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CASE REPORT

An ameloblastoma associated with cardiofaciocutaneous syndrome

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Abstract

This case describes the management of a plexiform unicystic ameloblastoma in a child with cardiofaciocutaneous syndrome. This was managed conservatively, which has allowed the patient to undergo normal dental development. There are no signs of recurrence 4 years post-operatively and the use of magnetic resonance imaging in monitoring has ensured the patient's exposure to ionising radiation is minimised. The patient's cardiofaciocutaneous syndrome was linked to a BRAF mutation. This gene is involved in cell proliferation and has recently been shown to have a link with mandibular ameloblastomas. As far as the authors are aware, this is the published first case of an ameloblastoma in a patient with cardiofaciocutaneous syndrome.

This case is the first of its kind to describe cardiofaciocutaneous syndrome patient presenting with a tumour and specifically an ameloblastoma.

A 4-year-old boy was referred to our Oral Surgery clinic from the Paediatric dentistry department. He was initially seen by his own general dental practitioner due to a right-sided facial swelling. This was initially treated with antibiotics. The patient's medical history included cardiofaciocutaneous syndrome linked with a BRAF mutation. This was confirmed by molecular genetic analysis.

Cardiofaciocutaneous syndrome is characterised by:

1 Distinctive facial appearance
2 Sparse, brittle and curly hair
3 A range of skin abnormalities
4 Heart abnormalities
5 Delayed growth
6 Foot abnormalities

Our patient had the characteristic appearance, sparse and curly hair and delayed growth. His echocardiogram, however, revealed no cardiac abnormalities. Until this point, there was no recorded predisposition to tumour formation in cardiofaciocutaneous syndrome[1].

The patient had a computerised tomography (CT) scan with contrast under general anaesthetic (GA) to characterise the area and eliminate a vascular component. This showed the radiolucent area to be non-vascular, well circumscribed, non-loculated, homogenous radiolucency related to the crown of the unerupted lower right first molar. There was buccal and lingual expansion of the mandible and the lesion was in close contact with the inferior dental nerve (Fig. 1). The differential diagnosis included dentigerous cyst, keratocyst and ameloblastoma.

Under the same GA, we then moved to biopsy and marsupialised the sizeable lesion and extracted the lower right second deciduous molar. Several specimens were submitted for histopathological examination and the area was packed with bismuth iodoform paraffin paste (BIPP)-impregnated ribbon gauze.

Histopathological examination showed a thin wall of fibrous tissue lined by epithelium. The epithelium

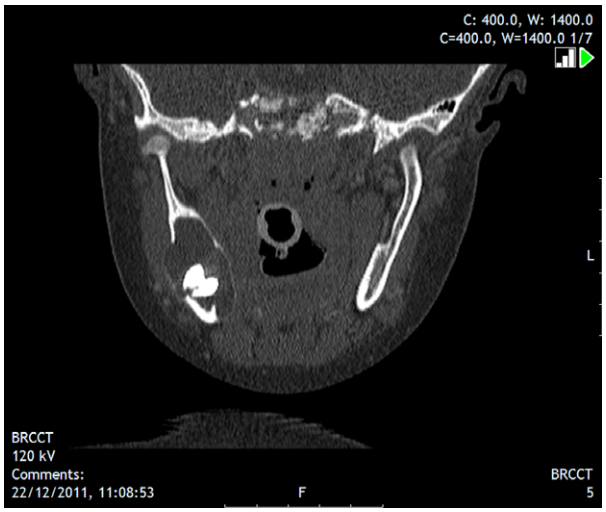

Figure 1 Coronal view of the pre-operative CT scan

was mostly 5–10 cells thick in a vague stratified pattern. The basal cell layer had a columnar morphology and displayed some palisading with a suggestion of increased nuclear hyperchromatism (Fig. 2). There was also a luminal projection of epithelium that comprised polygonal-, cuboidal- and spindle-shaped cells supported by fibro-vascular connective tissue (Figs 3 and 4). There was no evidence of mural involvement.

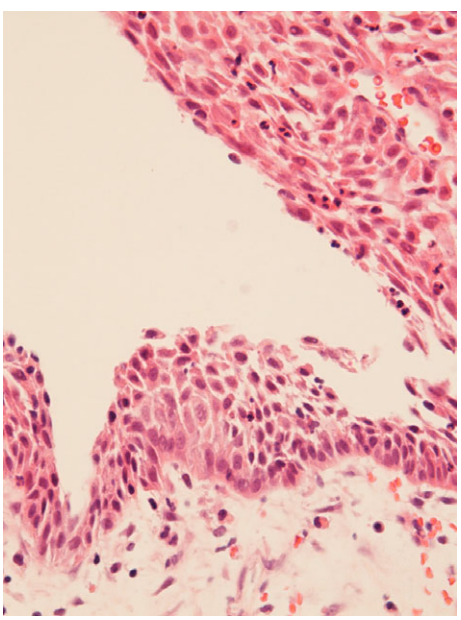

Figure 2 Wall of cyst showing subtle basal palisading at the base of the luminal projection, typical of unicystic ameloblastoma (H&E stain × 250)

These features were indicative of an ameloblastoma and were strongly suggestive of the intraluminal/plexiform unicystic subtype.

Following the diagnosis, we sought input from our pathologist, undertook a literature review regarding treatment of this subtype in children[2] as well as contacting a tertiary service for advice, in this case Great Ormond Street Hospital.

At the conclusion of the discussion, all parties felt it would be in the patient's best interest to manage this conservatively. Radical resection in a 4-year old would have left the patient with significant lifelong morbidity and because of the less aggressive nature of the plexiform type, it was decided it would be unnecessary. The options were discussed with the patient's parents and the treatment plan was agreed.

The patient was returned to theatre 6 weeks later to change the BIPP pack. The following month, the patient had a GA for a follow-up CT scan to monitor interval change and was brought to theatre after the scan for a pack change under the same GA. The CT scan had shown significant reduction in size (Fig. 5).

At this point, an impression was taken for a lower obturator to reduce the need for repeated general anaesthetics. In the light of these results and with further discussions, it was decided not to enucleate the area at this time. Three weeks later, the patient was brought to theatre for the last time to remove the pack and fit the lower obturator. The patient found this difficult to tolerate and, as his mother could clean the area with saline and a blunt syringe, the obturator was abandoned after 1 month.

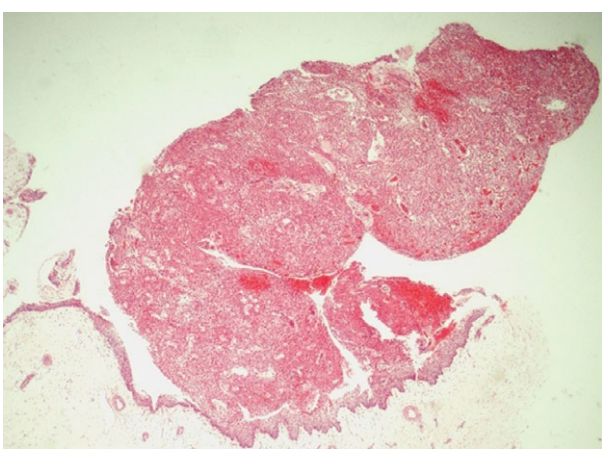

Figure 3 Wall of cyst with luminal proliferation (H&E stain ×40)

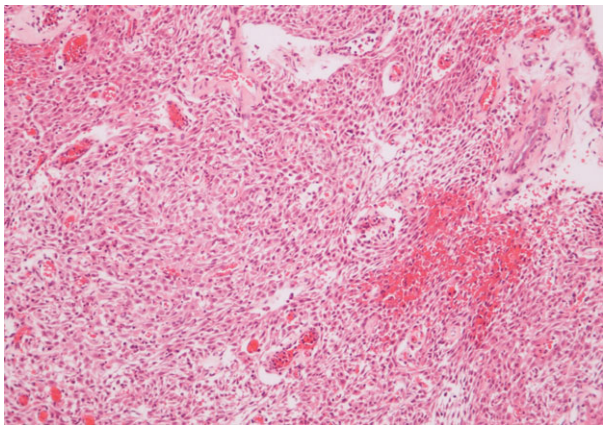

Figure 4 Confluent epithelial proliferation in intraluminal projection admixed with neutrophils and supported by vascular cores (H&E stain ×250)

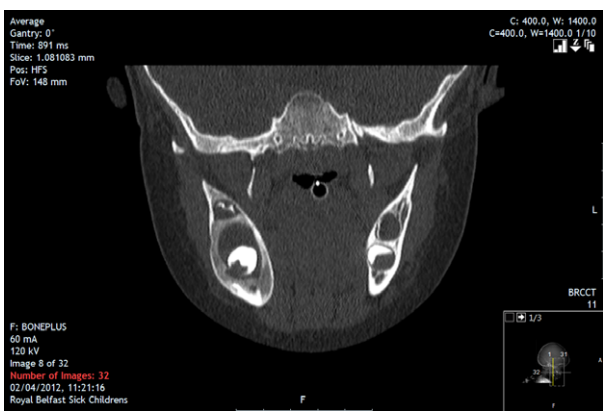

Figure 5 Coronal view of the CT scan 3 months post-operatively

The patient had a baseline magnetic resonance imaging (MRI) scan taken 9 weeks after his second CT scan so that monitoring could be undertaken without exposing the patient to ionising radiation.

Follow-up MRI (no 2) was undertaken 6 months later, 11 months post-operatively, under GA and the ameloblastoma remained intimately related to the lower right first permanent molar with no destruction or cortical expansion. The MRI (no 3) was repeated 9 months later, 20 months post-operatively, under GA and the lesion was no longer visible.

Our most recent MRI (4) was almost 4 years after the patient's original surgery and shows no evidence of recurrence. The patient has also been assessed clinically with the same frequency and shows no clinical signs of recurrence. An OPT taken 57 months post-operatively shows no sign of recurrence and continued dental development (Fig. 6).

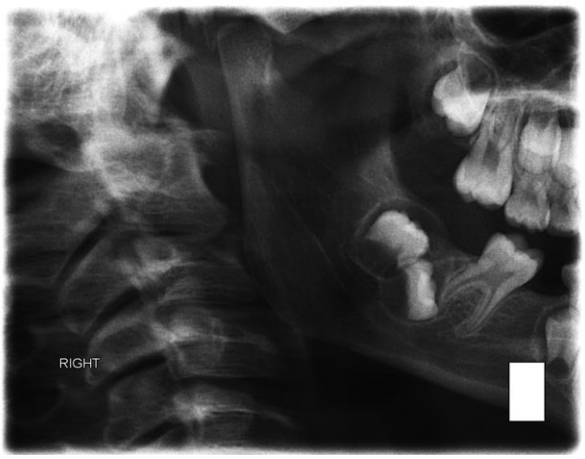

Figure 6 OPT taken 57 months post-operatively

Discussion

Ameloblastomas are benign odontogenic tumours and are classified by the World Health Organisation (WHO) as:

1 Solid/multicystic
2 Extraosseous
3 Desmoplastic
4 Unicystic[3]

The most common subtype is the solid/multicystic, accounting for 81% of ameloblastomas[4]. Unicystic ameloblastomas are the second most common, accounting for around 14%[4]. The WHO further divides unicystic ameloblastomas into different subtypes. These include:

1 Luminal
2 Intraluminal/Plexiform
3 Mural[3]

The luminal form is a cystic lesion with ameloblastomatous epithelium[3]. The intraluminal/plexiform variant has extensions of tumour cells into the cyst cavity[3]. In the mural variant, the cyst wall can be infiltrated by ameloblastomatous epithelium and can show varying degrees of invasion of the surrounding bone[3].

Some studies have shown that it occurs more frequently in males than in females[4,5]. The most commonly involved site was the mandible with the posterior aspect being the most frequently involved subsite[4].

Ameloblastomas most often occur between the ages of 30 and 50 but unicystic ameloblastomas tend to occur in a younger age group[4,6]. There are several ways that ameloblastomas present including with swelling and pain, but many are asymptomatic[4,5].

Solid/multicystic variants are best treated with resection due to their high recurrence rates[4]. Unicystic ameloblastomas have a lower recurrence rate and can be treated conservatively[4].

A systematic review comparing recurrence rates related to various treatments found resection to have the lowest recurrence rate, at 3.6%, followed by marsupialisation with or without a second procedure at 18%[2].

Enucleation alone had the highest recurrence rate of 30.5%[2].

The subtype also has an effect on the recurrence rates. The mural variant of unicystic ameloblastomas has a recurrence rate of 35.7%, while the other variants have a recurrence rate of around 6.7%[7]. In our case, it was decided that even with the comparatively increased recurrence rate compared with resection, marsupialisation was the preferred option given the child's developmental status and histological picture.

Resection of such a large ameloblastoma in a 4-year old would have caused significant morbidity on top of an already complicated syndromic picture. It was very important to make the implications clear to the patient's parents as they would need to bring the patient for reviews to ensure monitoring of the area. To date, through annual reviews both clinically and with MRI, there is no sign of recurrence. The use of non-ionising imaging alongside an improvement in behavioural management with age now means that monitoring with MRI without the need for a GA can occur, and in our hands has proved most useful adjunct to monitoring.

The child's dentition has continued to develop and he is able to function normally.

Cardiofaciocutaneous syndrome has been linked with several different mutations, with BRAF mutations being the most common[1]. The BRAF gene is involved with cell proliferation and this explains other clinical findings, such as hypertrophic cardiomyopathy[1].

Recent research has shown that BRAF mutations occur in 62–70% of ameloblastomas[8–10]. BRAF-associated ameloblastomas tend to occur in younger age groups and mainly in the mandible[9]. BRAF is part of the MAPK pathway which is a cascade that results in activation of transcription factors in the cell nucleus[11]. Other mutations of the MAPK pathway linked with ameloblastoma include KRAS, HRAS, NRAS and FGFR2[9]. Mutations in BRAF are significantly more common than the others, which results in the substitution of the V600E amino acid[9,11]. This case provides a previously unreported link between a recognised syndrome and ameloblastoma development. This is perhaps because of the rarity of cardiofaciocutaneous syndrome, which has only 60 published cases[1].

While BRAF mutations have also been linked with several different forms of cancer, including melanoma, there has been no previously established link between cardiofaciocutaneous syndrome and an increased incidence of tumours[1,12].

In the light of this, clinicians may wish to consider a referral for medical genetics assessment for patients with mandibular ameloblastomas to assess the presence of a mutation and where that mutation lies. This may have an effect on their future health and family planning. It may also provide a target for future therapy as BRAF inhibitors have been used effectively to improve clinical outcomes with melanoma[13]. This is supported by *in vitro* work on the effect of vemurafenib on ameloblastoma cells lines[9]. Vemurafenib was found to inhibit the proliferation of ameloblatoma cells even more profoundly than melanoma cells[9]. These medications may result in less invasive surgery as well as the associated reduction in morbidity. This may help to improve the patients' quality of life, which the profession is using more commonly as the treatment goal.

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