Central xanthoma of the jaws: a clinicopathologic entity?

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Objective. To investigate central lesions of the jaws dominated by foamy macrophages (foam cells), which are interpreted to be "central xanthomas of the jaws" and to differentiate this condition from reported cases of jaw nonossifying fibroma/fibrous cortical defect and benign fibrous histiocytoma of bone.
Study Design. The study is a literature review and a retrospective analysis of clinical, radiographic, microscopic, and immunohistochemical features of five new cases of this condition.
Results. The lesion has a predilection for the mandible in adults of variable ages, with the potential to become very large and destructive; however, it has a very low recurrence rate, if any, following surgical curettage.
Conclusion. We suggest that the "central xanthoma of the jaws" be considered a unique, although rare, clinicopathologic entity. It is unclear whether this lesion is a benign neoplastic process or a persistent reactive process. (Oral Surg Oral Med Oral Pathol Oral Radiol 2015;119:92-100)

In 1988, Harsanyi and Larsson[1] described seven mandibular lesions, dominated microscopically by xanthoma cells (foam cells) with supporting fibrous tissue, which were observed for 1 to 18 years in patients ranging in age from 12 to 72 years (mean: 25.4 years). None of the patients had lipidoses or glycogen storage diseases, and all lesions involved only the mandible. In all cases, the disease persisted, some with considerable, but slow, progression and bone destruction. Rudy and Scheingold[2] reported a solitary "xanthogranuloma" involving the right body and ramus of the mandible in a 49-year-old female with uncontrolled diabetes and considered it a unique pathologic entity. Mosby et al.[3] described a 28-year-old healthy male with a cystic lesion of the left posterior mandible, which was diagnosed as "xanthoma of bone." Slootweg et al.[4] described a "xanthomatous lesion of the mandible" in a 49-year-old man and ruled out benign fibrous histiocytoma (BFH) and nonossifying fibroma (NOF) because of bone formation in their case, which they interpreted to be an inflammatory, reactive lesion. Mateo et al.,[5] published a report of an expanding "primary mandibular bone xanthoma," which occurred in an otherwise healthy 11-year-old patient (gender not stated). Ramos-Perez et al.[6] reported a 2-cm "primary xanthoma of the mandible" in the left posterior mandible of a 25-year-old healthy male.

Similar lesions of the jaw bones containing more than occasional clusters of xanthoma cells have been diagnosed as NOF (fibrous cortical defect or metaphyseal fibrous defect). The two cases reported by Elzay et al.[7] in the left mandibles of two 11-year-old girls appear, from their illustrations, to be identical to the xanthoma of bone. The second case described by Abdelsayed et al.[8] in the mandible of a 27-year-old male as the "xanthic" variant of NOF appears to be a xanthoma of bone. The case reported by Bowers et al.[9] in the mandibular ramus of a 22-year-old female contained a significant proportion of xanthoma cells, and no storiform fibrous component was illustrated. It also appears to be a xanthoma of bone. However, other cases reported to contain more fibrous tissue with a storiform pattern and fewer xanthoma cells appear to be NOFs,[8,10-13] especially those occurring in young children.[11,12]

Further complicating the issue is the fact that NOF is considered microscopically identical to BFH of bone, including the presence of clustered or scattered xanthoma cells. The two conditions must be differentiated

Statement of Clinical Relevance

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. This article addresses these problems and makes recommendations for a consistent diagnosis by defining the lesion as a unique entity, which hopefully would lead to improved patient management.

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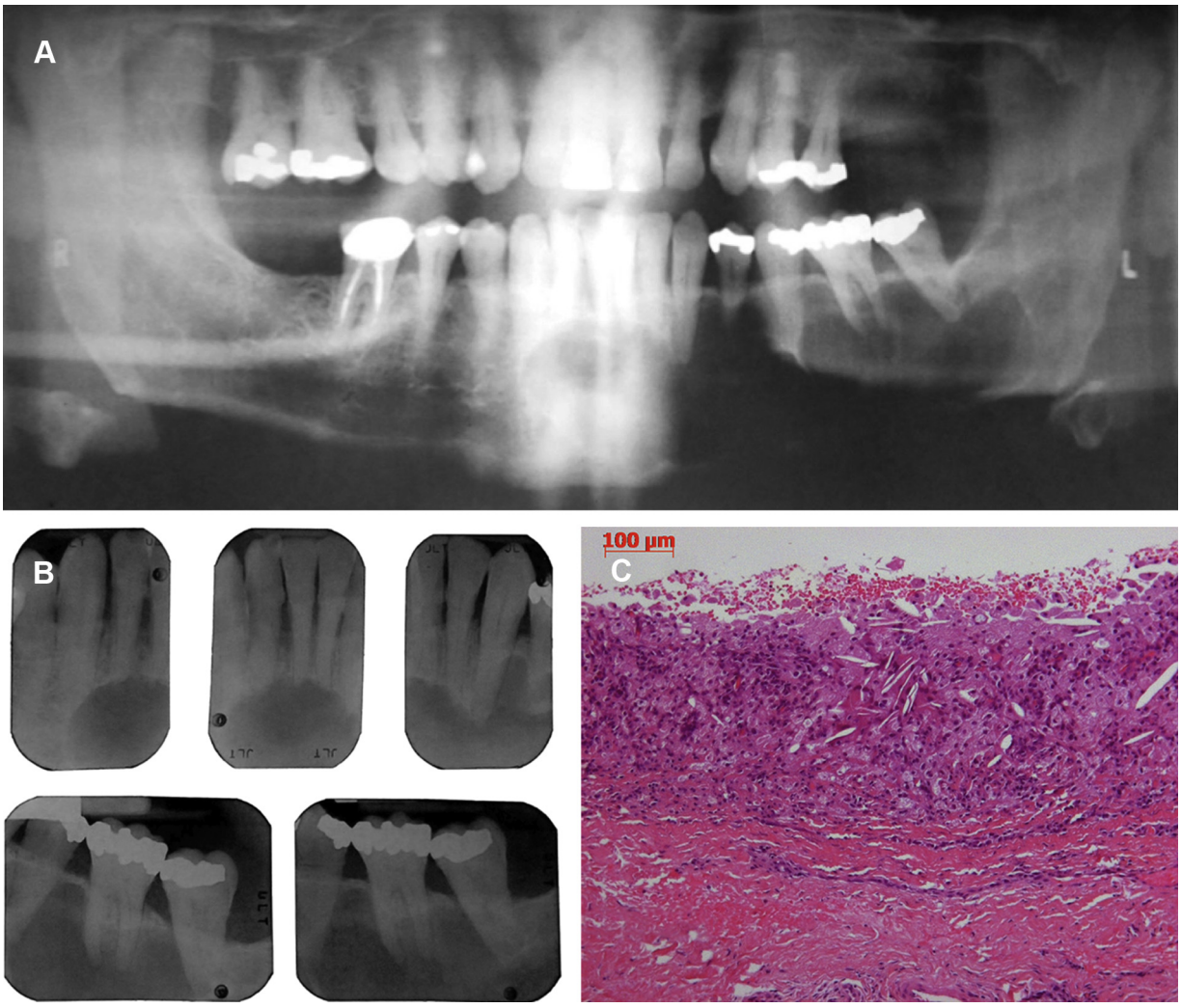

Fig. 1. (Case 1) **A**, Panoramic radiograph showing a large scalloped radiolucency of the central and left mandible. **B**, Periapical radiographs showing radiolucency scalloping between the roots of the mandibular molars resembling a traumatic bone cyst. **C**, Sheets of foamy macrophages with some scattered lymphocytes and plasma cells dominating the lesion. Typical giant cells were seen only associated with cholesterol clefts. Fibrous stroma was often seen, but never with a storiform pattern. (H&E; magnification as illustrated). A high-resolution version of the image is available as eSlide: VM00392.

on the basis of clinical and radiographic features.[14,15] BFHs of bone have been reported in the mandible,[16-19] although foam cells were not the dominant feature described or illustrated.

The objectives of this paper are (1) to describe five new cases of the central xanthoma of the jaws and (2) to compare the clinicopathologic features of these and other similar published cases with the known clinicopathologic features of NOF or BFH of bone in an attempt to determine if the central xanthoma of the jaws is a distinct clinicopathologic entity.

MATERIAL AND METHODS

The files of the Oral Pathology Diagnostic Service, University of Western Ontario/Western University, were searched for examples of intrabony lesions diagnosed as intrabony xanthomatous lesions for the 10-year period between 2003 and 2012 (both inclusive). Five micron hematoxylin and eosin (H&E)–stained tissue sections were reviewed by two of the authors (TD and MD), along with clinical, radiographic, and surgical data to confirm the diagnosis. Routine immunohistochemical staining was performed on 5-micron tissue sections for CD68, CD34, CD1a, and HLA-DR, using mouse antihuman monoclonal antibodies, and S100, using rabbit polyclonal antibodies (all from Dako Canada, Inc., Burlington, Ontario, Canada) in all cases. Follow-up data were sought for all cases. Ethics approval was obtained from Western University.

Table I. Clinical, radiographic, treatment and follow-up features of five cases of central xanthoma of the jaws

Case	*Age*	*Gender*	*Site*	*Radiographic features*	*Clinical*	*Treatment*	*Follow-up information*
1	56	M	Central and left body of mandible	Scalloped radiolucency 11 × 3.5 cm (Figure 1, A and B)	Buccal expansion Teeth vital Some numbness of left lower lip	Curettage Teeth not removed	NED at 2 years
2	24	M	Mandible at left cuspid root mesial–apical area	Radiolucency 2 × 2 cm, corticated	Tooth vital, unrestored No pain No expansion of bone	Curettage, tooth not removed	NED at 6 years
3	47	M	Left posterior mandible	3 × 2 cm radiolucency	Second molar had previous RCT. No pain, no expansion of bone	Curettage, teeth removed	NED at 5.5 years
4	48	M	Anterior maxilla at central incisors with bone expansion and perforation labially	Radiolucency, labial plate perforation	Central incisors were vital	Curettage Teeth not removed	Lost to follow-up
5	22	M	Right posterior mandibular body	radiolucency	Teeth vital except for RCT on the first molar, 10 years previously No pain and no numbness of the lower lip No expansion of bone	Curettage Teeth not removed	NED at 1 year.

M, male; *RCT*, root canal therapy; *NED*, no evidence of disease.

RESULTS

Five (0.01%) primary xanthomas of the jaws were diagnosed from a total of 51,382 accessions. None of the five patients had a history of systemic lipidosis, glycogen storage disease, or Erdheim-Chester disease. All lesions were monostotic at the time of diagnosis. The radiographic appearance was variable, consisting of nonspecific radiolucencies. Most lesions were larger than 2 cm in greatest dimension, with the largest extending through the central and left body of the mandible (case 1) (Figure 1, A and B). All lesions were reported to be painless. There were no dental symptoms, and all associated teeth were vital, with the exception of root canal–treated teeth: left mandibular second permanent molar in case 3 and right mandibular first permanent molar in case 5. The patients ranged in age from 22 to 56 years with an average age of 39.4 years. All lesions were treated with surgical curettage, and no recurrence was reported in follow-up periods ranging from 1 to 6 years (average: 3.6 years). Table I lists the salient clinical and treatment data.

The microscopic appearances of all lesions (Table II) were similar. The dominant feature was the presence of sheets of foamy cells with abundant cytoplasm and small hyperchromatic nuclei (Figure 1, C; Figures 2-5), sometimes clustered with surrounding fibrous tissue, which was always devoid of the characteristic storiform pattern seen in NOF and BFH. Foreign body–type giant cells were present in one case, associated focally with cholesterol clefts. There were occasional multinucleated cells with foamy cytoplasm in four of the five lesions. Recent hemorrhage, possibly surgical, was found in four cases, and hemosiderin was found in case 5. Case 2 was infiltrative between bony trabeculae (Figure 2), but the other four lesions were at least partially encapsulated. Complete encapsulation could not be assessed because of the fragmented nature of the specimens. Chronic inflammatory cells, such as lymphocytes and plasma cells, were usually seen and were sometimes a prominent feature.

Immunohistochemistry (Table II) showed that the xanthoma cells were activated macrophages (CD68 and HLA-DR positive) (Figures 6 and 7). The lack of S100 staining indicated that they were not fat cells, and the lack of S100 and CD1a staining indicated that they were not Langerhans cells.

DISCUSSION

Is the central xanthoma of the jaw a distinct entity?

Is the central xanthoma of the jaws a unique entity or simply a variant of NOF or BFH? All of these lesions are characterized by fibrous tissue, xanthoma cells, and inflammatory cells. Considerable confusion exists in the literature concerning these overlapping entities.[1-13,16-19]

Table II. Microscopic (H&E) and immunohistochemical staining features of five cases of central xanthoma of the jaws

Feature	*Case 1 (Figure 1, C)*	*Case 2 (Figure 2)*	*Case 3 (Figure 3)*	*Case 4 (Figure 4)*	*Case 5 (Figure 5)*
Sheets of xanthoma cells	++++	++++	++++	++++	++++
Fibrous tissue	++	+	++	++	+
Storiform pattern	No	No	No	No	No
Nonfoamy giant cells	+ With cholesterol granuloma	No	No	No	No
Lymphocytes and plasma cells	+++	+	++	+++	+++
Reactive bone	+ Focally	+++	No	No	+
Hemorrhage/hemosiderin	+	No	+	+	+
CD 68 cytoplasmic staining in xanthoma cells (Figure 6)	+++ Granular	++ Granular	++ Granular	++ Granular	++ Granular
S100, nonneural cells	+ Scattered	+ Scattered	+ Scattered	+ Scattered	None
CD 1a	+ Scattered	None	None	None	+ Scattered
CD 34	Vascular only	Vascular only	Vascular only	Vascular only	Vascular only
HLA-DR cytoplasmic staining in xanthoma cells (Figure 7)	+++	+++	+++	++++	++++

no/none: Feature not seen.
+: Occasionally found.
++: Few found.
+++: Moderate presence.
++++: Dominant feature.

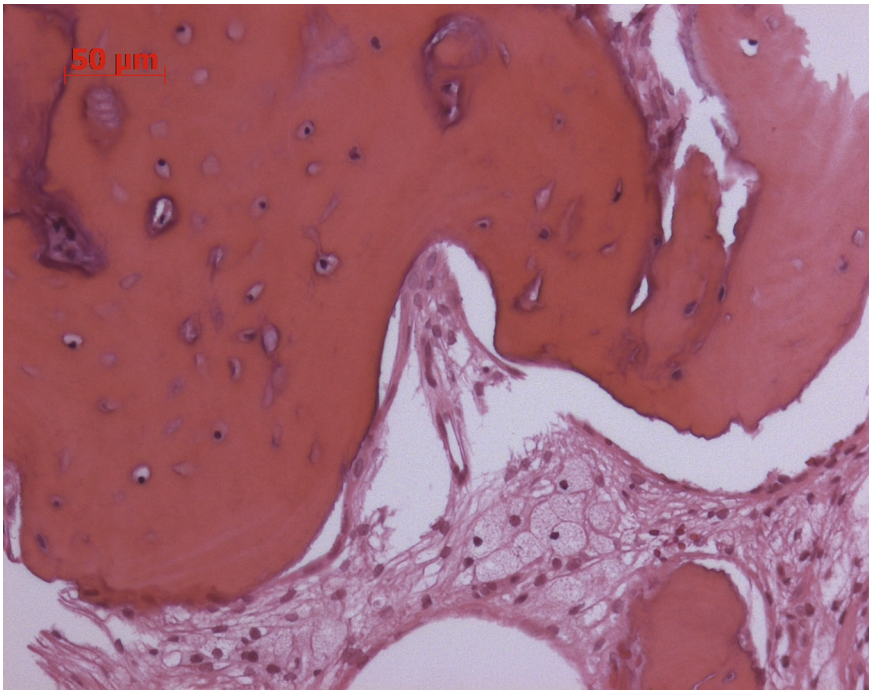

Fig. 2. (Case 2) Foamy macrophages are seen between trabeculae of bone in this case. (H&E; magnification as illustrated). A high-resolution version of the image is available as eSlide: VM00393.

For example, Harsanyi and Larsson[1] believed their lesions to be, paradoxically, a reactive form of fibrous histiocytoma, but Kishino et al.[19] disagreed, stating that Harsanyi and Larsson's cases were not BFHs. Abdelsayed et al.[8] considered his xanthomatous lesion simply to be one end of the spectrum of microscopic features of an NOF, apparently unaware of the xanthoma's biologic behavior. We suggest that central xanthoma of the jaws is a unique entity on the basis of the following criteria:

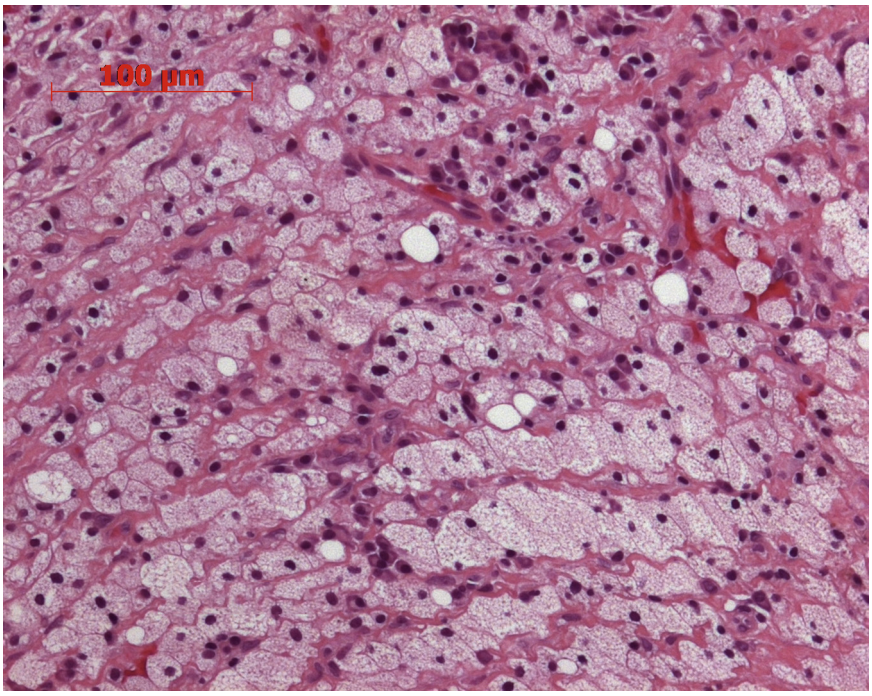

Fig. 3. (Case 3) The foam cells exhibited distinct cytoplasmic membranes and small, hyperchromatic nuclei. (H&E; magnification as illustrated). A high-resolution version of the image is available as eSlide: VM00394.

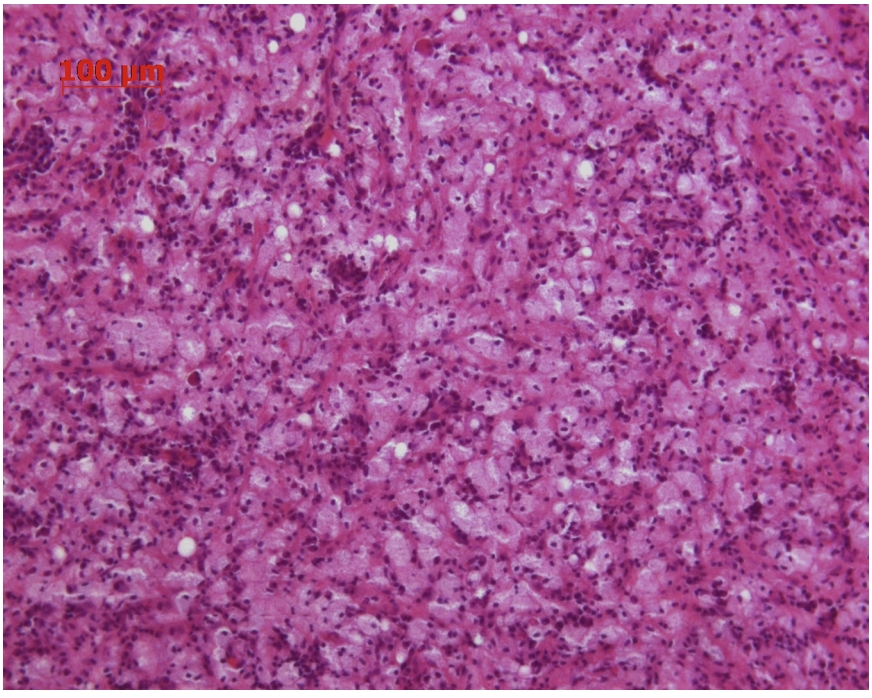

Fig. 4. (Case 4) Inflammation was always present, but variable in quantity. This case had a moderate amount mostly of lymphocytes. (H&E; magnification as illustrated). A high-resolution version of the image is available as eSlide: VM00395.

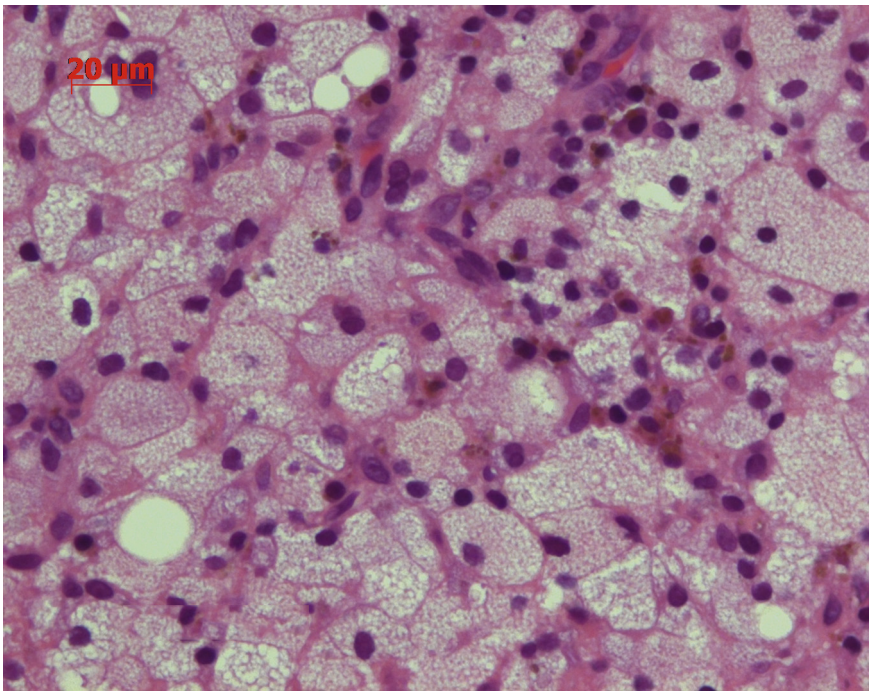

Fig. 5. (Case 5) Occasional, focal hemosiderin deposits were found in this case and 3 others, but this was never a prominent feature. (H&E; magnification as illustrated). A high-resolution version of the image is available as eSlide: VM00396.

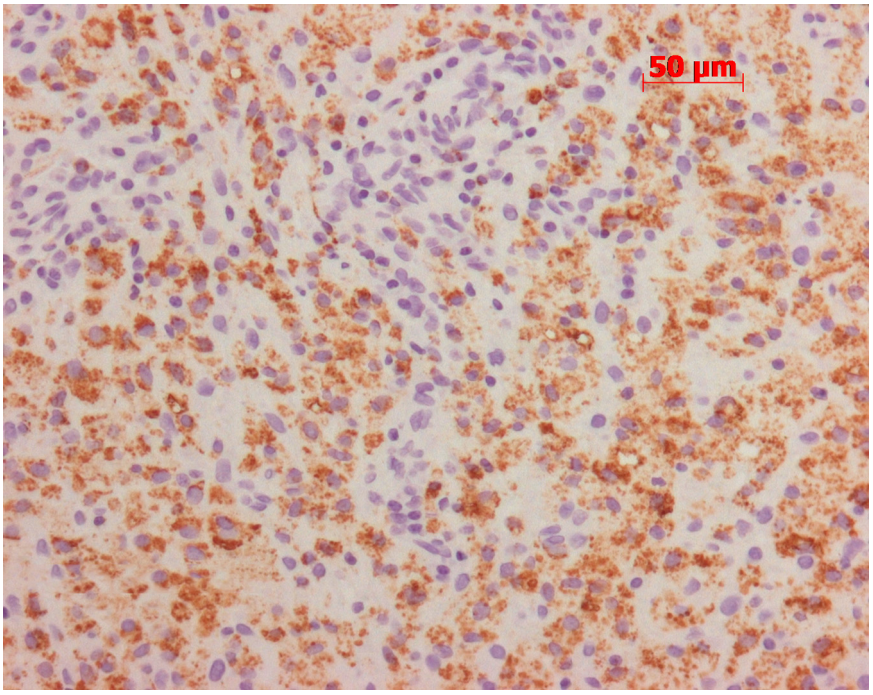

Fig. 6. (Case 4) Xanthoma cells exhibited granular cytoplasmic staining for CD68. (anti-CD68/hematoxylin; magnification as illustrated). A high-resolution version of the image is available as eSlide: VM00397.

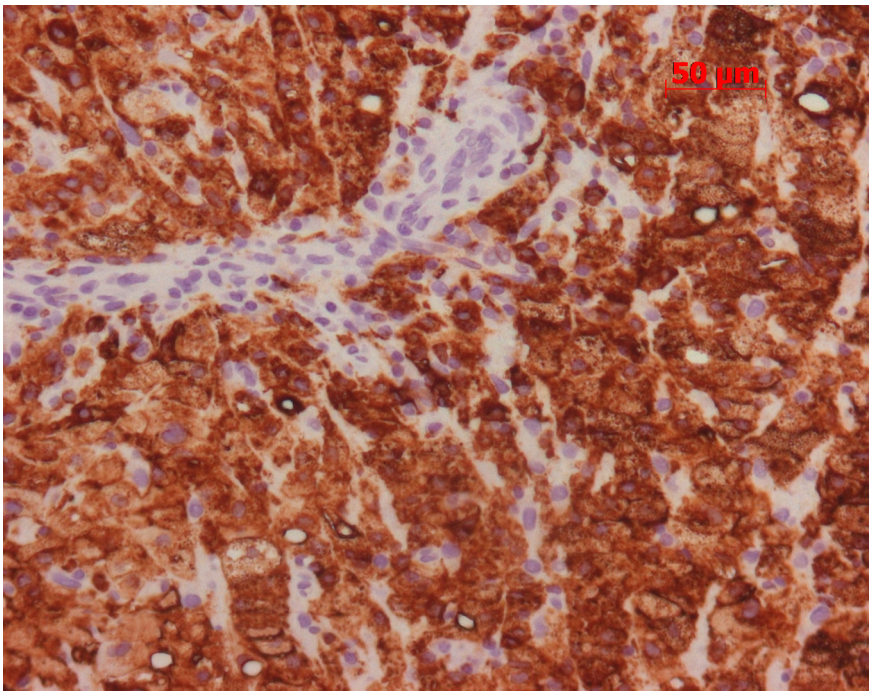

Fig. 7. (Case 4) HLA-DR staining was intense in xanthoma cells. (anti-HLA-DR/hematoxylin; magnification as illustrated). A high-resolution version of the image is available as eSlide: VM00398.

1. The lesion is dominated by xanthoma cells.
2. Fibrous tissue is present in variable proportions but does not show the characteristic storiform pattern seen in NOF and BFH.
3. Nonfoamy giant cells are not seen, unless associated with cholesterol clefts.
4. The lesions are CD68 positive, HLA-DR positive, S100 negative (ruling out fat cells), and CD1a negative (ruling out Langerhans cells).
5. Unlike NOF, which heals spontaneously and requires no treatment, central xanthoma of bone persists and progresses slowly,[1] requiring surgical curettage. Unlike BFH of bone, which may recur,[15] requiring appropriate close follow-up, central xanthoma of the jaws rarely, if ever, recurs. Only limited follow-up is required.
6. Central xanthoma of the jaws occurs in patients in a broader age range, including older adults, compared with NOF.

In agreement, Slootweg et al.[4] ruled out NOF and BFH in their xanthomatous case because of the presence of reactive bone. In addition, Cale et al.[16] considered the xanthoma-rich lesions reported by Harsanyi and Larsson[1] and by Rudy and Scheingold[2] not BFHs, since, among other reasons, they lacked the characteristic storiform pattern microscopically. Central xanthoma of the jaws has clinical features (older age distribution, expansion of bone, potential to become very large, no evidence of spontaneous resolution[1]) more consistent with BFH than with NOF, yet it lacks the characteristic storiform microscopic pattern of fibrous tissues (Table III).

Could these lesions represent an unusual lining of a traumatic bone cyst? The radiographic appearance of the lesion in our case 1, showing scalloping of the radiolucency between the roots of the posterior mandibular teeth (Figure 1, A and B), is very similar to the radiographic appearance of a traumatic bone cyst. However, this lesion occurred in a 56-year-old male and involved his entire left and central mandible, and the cavity was not “empty” at surgery. These clinical and surgical features argue against a diagnosis of traumatic bone cyst and favor an interpretation of a unique entity.

Could these lesions be within the spectrum of an aneurysmal bone cyst? This is unlikely, since nonfoamy giant cells are not a feature of central xanthoma. Further, the usual age of patients (adolescents vs adults) and the biologic behavior of the two lesions (often painful and rapid expansions of bone vs painless and indolent progress) are inconsistent.[20-22]

Is central xanthoma of the jaws a benign neoplastic process or a reactive process?

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

Table III. The differential diagnosis of the central xanthoma of the jaws (Central Xanthoma), nonossifying fibroma (NOF) and benign fibrous histiocytoma of bone (BFH)

	Central xanthoma	*NOF*	*BFH of bone*
Age predilection	Adults	Children and adolescents	Wide age range, usually adults
Site predilection	Mandible	Metaphysis of long bones	Pelvis, long bones
Clinical behavior	Usually painless. Slowly progressive	Painless Spontaneous healing	Often painful Progressive
Dominant histologic characteristics	Masses of foam cells in fibrous stroma	Fibrous tissue fascicles with foam cell clusters	Fibrous tissue fascicles with foam cell clusters
Giant cells	uncharacteristic	Usually present	Usually present
Storiform pattern of fibrous tissue	No	Characteristic feature	Characteristic feature
Treatment	Curettage	None	Curettage
Recurrence	Rare, if ever	No	Yes
Follow-up	Limited	Limited	Long term

process are the apparent spontaneous occurrence in the absence of trauma, infections, or precipitating systemic diseases. It occurs as a solitary lesion, does not regress,[1] shows progressive growth,[1] can expand the jaw, has the potential to cause considerable boney destruction[1,2] (case 1), and may show infiltrative growth[4] (case 2). Factors favoring a reactive lesion are the presence of inflammatory cells, hemorrhage or hemosiderin, potential for reactive bone, and occasional cholesterol granulomas. Most authors support a reactive or inflammatory process despite the clinical features.[1,4,6] The case reported by Rudy and Scheingold[2] may be related to their patient's uncontrolled severe diabetes. In our study, all lesions were monostotic at the time of diagnosis, and none of the patients was known to have any type of inherited storage disease or Erdheim-Chester disease. The possibility that the older patients in our study may have had hyperlipidemia cannot be ruled out, but the case reported by Mosby et al.[3] was specifically tested for serum cholesterol and triglycerides levels, which were found to be normal. Furthermore, two of our patients were young adults, who would not be expected to develop large lipid deposits. This evidence suggests that the source of the lipid was not via the bloodstream, as suggested by Weiss and Goldblum,[23] 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. Our immunohistochemical results indicate that the foamy cells are activated macrophages (CD68- and HLA-DR−positive 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-α , interleukin 6).[24]

Foam cells are commonly seen in periapical granulomas. Two of our cases (cases 3 and 5) had root canal−treated molars in the area of the lesions. In both cases, there were no dental symptoms, and one case was recorded to have had the root canal treatment done 10 years ago. In both cases, the radiolucency was 3 cm in greatest dimension and involved the roots of adjacent vital teeth. In case 5, the tooth was not removed at surgery, and there were no further dental problems in the 1-year follow-up period. The teeth were removed in case 3. The possibility that these two cases represent low-grade, longstanding, and asymptomatic chronic periapical inflammations cannot be completely ruled out, and this remains the primary differential diagnosis for central xanthomas of the jaws associated with a potential odontogenic inflammatory process. Yet, cases 1,2, and 4, as well as other cases reported in the literature,[1,4-6] occurred in the complete absence of any dental or significant periodontal pathology, supporting the concept that the lesion is a unique entity.

CONCLUSIONS

We suggest that central xanthoma of the jaws is a benign, slowly progressing lesion of activated macrophages containing foamy cytoplasm. 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.

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