Case Report

Radiation-Induced Olfactory Neuroblastoma

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Abstract

Olfactory neuroblastoma (ONB) is a rare, malignant neuroendocrine tumor with potential to develop outside the normal means and distribution of olfactory neuroepithelium. With four published cases, we present a patient with a frontal sinus ONB invading the dura after receiving whole brain radiation for non-Hodgkin Lymphoma 20 years before. Imaging and biopsy revealed a frontal sinus malignant neuroendocrine neoplasm with posterior table and dural involvement. She underwent a combined craniofacial resection with adjuvant stereotactic radiosurgery. She subsequently developed metastatic disease. The element of radiation introduced a variable that undoubtedly affected her loco regional control and overall survival.

INTRODUCTION

Olfactory neuroblastoma (ONB) is a rare and malignant neuroendocrine tumor that was first described by Berger and Luc in 1924 [1]. ONB arises from the olfactory neuroepithelium located within the superior nasal cavity and represents 3% of nasal neoplasms [2]. The Kadish radiologic staging system and the Hyams histopathologic grading system have historically been used to characterize the extent and aggressiveness of the disease [3-5]. Extension beyond the nasal cavity via transit through the cribriform plate to the dura or parenchyma beyond often dictates the aggressiveness of treatment [6]. One possible etiologic factor for ONB development outside the normal distribution of olfactory neuroepithelium is a history of prior radiation. With four published cases [7], we present a patient with a frontal sinus ONB invading into the dura after receiving whole brain radiation over 20 years ago.

CASE REPORT

The patient is a 49-year-old female who received 24-Gy whole brain radiation for stage 4 non-Hodgkin lymphoma in 1987. Twenty three years later, she developed two years of worsening frontal headaches and was treated for chronic sinusitis and frontal bone osteomyelitis with multiple courses of intravenous antibiotics at an outside institution. Secondary to worsening symptoms, computed tomography (CT) and magnetic resonance imaging (MRI) scans were obtained that revealed a left frontal sinus mass with posterior table and dural involvement (Figures 1A, 1B, 1C). A frontal trephine biopsy showed a malignant neuroendocrine neoplasm consistent with olfactory neuroblastoma and she was referred to our institution for further treatment. The patient underwent a combined craniofacial resection with left frontal craniotomy, excision of the

Figure 1 CT non-contrast paranasal sinuses with coronal and sagittal reformats: left frontal sinus contains a soft tissue mass local osseous destruction and erosion through the inner table of the skull, and a 4mm component extending intra-axial.

CT: computed tomography
mass with associated frontal bone and dura, and pericranial and calvarial graft reconstruction. Pathologic examination revealed cytomorphologic and immunohistochemical characteristics consistent with olfactory neuroblastoma having a high mitotic rate and no necrosis (Hyams grade 3) and negative surgical margins (Figure 2). The patient then underwent adjuvant stereotactic radiosurgery of five 500-cGy daily fractions to the frontal bone. Six months after completing radiation therapy, the patient developed multiple left sided dural based enhancing lesions consistent with metastatic neuroendocrine carcinoma. She underwent an additional five 500-cGy fractions of stereotactic radiosurgery. She had complete resolution of the lesions on surveillance imaging. Approximately 6 months later she developed severe back pain, loss of rectal tone, urinary retention, and lower extremity weakness and sensory loss with extensive intramedullary, epidural, leptomeningeal disease throughout the spine on MRI, likely representing drop metastases from her neuroendocrine tumor. She was given intravenous steroids, elected to forgo palliative radiation therapy, and died several weeks later on inpatient hospice.

**DISCUSSION**

Olfactory neuroblastoma (ONB), also known as an esthesioneuroblastoma, is an uncommon tumor of the sinonasal cavity arising from neural crest olfactory neuroepithelium. While this tumor is rare in and of itself, radiation exposure is an even more uncommon etiology for ONB with only four documented cases within the literature.

1. A 43-year-old female with low-grade astrocytoma was treated with 58Gy radiotherapy developed anosmia, rhinorrhea, and right nasal obstruction 9 years later. Imaging revealed a large mass involving the superior nasal cavity and ethmoid, maxillary, and frontal sinuses. She underwent functional endoscopic sinus surgery for debridement followed by adjuvant radiation (50 Gy) and chemotherapy (docetaxel, cisplatin, and fluorouracil) for a malignant sinonasal small-cell tumor. Approximately 10 months later she developed similar symptoms with a recurrence involving the paranasal sinuses, crista galli, and right orbit. A resection of the cribiform plate, anterior cranial fossa, and right orbit was performed to clear the high-grade olfactory neuroblastoma. Approximately 1 year later on routine imaging, a new large tumor involving the paranasal sinuses and the left orbit was identified; the patient was placed on palliative chemotherapy [7].

2. A 19-year-old female with childhood acute lymphoblastic leukemia was treated with autologous bone marrow transplantation with prophylactic cranial and whole body irradiation (total 36 Gy) 9 years earlier. She was ultimately diagnosed with widely osseus metastatic ONB. She was treated with chemotherapy but died 11 months later.

3. A 59-year-old female with a pituitary prolactinoma was treated with 2 subtotal resections and adjuvant radiation totaling 54 Gy. She subsequently received additional treatment with bromocriptine. Approximately 20 years later she developed nasal obstruction and epistaxis with a superior nasal cavity and ethmoid sinus mass that invaded the frontal lobe through the skull base. Biopsies showed a malignant small-cell tumor and the patient underwent a transcranial and transnasal resection. The tumor was identified as a high-grade ONB, Kadish stage C. The patient was given chemotherapy (ifosfamid, cisplatin, etopoide) and remained disease free [8].

4. A 36-year-old female was diagnosed with diffuse large cell poorly differentiated lymphocytic lymphoma of the left tonsil and was treated with cobalt-60 parallel opposing radiation therapy (60 Gy). She received an additional 30 Gy with chemotherapy (m-BACOD) to her thoracic spine for cord compression. Approximately 25 years later she developed left maxillary swelling, nasal obstruction, and epiphora. She was diagnosed with a Hyams’ grade 3-4 ONB with diffuse FDG-avid pulmonary lesions consistent with distant metastatic disease. She was placed on palliative carboplatinum-etopoide and died shortly after diagnosis [9].

Olfactory neuroblastoma, accounting for about 3% of tumors identified within the nasal cavity, has a slightly higher male predominance with diagnosis peaking in the fifth and sixth decades [10,11]. While locally aggressive, there is an approximate 10% risk of cervical metastases at presentation [12]. The overall 5-year survival for patients with de novo ONB is 45-62% with higher Kadish radiologic and Hyams histopathologic grading portending a worse prognosis [10,11,13]. The Kadish staging system stratifies patients into 3 categories based on location of the lesion: stage A tumors are limited to the nasal cavity, stage B tumors involve the paranasal sinuses, and stage 3 tumors extend beyond the nasal cavity and paranasal sinuses [12]. The Hyams grading system utilizes the histopathologic evidence (or absence) of lobular preservation, mitotic index, nuclear polymorphism, fibrillary matrix, Homer Wright or Flexner-Wintersteiner rosettes, and necrosis to stratify aggressiveness. When the tumors appear dedifferentiated or appear in aberrant locations, a boarder differential diagnosis of small round cell tumors is necessary [14]. Malignant melanoma, rhabdomyosarcoma, lymphoma, extramedullary plasmacytoma, sinonasal undifferentiated carcinoma (SNUC), neuroendocrine...
sinonasal carcinoma (NEC), Ewing’s sarcoma, and primitive neuroectodermal tumors (PNET) must be differentiated from ONB through the use of an immunohistochemical profile [14]. ONB is generally diffusely positive for neuron-specific enolase and synaptophysin. Chromogranin and peripheral S-100 staining limited to the sustentacular network are also found. While ONB stains for S-100, malignant melanoma and Ewing’s sarcoma show diffuse tumor cell positivity. Malignant melanoma also stains for HMB-45. Rhabdomyosarcoma shows evidence of desmin, myogenin, vimentin, and myo-D2, while SNUC and NEC show evidence of epithelial markers. Ewing’s sarcoma can be identified with antibodies to the myc-2 protein.

Given that radiation-induced ONB patients show evidence of tumor development beyond the expected distribution of olfactory neuroepithelium, it is important to make a timely and accurate diagnosis for treatment and prognostic purposes. Although a small sample size of 5 cases, 100% of patients with radiation-induced ONB have been female with an average age of 52 years at time of discovery (range 19 to 79 years). The average latency between radiation to diagnosis of the ONB was approximately 17 years (range 9 to 25 years).

To help facilitate determination if malignancy is a result of previous radiation exposure, Murray and colleagues [15] revised the original criteria proposed by Cahan et al in 1948 to describe post-radiation sarcomas originating from irradiated bone. These criteria include:

1. Microscopic or radiographic evidence of non-malignant nature of the initial tissue condition.
2. The cancer developing after radiotherapy must have arisen in the area included within the 5% isodose line.
3. A relatively long, asymptomatic period must have elapsed after radiotherapy and before the clinical appearance of the second malignancy (at least 5 years, but ranging from 10-20 years).
4. All post-therapy malignancies must be confirmed histologically and clearly be a different etiology than the primary condition

Most of the research related to radiation-induced malignancy is related to the development of sarcoma with a 19.1% 3-year overall survival based a large series after treatment of nasopharyngeal carcinoma in an endemic region of China [17,18]. With an incidence of sarcoma up to 0.3% after radiation therapy [16], it would be difficult to extend sarcoma data to ONB, let along ascertain prognostic information from olfactory neuroblastoma in a previously irradiated patient. Despite a recent metaanalysis of 26 studies showing an overall 5-year survival of 45%, the larger studies quote a 70% 5-year survival with a local recurrence rate of 30%. Treatment paradigms including a combination of surgery and radiotherapy with or without chemotherapy are the mainstay of therapy. Based on the 5 cases of radiation-induced ONB, it appears there is a predilection to distant metastases and low disease free or overall survival and therefore warrants aggressive treatment.

**CONCLUSION**

While sarcoma of the head and neck is a rare complication of radiation therapy, the development of olfactory neuroblastoma outside of the usual distribution of olfactory neuroepithelium is an extremely rare but possible outcome. While staging, histologic grade, and treatment modality often dictate disease free and overall survival, the element of radiation-induced malignancy introduces a negative prognostic variable in olfactory neuroblastoma.

**REFERENCES**

14. Kahmke et al. (2016) Email: russell.kahmke@duke.edu

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