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Inflammatory Pseudotumor and/or Xanthoma Involving The Maxilla And Maxillary Sinus: An Unusual Case Report

Case Report

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Abstract

Fibro inflammatory pseudotumors are histologically benign, locally destructive lesions composed of fibrovascular tissue admixed with chronic inflammatory cells. They are unencapsulated mass-like aggregates of myofibroblastic spindle cells and inflammatory cells including both B-cell and T- cell lymphocytes. Xanthomas are soft tissue benign lesions, commonly seen involving the skin or over subcutaneous tissue of tendon sheaths and extensor surfaces following minor trauma or friction.
In this article, we report an unusual and interesting case which reported to our institute, in which the incisional and excisional biopsy and immunohistochemistry analysis showed varying results. In our patient, the incisional biopsy and ImmunoHistochemistry gave the impression of a Low Grade Spindle Cell tumor with features suggestive of Myofibroblastic tumor/ Inflammatory pseudo tumor. After reviewing literature and understanding the high incidence of recurrences in patients with IPT, a more aggressive approach was implemented (surgical excision with margins). The post-operative histopathology and immunohistochemistry identified the lesion as a Xanthoma (positive for CD68 and foamy histiocytes).

Keywords: Pseudotumor; Xanthoma; Myofibroblastictumor; Inflammatory Pseudotumor; Xanthomatosis; Head And Neck.

Introduction

Fibroinflammatorypseudotumors are defined as histologically benign, locally destructive lesions composed of fibrovascular tissue admixed with chronic inflammatory cells [1]. They are benign unencapsulated mass-like aggregates of myofibroblastic spindle cells and inflammatory cells including both B-cell and T- cell lymphocytes. They have been reported in virtually any tissue or organ in the body, the orbit and lungs, being the most commonly affected. First characterized by Brunn in 1939, the clinical presentation and imaging appearances of IPT can mimic other benign conditions including menangiomas, xanthomas and granulomatous diseases, such as sarcoidosis [2]. Alternatively, IPT's pose a diagnostic and therapeutic dilemma as they can be aggressive and mimic malignancies such as lymphomas, fibrosarcomas and metastases. Therefore, their diagnosis is ambiguous and a cause of confusion, requiring further elaboration.

Xanthomas are soft tissue benign lesions, commonly seen involving the skin or over subcutaneous tissue of tendon sheaths and extensor surfaces following minor trauma or friction. It most frequently occurs in patients with endocrine and metabolic diseases. Xanthoma is derived from the Greek xantho´s, which means yellow, and is related to the altered metabolism of lipids and the accumulation of yellow pigment in skin and other internal organs [3].

Histiocytic diseases have been divided into Langerhans cell related histiocytic disease (LCH) and non-Langerhans histiocytic processes. The xanthoma is a non-Langerhans histiocytic process and is characterized microscopically by lipid-containing macrophages,

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or foam cells.

The primary xanthoma of bone is extremely rare, and when present is often secondary to hyperlipidemia type II or III or diabetes mellitus. When systemic metabolic disease and lipid disease are ruled out, the bony lesion is termed primary xanthoma of bone. Only a few more than a handful of cases have been reported in literature.

However, lesions have been described in the axial and appendicular bones in patients with and without hyperlipidemia. Xanthomatosis is a term used for multiple bone lesions and for xanthomas with accompanying soft tissue involvement [4].

In this article, we report an unusual and interesting case which reported to our institute, in which the incisional and excisional (post-operative) biopsy and immunohistochemistry analysis showed varying results.

Case History

A 40 year old male patient reported to our institute with a swelling on the right side of the face since 5 days. The swelling developed 2 months back following an upper molar extraction (17) and continued to grow progressively to its current size. On examination, the swelling was extending from the infraorbital region to the imaginary line joining the angle of the mouth to the tragus of the ear superoinferiorly and 2 cm posterior to the commissure of the lip to the tragus, anteroposteriorly. The swelling was soft in consistency, non-fluctuant and tender on palpation with evidence of local rise in temperature [Fig 1].

Intraorally, there was vestibular obliteration in Upper Right Buccal Vestibule from the 14-18 region and unhealed socket in the region of the extracted right upper second molar.

CT Maxilla revealed a large peripherally enhancing hypodense lesion measuring 3.1 x 3.2 cm occupying the right maxillary sinus, mildly expanding it. There was erosion of the right posterolateral wall of the maxillary sinus with lesion extending into the right infratemporal fossa and buccal spaces. The lesion erodes into the alveolar process of maxilla uptoperiapical region of right upper 2nd and 3rd molar tooth. Sinusitis of the ethmoidal and left frontal sinuses was evident [Fig 2].

An incisional biopsy and ImmunoHistochemistry gave the impression of a Low Grade Spindle Cell tumor with features suggestive of Myofibroblastic tumor/Inflammatory pseudo tumor (positive for ALK and p53 desmin).

As per literature, a sub-total maxillectomy of the lesion followed by reconstruction using a split thickness skin graft and surgical obturator was planned and carried out under general anesthesia [Fig 3,4].

The specimen was sent for post-operative histopathology and immunohistochemistry which identified the lesion as a Xanthoma (positive for CD68 and foamy histiocytes) or a Cholestrol granuloma pending investigations (lipid and cholesterol profile) to rule out Hyperlipidemia and paraproteinemia.

Discussion

The term "inflammatory pseudotumor" was coined by Umiker et al. in 1954 who described four inflammatory tumors of the lung simulating xanthoma, fibroma, or plasma cell tumor.

IPT has been most commonly reported in lungs, but it is uncommon in the head and neck region. Orbital pseudotumor most commonly occurring with head and neck lesions, can be localized or diffuse and can affect any position of the orbit but is typically unilateral rather than bilateral [5].

The most critical feature of IP on pathologic exam is the presence of spindle cells, plasma cells, and lymphocytes. Fibroblasts, myofibroblasts, histiocytes, and inflammatory infiltrate may also

Figure 1.

Figure 2.

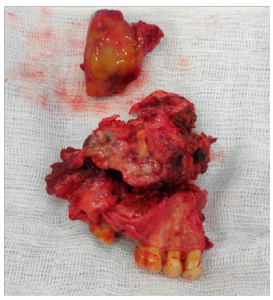

Figure 3.

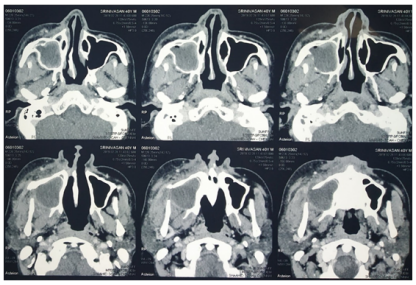

Figure 4.

be present. In a literature review of 84 cases of IPs, three basic patterns were recognized: (a) myxoid, vascular, and inflammatory; (b) spindle cells with lymphocytes and plasma cells; and (c) dense collagenous type resembling scar tissue. However, as opposed to hematologic malignancy, mitotic figures and necrosis are usually absent [6].

There are a variety of disease entities noted within the spectrum of Pseudotumors. IgG4 sclerosing disease is one such subtype that involves lymphocytes, IgG4-positive plasma cells, and fibrosis. This has been reported in several sites in the head and neck and has a favorable response to corticosteroids if diagnosed early [2].

Other disease subtypes within the umbrella of IP include benign tumors such as calcifying fibrous tumors as well as inflammatory myofibroblastic tumor (IMT). More aggressive and malignant tumors with similar histopathologic features include IMT-like dedifferentiated liposarcoma and Epstein–Barr virus (EBV)-associated IP-like follicular dendritic cell tumor. Numerous studies have attempted to characterize and prognosticate these IP subsets.

Con et al. showed that half of IMTs express cytoplasmic anaplastic lymphoma kinase (ALK), a receptor tyrosine kinase. All patients with metastatic IMTs were ALK negative. Furthermore, nuclear expression of p53 occurred in 80% of IMTs, but only in 25% of the metastatic subset. As a result, ALK and p53 expression may predict a favorable prognosis. On the other hand, presence of ganglion-like cells, aneuploidy, and perinuclear ALK expression portend a more aggressive course. Infection, trauma, and foreign bodies are among the numerous etiologies that may be involved in the pathogenesis of IP [7].

Organisms such as mycobacteria, Rhodococcusequi, Klebsiellarhinoscleromatis and Actinomycetemcomitans have been shown to cause IPs.

The main treatment regimens of IMT include surgery, glucocorticoids, chemotherapy, and radiotherapy, which were used alone or in combination empirically. Approximately 80% of IPs respond to corticosteroid treatment but there is a 50 to 60% chance of disease recurrence. Maintenance-dose corticosteroids are recommended for at least six months to prevent recurrence of disease. Patients unresponsive to systemic corticosteroids may benefit from intralesional steroids. A favorable response with corticosteroids is seen especially in IPs that are predominated by lymphocytes and plasma cells.

Alternative treatments include radiotherapy, small molecule inhibitors, and Igs. In a clinical trial involving orbital pseudotumors, 75% of patients responded to radiotherapy treatment. Small molecule inhibitors have shown results in small subsets of patients. For example, rituximab is a chimeric antiCD20 antibody that provoked a sustained response in a recurrent IP of the mandible. Crizotinib, an ALK inhibitor, induced a partial response in a patient with ALK-translocated inflammatory myofibroblastictumor [2].

A xanthoma is a rare soft tissue and bone condition consisting of a predominant collection of lipid-rich foamy histiocytes. Increasingly, the central xanthoma of the jaw bones is being recognized as an entity with features unique enough to warrant separation from conditions such as the benign fibrous histiocytoma (BFH) and non-ossifying fibroma (NOF), with which it is often confused. In all 29 cases of central xanthoma of the jaw bones reported so far there has no association with any other bony or soft tissue lesions. Also, from the available data, none of the patients had hyperlipidemia and no myofibroblasticcomponent [4].

There is considerable confusion concerning the diagnosis of an unusual lesion of the jaws dominated by xanthoma cells. The various diagnoses, usually related to somewhat similar lesions of other bones, have different treatment protocols, leading to an increased risk of inappropriate treatment for some patients.

It is unclear whether the central xanthoma of the jaws is a benign, low-grade neoplastic process or a persistent, reactive process. Fac-

tors favoring a benign neoplastic process are the apparent spontaneous occurrence in the absence of trauma, infections, or precipitating systemic diseases. It may be infiltrative within marrow spaces. The lesion is capable of considerable destruction of the jaw and may cause bony expansion. It usually occurs in adults in a wide age range. There is a male predilection, and most lesions occur in the mandible. The lesion is treated with curettage, and recurrence has not as yet been reported. Spontaneous resolution has not yet been observed.

Most authors support a reactive or inflammatory process despite the clinical features. Factors favoring a reactive lesion are the presence of inflammatory cells, hemorrhage or hemosiderin, potential for reactive bone, and occasional cholesterol granulomas.

A case reported by Mosby et al. was specifically tested for serum cholesterol and triglycerides levels, which were found to be normal. This evidence suggested that the source of the lipid was not via the bloodstream, as suggested by Weiss and Goldblum, in soft tissue xanthomas. The source of the lipid remains unknown, and the possibility that the macrophages may produce lipids internally has not been disproven.

Immunohistochemical results indicate that the foamy cells are activated macrophages (CD68- and HLA-DRepositive staining). The activation may be secondary to lymphokine stimulation, but alternatively, the presence of inflammatory cells may be directly and/or indirectly secondary to cytokines produced by the foamy cells (e.g., interleukin 1, tumor necrosis factor-a, interleukin 6).

The central xanthoma of the jaws is characterized primarily by a proliferation of histiocytes that may be accompanied with a mild inflammatory cellular infiltrate. Based on the sampling of tissue, these findings are seen in a diverse list of conditions including periapical inflammatory lesions, benign fibrous histiocytoma, non-ossifying fibroma of bone, and fibrous dysplasia. Foamy histiocytes also populate intrabony lesions of lipid reticuloendotheliosis. Cases of Langerhans cell histiocytosis and Rosai-Dorfman disease also show a proliferation of histiocytic cells. Cases of a rare bone condition with histiocytes, Erdheim-Chester disease of the jaw bones have also been described. Therefore, a diagnosis of a central xanthoma of the jaw bones is challenging and requires elimination of the aforementioned conditions. This process of elimination requires careful assessment of the clinical, radiographic, and histopathological findings in each case individually.

Periapical inflammatory conditions such as granulomas and cysts may show a variable presence of foamy histiocytes. Periapical cysts show an epithelial lining and both cysts and granulomas may show the presence of a rich inflammatory cellular infiltrate that may also contain plasma cells, Russell bodies, pyronine bodies, neutrophils, eosinophils and mast cells. Cholesterol clefts and cholesterol granuloma formation with multinucleated foreign body giant cells may also be seen frequently as would pieces of root canal filling material. Also, these lesions are associated with non-vital teeth secondary to trauma or dental caries or with failing endodontically treated teeth [13].

CD68 positive histiocytes may be seen in both the benign fibrous histiocytoma (BFH) and the non-ossifying fibroma (NOF). The BFH is the intrabony counterpart of the more common soft tissue BFH. Most cases are diagnosed from the 4th to the 8th decade of life. The ilium and the ribs are the most frequently affected bones in the body. Pain is the most frequent presenting symptom at these locations [2].

Jaw lesions may or may not be painful but show progressive expansion of the posterior mandible including the angle and ramus. Histopathologically, the foam cells are usually seen in small focal clusters and the dominant microscopic appearance is of a spindle cell proliferation arranged in whorls and storiform fascicles [8, 9]. Thick collagen band entrapment and multinucleated giant cells are almost always seen. Hemorrhage and hemosiderin pigment may also be found [8, 9]. However, rare jaw lesions present as expansile, asymptomatic radiolucencies with a sclerotic border [10]. The histopathological appearance is identical to that of the BFH. The predominant cells are fibroblastic spindle cells arranged in a storiform pattern with interspersed giant cells. Foamy histiocytes are seen in small clusters [10]. Hemorrhage and hemosiderin pigment with aneurysmal bone cyst-like areas may also be seen. Absence of a whorling or a storiform fascicular spindle cell population, multinucleated giant cells and thick collagen band entrapment and presence of sheets of xanthoma cells rather than small focal clusters of foamy histiocytes distinguishes the central xanthoma of the jaw bones from the BFH and the NOF.

In fibrous dysplasia, depending on the biopsy sampling, a sheet-like infiltrate of foamy histiocytes may be seen. This is a secondary change that may be accompanied by giant cells, hemorrhage, and myxoid areas. These changes occur in association with an expansile lesion that in the craniofacial bones tends to be radiopaque with a ground glass appearance. A biopsy of the more opaque bone tends to show the characteristic woven bone within cellular fibrous connective tissue. The woven bone shows a haphazard pattern of mineralization under polarized light microscopy [2].

Sheets of lipid filled histiocytes are seen in the bone marrow of lipid reticuloendotheliosis such as Gaucher and Niemann-Pick disease. These rare inherited disorders are mostly encountered in the Ashkenazi Jewish population. In Gaucher disease, the histiocytes show abundant bluish cytoplasm whose texture resembles wrinkled silk. These cells replace the bone marrow resulting in anemia and thrombocytopenia. Patients show growth retardation, painful bone infarcts, hepatosplenomegaly, and bone deformities [2]. The “sea blue” histiocyte is the predominant cell type seen in Niemann-Pick disease. Patients present with hepatosplenomegaly and neurologic features. Life expectancy is limited to the first two decades, especially in the neuronopathic form of the disease [13]. Therefore, correlation of the histopathological findings with the clinical presentation easily distinguishes these conditions from the primary xanthoma of the jaw bones.

Posterior mandibular radiolucencies with a well-demarcated border are the presenting jaw lesions in Langerhans cell histiocytosis. The cell that defines this process is the Langerhans cell histiocyte with an abundant eosinophilic cytoplasm containing a kidney bean or coffee bean shaped indented nucleus. When seen ‘face on’, the nucleus shows a prominent linear groove across its length. Sheets of these cells are admixed with other macrophages, lymphocytes and a rich population of eosinophils. The eosinophils may be focally plentiful producing the so called eosinophilic abscesses. The Langerhans cell histiocyte demonstrates a highly specific reactivity to CD207 (langerin). Rarely, demonstration of the Birbeck-Broadbent granules by electron microscopy may be

required to confirm the diagnosis [11].

In addition to macrophage markers CD68 and CD163, the large foamy histiocytes of Rosai-Dorfman disease are also reactive to S100 protein. Their cytoplasm shows vacuoles containing unaltered leukocytes (emperipolesis or lymphophagocytosis). Phagocytosed plasma cells, red blood cells and neutrophils may also be seen within such intracytoplasmic vacuoles [11, 12]. The phagocytosed cells are conspicuous because they are S100 negative [12].

Rare cases of Erdheim-Chester disease of the jaws have been described. Sheets of foamy histiocytes with a finely granular cytoplasm are associated with bone trabeculae in this disorder. Occasional multinucleated giant cells may be seen. The histiocytes express macrophage markers CD68 and CD163 and are negative to S100 protein and Langerhans cell markers. Rare cases may show admixed clusters of Langerhans cells. Erdheim-Chester disease is a multi-system condition affecting mostly adult males who present with bilateral lower appendicular long bone pain. Other common systemic findings include diabetes insipidus, neurologic symptoms, exophthalmos, and a retroperitoneal mass. Virtually any organ may be affected. 100 % of cases express a BRAF V600E mutation [13].

In our patient, the incisional biopsy and ImmunoHistochemistry gave the impression of a Low Grade Spindle Cell tumor with features suggestive of Myofibroblastic tumor/ Inflammatory pseudo tumor. After reviewing literature and understanding the high incidence of recurrences in patients with IPT, a more aggressive approach was advocated and implemented (surgical excision with margins). The post-operative histopathology and immunohistochemistry identified the lesion as a Xanthoma (positive for CD68 and foamy histiocytes).

As per the Atlas of Orthopedic Pathology, Over 50 % of the central xanthomas of the jaw bones occur in the 2nd and 3rd decades of life while the highest relative incidence of extragnathicxanthomas and xanthomatosis is in the 4th to 6th decades of life.

1. Central xanthomas of the jaw bones have a 9:1 predilection for the mandible over the maxilla.
2. Lesions affect males and females equally while the extragnathicxanthomas and xanthomatosis are predominantly a male disorder with a male to female ratio of 2:1.
3. Xanthomas of both primary and secondary hyperlipidemia, hypercholesterolemia and systemic lipid diseases have distinct reported mechanism and etiology. The intrabonyxanthomas reported with hyperlipidosis also have a genetic mutation of the Low Density Lipoprotein Receptor. The central xanthoma of the jaw bones is not associated with a systemic lipid disorder and the hypothetical lipid leakage from the vascularity into the surrounding tissue is therefore not expected in these individuals.
4. Lesions contain sheets of xanthoma cells with little fibrous tissue.
5. There is no history of trauma, infection or other preexisting intrabony pathology.

In addition, the following findings might suggest that the central xanthoma of the jaw bones is an aggressive or neoplastic process that is distinct from the extragnathic lesions including those associated with xanthomatosis.

6. The growth is progressive and when large enough to be associated with teeth, causes splaying and resorption of roots. The inferior dental canal is also displaced.
7. It causes significant bone destruction, cortical perforation and extension into surrounding structures.

Conclusion

Xanthomas and Inflammatory pseudotumors are rare pathologies of the head and neck. The histopathological traits to differentiate between the two are clear but the process of elimination to reach a conclusive diagnosis requires careful assessment of the clinical, radiographic, and histopathological findings in each case individually.The treatment for Xanthoma is generally more conservative.

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