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ORIGINAL PAPER

Aneurysmal Bone Cyst of the Maxillary Sinus with *USP6* Rearrangement: Case Report of a Rare Entity and Review of the Literature

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Abstract
Aneurysmal bone cysts (ABCs) are benign lesions which most frequently occur in the long bones of pediatric patients. Long thought to be reactive, recent molecular advances have demonstrated that the majority of primary ABCs harbor rearrangements of the USP6 gene, confirming their neoplastic nature. Secondary ABCs arising from other lesions do not demonstrate this recurrent genetic anomaly. ABCs rarely occur in the craniofacial bones, and sinonasal ABCs are exceedingly rare. We report a case of a primary ABC arising the maxillary sinus of a 14-year-old female, which was found to harbor USP6 rearrangement. We describe the clinical, radiologic, and pathologic features of this case, and review the current literature on craniofacial ABCs. Careful histologic evaluation and genetic studies are warranted in order to confirm the rare occurrence of a primary sinonasal ABC.

Keywords Aneurysmal bone cyst · USP6 rearrangement · Maxillary sinus

Introduction

Primary aneurysmal bone cyst (ABC) is a benign, clonal neoplasm commonly found in the long bones of the extremities in pediatric patients, which can rarely undergo malignant transformation [1, 2]. Only 2% of ABCs occur in the head and neck region, with 66% being found in the mandible or maxilla [3]. ABCs of the sinonasal cavity are exceedingly rare, documented in scattered case reports and literature reviews [1–5]. ABCs arising within the paranasal sinuses appear to affect patients of a wide age range, and exhibit no predilection for either sex [3]. The clinical signs and symptoms are often nonspecific and varied, ranging from asymptomatic lesions to nasal obstruction to anosmia, proptosis, and/or neurologic symptoms [4, 5]. Pain is an uncommon feature of sinonasal ABC, although pain to palpation or passive pain can be present [3–5]. ABCs can arise de novo (primary ABC), or as a degenerative change in the setting of another underlying bony lesion (secondary ABC). Lesions giving rise to secondary ABCs in the head and neck region include cemento-ossifying fibromas [6–8], fibrous dysplasias [9], and giant cell granulomas [10]. While the origin of these lesions was elusive for many years, it is now known that a majority of primary ABCs exhibit a recurrent translocation t(16;17)(q22;p13) leading to fusion of the *CDH11* and *USP6* genes or a variant thereof [11–14], underscoring the neoplastic nature of primary ABCs.

Herein we report a rare case of primary ABC of the maxillary sinus presenting in an adolescent female. The lesion exhibited a characteristic radiographic appearance, and was histologically consistent with ABC. Fluorescent in situ hybridization (FISH) revealed the presence of a *USP6* rearrangement, genetically supporting the diagnosis of primary ABC. The clinical, radiologic, and pathologic characteristics of this unusual lesion are described.

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Case History

The patient was a 14-year-old female with no significant past medical history who was referred to our institution for evaluation of a right maxillary sinus mass. Upon evaluation by a head and neck surgeon, the patient endorsed pain of the right face and jaw, right-sided nasal congestion, right-sided lacrimation, and a long history of headaches that often localized to the posterior right side of her head. She also reported decreased sensation on the right side of her face but denied any recent weight changes or other constitutional symptoms.

Physical exam revealed a palpable, firm, tender mass in the right premaxillary region, directly adjacent to the right maxilla and zygomatic bone. There was decreased sensation in the region of the right V2 cranial nerve. A CT scan was revealed a 3.8 × 3.0 cm irregularly-marginated, expansile mass that encompassed most of the right maxillary sinus. The right orbital floor was elevated secondary to mass effect, and the mass involved the roots of the right lateral maxillary teeth (Fig. 1a, b). An MRI demonstrated a mixed multicystic-and-solid lesion with bony septae, chronic sinus

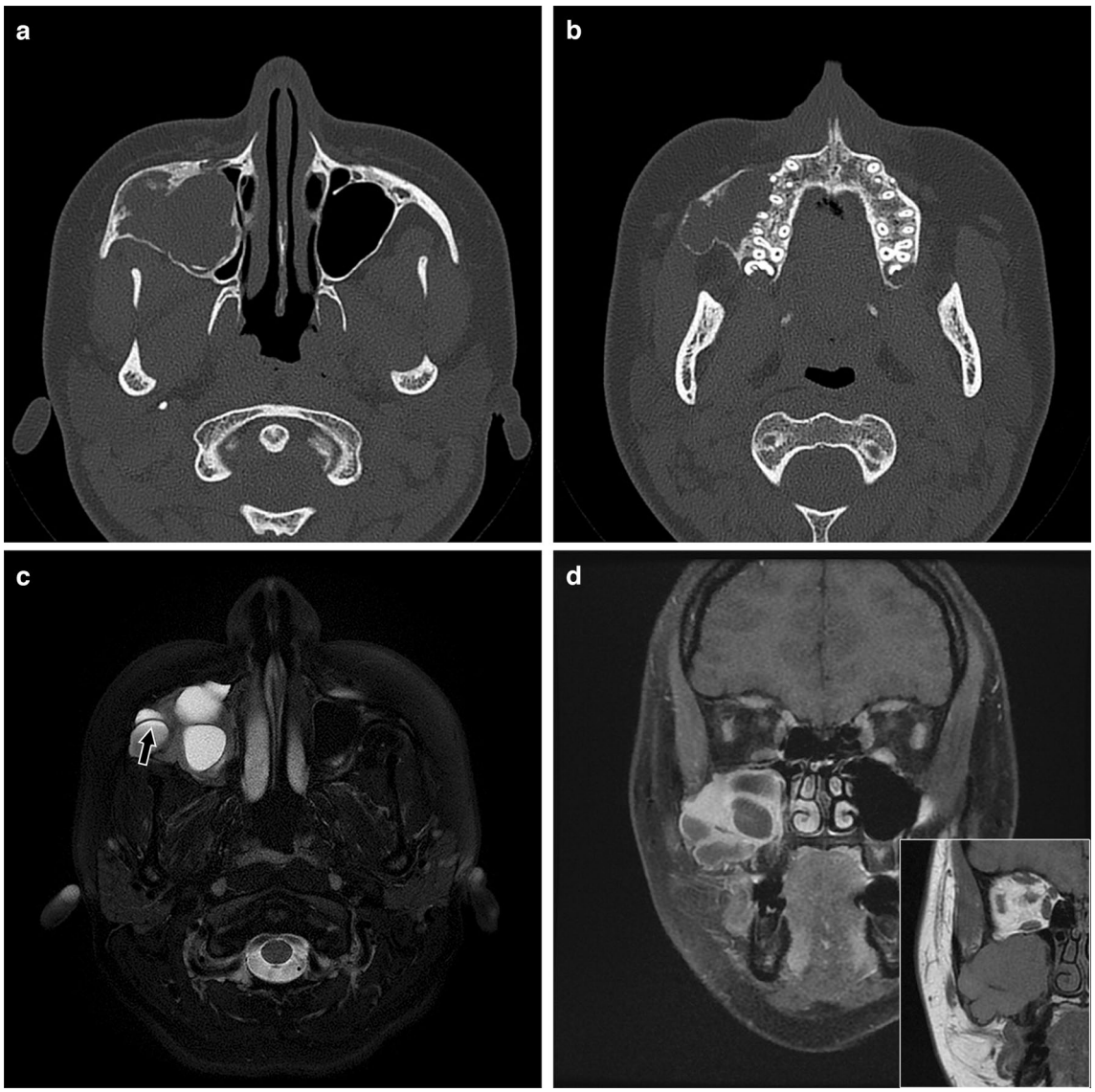

Fig. 1 Representative axial computed tomography images in bone algorithm demonstrating an irregularly-marginated, variably hypo- to hyperdense expansile mass (3.8 × 3.0 cm) involving most of the right maxillary sinus (**a**). There is involvement of the alveolar process of the right maxilla without dental root resorption (**b**). Axial T2-weighted MRI demonstrates a multicystic and solid lesion filling the right maxillary sinus. The cystic components are hyperintense, with a possible fluid-blood level (arrow, **c**). Coronal T1 fat-saturated postcontrast (**d**) and pre-contrast (inset, **d**) images demonstrate the solid components with avid enhancement

expansion, and bone remodeling. The cystic components were T2 hyperintense (Fig. 1c, d). The radiologic differential for the collective findings included giant cell granuloma, Langerhans cell histiocytosis, aneurysmal bone cyst, chronic organized hematoma, allergic fungal sinusitis, and unspecified neoplasm.

An open biopsy of the maxillary lesion was performed under general anesthesia. At gross examination, the tissue was composed of aggregates of red-tan soft tissue admixed with bone fragments. A frozen section demonstrated bland-appearing fibrous tissue with a scant amount of bone and was diagnosed as "inflammatory fibrovascular tissue with no evidence of malignancy." On permanent sections, there were fragments of variably cellular tissue with scattered stromal osteoid deposition (Fig. 2a, b). In occasional areas, plump mononuclear cells were admixed with osteoclast-like giant cells (Fig. 2c). Immunostains for CD1a and Langerin were negative. The majority of the tissue demonstrated bland, spindled to stellate-shaped fibroblasts. Plump to spindled histiocytoid cells were clustered at the tissue edges (consistent with a pseudocyst wall), and a true epithelial or endothelial lining was not identified. Occasional osteoclast-like giant cells were located adjacent to the cyst wall (Fig. 2d). Given the radiologic appearance of a multiloculated expansile lesion in conjunction with the histologic findings, a diagnosis of aneurysmal bone cyst (ABC) was considered. Fluorescence in-situ hybridization (FISH) analysis was performed on a representative 4 micron-thick, formalin-fixed, paraffin-embedded (FFPE) tissue section using a custom *USP6* (17p13) Dual Color, Break Apart Rearrangement Probe as previously described [11]. Strong, well-delineated hybridization signals were independently scored by two individuals

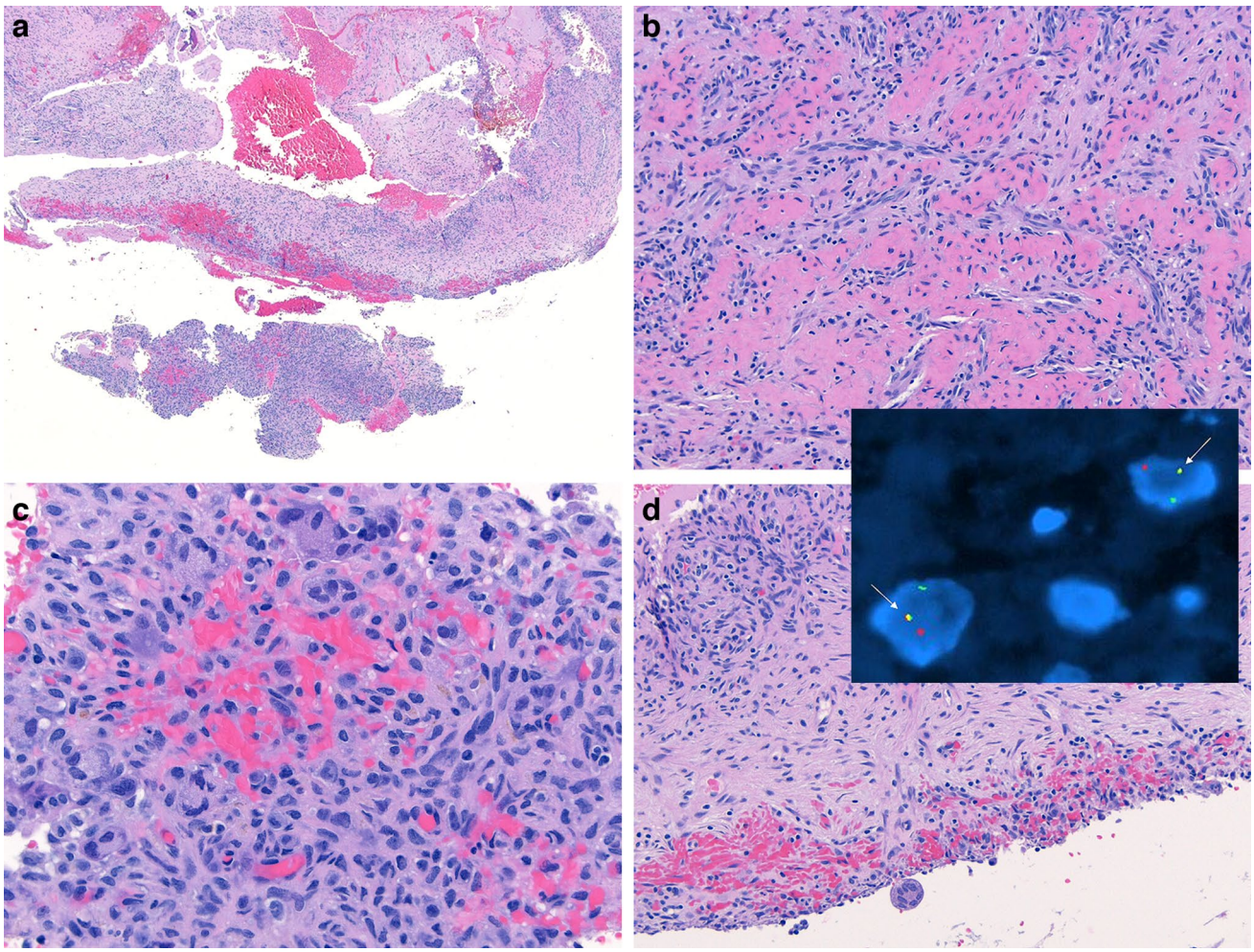

Fig. 2 Representative hematoxylin and eosin stained sections from the initial curettage specimen demonstrate strips of tissue of varying cellularity (**a**). Osteoid and bland spindle cells are seen (**b**) while other areas exhibit osteoclast-like giant cells with plump mononuclear cells and blood (**c**). Focal histiocytoid cells are present at tissue edges with loosely-adherent giant cells (**d**). FISH study (inset, **b** & **d**) reveals lesional cells exhibiting one fused set of orange and green signals per nucleus (arrow) corresponding to a normal 17p *USP6* locus, as well as a pair of split orange and green signals, indicating rearrangement of the *USP6* locus

in 200 interphase nuclei. The specimen was interpreted as abnormal if a split of the normally juxtaposed 5′ and 3′ *USP6* probe signals was detected in greater than 15% of the interphase cells analyzed. Images were acquired by use of the CytoVision Image Analysis System (Applied Imaging, Santa Clara, CA). FISH analysis conducted on the permanent section specimen revealed one set of juxtaposed orange and green signals and one set of distanced orange and green signals (indicative of rearrangement of the *USP6* locus) in 31% of the 200 interphase cells analyzed, confirming the diagnosis of ABC (Fig. 2 inset).

Approximately 1 month following the initial biopsy, the patient presented for definitive resection. Final histologic analysis of the curetted tissue revealed features similar to that seen on initial biopsy, with the addition of solid areas containing spindle cells in a storiform arrangement with admixed blood and osteoclast-like giant cells (Fig. 3). There was no histologic evidence of a precursor lesion. At 2 months following the final resection, the patient was asymptomatic with no clinical or radiologic evidence of recurrence.

Discussion

ABCs are relatively rare lesions which typically present in the first two decades of life, and have a predilection for the long bones. These lesions are often expansile and destructive and can arise either de novo (primary) or in the setting of a precursor lesion (secondary). Occurrence in the head and neck and paranasal sinuses is rare, with mandibular lesions being approximately three-times more frequent than maxillary lesions [3–5]. Despite their rarity in the craniofacial bones, ABCs exhibit radiographic and histologic features similar to those in the long bones [15]. Radiologically, they often present as multiloculated cystic masses, with expansile borders, and typically exhibit a lytic appearance on X-Ray. Periosteal reaction resulting in thinning and "ballooning" of the cortex are common findings. By CT scan or MRI, fluid–fluid levels may be appreciated, and these modalities may additionally suggest an underlying lesion associated with the ABC [15]. Fibrous septations can often be identified radiologically, which are classically oriented perpendicular to the cortex and exhibit enhancement after administration of contrast. Although radiologic features of ABC are often characteristic, they may overlap with a number of other lesions, including malignancies such as telangiectatic osteosarcoma. Therefore, pathologic examination is required to confirm the diagnosis, even in cases where the radiologic and clinical features are suggestive.

Gross findings of ABCs are often non-specific. They typically exhibit a well-circumscribed edge, and may contain hemorrhage, thrombi, or multiple fibrous septations of varying thickness. Microscopically, ABCs may exhibit features approximating granulation tissue or reactive fibrosis. Key features that aid in the diagnosis are cystic spaces not lined by endothelium, and fibrous septae containing bland spindle cells. It is not uncommon for the spindle cell population to be mitotically active, but they should not exhibit atypical mitoses. Osteoclast-like giant cells are usually present within the fibrous septae and at the tissue edges toward the lumen of the cyst, but are not uniformly distributed and may not be present in scant specimens such as biopsies. Their presence, however, is extremely suggestive of ABC. There may be focal osteoid formation, which should prompt exclusion of osteosarcoma. Aside from expression of histiocyte markers in giant cells, SMA in spindled fibroblasts/myofibroblasts, and occasional p63 in mononuclear cells, immunostains are not specific [16, 17].

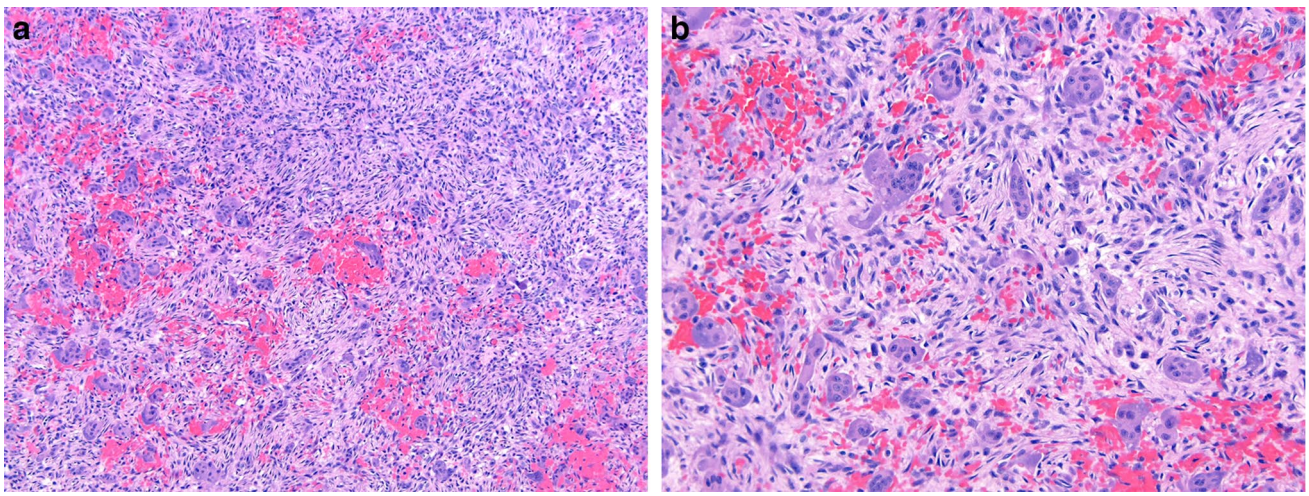

Fig. 3 Representative hematoxylin and eosin stained sections from the subsequent surgical resection specimen demonstrating increased solid areas with a storiform arrangement of spindle cells (**a**) with admixed hemorrhage and irregularly-dispersed osteoclast-like giant cells (**b**)

The histopathologic differential diagnosis primarily includes giant cell granuloma (GCG) and telangiectatic osteosarcoma (TO). GCG are lobulated lesions composed of osteoclast-like giant cells within a bland spindle-cell background with associated areas of hemorrhage and hemosiderin deposition. They can mimic the solid component of ABC, however, they are not usually cystic. On biopsy specimens, ABCs are typically cystic, and the solid portions tend to exhibit more prominent woven bone trabeculae, with less hemorrhage compared to GCGs. GCGs tend to have sporadic genetic mutations and lack the *USP6* rearrangement characteristic of ABCs. Many cases of would-be GCGs located in the hands and feet exhibit *USP6* rearrangements and are best classified as solid ABCs [14]. TO can exhibit cystic spaces and fibrous septae, mimicking ABC both grossly and histologically. However, significant atypia within the spindle cell population (nuclear enlargement, hyperchromasia, increased mitoses, atypical mitoses) as well as malignant cells within osteoid support TO over ABC.

To date, only three prior examples of *USP6*-rearranged ABCs of the craniofacial bones have been reported: one in the ethmoid and maxillary sinus of a 24-year-old female [13], one in the orbit of a 27-year-old female [14], and one in the temporal bone of a 54-year-old female [14]. Fusion partners for *USP6* include *CDH11* (the most common), which results in overexpression of the *TRE17* oncogene [18]. Additional variant translocation partners include *ZNF9* (Zinc-finger 9), *COL1A1* (Collagen 1A1), *TRAP150* (Thyroid Receptor Associated Protein 150), and *OMD* (Osteomodulin) [18]. Heterogenous genomic pathways can be involved, but the common aberration among most ABCs is *USP6*. Only rare cases show rearrangement of CDH11 without USP6, or lack of rearrangement [12]. Demonstration of *USP6* rearrangement should be used to confirm the diagnosis in cases where histology may be inconclusive. To date, *USP6* rearrangements have been described in nodular fasciitis and ABC, and have not been reported in TO, GCG, chondroblastoma, or other lesions entering the differential diagnosis [11–15].

Conclusion

While ABCs may have characteristic clinical and radiologic presentations, they may occasionally present in atypical sites such as craniofacial bones and may present a diagnostic challenge. Careful review of the clinical and radiologic characteristics, combined with thorough pathologic evaluation (including genetic studies), is required for definitive diagnosis. *USP6* rearrangement associated with primary ABC can be used to confirm the diagnosis in suggestive cases.

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