Case Report

Unusual presentation of primary central xanthoma of the maxilla associated with impacted canine: An update on immunohistochemistry in the diagnosis

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Abstract

A xanthoma is an extremely rare condition that affects the soft tissues and bones and is characterized by a predominance of lipid-rich foamy histiocytes. The onset of xanthomas is frequently accompanied by primary or secondary hyperlipidemia. Primary bone xanthomas are very uncommon benign bone lesions that are not linked to hyperlipidemia. Histopathologically, they are distinguished by histiocytes, an abundance of foam cells or xanthoma cells that contain lipids, and a paucity of multinucleated giant cells. There have only been four reports of primary maxillary xanthoma in the medical literature. We present a rare primary intrabony xanthoma of the anterior maxilla in a 23-year-old normolipidemic female patient with solitary radiolucency. Using CD68, S-100, and CD1a immunohistochemical staining, it is possible to distinguish between macrophage/non-Langerhans histiocytes and Langerhans histiocytes. Therefore, a diagnosis of a central xanthoma of the jaws must be made.

Keywords: Bone, CD68, foamy histiocytes, maxilla, non-Langerhans histiocyte, xanthoma

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INTRODUCTION

Xanthomas are benign soft tissue lesions commonly found in the epidermis or over the subcutaneous tissue of tendon sheaths and extensor surfaces due to trauma or friction. Bone xanthomas are rare, are often accompanied by skin symptoms, and are associated with endocrine or metabolic disorders, including hyperlipoproteinemia, hyperlipidemia, and diabetes mellitus; consequently, they are referred to as reactive or metabolic lesions. The primary xanthoma is extremely uncommon when there are no underlying systemic diseases.[1,2]

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The word "xanthoma," which means yellow in Greek, is associated with abnormal lipid metabolism and the deposition of yellow pigment in the skin and other internal organs. Langerhans cell-related histiocytic disease (LCH) and non-Langerhans histiocytic diseases are two categories of histiocytic diseases. The xanthoma is a non-Langlenhans histiocytic condition distinguished microscopically by macrophages, or foam cells containing lipids.[3] In 1988, Harsanyi and Larsson described the first well-documented series of seven cases involving the mandible, which were dominated microscopically by xanthomatous cells in fibrous

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connective tissue.[4] We present a case of central xanthoma in a 23-year-old female patient. This case represents the clinical, biochemical, radiographic, histopathological, and immunohistochemical studies of a lesion associated with an impacted canine.

CASE REPORT

A 23-year-old female patient complains of swelling and mild pain in the right upper anterior region of the maxilla for two months with no history of notable local trauma or prior medical or surgical history. The extraoral examination showed an expansion of the right face in the area of the anterior maxilla. There was no facial paralysis or paraesthesia. On intraoral examination, the patient presents with swelling from the central incisor to the first premolar on the free gingiva to the labial sulcus, which also extends from the incisor canal to the mid-palatine region. A retained deciduous tooth was present, and all teeth were vital.

Cone beam computed tomography (CBCT) showed an enlarged lesion measuring 1.5 × 1 × 1.4 cm, along with an impacted permanent canine. The roots of the first premolar and the lateral incisors were minimally displaced. The buccal and lingual cortical borders of the lesion were eroded, and the buccal plate showed slight expansion and thinning [Figure 1].

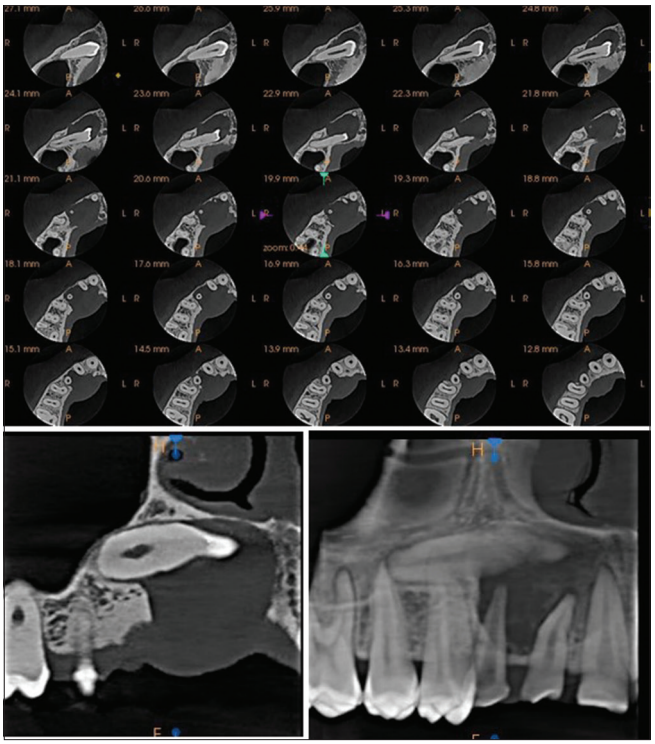

Figure 1: CT shows a well-defined, circumscribed, and low-density lesion at the right anterior maxilla with impacted teeth and mild displacement of the first premolar and lateral incisor

Under local anesthesia, the buccal cortical plate widow was created, and a tissue specimen was removed using a bone curette and bone gauge. Clinical examination revealed yellow "granules" in the cancellous bone. The biopsy specimen, preserved in 10% formalin, was sent for a histologic investigation and diagnosis. Histologic examination showed connective tissue devoid of epithelium. Connective tissue is composed of histiocytic cells and chronic inflammatory cells infiltrating a background of loose fibrous connective tissue [Figure 2]. High-power examination demonstrated an abundance of foam cells or xanthoma cells which were demarcated on the cell border with eosinophilic granular cytoplasm and small hyperchromatic nuclei [Figure 3]. Immunohistochemistry showed diffusely significant cytoplasmic positivity of the histiocytes with the CD68 antibody and negative immunostaining with the S-100 and CD1a antibodies, efficiently eradicating Langerhans histiocytic diseases [Figure 4]. These results were consistent with xanthoma.

The biopsy site was healed without any complications. The patient was referred to her general physician for an evaluation of hyperlipidemia. Amylase, vitamin D, hemoglobin A1C, and the total lipid profile (total cholesterol, LDL, HDL, and cholesterol triglycerides) were all within normal ranges. A physical examination found no other xanthomatous lesions in other body regions.

Based on the diagnosis, an impacted canine and pathologic lesion were removed, and no additional therapy was provided. The patient visited the hospital every 6 months following surgery for 2 years to rule out any recurrence or complications.

DISCUSSION

The term "secondary xanthoma" is used to describe xanthomatous lesions of the skin, subcutis, and tendon sheaths that are frequently linked to abnormalities of lipid storage or metabolism.[3] The other diseases, like Vitamin D deficiency, hyperlipidemia, chronic cholestasis, primary biliary cirrhosis, hypothyroidism, lipoprotein lipase deficiency, and Noonan syndrome, are all associated with CX of the jaw.[5] They frequently indicate that there is an alteration in biochemical values like bilirubin, serum alkaline phosphatase, AST, and ALT[6] and associate with the abnormal metabolism of lipids, cholesterol, or glucose.[7] Primary intraosseous xanthoma or primary central xanthoma (PCX) of the gnathic bones is rare, but common in the axial and appendicular bone and are not associated with lipid disorders, as listed in the Table 1.

Table 1: Central xanthoma cases in maxilla in the literature

Year	Etiology	Age	Sex	Symptom	Radiographic feature	Treatment
2017	No etiology	48	Male	• Painless swelling at anterior maxilla • Bone resorption with mobile teeth • Swelling extends from premolar root to the left pterygomaxillary fissure	Radiolucency with diffuse border	Curettage
2017	No etiology	58	Female	• Swelling with pain at left maxilla	Unilocular radiolucency with diffuse border	Curettage
2015	Unknown	48	Male	• Pain with swelling at anterior maxilla • Labial bone perforation	Radiolucency with labial bone perforation	Curettage
2010	Unknown	66	Female	• Cystic lesion in the left anterior region of the maxilla	Radiolucency with demarcated border	Surgical excision

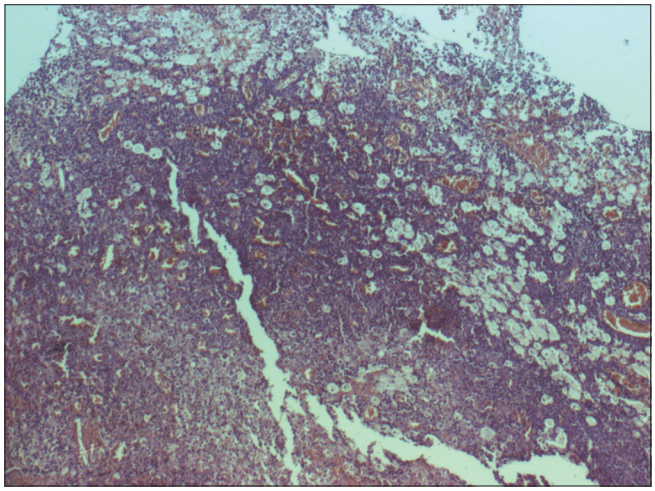

Figure 2: Low power magnification (100×) HE stained tissue section showing numerous xanthoma cells in a background of loose fibrous stroma

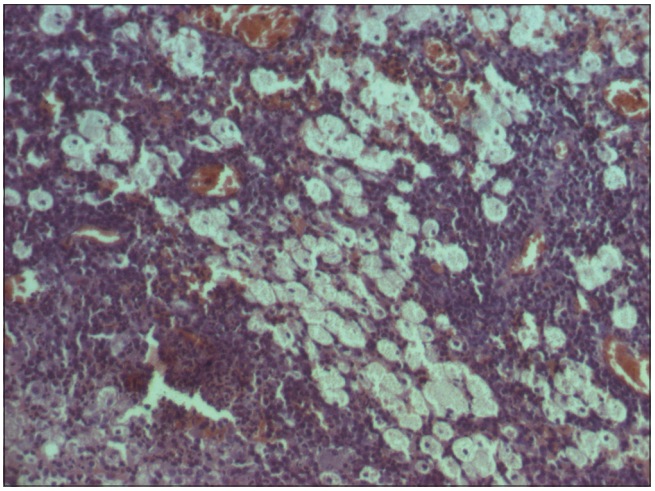

Figure 3: High magnification (450×) HE stained tissue section demonstrating the abundant xanthoma cells showing distinct cytoplasmic membranes with granular cytoplasm and small, hyperchromatic nuclei

There are various hypotheses regarding the pathophysiology of xanthoma. Whether the xanthoma is a benign neoplastic process or a reactive process is a controversial issue. According to one hypothesis, lipid leakage from arteries occurs after local trauma or hemorrhage. Foam cells are formed histologically by lipid accumulation within macrophages, and extracellular cholesterol crystallizes in clefts.[3] Minor trauma could be the etiology involved in the development of xanthomas.[1,7] Dahlin proposed that the lesion is secondary to a pre-existing pathology such as fibrous dysplasia, aneurysmal bone cysts, simple bone cysts, idiopathic bone cavities, giant cell tumors, or brown tumors of hyperparathyroidism.[1,3] However, few authors suggested that there is no history of trauma, infection, or other pre-existing intraosseous pathologies.[2] Weiss and Goldblum suggested that the bloodstream was the source of the lipid in soft tissue xanthoma.[2,8] Another theory suggests the xanthomatous transformation of undifferentiated mesenchymal cells by lipotrophic factors in the blood in patients with autoimmune conditions.[3] Few authors identified the genetic mutation among intrabony xanthomas reported to have hyperlipidosis. Alternately, the existence of inflammatory cells may be directly and/or indirectly secondary to the cytokines released by the foamy cells. The activation of foamy cells may be secondary to lymphokine stimulation (e.g., interleukin 1, tumor necrosis factor-a, interleukin-6).[9] So, according to Tom Daley *et al*., central xanthoma of the jaws is a benign, gradually progressive lesion of activated macrophages with foamy cytoplasm. The lesion has the potential to penetrate the marrow spaces and damage the jaw, which may lead to bone destruction.[10]

Intraosseous xanthoma has been widely documented at any age from 20 to 70 years[2] but is uncommon in children.[3] The majority of those were reported in the second and third decades, but maxillary central xanthoma first manifested in the fifth and sixth decades of life.[2] There does not appear to be a gender bias; however, some literature indicates that males are more affected when the male-to-female ratio is 2:1.[2] However, our present case report shows the second decade of female patients.

The hand, temporal bone, pelvic bones, rib, skull, and vertebrae are the areas where the lesion most commonly develops. The ratio of mandibular to maxillary xanthoma of the jaw bones is 9:1.[2,3,7] Pain is a rare finding in documented mandibular xanthoma, although it is present in

up to 60% of non-gnathic bone xanthomas.[3] The maxillary xanthoma shows variable degrees of pain with an expansive osteolytic process.[2,6] In our present case report, there was swelling with pain in the maxilla.

The radiographic appearance that was described in the cases that had previously been documented varied greatly. The radiographic appearance may be diffuse with small, well-demarcated, or poorly defined radiolucency and areas of increased density. In the osteolytic regions, calcifications or thin, opaque foci have been observed. As in the previously described case, the lesion could enlarge the cortices and, when lytic, may resemble a malignant process.[2,3] Computed tomography shows the absence of the typical trabecular pattern, and the lesion may have a higher density than the normal bone marrow. Using magnetic resonance imaging shows mixed hypo- and hyper-intensity.[3] These features are also present in primary or metastatic malignant neoplasms, early-stage fibro-osseous disease of the jaw, and odontogenic cysts and tumors.[11] Because of its rarity, nonspecific radiological characteristics, and abnormal radiological appearance, xanthoma is difficult to detect by imaging findings.

Histopathologically, sheets of histiocytes and lipid-containing macrophages, foam cells, or xanthoma cells are occasional multinucleated giant cells in the fibrous connective tissue. These xanthoma cells have a well-defined cell membrane with granular cytoplasm and hyperchromatic nuclei. Cholesterol clefts may or may not be present. Occasional intralesional hemorrhage with inflammatory cells is seen.[2] On immunohistochemistry, positive staining for CD68 and CD163, negative staining for S100, CD1a, and CD207, and minimal inflammation are seen in the central xanthoma of the jaws.[2] All the features are inconsistent with our case. The histological differential diagnosis of central xanthoma is considered to exclude other diseases, such as Langerhans cell histiocytosis, non-ossifying fibroma (NOF), and benign fibrous histiocytoma (BFH), as mentioned in Table 2.[7]

After the diagnosis of intrabony xanthoma, a comprehensive clinical and hematological investigation is required to rule out systemic endocrine or metabolic disorders. A lipid profile, an amylase test, blood chemistry, and hemoglobin A1c are the main hematologic tests.[3]

If the lesion is a secondary xanthoma caused by hyperlipidemia, the patient must be on medication and on a restricted diet. After treating the hyperlipidemia, the lesion will resolve.[3] The line of treatment for primary intraosseous xanthoma of the jaw is treated with curettage,

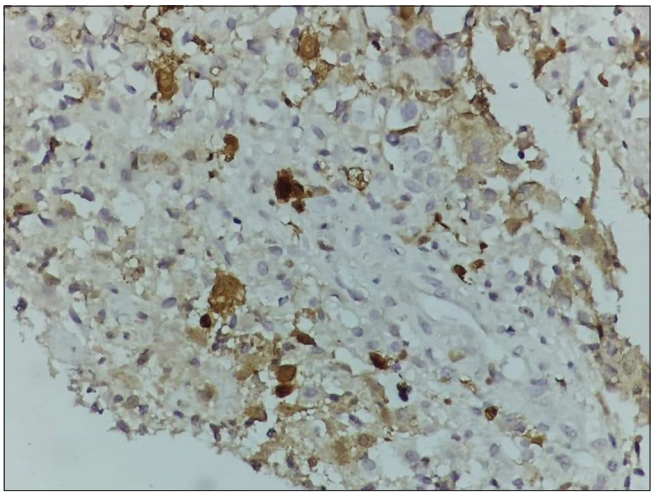

Figure 4: Xanthoma cells exhibiting strong positive CD68 IHC staining and negative for S-100 and CD1a IHC staining

Table 2: Differential diagnosis for central xanthoma

Features	Langerhans cell histiocytosis (LCH)	Non-ossifying fibroma (NOF)	Benign fibrous histiocytoma (BFH)	Xanthoma
Clinical findings	• Seen in younger age • Both jaws affected • Mobile teeth	• Common in children and teens • Asymptomatic expansile lesion	• 4th to the 8th decade of life • Pain • progressive expansion of the posterior mandible	• Occur at any age group with no sex predilection
Radiographic findings	Punched out or floating in air appearance	Multilocular radiolucency with a sclerotic border	Radiolucency with irregular sclerotic margins	Small unilocular radiolucent with sclerotic border to diffuse border
Histopathology	• Histiocytic cell which shows Birbeck granule granules • Eosinophils • Necrosis • Giant cell	• Focal clusters of foamy histiocytes • Fibroblastic spindle cells arranged in a whorling or a storiform pattern • Multinucleated giant cells, • Thick collagen band	• Foam cells are seen in small focal clusters • spindle cell proliferation arranged in whorls and storiform fascicles • Thick collagen band	• Presence of sheets of xanthoma cells • Loose connective tissue
Immunohisto chemistry	Positive for S-100 and CD1a	positive for CD68	positive for CD68	Positive for CD68, CD163, and negative for S-100, CD1a, CD207
Treatment	Surgical excision, Radiotherapy chemotherapy	Surgical excision	Curettage Surgical excision	Curettage
Prognosis	Good	Good	Good	Good

and a complete excision can be performed. Radiotherapy and chemotherapy are not recommended because xanthoma is not considered a neoplasm. The prognosis of central xanthoma of the jaw is satisfactory without any recurrence or complications.[3] However, in a few cases, the recurrence was observed due to incomplete removal of the lesion, inadequate treatment, or an unidentified causative agent.[2,11] In our case, the primary intraosseous xanthoma was treated by surgical curettage along with the removal of the impacted canine, and follow-up was done every 6 months for 2 years.

Debatable on the central xanthoma

It is unknown whether central jaw xanthoma is a benign, neoplastic, or reactive process. Indeed, the apparent spontaneous development and progressive and infiltrative growth with bony destruction of the lesion in the absence of trauma, infection, or other systemic disease are factors favoring benign neoplastic progression. The presence of inflammatory cells, hemorrhage or hemosiderin, the potential for reactive bone, and the occasional presence of cholesterol granulomas are factors that favor a reactive lesion.[10]

We proposed the following criteria to diagnose the central xanthoma of the jaws:

- CX can occur in any age group with no sex predilection.
- Histopathologically, the lesion should show foamy cells or xanthoma cells in fibrous connective tissue.
- Positive for CD68, CD163, and negative for S-100, CD1a, and CD207 IHC staining.

CONCLUSION

Primary intraosseous xanthomas are uncommon and typically not linked to metabolic or endocrine disorders. It is challenging to diagnose xanthoma due to its rarity, non-specific clinical features, and radiological appearance. Therefore, histopathologic and immunohistochemical studies are necessary to provide a final diagnosis and serve as a critical diagnostic tool.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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