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Incidental ameloblastoma diagnosed after treatment for childhood tumor

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ABSTRACT

Ameloblastoma is a rare odontogenic neoplasm accounting for 1% of all tumors of the jaws. It is rarely diagnosed in pediatric and adolescent age. Cancer treatment is a well-known risk factor for the onset of secondary malignancies among childhood cancer survivors, but any link between ameloblastoma and prior cancer treatments has yet to be explored. Here we report on two cases of ameloblastoma diagnosed in patients previously treated for tumors in pediatric age.

1. Introduction

Ameloblastoma is a slow-growing benign tumor arising from odontogenic epithelium, characterized by a locally aggressive behavior [1–4]. It is a rare neoplasm, accounting for 1% of all tumors of the jaws [1]. It is seen primarily in adults in their 3rd to 5th decades of life [5] (median age at diagnosis: 36.1 years) [5–7], with a balanced male-to-female ratio (51.9% males) [5–7]. Ameloblastoma is infrequently diagnosed in children and adolescents [8], who are involved in 10–15% of all reported cases [9]. Owing to its rarity, there is no consensus on factors promoting its genesis. Although general guidelines for ameloblastoma treatment exist, the onset of this disease in pediatric age represent a challenge, considering the benign nature of this lesion and the possible effects of extensive surgical excision on a growing bone.

Accumulating evidence from the world of pediatric oncology suggests that children and adolescents given chemotherapy and/or radiotherapy for neoplastic disease are at higher risk of developing secondary malignancies [10–13]. There have been no reports of a link between prior cancer treatments and incidental ameloblastoma to date. Here we describe two cases of ameloblastoma diagnosed in patients previously treated for childhood tumors.

1.1. Case #1

A male patient diagnosed at one year old with stage I neuroblastoma (right adrenal gland, Shimada favorable stage, N-myc not amplified, absence of del1p) was treated with radical surgery, and was subsequently given chemotherapy for recurrent skeletal disease (1^{st}-line treatment with standard dose chemotherapy consisting of: vincristine + cisplatin + etoposide + epi-adriamycin alternated with ifosfamide; 2^{nd}-line treatment with standard doses of carboplatin + etoposide followed by high-dose cyclophosphamide and etoposide, and consolidation with high-dose mitoxantrone + melphalan followed by autologous stem cell rescue).

At 18 years of age (17 years after neuroblastoma diagnosis, 15 years after completing his cancer treatments), the patient presented with a left facial swelling. He underwent orthopantomography (OPT) and computed tomography (CT), which revealed a gross osteolytic lesion of the jaw with thinning of the vestibular cortical bone. Conservative surgery was performed (Fig. 1A–B), consisting of excision of the mandibular angle (bone

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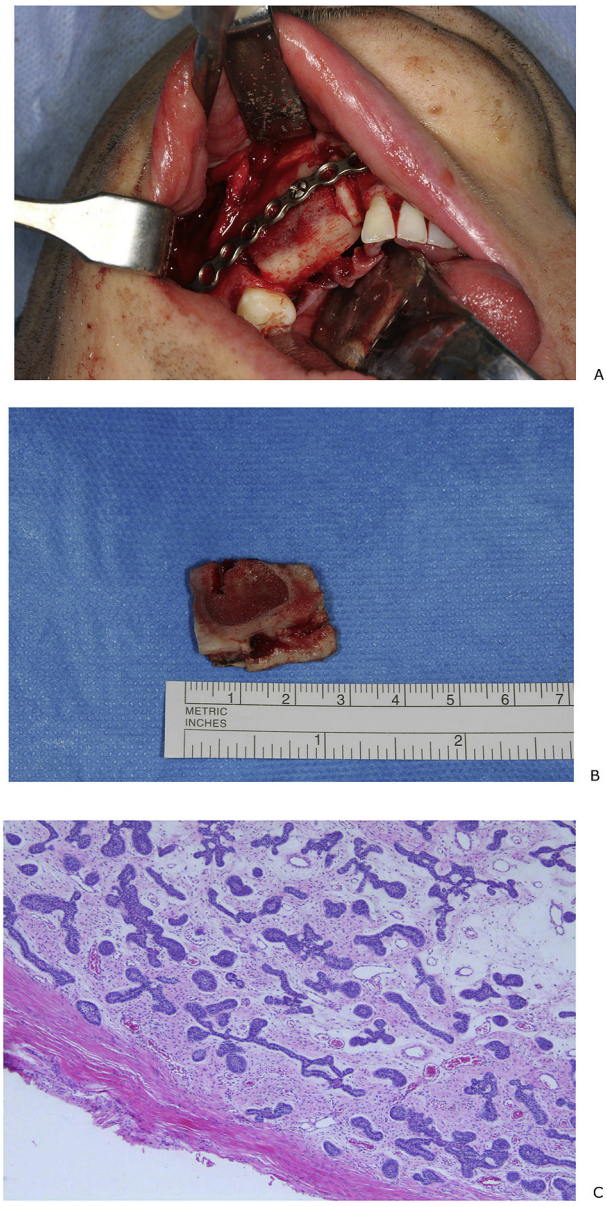

Fig. 1. Case #1: (A) Intraoperative capture of mandibular cortical perforation. (B) Pathological specimen of radically resected ameloblastoma. (C) Conventional ameloblastoma with plexiform growth pattern and pushing margins (H&E, 50x).

margins > 1 cm). Histological examination led to a diagnosis of classic (multicystic) ameloblastoma (Fig. 1C). No local recurrences occurred during a 9-month follow-up.

1.2. Case #2

A male patient diagnosed with medulloblastoma (T3a M0) at 5 years of age underwent radical surgery, adjuvant chemotherapy (a personalized treatment with cisplatin and etoposide due to his poor clinical conditions after surgery), and craniospinal irradiation (total fractionated dose: 23.4 Gy), with a boost to the posterior fossa (total fractionated dose: 54 Gy).

At 18 years old (13 years after being diagnosed with cancer, and 12 years after completing his cancer treatments), the patient presented with a left jaw swelling. An OPT revealed a radiolucent lesion of the left mandibular body (Fig. 2A). CT scan showed an osteolytic lesion of the jaw with evidence of cortical disruption (Fig. 2B–C). Surgery was performed with excision of the left mandibular body (bone margins > 1 cm) and reconstruction with a bone graft. Histological examination led to a diagnosis diagnosis of classic (multicystic) ameloblastoma. No disease recurrences were observed during a 6-month follow-up.

2. Discussion

To the best of our knowledge, this report of two cases of incidental ameloblastoma in patients treated for childhood cancer is the first to support a possible link between previous oncological treatments and ameloblastoma.

Ameloblastoma is a rare epithelial odontogenic tumor that usually occurs in the mandible and maxilla; other osseous sites are exceedingly uncommon [1–4]. According to the recently updated classification of the World Health Organization (WHO) [14], there are four histological subtypes: (1) solid/multicystic ameloblastoma (including desmoplastic ameloblastoma), which is the most common; (2) unicystic ameloblastoma; (3) extraosseous/peripheral ameloblastoma; and (4) metastasizing ameloblastoma, which appears as benign proliferation but has aggressive behavior.

A specific etiology for ameloblastoma has yet to be identified [15–17]: its pathogenesis is a complex multifactorial process involving numerous cellular pathways [18] and certain predisposing factors for its onset have not been observed. Due to its rarity in pediatric age [8,9], several aspects of childhood ameloblastoma remain to be fully understood.

Even though guidelines for ameloblastoma treatment exist, management during pediatric age often needs to be patient-tailored. This primarily considering the benign nature of the lesion and the possible surgical consequences on a growing skeleton [19].

The preoperative diagnostic workup includes imaging (OPT, CT, and possibly also magnetic resonance imaging [MRI]), and biopsy in some cases [20]. Histological examination of the whole excised specimen is of paramount importance to the diagnostic process [2]. Surgical excision is the mainstay of treatment, and achieving free margins is essential to disease control [20], aiming for resections with at least 1.0 to 1.5- cm margins of normal bone. This can pose a major problem in pediatric patients because extensive radical excisions may lead to deformity, poor mastication and occlusion anomalies. In fact, some authors argue that a more conservative, less demolitive approach might be recommended for pediatric patients [19,21] albeit considering the site and size of the lesion. Also histologic subtype can guide treatment choices, considering that unicystic variants often show a less aggressive behavior [22]. Shi et al. also made the point that recurrent disease is generally easy to control due to the small size of any (benign) relapsing lesions [23]. Expanding knowledge about oncogenic pathways and possible therapeutic targets in ameloblastoma (e.g. arsenic trioxide [ATO] to inhibit the Hedgehog signaling pathway activity in cells harboring SMO activation, or vemurafenib in cells harboring BRAF mutation) [15–17] entitle us to speculate that neo-adjuvant treatment might be considered with a view to reducing surgical sequelae.

Prompt diagnosis and appropriate treatment are essential to ensure cure without impairing patients' quality of life as a result of more aggressive radical treatments being needed in the event of a delayed diagnosis and more extensive disease. Hence the importance of improving awareness of the possibility of ameloblastoma occurring in the pediatric setting.

There is a growing body of evidence of pediatric cancer survivors being at far from negligible risk of developing secondary

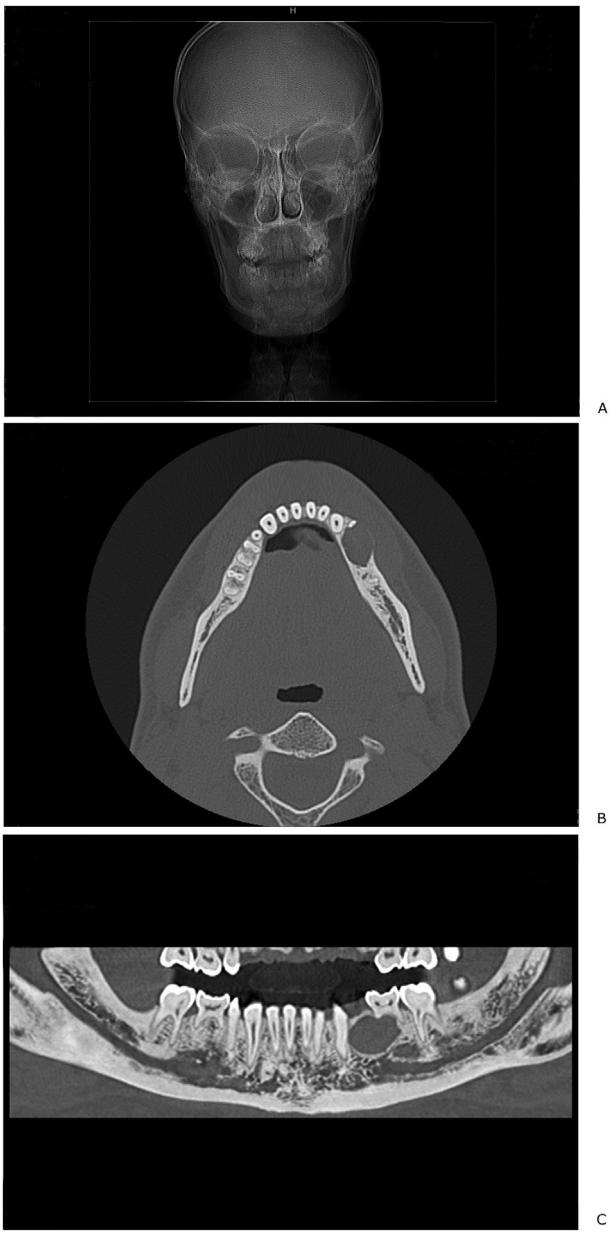

Fig. 2. Case #2: Radiology showing left mandibular ameloblastoma. (A) X-ray. (B) Axial and (C) coronal CT scan.

benign and malignant tumors [10–13]. Their additional risk is related partly to individual factors (i.e. cancer predisposition syndromes), but mainly to past cancer treatments, and radiotherapy in particular. In a recent investigation by our study group, it emerged that patients treated with high-dose chemotherapy and craniospinal irradiation for childhood medulloblastoma and PNET carried a significant (12%) risk of developing secondary malignancies, most of them within the irradiation field [10]. Neither of the two patients considered in the present report underwent genetic testing for underlying cancer predisposition syndromes because their family history was negative. Patient #1 had previously been given high-dose chemotherapy with alkylating agents, and Patient #2 had received radiotherapy, plausibly with a scattered delivery of the radiation to the site where the ameloblastoma subsequently developed. No studies to date have suggested a higher risk of ameloblastoma developing in individuals with a history of pediatric cancer treatments, but this association deserves attention.

3. Conclusions

This report regards two cases of ameloblastoma in patients who had been treated for cancer in pediatric age. One of the main merits of our report lies in raising awareness of a rare entity that might be encountered in oncological patients under surveillance. Further investigations are needed to clarify the possible link between ameloblastoma and chemo/radiotherapy administered for childhood tumors, and promote awareness of this occurrence among physicians.

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