotherapy.[9] Patients received intravenous carboplatin (70 mg/m^2), intravenous vincristine (2 mg), and oral lomustine (70 mg/m^2) on day 1, followed by intravenous vincristine (2 mg) on days 8 and 15, every 6–8 weeks as the patient's condition tolerated. The intrathecal chemotherapy was based on a treatment protocol established for AIDS-related lymphomatous meningitis:[8] Two milligrams of intrathecal methotrexate every day for 5 days, repeated every other week for 8 weeks, or 20 doses. If patients improved or remained stable during induction, they received 2 mg of intrathecal methotrexate every day for

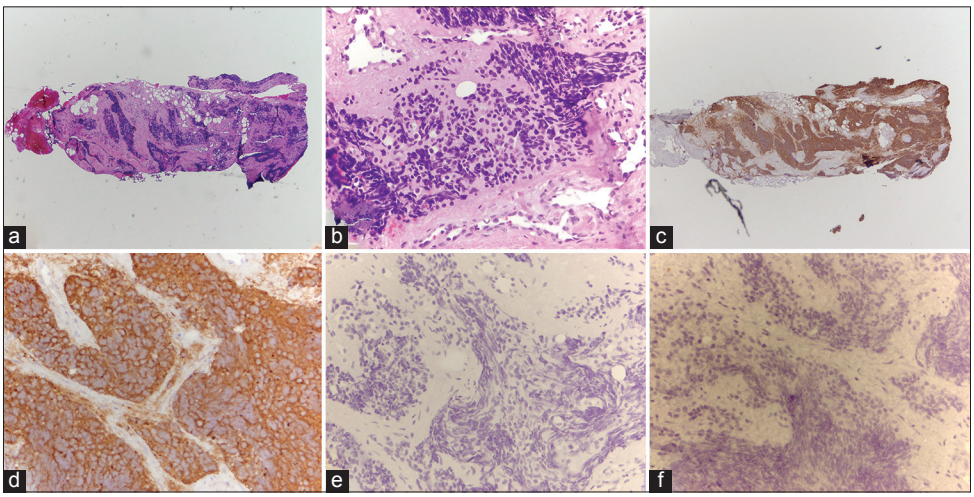

Figure 5: Photomicrographs from spinal mass at T9–10. H and E staining shows well-defined clusters of cells separated by a fibrovascular stroma (a). Higher magnification (b) shows small, round cells with large nuclei and scant cytoplasm. Immunohistochemical staining for synaptophysin, a neuronal cell marker, is strongly positive in all lesional cells (c) and is completely within the cytoplasm (d). Staining for CD45 (e), a lymphoid tissue marker, and cytokeratin, a marker for adenocarcinoma, were both negative. Magnification: (a and c) ×2, (b, d–f) ×40

Table 1: Modified Kadish staging system for esthesioneuroblastoma

Stage	Description
A	Confined to nasal cavity
B	Involvement of nasal cavity with extension into paranasal sinuses
C	Extension beyond nasal cavity and into paranasal sinuses. Involvement of cribriform lamina, orbit, skull-base, or intracranial cavity
D	Cervical lymph node or neck involvement or distant metastasis

5 days, repeated every other week for 4 weeks, or 10 doses. If patients showed clinical improvement or remained stable during this consolidation period, they went on a maintenance dose of 2 mg of intrathecal methotrexate every day for 5 days repeated monthly for 4 months, for 20 doses. If disease progression was noted while the patients were on methotrexate, they were transferred to a regimen involving cytosine arabinoside or thiotepa. Packer *et al.*[18] reported responses lasting 2–11 months and an overall survival of 4–13 months. Two patients had disease progression while on intrathecal methotrexate and were transferred to cytosine arabinoside. One patient proceeded then to thiotepa. All three patients responded to the treatment, as defined by a CSF cytology conversion of positive to negative at all sites tested, as well a stable neurological examination at the end of the induction trial. No treatment-related deaths were noted. All three patients experienced aseptic meningitis, which was managed using analgesics, antipyretics, antiemetics, and steroids. The symptoms resolved in 2–3 days.[9]

This treatment protocol, which we used in our second patient, stemmed from a treatment designed for medulloblastoma displaying CNS metastasis.[18] Esthesioneuroblastoma, like medulloblastomas, are considered a subtype of the primitive neuroectodermal tumors (PNETs), which show varying degrees of cellular differentiation and a propensity to disseminate along the pathways of CSF.[3] Even with systemic and intrathecal chemotherapy and radiation therapy to the neuraxis, the prognosis after the diagnosis of CNS metastasis is extremely poor. While new treatment investigations are relatively rare, understanding drivers of leptomeningeal dissemination in PNETs may hold the key to metastasis-targeted treatment. Transposon insertion mutagenesis studies have been used to discover multiple candidate genes (Eras, Lhx1, Ccrk, Akt, Arnt, and Gdi2) that, when overexpressed in Sonic hedgehog-induced medulloblastoma mouse models, showed a significantly increased propensity for leptomeningeal dissemination.[14] While still early in the clinical translational research paradigm, this represents, to our knowledge, the most progressive attempt at metastasis-targeted therapy in PNETs.

CONCLUSION

Although rare, distant metastasis from leptomeningeal dissemination in esthesioneuroblastoma can occur and portend a poor prognosis. We describe two patients with esthesioneuroblastoma treated previously with multimodal therapy who developed distal metastatic recurrence, one who went on to have long-term success. The possibility of leptomeningeal dissemination should be kept in mind when monitoring patients with esthesioneuroblastoma and early detection from surveillance CSF analysis should be the goal. Understanding the drivers of leptomeningeal dissemination in PNETs may hold the key to developing successful treatment strategies.

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Conflicts of interest

There are no conflicts of interest.

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