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Case report

Primary aneurysmal bone cyst of the mandibular condyle with USP6-CDH11 fusion

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ABSTRACT

Primary aneurysmal bone cyst (ABC) is a cystic bone neoplasm characterized by disease-defining gene fusions involving the *USP6/Tre2* gene. The literature describing gnathic ABC is limited. This case report describes a 27-year-old man presenting with a long-standing left-sided facial asymmetry. Multi-detector computed tomography imaging demonstrated a large expansile lesion positioned within the left condylar head. The lesion was biopsied and resected. The specimen showed a giant cell-rich cystic neoplasm, with fibrous tissue lined by multinucleated giant cells. Next-generation sequencing confirmed the presence of a *USP6-CDH11* fusion gene, consistent with classification as a primary ABC, the first reported to be translocation-positive in the head of the mandibular condyle.

1. Introduction

Aneurysmal bone cyst (ABC) was originally reported by Van Arsdale in 1893 as an ossifying hematoma. It was renamed in 1942 by Jaffe and Lichenstein, based on its intraosseous and expansile nature [1,2]. ABC is a primary benign neoplasm of bone; however, soft tissue counterparts exist [3]. Secondary ABC is a term used to describe hemorrhagic cystic change that appears histologically identical to the primary ABC, but arises in conjunction with other benign and malignant tumors. Secondary ABC is not considered a neoplasm in itself, as it does not show the characteristic gene fusion. The majority of primary ABCs are observed in individuals younger than 30 years of age, with a slight male predilection reported in the jaws [4,5]. Commonly occurring within the vertebral column and the long bones, such as the femur, tibia, and humerus, ABCs of the gnathic complex are rare and represent approximately one percent of all cases [6,7]. Clinical manifestations include localized swelling which may be associated with pain or pathological fracture. The radiographic appearance is varied and lesions are typically multilocular and radiolucent [8]. Internally, septations may be present and are both wispy and ill-defined. Multi-detector computed tomography (MDCT) and magnetic resonance imaging may demonstrate classic findings of multiple cysts with fluid-fluid levels [9].

Histologically, ABCs are well-circumscribed neoplasms with hemorrhagic cystic spaces separated by fibrous septae [10]. The fibrous septae are composed of spindled fibroblast-like cells that exhibit bland nuclei with mitotic figures, with areas of reactive woven bone. There is significant histological overlap with other gnathic giant cell lesions including central giant cell granuloma (CGCG), cherubism, giant cell tumor of bone, brown tumor of hyperparathyroidism and telangiectatic osteosarcoma.

Cytogenetic abnormalities were identified in primary ABCs in 1999 [11,12]. The chromosomal translocation t(16;17)(q22;p13) was later identified to be gene fusion partners between osteoblast cadherin 11 (*CDH11*) on chromosome 16q22, and ubiquitin-specific protease 6 (*USP6* or *Tre2*) [13]. There are three other reports of gnathic giant cell-containing lesions possessing the *USP6* gene rearrangement [14,15]. Here we report the fourth translocation-positive primary ABC in the jaws, and the first located in the condylar head of the mandible.

2. Clinical presentation and radiographic findings

A 27-year-old male patient with a past medical history of hypothyroidism presented with a three-year history of left-sided facial asymmetry. Clinical examination revealed limited jaw opening,

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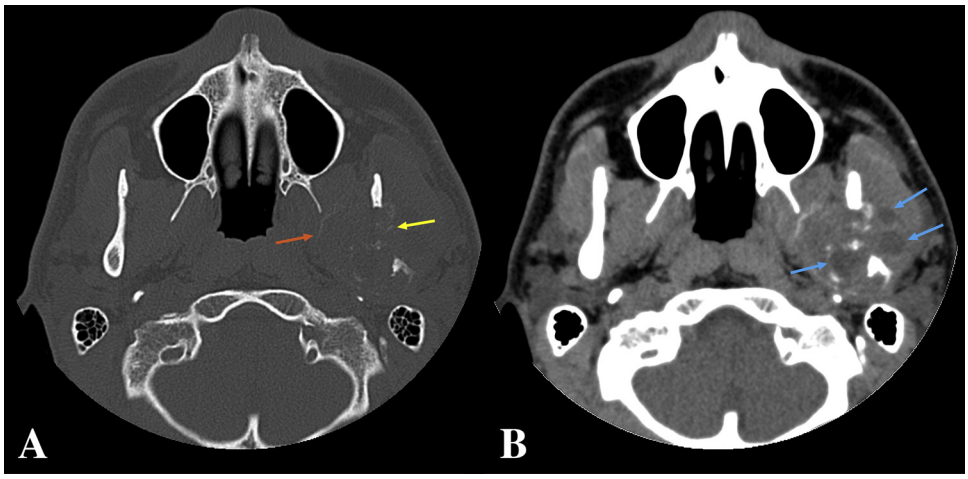

Fig. 1. Axial (A, B) MDCT images in the bone (A) and soft tissue (B) windows demonstrating a large and expansile lesion within the left condylar head possessing a discontinuous granular cortex (orange arrow), internal deposition of granular bone (yellow arrow) and cyst-like spaces (blue arrows). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

paresthesia of the left lower lip, and a firm swelling in the left preauricular region.

Plain film and non-contrast enhanced MDCT imaging revealed a relatively well-defined, heterogeneous and expansile entity positioned within the left mandible (Fig. 1). Internally, delicate granular septations surrounded well-defined low-attenuation regions with an attenuation similar to that of fluid.

3. Diagnosis and treatment

Incisional biopsy showed a cellular and vascular lesion composed of multinucleated giant cells and mononuclear spindled and polygonal cells, with osteoid and hemosiderin deposits (Fig. 2). The diagnosis was central giant cell lesion. Blood calcium and parathyroid hormone levels were subsequently found to be normal, excluding brown tumor of hyperparathyroidism.

The lesion was resected, with placement of a temporary left temporomandibular joint prosthesis. The resection specimen showed blood-filled cystic spaces lined by spindle-shaped cells, and cellular solid areas composed of spindled cells and osteoclast-like multinucleated giant cells (Fig. 3). Reactive basophilic bone and osteoid followed the contours of the fibrous septa. The diagnosis was ABC. Confirmatory FISH testing confirmed the presence of *USP6* rearrangement. Subsequent, NGS testing confirmed the presence of a *USP6-CDH11* fusion gene [16].

4. Discussion

There are thirteen reports of primary ABC arising in the condylar head, and this is the first such case with a documented *USP6-CDH11* fusion gene [14]. Herein we report the fourteenth case of primary ABC, which we confirm by FISH and NGS.

There is a broad differential diagnosis for giant cell rich lesions of the head and neck which includes CGCG, brown tumor of hyperparathyroidism, giant cell tumor, giant cell tumor of low malignant potential, and the giant cell lesions of cherubism and Noonan syndrome. Giant cell-rich lesions can be diagnostically challenging in the context of limited sampling and/or clinical history. Diagnostic imaging in this location is often of limited value. While MRI may be useful in identifying fluid levels within the lesion, these are not diagnostic for ABC.

Accurate classification of these lesions is necessary for their appropriate management. Primary ABCs are typically managed by curettage or enucleation and show a recurrence rate of 10% [10]. CGCGs arising in the jaws are treated with curettage and when treated this way show a recurrence rate of 11–49%, which increases significantly with the aggressive variants of this lesion [17–19]. Giant cell tumor of bone is a locally aggressive neoplasm, most often occurring in the long bones, that has malignant potential. This lesion is normally treated by curettage and has been shown to have a 25% recurrence rate [20]. The driver mutation, *H3F3A*, is present in 92% of giant cell tumor of bone, and allelic losses of 1p, 9q, and 19q in primary, recurrent and metastatic giant cell tumors, respectively [21,22]. The identification of this mutation aids in identifying GCTs. Cherubism is a self-limiting condition characterized by SH3BP2 mutations, which are usually inherited in autosomal dominant fashion. Affected children develop slow bilateral maxillary and mandibular expansion [23]. Similar such bilateral giant cell lesions have been reported in Noonan syndrome [17]. Brown tumor of hyperparathyroidism should always be considered in the differential diagnosis of a giant cell-containing lesion, however serology can easily rule out this entity [23]. The giant cell tumor of soft tissues of low malignant potential histologically resembles the giant cell tumor of bone but its localization within the superficial and deep soft tissues aids in the discrimination of these entities [24]. Therefore, correlation with clinical information, radiographic imaging and the use of molecular investigations is exceedingly important for the accurate histologic diagnosis of giant cell-containing lesions.

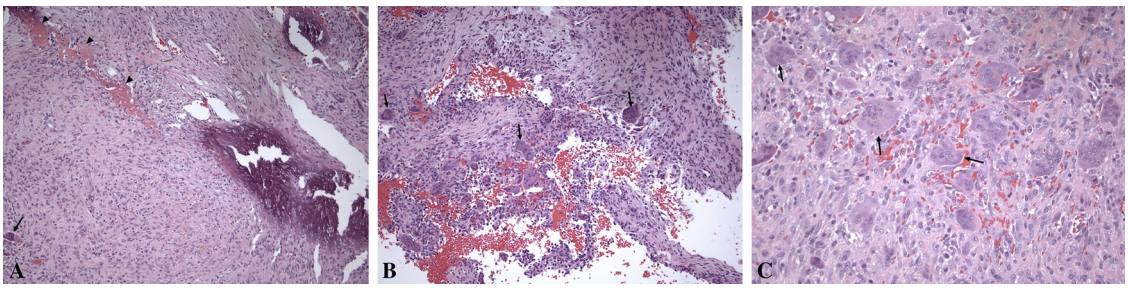

Fig. 2. Incisional biopsy photomicrographs show cellular and vascular mesenchymal stroma with multinucleated giant cells (arrow) with areas of osteoid (arrowhead). (H & E, magnification A:5X, B: 10X, C: 20X).

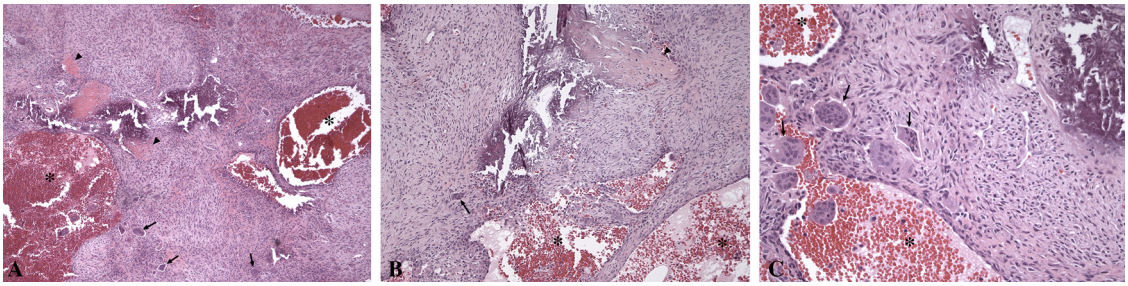

Fig. 3. Resected specimen photomicrographs exhibits blood-filled cyst-like spaces (asterisk) lined by spindle-shaped cells, with basophilic bone and osteoid formation (arrowheads) and solid areas of a cellular spindle cell stroma containing multinucleated giant cells (arrows). (H & E, magnification A: 5X, B: 10X, C: 20X).

An ABC within the region of the mandibular condylar head is exceptionally rare. The presence of a disease-defining translocation can be exploited to facilitate diagnosis. The cytogenetic abnormality in primary ABCs is associated with a gain-of-function translocation of the ubiquitin protease gene *USP6* on chromosome 17p13 (TRE17). The pathogenesis of ABC was challenged when the t(16;17)(q22;p13) translocation was found to be associated with these lesions. The most common fusion partner, *CDH11* on chromosome 16q22, was later identified by fluorescence in situ hybridization (FISH). *TRE17* activates canonical NF-kB independently of IkB phosphorylation and regulates plasma membrane endosomal trafficking and actin remodeling through Rho GTPases, leading to increased cellular invasiveness through effects on cellular motility [25]. Furthermore, *TRE17* may deregulate osteoblastic maturation pathways and upregulate matrix metalloproteinase (MMP)-9 and MMP-10 which may play a role in angiogenesis, inflammation and the degradation of the extracellular matrix thus allowing for rapid lesional expansion [26]. The reversal of protein ubiquitination, a critical step in multiple cellular processes, is catalyzed by a diverse number of enzymes from the multiple families including *USP6/TRE17* from the *USP* family, which is associated with human tumorigenesis [27]. Deubiquinilation and stabilization of Jak1 and subsequent NF-κB-independent STAT3 activation serves as a component of the pathogenic mechanism of the upregulation of USP6 [28].

The *USP6* translocation is not unique to primary ABCs. Entities that possess both the USP6 translocation and multinucleated giant cells include CGCG, also called giant cell reparative granulomas, nodular fasciitis, and cellular fibroma of tendon sheath [29,30]. The CGCG shows a *USP6* translocation when present in the hands and feet, but not in the gnathic structures [31]. While nodular fasciitis and cellular fibroma of tendon sheath both typically occur in very specific sites, they should be considered if the epicentre of the lesion or proximity to the temporomandibular joint is in question. Nodular fasciitis is a self-limited soft tissue lesion that is composed of myofibroblastic cells arranged in a "tissue culture-like" growth pattern. While predominantly composed of spindle cells, nodular fasciitis lesions may contain multinucleated osteoclast-like giant cells [32]. The most common chromosomal translocation breakpoint for this lesion results in promoter swapping of the *USP6* coding and MYH9 promoter regions [33]. The USP6 translocation has also been shown to be positive in the cellular variant of the fibroma of tendon sheath, a benign myofibroblastic neoplasm of the tenosynovial soft tissues [29]. While the fusion partner *MYH9* has not been detected in cellular fibromas of tendon sheath, it is proposed that those with nodular fasciitis-type areas may in fact be a tenosynovial subset of nodular fasciitis. The determination of the fusion partner therefore is useful in elucidation of some lesions bearing *USP6* rearrangements. Several other ABC fusion partners have been identified in addition to *CDH11* and include zinc finger 9 (*ZNF9*), thyroid receptor-associated protein 150 (*TRAP150*), osteomodulin, and collagen 1A1 (*COL1A1*) [34]. These fusion partners result in a similar oncogenic mechanism in that *USP6* is juxtaposed to the promoter region of these genes, thereby driving USP6 transcription.

If the diagnosis is in question, identification of the fusion partner along with obtaining clinical and radiographic information are important to rule out the presence of more rare entities. Furthermore, the identification of a target protein for USP6 may serve as a basis for immunomodulatory therapy against *USP6* translocation-associated neoplasms.

Conflict of interest

The authors do not have any conflicts of interest to declare.

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