Late occurrence of drop metastasis to the spine in a case of esthesioneuroblastoma

Case report

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Esthesioneuroblastoma is an aggressive neuroectodermal tumor that originates from the olfactory mucosa and often recurs locally. Distant metastasis of esthesioneuroblastoma has been described, but there are few reports of drop metastasis to the spinal cord. Here, we report a case of multiple drop metastases to the cervical, thoracic, and lumbar regions of the spinal cord that occurred 18 years after resection and radiotherapy of the original anterior cranial fossa lesion. There was no evidence of local recurrence. The symptomatic lesion was treated with resection and adjuvant chemotherapy. The options available for treatment of this disease are summarized with a review of the few reported cases of spinal metastasis of esthesioneuroblastoma. (DOI: 10.3171/2011.6.SPINE11157)

Key Words • esthesioneuroblastoma • recurrence • drop metastasis • olfactory neuroblastoma • spine • oncology

Esthesioneuroblastoma is a rare malignant neuroectodermal tumor that arises from the olfactory mucosa in the superior nasal cavity. This aggressive tumor exhibits a variety of potential behaviors, at times invading locally into the paranasal cavities, oropharynx, anterior skull base, and frontal cerebral lobes and in other cases metastasizing to the cervical lymph nodes, lungs, or distant CNS. Although this tumor may occur in patients of any age, the literature points to a bimodal distribution, with peaks in the 2nd and 3rd decades and the 6th and 7th decades of life. There is no evidence of predilection for either sex. Since esthesioneuroblastoma was first described in 1924, about 1000 cases have been reported. This locally aggressive tumor can be classified using the Kadish staging and Hyams grading systems, which correlate with 5- and 10-year survival.

Resection is the mainstay of treatment for esthesioneuroblastoma. Given the rarity of this tumor, there exists no widely accepted consensus for multimodal treatment, although many authors advocate considering adjuvant or neoadjuvant radiation and/or chemotherapy. Despite aggressive therapy, the local recurrence and distant metastasis rates are approximately 50%–60% and 10%–20%, respectively. Metastatic CNS disease typically is identified between 0 and 10 years after diagnosis, with survival after identification of metastatic disease being typically less than 2 years. Spinal cord metastasis of esthesioneuroblastoma is particularly unusual, with a total of 22 documented cases of spread to the vertebral bodies, spinal cord, or spinal leptomeninges; the vast majority of these masses occurred in the thoracic or lumbar spine. Here, we report a case of multiple drop metastases to the spine presenting nearly 20 years after initial diagnosis and treatment.

Case Report

History and Examination. This 59-year-old man presented to the neurosurgical clinic at our institution with a several-month history of upper-extremity weakness manifesting as hand clumsiness, numbness and tingling of the arms and upper chest, and a feeling of imbalance while walking. The hand clumsiness was progressive, causing him to seek medical attention. There were no bowel or bladder changes and no lower-extremity symptoms. The patient's medical history was significant for esthesioneuroblastoma of the anterior cranial fossa and right nasal cavity with dural involvement, which had been surgically treated via bifrontal craniotomy and anterior skull base resection at our institution in 1991. He also had completed postoperative radiation therapy of 61 Gy to the tumor bed and experienced radiation-induced retinopathy of the right eye and anosmia. Magnetic resonance imaging 5 years after the initial operation showed no recurrence.

This article contains some figures that are displayed in color online but in black and white in the print edition.
Physical examination at the time of re-presentation was notable for pallor of the right optic disc; 4 to 4+/5 strength of the C-7, C-8, and T-1 muscle groups bilaterally; and diminished sensation to light touch in the C-6, C-7, C-8, T-1, and T-2 dermatomes bilaterally. His deep tendon reflexes were 2+ and symmetric throughout and no pathological reflexes were elicited. Magnetic resonance imaging of the cervical spine showed 3 dural-based, homogeneously enhancing intradural extramedullary masses located at C-2, C-3, and C4–6 (Fig. 1A–C). This last mass caused severe cord compression, worst at C-5, with subtle cord signal abnormalities. In addition, multilevel degenerative disc disease was noted. Magnetic resonance imaging of the thoracolumbar spine showed 4 avidly enhancing intradural extramedullary masses, several of which were associated with the nerve root or

![Fig. 1. A: Sagittal T1-weighted MR image of the cervical spine showing 2 intradural extramedullary masses that extend into the spinal canal and displace the spinal cord. B: Sagittal T2-weighted MR image obtained after administration of contrast agent showing that both masses enhance homogeneously. C: Axial T1-weighted sequence obtained before contrast enhancement showing that the mass centered at C-5 appears ventrally based and invades the right neuroforamen. D and E: Contrast-enhanced sagittal T1-weighted sequences of the thoracic and lumbar spine showing multiple intradural extramedullary masses that also intensely enhance homogeneously. These masses do not demonstrate any nerve root involvement or spinal canal compromise. F: Gadolinium-enhanced coronal MR image showing small enhancing dural-based nodules superficial to the right parietal lobe and left cerebellar hemisphere. No evidence of recurrence was observed in the anterior cranial fossa. G–I: Sagittal precontrast (G), sagittal postcontrast (H), and axial precontrast (I) T1-weighted images of the cervical spine obtained at 9 months after the operation described in this article showing a residual ventral dura-based mass centered at the C-5 level, associated with slight displacement of the spinal cord to the right and enhancement along the left C-4 nerve root. The ventral lesion at the level of C-2 is stable in size compared with preoperative images.]
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neural foramina and thus thought to be concerning for schwannomas or meningiomas (Fig. 1D–E).

**Operation.** Given the patient’s symptoms, spinal cord compression, and tumor history, resection of the tumor located at C4–6 was indicated to obtain decompression and a tissue diagnosis. The patient underwent a C4–5 complete laminectomy, inferior hemilaminotomy at C-3, and superior hemilaminotomy at C-6, with resection of the tumor. Intraoperatively, the tumor was noted to be hard and white in color, with broad-based attachment to the right ventrolateral dural surface. A tongue of tumor extended up the right C5–6 neuroforamen and interdigitated with nerve roots which, when stimulated, showed motor function. Frozen pathological sections showed a fibrous tumor with small cells most consistent with metastatic esthesioneuroblastoma. Subtotal resection was obtained, and a dural patch graft was used to expand the thecal sac. Given the intraoperative pathological findings, we elected not to use instrumentation. Although the incidence of postlaminectomy kyphosis in the cervical spine ranges from 14%–33% over a follow-up period of roughly 2–7 years, we felt that the intraoperative tissue findings indicated poor prognosis and that the need to obtain postoperative surveillance MR imaging without instrumentation artifact outweighed the benefit of instrumentation to prevent postlaminectomy kyphosis at this point in time.

The patient tolerated the surgery well and was discharged home 3 days later. However, he presented about 1 week later with fever, anorexia, hyponatremia, hallucinations, and confusion. Magnetic resonance imaging of the brain showed nodular enhancing foci along the lateral aspect of the left cerebellar hemisphere and the convexity of the right parietal lobe (Fig. 1F). In addition, there was a small infarct in the pons. Positron emission tomography scans showed mildly hypermetabolic intradural extramedullary lesions consistent with drop metastases at C-2, C6–7, and L-1; the results of CT angiography were unremarkable. The patient’s fever, altered mental status, and hyponatremia resolved with medical management, and he was discharged home 1 week later.

**Histopathological Findings.** Hematoxylin and eosin staining showed that the tumor was composed of well-defined nests and lobules of tumor cells separated by a fibrovascular stroma (Fig. 2A). The neoplastic cells consisted of 2 distinct groups: one group had vesicular nuclei and single nucleoli (Fig. 2B), the other group had darker and coarser chromatin (Fig. 2C). Microcalcifications were present. Mitoses were rare, and necrosis was not identified. Gland formation was not present. Neurofibrillary matrix and rosette formation were not prominent. Results of testing for synaptophysin (Fig. 2D), CD56 (Fig. 2E), chromogranin, and neuron-specific enolase were all strongly and diffusely positive in the tumor cells. Approximately 5% of cells stained positively for Ki 67 (not shown). Results of immunohistochemical staining for markers of glioma, meningioma, melanoma, Ewing sarcoma, and carcinoma all were negative. These findings were consistent with Hyams Grade II–III

![Fig. 2. Photomicrographs of sections from the mass at C4–6. Hematoxylin and eosin staining shows that the tumor is composed of well-defined nests and lobules of cells separated by a fibrovascular stroma (A). The neoplastic cells consisted of 2 distinct groups: one group had vesicular nuclei and single nucleoli (B) and the other had darker and coarser chromatin (C), prone to considerable crush artifact. Microcalcifications were present. Mitoses were rare, and necrosis was not identified. Gland formation was not present. Neurofibrillary matrix and rosette formation were not prominent. Results of immunohistochemical staining for the neuronal markers synaptophysin (D) and CD56 (E) were positive, whereas results of staining for keratin were negative (F). Original magnification × 100 (A), 400 (B–D and F), and 200 (E).](image-url)
esthesioneuroblastoma. Histopathological samples from the patient's initial biopsy in the sinonasal area were re-examined. The spinal lesion described here was histologically identical to the previous sinonasal tumor.

**Postoperative Course and Adjuvant Therapy.** Post-operatively, the patient was evaluated by the radiation oncology and neurooncology services. Given the extent of the patient's radiological disease burden and his prior radiation therapy, we elected to initiate chemotherapy prior to radiation therapy to lessen the tumor burden and better target any radiation therapy. The patient received 6 cycles of intravenous carboplatin (400 mg/m²), etoposide (400 mg/m²), and cyclophosphamide (660 mg/m²) over 6 months, which he tolerated well. Magnetic resonance images of the brain and spine obtained 12 months after chemotherapy showed that all the other lesions were either stable or very slightly increased in size and there were no new lesions (Fig. 1G–I). Clinically, the patient's upper-extremity weakness has improved, and his sensory deficits in the upper extremities have resolved. The patient has experienced some anemia, fatigue, hypotension, and lightheadedness secondary to chemotherapy and possible adrenal insufficiency related to dexamethasone doses associated with the chemotherapy regimen. For this he is being treated with iron supplementation and hydrocortisone. At 14 months postoperatively, he has not received further irradiation.

**Discussion**

Esthesioneuroblastoma is a rare neoplasm composed of neuroectodermal cells originating from the olfactory mucosa in the area of the cribiform plate, upper third of the nasal septum, and superior turbinates. Many authors cite its incidence as approximately 2%–3% of all intranasal neoplasms. As may be expected from a locally aggressive tumor, patients typically present with nonspecific symptoms such as nasal obstruction and epistaxis, as well as headache, nasal pain, proptosis, increased lacrimation, anosmia, or visual field defects. Resection for symptom relief and tissue diagnosis is the mainstay of treatment, although it is often supplemented with adjuvant radiation and/or chemotherapy. Recent meta-analyses and large case series have shown conflicting data with regard to the 5-year survival benefit of adjuvant radiotherapy after surgical resection, but most authors advocate the inclusion of adjuvant radiotherapy, usually in the range of 55–65 Gy to the tumor bed. Most case series of esthesioneuroblastoma report end points of 5- or 10-year survival, and in a 49-case series from the Mayo Clinic, the longest duration to first recurrence after initial treatment was 10 years.

Metastatic disease occurs in about 20%–30% of patients, usually in the cervical lymph nodes or lungs (as reviewed by Klepin et al.). Most studies do not report the length of time after initial treatment at which CNS metastasis is detected, although 1 case of metastasis to the lumbar spine was detected 15 years after initial diagnosis. In addition, in a series of 50 patients, 17 patients (34%) had recurrent disease after initial treatment; 5 of these cases were distant recurrences, with only 1 case of recurrence in the spine. Finally, the most comprehensive review of esthesioneuroblastoma metastasis to the spine describes 20 patients, the majority of whom had vertebral body or cauda equina disease; in many cases, the lesions were incidentally noted either radiographically or at autopsy. To our knowledge, the case described in this paper is the first reported case of symptomatic intradural extramedullary cervical spine disease.

Another salient feature of the case reported here is the delayed onset of CNS metastasis, particularly in the absence of radiographically identifiable local recurrence. A large meta-analysis of 225 cases of esthesioneuroblastoma by Kane et al. in 2010 showed that there was a statistically significant survival benefit at 10 years when radiotherapy was used as an adjuvant to resection. This study and other large case series do not report the time to detection of metastatic disease, but the average time to disease recurrence appears to be 5 years or less (as reviewed by Klepin et al.), and metastatic disease has been reported anywhere from 1 month to 10 years after disease diagnosis. Because of the rarity of this tumor, there does not appear to be a consensus protocol for surveillance imaging to monitor for recurrence or metastasis, and thus, it is difficult to determine whether delayed diagnosis of late metastasis confounds these figures. Nonetheless, our case of an intradural cervical spine lesion detected 18 years after initial diagnosis and treatment of esthesioneuroblastoma represents late metastasis that, based on the imaging characteristics shown here, may be initially misdiagnosed as meningioma or schwannoma. Thus, when surgically treating lesions that may represent esthesioneuroblastoma metastases, it is important to recognize the response of this tumor to chemotherapy.

Adjuvant or neoadjuvant platinum-based chemotherapy for esthesioneuroblastoma generally has been used for local control of recurrent or metastatic disease, as was undertaken with our patient, and does not appear to be curative. For example, 13 of 19 patients treated with cisplatin and etoposide, most of whom had Kadish Stage C disease (direct regional spread to surrounding structures), had partial or complete radiological response to chemotherapy. In addition, published series from the University of Virginia advocate routine use of preoperative cyclophosphamide and vincristine in Kadish Stage C disease, followed by surgery and radiation therapy. On the other hand, a large meta-analysis showed that adjuvant chemotherapy did not confer a statistically significant survival benefit in patients with histologically high-grade disease, but the authors concluded that there was inadequate power, given the rarity of the disease, to exclude consideration of chemotherapy. Moreover, there exists evidence that the addition of chemotherapy or radiation therapy after resection of CNS metastases confers a survival advantage of, on average, about 15 months. Given the small number of reported cases of CNS metastasis and the lack of consensus opinion or protocol on the use of chemotherapy in primary, recurrent, or metastatic esthesioneuroblastoma, our case serves as an example in which adjuvant chemotherapy aids in symptom control and possibly in survival.
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Conclusions

We report here a case of esthesioneuroblastoma in which multifocal CNS drop metastases occurred 18 years after initial diagnosis. The symptomatic lesion was treated with surgical decompression and adjuvant chemotherapy, and 14 months after surgery, the patient continues to do well clinically and enjoy relief of his symptoms. This case demonstrates that cases of esthesioneuroblastoma may warrant long-term follow-up or periodic radiographic surveillance beyond 10 years.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Ragel. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Ragel. Study supervision: Ragel.

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References


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