Angiosarcoma Arising from the Tongue of an 11-Year-Old Girl with Xeroderma Pigmentosum

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Abstract Xeroderma pigmentosum (XP) is a rare autosomal recessive defect in DNA endonuclease activity that is associated with the development of cutaneous malignancies, at sun exposed sites, including basal cell carcinoma, squamous cell carcinoma, and melanoma. Squamous cell carcinomas are also known to target the anterior tongue. Patients sometimes develop angiosarcomas, and these invariably arise from sun-exposed skin. A biopsy was taken from a large mass arising in the anterior tongue of an 11-year-old girl with XP and a history of cutaneous basal cell carcinomas. The histopathologic findings demonstrated a high grade epithelioid neoplasm resembling a poorly differentiated squamous cell carcinoma, but the immunohistochemical profile (AE1/AE3 negative, p63 negative, CD31 positive, CD34 positive) established the diagnosis of angiosarcoma. Angiosarcoma is an XP-related tumor that usually arises in sun-exposed skin but can also arise in the oral cavity. For patients with XP who develop epithelioid neoplasms of the

oral cavity, epithelioid angiosarcoma should be considered in the differential diagnosis.

Keywords Xeroderma pigmentosum · Angiosarcoma · Head and neck cancer · Squamous cell carcinoma

Introduction

Xeroderma pigmentosum (XP) is a rare autosomal recessive defect in endonuclease activity that leads to abnormal DNA repair in response to ultraviolet (UV) radiation-induced damage. Early cataract formation and blindness are hallmarks of the disease, and intellectual impairment is occasionally present [1]. Cutaneous manifestations of XP include lentigines, freckling, premature aging, severe photosensitivity, and cutaneous neoplasms including squamous cell carcinoma, basal cell carcinoma, and melanoma [2]. Angiosarcoma infrequently occurs in patients with XP, where it invariably arises in sun-exposed skin. The first presentation of XP-associated angiosarcoma in the oral cavity is herein presented along with diagnostic considerations.

Case Report

An 11-year-old girl who had immigrated to the United States from central Africa presented at our institution with cataracts leading to complete visual loss in the right eye and partial visual loss in the left eye, a history of numerous basal cell carcinomas of the face and scalp, and a recurrent lesion of the tongue. She had undergone surgical excision and radiation of a tongue lesion in her home country, but the lesion had recurred.

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Fig. 1 Clinical image of the lesion on the anterior tongue

Physical examination was remarkable for a fungating polypoid mass along the dorsal aspect of the anterior tongue (Fig. 1), a large friable mass on the nasal tip, multiple smaller eroded plaques on the face, and bulky cervical lymphadenopathy. Tests for tuberculosis and human immunodeficiency virus (HIV) were negative. The patient also had a normal blood count and peripheral blood smear. A computed tomographic scan of the head and neck demonstrated a 2.4 cm fungating mass of the anterior tongue, a 2.5 cm exophytic mass of the left nasal wall and nasal tip, and enlarged lymph nodes at level II bilaterally.

The nasal and tongue lesions were biopsied. The nasal lesion was found to be a basal cell carcinoma. By contrast, microscopic analysis of the lesion on the tongue revealed the presence of a poorly differentiated tumor composed of rounded epithelioid cells with abundant eosinophilic

cytoplasm, large vesicular nuclei, and prominent nucleoli. The tumor infiltrated the submucosal and skeletal muscle of the tongue as solid sheets and irregular cords. The tumor focally formed irregular anastomosing channels. The overlying squamous mucosa was inflamed but did not exhibit dysplastic changes. A panel of immunohistochemical stains showed that the oral tumor was positive for the vascular markers CD31 and CD34; and it was negative for AE1/AE3, p63, and HHV-8. Based on the morphologic features together with the immunohistochemical profile, the tumor of the oral tongue was diagnosed as a high-grade epithelioid angiosarcoma (Fig. 2).

Discussion

Angiosarcomas are malignant neoplasms that express endothelial differentiation. Well-recognized risk factors for the development of angiosarcomas include longstanding lymphedema, therapeutic radiation, and the chemical carcinogen thorium dioxide (Thorotrast). Although cutaneous angiosarcomas unassociated with lymphedema preferentially target the upper part of the face and scalp (areas of high sunlight exposure) the role of ultraviolet light in the development of these tumors is uncertain. Angiosarcoma has previously been reported in five other patients with Xeroderma pigmentosa (XP)—a rare autosomal recessive defect in endonuclease activity that leads to abnormal DNA repair in response to ultraviolet (UV) radiation-induced damage (Table 1) [3–7]. Patients with XP are very prone to developing UV-associated cutaneous malignancies including basal cell carcinomas, squamous cell carcinomas, and melanomas. The development of angiosarcomas in a small

Fig. 2 The angiosarcoma consisted of a submucosal tumor consisting of plump epithelioid cells (a). Tortuous anastomosing vascular spaces were best seen at higher power (b). The tumor was immunoreactive for CD31 (c) but not p63 (d)

Table 1 Age, gender and site of all reported cases of XP-associated angiosarcoma

Author	Age (years)	Gender	Site
Leake et al. [9]	15	Female	Scalp
De Silva et al. [8]	63	Male	Cheek
Ludolph-Hauser et al. [7]	13	Female	Shin
Marcon et al. [6]	15	Male	Nose
Arora et al. [5]	40	Male	Eyebrow
Present case	11	Female	Tongue

subset of patients with XP, including young patients with no other risk factors, provides some presumptive evidence in support of UV-induced damage as a risk factor.

Our case is unique from the other reported cases of XP-associated angiosarcoma in that the tumor arose from a non-cutaneous intra-oral site. Its origin from the anterior tongue, however, does not exclude the role of UV-damage as a contributing factor. Unlike other regions of the upper aerodigestive tract, the anterior portion of the tongue has limited exposure to sunlight. Indeed, the anterior tongue is a well-recognized site of origin for patients with XP-associated squamous cell carcinomas.

Although this is the first reported case of angiosarcoma arising in the tongue of a patient with XP that we are aware of, it is conceivable that other cases of intraoral angiosarcomas have been misdiagnosed as squamous cell carcinomas. There are several factors that may contribute to this confusion. First, squamous cell carcinomas are much more common, and they frequently target the anterior tongue in patients with XP. Given the overwhelming preponderance of oral squamous cell carcinomas, epithelioid angiosarcomas may not be routinely considered in the differential diagnosis of poorly-differentiated epithelioid neoplasms at this site. Second, its epithelioid morphology and limited vasoformation often render the histologic appearance of epithelioid angiosarcoma more akin to non-keratinizing squamous cell carcinoma than to classic angiosarcoma [8–10]. Third, squamous cell carcinomas, particularly those arising in sun-exposed sites, sometimes exhibit acantholytic spaces that mimic the vascular channels of angiosarcoma. In effect, the focal presence of vascular channels in an angiosarcoma may be erroneously interpreted as acantholysis in a squamous cell carcinoma.

Reliable distinction of an epithelioid angiosarcoma from poorly-differentiated squamous cell carcinoma may require immunohistochemical evaluation. Considerable caution is needed when using cytokeratin expression as sole evidence of epithelial origin as the majority of epithelioid angiosarcomas are positive for pancytokeratin. P63 is strongly and diffusely expressed in oral squamous cell carcinomas, but it is not expressed in the limited number of epithelioid

angiosarcomas tested to date [11, 12]. Endothelial differentiation can be confirmed by the vascular markers CD31 and CD34. These markers are expressed in most angiosarcomas of the oral cavity [11, 13] but not in squamous cell carcinomas.

In summary, this case is the first reported instance of angiosarcoma presenting in the oral cavity of a patient with XP. This and other reports of angiosarcoma arising in sun exposed sites of patients who are unable to properly repair UV-induced DNA damage draws attention to sunlight as a possible etiologic factor in the development of some angiosarcomas. In patients with XP, distinguishing angiosarcoma from squamous cell carcinoma may be difficult, particularly in those sarcomas that exhibit prominent epithelioid morphology with minimal vasoformative features.

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