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Sinonasal carcinoma after irradiation for medulloblastoma in nevoid basal cell carcinoma syndrome

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Abstract

Background: Nevoid basal cell carcinoma syndrome (NBCCS) is associated with multiple basal cell carcinomas, odontogenic cysts, craniofacial anomalies, and childhood medulloblastomas. In addition, it has been associated with irradiation-induced neoplasms including, meningiomas, sarcomas, and gliomas.

Methods: We present a 19-year-old man with NBCCS who presented with a sinonasal carcinoma 17 years after receiving craniospinal irradiation for treatment of medulloblastoma.

Results: To our knowledge, this is the first report of a sinonasal tumor after irradiation in a patient with NBCCS.

Conclusions: With this case, the authors examine the genotype of NBCCS patients and their propensity for radiation-induced tumors. In addition, the management of neoplasms in these tumor-sensitive patients is reviewed.

1. Introduction

Gorlin syndrome or nevoid basal cell carcinoma syndrome (NBCCS) was discovered shortly after 1958 when Dr Robert Gorlin and his colleague, Dr Robert Goltz, encountered a patient with multiple skin lesions and with what was then called primordial cysts of the maxilla [1]. Currently, this autosomal dominant syndrome is known to represent 0.4% of all cases of basal cell carcinoma and has a minimal prevalence of 1 per 57,000 [2,3]. This relatively rare condition is characterized by a proclivity of multiple basal cell carcinomas between puberty and 35 years of age, odontogenic cysts, medulloblastomas, frontal bossing, skeletal anomalies, and fibromas [4]. Children younger than 5 years and presenting with medulloblastoma have a 4.5% chance of also having NBCCS [5].

Patients with NBCCS treated with irradiation often develop late-onset neoplasms with differing histology from the primary tumor. Documented cases of irradiation-induced tumors in patients with NBCCS include basal cell carcinomas, meningiomas, schwannomas, and liposarcomas [6,7]. We present a unique case of sinonasal carcinoma that most likely represents a late-onset neoplasm from craniospinal irradiation. Less likely, but possible, this neoplasm may represent a primary tumor that occurs in association with Gorlin syndrome.

2. Case

A 19-year-old African American man, with a complicated history of nevoid basal cell carcinoma, was referred for evaluation of a 1-month history of nasal congestion and intermittent epistaxis. Nasal endoscopy revealed a red-pink mass obstructing the left posterior nasal cavity. Magnetic

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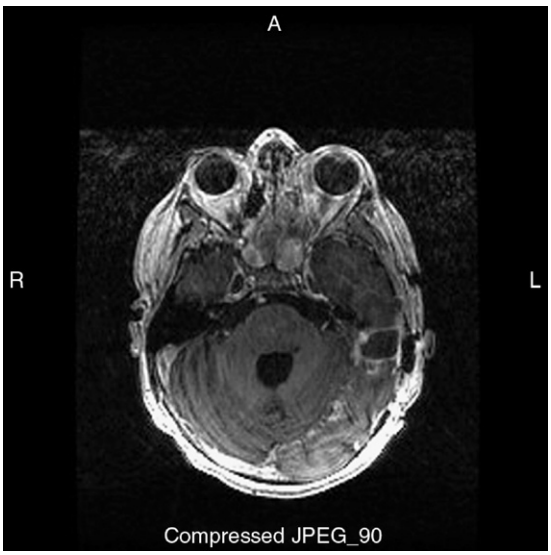

Fig. 1. Postcontrast axial magnetic resonance image demonstrates a poorly defined irregular soft tissue mass with heterogeneous enhancement involving the ethmoid sinuses and sphenoid sinuses bilaterally.

resonance imaging confirmed a large irregular-enhancing mass involving the ethmoid and sphenoid sinuses bilaterally (Fig. 1). Opacification of the left maxillary sinus represented partial invasion and/or obstructive sinusitis. In addition, there is evidence of bilateral temporal craniotomies with areas of cystic encephalomalacia.

Biopsy of the intranasal mass demonstrated a poorly differentiated carcinoma with neuroendocrine features.

At 30 months of age, the patient was treated with craniospinal irradiation for a T2N0 medulloblastoma. A total dose of 45 Gy was administered, 23.4 Gy to the spine and 21.6 Gy to the posterior fossa. Two years later, at age 4, he required excision of odontogenic keratocyts. At 14 years of age, he underwent a partial resection of the liver for a benign mesenchymal tumor and a right rib resection for a cystic lesion. At the age of 18, he underwent surgery to remove a meningioma in the left parietal region.

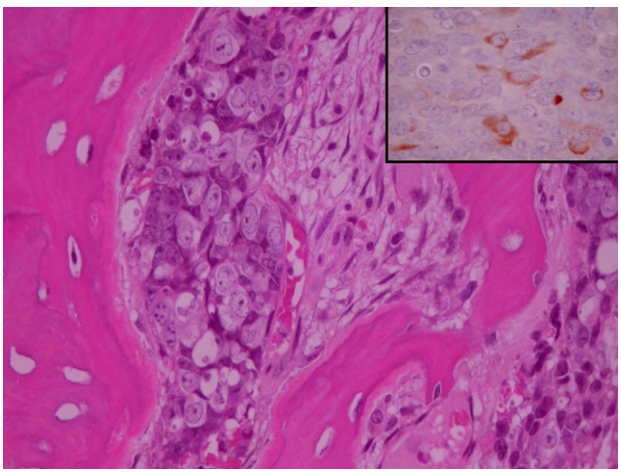

Fig. 2. Poorly differentiated neuroendocrine carcinoma invading the bone. There are pleomorphic cells with prominent nucleoli (hematoxylin-eosin, original magnification, ×400). Inset: positive immunoreactivity for synaptophysin in cells with neuroendocrine features (original magnification, ×400).

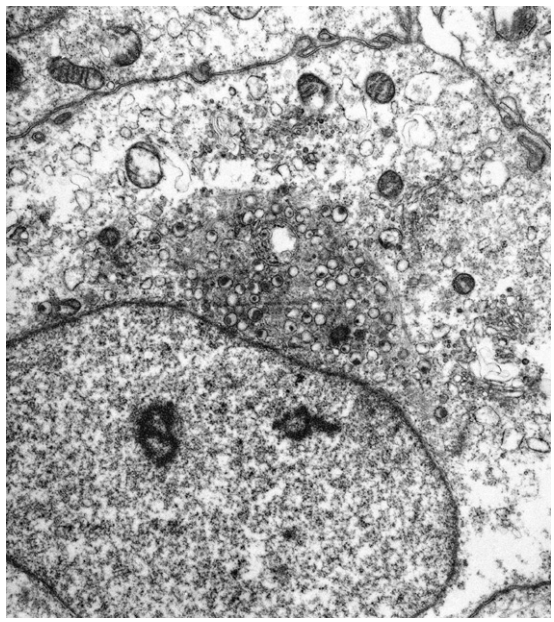

Fig. 3. There are vacuoles that range from empty to having varying amounts of fine, electron-dense contents in a background that is more electron-dense than the surrounding cytoplasm. They likely represent early formation of dense core, neuroendocrine type granules (transmission electron microscopy, original magnification, ×26,000).

A resection of the gross tumor was performed involving the nasal cavity, sinuses, and the skull base. At that time, it was estimated that 95% of the tumor was resected. Pathological analysis of the surgical specimen identified a poorly differentiated carcinoma (Fig. 2). A synaptophysin immunohistochemical stain was positive. Chromogranin CD 56 and S-100 protein stains were negative. Electron microscopy displayed no classic dense core granules but displayed neuroendocrine type granules with clear vacuoles associated with the Golgi, which were consistent with precursors of neuroendocrine granules (Fig. 3). These findings were most consistent with a poorly differentiated neuroendocrine carcinoma.

The hospital course was uneventful. He has continued to do well postoperatively with cessation of epistaxis. He has occasional headaches, mainly over the frontal sinuses, but otherwise remains without diplopia or other vision changes. Although radiation can be considered postoperatively, a dose of nearly 60 Gy would be needed to deliver any meaningful effect. In light of his history with the adverse effect of radiation therapy, the decision was made to forgo irradiation.

3. Discussion

From establishment of NBCCS with basal cell carcinomas and odontogenic cysts, this relatively rare syndrome has since been associated with medulloblastomas, frontal bossing, skeletal anomalies, and fibromas [4]. The first

population-based study on medulloblastoma showed the overall incidence of NBCCS among those with medulloblastoma to be 1% to 2%. However, when controlling for age, the incidence increases to 4.5% for those younger than 5 years [5]. Viewed differently, 5% to 20% of all NBCCS patients will develop medulloblastoma [5].

Since the discovery of the Patched, or PTCH, gene in 1996, over 68 mutations have been associated with NBCCS. These occur in the form of deletions, insertions, missense mutations, errors in splicing, and premature stop codons [8]. PTCH is located on chromosome 9q22.3 and follows the Knudson 2-hit hypothesis [9]. Those born with NBCCS have a mutation in one of the PTCH alleles. A second hit occurs later because of random genetic or environmental mutations [1]. Normally, PTCH receptors on plasma membranes are in close association with smoothened (SMO) receptors, which suppress transcription of GLI1 leading to cessation of unregulated cellular division [10]. When the PTCH receptor becomes nonfunctional, secondary to mutation, the Sonic Hedge Hog ligand is unable to control cell growth. As a result, uncontrolled activation of downstream transcription occurs through the SMO receptor [10].

In addition to loss of control found with mutations of the PTCH gene, it is recognized that about 30% of those with NBCCS have mutations in the p53 tumor suppressor gene [11]. It is considered that the p53 gene plays an important role in human carcinogenesis, with over 50% of human neoplasms having a mutation in this gene [12]. Certain individuals with an inherited mutation of a single p53 gene, known as Li-Fraumeni syndrome, have a 25-fold greater chance of developing a malignant tumor by the age of 50 [13]. Those with Li-Fraumeni syndrome develop a variety of tumors, including those that affect the central nervous system.

An association between early irradiation and secondary cancers has been witnessed. These radiation-induced tumors typically occur after a long latency period, develop at the edge of the irradiated field, and are indistinguishable morphologically from the original cancer [14]. Irradiation usually results in large deletions, causing inactivation of tumor suppressor genes such as p53 [14]. It is speculated that patients with abnormal p53 would therefore have a decreased ability to detect damaged DNA. As a result, sublethal irradiation would lead to amplification of cells with damaged DNA [14]. The improper function of p53 has been indicated in the occurrence of meningiomas and nasopharygeal carcinomas [15,16].

Because of the propensity toward multiple late-onset tumors after craniospinal irradiation, it is imperative that those with NBCCS receive minimal irradiation for the treatment of medulloblastoma. Chemotherapy now plays a larger role in treating those with a genetic predisposition to develop cancers, such as those with NBCCS [17]. Children who present with medulloblastoma, especially those younger than 5 years, should have a thorough evaluation including familial history and genetic screening for NBCCS to help reduce late-onset irradiation-induced tumors.

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