Primary Intraosseous Xanthomas of the Jaws: A Series of Six Cases Including an Example with Formation of Apoptosis-Related Hyaline Globules, So-Called “Thanatosomes”

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Abstract

Primary intraosseous xanthomas of the jaws (PIXJ) are rare and predominantly affect the posterior mandible (86%) of normolipemic patients, with a mean age of 30 years and no gender predilection. Clinically, PIXJ exhibit indolent biologic behavior; curettage is considered treatment of choice. Only 36 PIXJ have been reported. Apoptosis-related hyaline globules (HGs), also known as “thanatosomes”, have not been previously reported in PIXJ. Cases diagnosed as xanthoma of bone were retrieved. Six cases fulfilling currently accepted criteria were identified and their clinicopathologic and immunohistochemical properties are presented herein. Mean age for PIXJ was 21.8 years (range = 12–33) and F:M ratio = 2:1. All cases presented as well-demarcated, unilocular or multilocular radiolucencies. Microscopically, PIXJ featured sheets of lipid-laden macrophages with eosinophilic or foamy cytoplasm. A secondary fibroblastic population lacking storiform pattern was evident in two cases. Adipocytes (3/6), peripheral neurovascular bundles (1/6), bone fragments (3/6) and dystrophic calcifications (3/6) were observed enclosed by the xanthoma cells. Notably, one case exhibited numerous, spherical, eosinophilic HGs containing apoptotic nuclei. PIXJ were consistently CD68(+) and negative for CD1α and S100. CD45 decorated lymphocytes and the membrane of foamy histiocytes. Xanthoma cells stained for lysozyme and plasma proteins including alpha-1 antitrypsin (AAT), IgG and IgA in one probed case. HGs were lysozyme(+), AAT(+), IgG(+), IgA(+), PAS(+) and diastase-resistant, and fuchsinophilic with Masson’s trichrome. PIXJ represent infrequent, solitary, mandibular lesions with a predilection for the second and third decade of life. Thanatosomes associated with cell injury and death can be present in PIXJ.

Keywords Xanthoma · Non-ossifying fibroma · Benign fibrous histiocytoma · Jaws · CD68 · Hyaline globules · Thanatosomes · Dead bodies

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Introduction

Primary intraosseous xanthomas of the jaws (PIXJ) represent a rare pathologic entity with unique characteristics which warrants separation from other conditions that may affect the gnathic bones, such as benign fibrous histiocytoma (BFH) and non-ossifying fibroma (NOF) [1, 2]. The clinicopathologic and radiographic features of PIXJ were delineated in 1988 by Harsanyi and Larsson [3]. Prior to this case series, a single example of mandibular xanthoma was reported by Mosby et al. [4] in a 28-year-old African American male. The pathogenesis of PIXJ is controversial; both a reactive or degenerative and a neoplastic etiology have been suggested [1, 2]. Notably, PIXJ have been previously reported in association with a pre-existent condition such as simple bone cyst, aneurysmal bone cyst and benign fibro-osseous lesion [4, 5].

Herein, we aimed to further elucidate the spectrum of clinicopathologic and immunohistochemical properties of PIXJ by presenting six additional examples involving the mandible, including a case featuring accumulation of cytoplasmic and extracellular apoptosis-related hyaline globules (HGs), so-called “thanatosomes”.

Materials and Methods

Case Selection

All cases diagnosed as xanthoma of the jaws between 2002 and 2019 at the Division of Oral and Maxillofacial Pathology, University of Minnesota, were retrieved. Hematoxylin and eosin (H&E) stained slides of each case were examined and the histopathologic characteristics of the lesions were correlated with available clinical and radiographic information. Criteria for exclusion included limited amount of biopsied tissue, lack of proper radiographic documentation, microscopic features suggestive of a concomitant cystic or fibro-osseous lesion in addition to the xanthomatous component, and the presence of a prominent spindle cell population with storiform or fascicular architecture.

Six cases fulfilling these criteria were identified; the demographic features (age and gender of the patients) as well as the location, size, radiographic appearance of the lesions, and treatment information were collected and tabulated (Table 1). All six PIXJ were immunohistochemically stained for CD68 and CD1 α , surrogate markers of histiocytic and Langerhans-cell lineage, respectively. Five out of six cases were also stained for S100, while for lesions featuring a secondary fibroblastic proliferation additional

immunohistochemical markers were requested including α -smooth muscle actin (α -SMA), desmin, CD99, myogenin and pancytokeratin. Finally, the immunohistochemical and histochemical properties of HGs observed in one case of PIXJ were further explored with lysozyme, alpha-1 antitrypsin (AAT), IgG, IgA, Periodic acid–Schiff (PAS) with and without diastase digestion, and Masson’s trichrome stain.

Literature Review

A thorough Pubmed search using the keywords “xanthoma of bone”, “xanthoma of the jaws”, “xanthoma of the mandible”, “xanthoma of the maxilla” and “central/ intraosseous xanthoma” was performed and revealed 36 well-documented PIXJ.

Results

Clinical Findings

Among the six cases of PIXJ, four were seen in females and two in males (M:F ratio = 1:2) with mean age = 21.8 years (age range = 12–33). All six cases were located in the posterior body of the mandible (Figs. 1a, 2a), with two extending into the ramus (Fig. 3a, Table 1). The lesions presented radiographically as multilocular or unilocular, well-circumscribed, radiolucencies with frequently sclerotic borders and measured 1–2 cm in greatest dimension (Figs. 1a, 2a, 3a). All PIXJ were asymptomatic and produced no bone expansion. Although no previous history of trauma was reported in any of the cases, one of the patients (case 5) had orthodontic

Table 1 The demographic and clinico-radiographic characteristics of PIXJ presented in this cohort

Case #	Age (years)	Gender	Site	Radiographic features	Size (cm)	Clinical impression	Treatment
1	28	F	Posterior body of mandibular (L)	Multilocular radiolucency	1.0	Ameloblastoma, odontogenic keratocyst	Curettage
2	17	F	Posterior body of mandibular (L)	Well-circumscribed, unilocular radiolucency, area of teeth #18,19	NA	Dentigerous cyst, odontogenic keratocyst	Curettage
3	27	M	Posterior body and ramus of mandible (L)	Multilocular radiolucency with honeycomb pattern and sclerotic margins	2.0	Fibro-osseous lesion	Incisional biopsy
4	33	M	Mandibular ramus (L)	Multilocular radiolucency with honeycomb pattern	2.0 × 1.5	Odontogenic keratocyst	Enucleation with aggressive curettage
5	14	F	Posterior body of mandible (R)	Well-defined, multilocular radiolucency with sclerotic margins	1.0 × 0.5	NA	Curettage
6	12	F	Posterior body of mandible (L)	Radiolucency	1.5 × 0.8	Neoplastic process	Curettage

PIXJ primary intraosseous xanthomas of the jaws, NA not available

Fig. 1 Case 1 **a** Radiographic appearance of primary intraosseous xanthoma (white arrow) presenting as multilocular radiolucency of the posterior mandible. **b, c** Microscopic features of PIXJ. The lesion is comprised of sheets of lipid-laden foamy histiocytes. Note the presence of bone fragments and mature adipocytes within the lesion (H&E stain, original magnification **b** $\times 100$, **c** $\times 400$). **d, e** Immunohistochemical properties of PIXJ. The xanthoma cells are strongly and diffusely positive for CD68 but negative for CD1 α (original magnification **d, e** $\times 400$)

treatment. Five cases of PIXJ were treated with curettage, while in one (case 3) the lesion was incisionally biopsied and the patient was lost to follow-up. Serum lipid levels were not available for any of the patients.

Histopathologic Characteristics

The histopathologic features are summarized in Table 2. Specimens featured sheets or aggregates of large, round or ovoid cells with condensed occasionally vesicular or basophilic nuclei (Figs. 1b, 2b, 3b). The cytoplasm of the xanthoma cells was eosinophilic and ranged from foamy to granular, whereas the cytoplasmic membrane was, overall, well-defined (Figs. 1c, 2c, 3d). The xanthomatous component comprised $> 80\%$ of the lesional tissue in five out of six cases (Table 2). The packed sheets of lipid-laden xanthoma cells were separated by delicate fibrous connective tissue septae. A secondary, spindle-cell, fibroblastic population was evident at the periphery of the xanthomatous population in two cases (cases 4 and 5). It lacked a storiform or whorled pattern.

Fig. 2 Case 5: **a** An example of PIXJ presenting as well-defined, multilocular radiolucency with sclerotic borders (white arrow). This patient has history of orthodontic treatment. **b, c** Sheets of lipid-laden foamy cells are seen in the medullary spaces adjacent to lamellar and woven bone (H&E stain, original magnification **b** $\times 100$, **c** $\times 400$). **d, e**; CD68 highlights the cytoplasm and CD45 the cell membrane of the xanthomatous cells. **f, g** The fibroblastic proliferation identified at the periphery of the xanthoma cells in this case lacked a fascicular pattern and stained positively for α -SMA and CD99 (original magnification **d–g** $\times 400$)

Mature adipocytes enclosed by the xanthoma cells were observed in three PIXJ (Figs. 1c, 3b), while large peripheral neurovascular bundles surrounded by xanthoma cells were seen in one case (Fig. 3c, black arrows). Frequently, the xanthomatous cells were identified in the medullary spaces of the mandible (Fig. 2c). Three PIXJ showed lamellar and woven bone fragments surrounded by foamy histiocytes, while varying amount of dystrophic calcifications were seen in three out of six cases. Mild chronic inflammation and foci of hemorrhage were present in all lesions. Cholesterol clefts with an associated multinucleated giant-cell reaction (cholesterol granuloma) were observed only in case 1.

Fig. 3 Case 4: **a** Radiographic presentation of primary intraosseous xanthoma as well-demarcated, multilocular radiolucency with a honeycomb pattern involving the left mandibular ramus (black arrow). **b** Low-power photomicrograph depicting a xanthomatous lesion with entrapment of fat cells (H&E stain, original magnification $\times 100$). **c** Large peripheral neurovascular bundles (black arrows) are surrounded by the xanthomatous cells (H&E stain, original magnification $\times 100$). **d** Medium-power photomicrograph showing large foamy histiocytes with eosinophilic or granular cytoplasm and numerous, dispersed, red hyaline globules (HGs) (H&E stain, original magnification $\times 400$). **e** High-power photomicrograph displaying an area with multiple bright red, spherical intracellular and extracellular HGs. Note the edematous changes in the stroma (H&E stain, original magnification $\times 600$)

Interestingly, multiple xanthoma cells in case 4 exhibited HGs (thanatosomes) which presented as round or ovoid, varying in size, eosinophilic structures (Fig. 3d, e). The HGs were often numerous and located intracellularly or extracellularly, while the intensity of staining varied from light pink to bright red (Figs. 3e and 4a–d). Occasionally, the lesional cells showed pronounced cytoplasmic hyalinization which enveloped a dark and pyknotic nucleus (Fig. 4a). In numerous instances, HGs contained condensed (apoptotic), angular or elongated, nuclear fragments (Fig. 4b–d). Often, the thanatosomes were circumferentially located and appeared to become extracellular by bursting out of the cellular membrane (Fig. 4c and d). Overall, the presence of thanatosomes within the lipid-laden foamy histiocytes associated with increased apoptotic phenomena and edematous changes in the stroma (Figs. 3e and 4d).

Immunohistochemical and Histochemical Findings

The immunohistochemical properties of PIXJ are tabulated (Table 2). By immunohistochemistry, the lipid-laden xanthoma cells demonstrated strong and focal to diffuse, coarse, cytoplasmic immunopositivity for CD68 in all cases (Figs. 1d, 2d, 5a), suggestive of a histiocytic/phagocytic lineage. The xanthoma cells were consistently negative for CD1 α (Fig. 1e) and S100. CD45 (leucocyte common antigen, LCA) staining was available for 2 PIXJ and decorated lymphocytes, plasma cells and the cytoplasmic membrane of the foamy histiocytes (Figs. 2e, 5c).

The xanthoma cells of case 4, for which additional immunohistochemical markers were available, stained weakly to moderately for lysozyme (Fig. 5b) and plasma proteins including AAT (Fig. 5d), IgG and IgA (Fig. 5e and f). The fibroblastic proliferation present in cases 4 and 5 failed to stain for desmin, myogenin and pancytokeratin, but showed selective immunoreactivity (case 5) for α -SMA (Fig. 2f) and CD99 (Fig. 2g).

The globular eosinophilic structures observed in case 4 displayed strong lysozyme (Fig. 5b), AAT (Figs. 5d), IgG and IgA immunostaining (Fig. 5e and f, black arrows). Additionally, HGs stained for PAS and showed resistance to treatment with diastase (Fig. 6a, black arrows). Masson's trichrome stain highlighted the fuchsinophilia of the thanatosomes (Fig. 6b, black arrows).

Discussion

Intraosseous xanthoma, xanthogranuloma and xanthofibroma of bone are terms which have been previously utilized interchangeably in the English literature to describe benign intraosseous tumorous growths characterized, microscopically, by the presence of lipid-laden foamy histiocytes [2, 6–8]. Xanthoma of bone is rare and has been reported in the metaphysis of axial and appendicular bones of patients with abnormal lipid metabolism [7, 9]. The majority of cases are associated with hyperlipidemia type II and III, diabetes mellitus, hypothyroidism and nephrotic syndrome (secondary xanthomas) [7]. However, normolipidemic forms are well-documented [1, 9]. Whereas xanthoma refers to isolated lesions, xanthomatosis is the term used to describe multiple bone and soft tissue xanthomas [7, 9]. Solitary involvement of the pelvis, ribs and skull is usually observed in the normolipidemic variant of the disease (primary xanthomas of bone) [7].

PIXJ are rare with only 36 well-documented examples in the English literature (Table 3) [1–4, 10–17]. PIXJ manifest in their vast majority in normolipidemic individuals. A singular exception represents the case of mandibular xanthoma presented by Brooks et al. [14] involving a 16-year-old male

Table 2 The histopathologic and immunohistochemical properties of PIXJ included in this study

Case	Percent of xanthomatous component	Fibroblastic proliferation	Presence of fat tissue and bone	Intracytoplasmic eosinophilic globules	Inflammation	Cholesterol clefts	Multinucleated giant cells	Dystrophic calcifications	IHC and histochemical features
1	> 80%	Absent	Present	Absent	Chronic lymphocytic	Present	Present in association with cholesterol clefts	Present	CD68(+), CD1a(–), S100(–)
2	> 80%	Absent	Absent	Absent	Chronic lymphocytic	Absent	Absent	Present	CD68(+), CD1a(–), S100(–)
3	> 60%	Absent	Absent	Absent	Chronic lymphocytic	Absent	Absent	Present	CD68(+), CD1a(–)
4	> 80%	Present at the periphery. Lack of a storiform pattern	Present. Neurovascular bundles enclosed by xanthoma cells were also noticed	Numerous	Chronic lymphocytic with rare plasma cells	Absent	Absent	Absent	Xanthoma cells: CD68(+), CD1a(–), CD45(+), S100(–), Lysozyme(+), AAT(+), IgG(+), IgA(+) Spindled cells: α -SMA(–), Desmin(–) Hyaline globules: Lysozyme(+), AAT(+), IgG(+), IgA(+), Pas-diastase(+), Masson's trichrome (Bright red)
5	> 80%	Present at the periphery. Lack of a storiform pattern	Absent	Absent	Chronic lymphocytic	Absent	Absent	Absent	Xanthoma cells: CD68(+), CD1a(–), CD45(+), S100(–), HMB45(–) Spindled cells: CD99(+), α -SMA(+), Desmin(–), Myogenin(–), Pancytokeratin(–)
6	> 80%	Absent	Present	Absent	Chronic lymphocytic	Absent	Absent	Absent	CD68(+), CD1a(–), S100(–)

PIXJ primary intraosseous xanthomas of the jaws, IHC immunohistochemistry, AAT alpha-1-antitrypsin, α -SMA α -smooth muscle actin

Fig. 4 Case 4: Histopathologic variations of HGs. **a** Pronounced cytoplasmic hyalinization surrounding a dark and pyknotic nucleus. **b** Multiple perfectly round HGs containing condensed, angular nuclear fragments. **c** HGs showing circumferential localization in the cytoplasm adjacent to the cellular membrane. **d** HGs become extracellular following collapse of the cell membrane (H&E stain, original magnification **a–d** $\times 1000$)

Fig. 5 Case 4: **a** The xanthoma cells show selective positivity for CD68. **b** Lysozyme highlights both foamy histiocytes and thanatosomes. **c** CD45 decorates xanthoma cells and inflammatory cells. **d** Alpha-1 antitrypsin (AAT) is positive in foamy histiocytes and thanatosomes. **e, f** Plasma proteins IgG and IgA are staining the xanthomatous cells weakly to moderately but are strongly expressed in the thanatosomes (black arrows, original magnification **a–d** $\times 400$, **e, f** $\times 600$)

Fig. 6 Case 4: Histochemical features of the HGs. **a** HGs (black arrows) stained for Periodic acid–Schiff (PAS) showing resistance to diastase digestion. **b** Masson's trichrome stain highlighted the fuchsinophilia of the HGs (black arrows, original magnification **a, b** $\times 400$)

with occult hyperlipidemia and vitamin D deficiency. In the same patient, no other bone lesions were reported [14].

Clinically, despite the presence of pain in up to 60% of non-gnathic xanthomas, PIXJ manifest in an indolent and, generally, asymptomatic way [3, 18], as confirmed in the current study as well. Notably, most of the lesions are discovered as incidental findings during routinely examination [1]. The radiographic appearance of PIXJ may vary. The majority of the lesions, however, have been described as circumscribed, unilocular radiolucencies (approximately 70%) [17] with sclerotic and well-defined, punched-out margins [1, 2]. Honeycomb-like pattern, mixed radiolucent/radiopaque features, scalloping between the roots of adjacent teeth and poorly-defined borders have also been reported [1, 11, 17]. Rarely, PIXJ have been associated with tooth resorption, root displacement, perforation of the labial plate of the mandible and numbness of the lower lip [1, 2].

All previous cases of PIXJ including the ones in the current cohort were solitary. PIXJ exhibit a strong predilection for the posterior portion of the mandible and the ascending ramus (31/36, 86%) [1–4, 10–17]. Involvement of the maxilla, although infrequent (4/36, 11%) [1, 2, 19], appears to associate with more extensive, locally aggressive lesions [1]. The latter, may possibly be due to the presence of cancellous bone in the maxilla allowing for the xanthomatous lesions to expand further and acquire larger dimensions. Notably, the gnathic bones are not the only bones of the head and neck where central xanthomas develop. At least 17 cases of temporal bone xanthoma and one example affecting the inferior orbital rim [20] have been reported [21]. However, in contrast to PIXJ, most xanthomas of the temporal bone are secondary to lipid or metabolic disorders, e.g. hypercholesterolemia [21, 22].

PIXJ show a strong predilection for the 2nd and 3rd decades of life (22/36, 61% of all cases) and a mean age of 30 years (age range 11–72) [1–4, 10–17]. This is in complete agreement with the age demographics presented in our cohort. Interestingly, these data are also consistent with the reported age distribution of primary (non-hyperlipidemia)

Table 3 The epidemiologic and clinical features of all previously reported (n=36) examples of PIXJ

Author	Year	# of Cases	Age (range, mean)	Gender	Location	Treatment	Follow-up
Mosby et al.	1983	1	28	M	Mandible	NA	No recurrence
Harsanyi et al.	1988	7	12–72, 25.4	1 M:6 F	7 Mandible	4 with biopsy, 3 with enucleation	No remission for biopsied lesions; no recurrences for enucleated lesions
Marqués Mateo et al.	2004	1	11	M	Mandible	Enucleation	5 years, no recurrence
de Moraes Ramos-Perez et al.	2011	1	25	M	Mandible	Curettage	2 years, no recurrence
Daley et al.	2015	5	22–56, 39.4	5 M	4 Mandible, 1 Maxilla	Curettage	No recurrence, 1 NA
de Araujo et al.	2015	1	14	F	Mandible	Curettage	1 year, no recurrence
Morel et al.	2016	1	40	F	Mandible	Excision	6 months, no recurrence
Rawal et al.	2017	10	12–63, 36.8	4 M:6 F	8 Mandible, 2 Maxilla	NA	NA
Brooks et al.	2018	1	16	M	Mandible	Surgical excision	16.5 months, no recurrence
Olson et al.	2018	1	15	M	Mandible	Excision and curettage	Normal healing
Saha et al.	2018	1	30	M	Mandible	Excision and debridement	1 year, no recurrence
Cunha et al.	2018	1	35	F	Maxilla	Excision and curettage	18 months, no recurrence
de Arruda et al.	2019	5	13–45, 23.3	1 M:4 F	5 Mandible	Curettage	No recurrences
		36	11–72, 29.9	17 M:19 F	32 Mandible 4 Maxilla		

PIXJ primary intraosseous xanthomas of the jaws, NA not available

osseous xanthomas of long bones (range 8–62 years, mean = 27.8) [23]. No gender predilection is observed in PIXJ (Table 3).

The predominant feature of frank PIXJ is the presence of sheets and aggregates of foamy histiocytes with abundant cytoplasm and small hyperchromatic nuclei, which may be accompanied by a mild chronic inflammatory cellular response [1, 2]. In the current cohort, the xanthomatous proliferation comprised > 80% of the biopsied specimen in the majority of PIXJ. The xanthoma cells, typically exhibiting compact arrangement, are immersed in and surrounded by loose or dense fibrous connective tissue stroma [1, 2]. Although a sparse amount of fibroblastic component, as seen in two of our cases, can be observed in PIXJ, a fascicular or storiform pattern is not anticipated [1, 2]. As we and others have reported, the foamy histiocytes show strong cytoplasmic immunopositivity for CD68, CD163 [1, 2, 12, 24], lysozyme and plasma proteins, and membranous reactivity for CD45. Focal and weak reactivity for S100 has rarely been reported in PIXJ, whereas CD1α and CD207 (langerin) are consistently negative [1, 2, 12].

The differential diagnosis of PIXJ encompasses NOF and BFH of the jaws [13]. The presence of fascicles of slender,

spindle-shaped fibroblasts (Fig. 7a), scattered foamy cells (Fig. 7b), and non-foamy multinucleated giant cells is supportive of NOF (Fig. 7a, b) rather than PIXJ [13]. NOF, also referred to as metaphyseal bone defect, and BFH are, histologically, indistinguishable and the diagnosis is rendered upon evaluation of the clinical and radiographic appearance [13]. Approximately 16 cases of NOF of the jaws have been reported with a mean age of 19 years (range = 6–49 years) and a predilection for the posterior mandible [25]. BFH, which microscopically features aggregates of CD68(+) foamy histiocytes, scattered spindle cells and moderate lymphoplasmacytic infiltrates (Fig. 7c, d), is painful and affects adults between their 4th and 8th decade of life [26]. BFH has a tendency to recur [13, 26, 27]. BFH of the jaws is unusual, can be painful and demonstrates progressive expansion of the posterior mandible [28, 29].

PIXJ also need to be differentially diagnosed from extranodal Rosai-Dorfman disease of the mandible [30] and Langerhans cell histiocytosis [1, 13]. For patients with multiple bone xanthomas investigation for systemic Erdheim-Chester disease [24], Gaucher's disease, the most common of the lysosomal storage diseases [1, 31], hyperlipidemia type II and III and diabetes mellitus is warranted.

Fig. 7 **a, b** Histopathologic features of non-ossifying fibroma (NOF) affecting the mandible of a 14-year-old female. Fascicles of slender, spindle-shaped fibroblasts exhibiting rare mitotic figures. Clusters of foamy histiocytes are also present (H&E stain, original magnification **a** × 400, **b** × 800). In contrast to PIXJ where xanthoma cells represent the predominant feature, in NOF only scattered xanthoma cells are seen. **c, d** Histopathologic characteristics of benign fibrous histiocytoma (BFH) presenting in the maxilla of a 45-year-old female. The lesion is characterized by aggregates of foamy histiocytes, lymphocytes and spindle cells (H&E stain, original magnification **c** × 400, **d** × 800). Strong and diffuse CD68 immunostaining highlights the presence of macrophages (inset, original magnification × 400)

The clinical, radiological, histopathologic and immunohistochemical discrepancies between the aforementioned conditions and PIXJ have been thoroughly delineated by other authors [1, 13, 19], and may aid in rendering an accurate diagnosis.

HGs which we report here in an example of PIXJ have been described in various types of malignant and benign tumors, as well as non-neoplastic tissues [32, 33]. HGs were initially studied in human liver [34, 35] and the adrenal medulla [35, 36], and subsequently in breast, lung, colon and renal cell carcinomas, astrocytomas and glioblastomas [37–41]. HGs are considered useful in the diagnosis of yolk sac tumor [42], pheochromocytoma [43] and Kaposi's sarcoma, in which they are postulated to associate with erythrophagocytosis [44]. The term “thanatosomes”, which means dead bodies, was coined by Papadimitriou et al. [32] to emphasize the association of HGs with apoptotic cellular changes including cytoplasmic blebbing and condensation, and membrane permeability. Thanatosomes seem to represent distinct intracellular “hyalinized” fragments following plasma protein influx as a result of ischemic injury, cell turnover and death [32, 33]. As a sequela of cell fragmentation, thanatosomes are extruded in the extracellular space where they can be found connected to a fibrin fibril network [32]. Ultrastructural studies have confirmed that HGs are consistent with phagosomes or secondary lysosomes and contain membrane or nuclear debris in various stages of digestion

[32, 33]. By immunohistochemistry, thanatosomes are immunoreactive for lysozyme and all plasma proteins probed (e.g. AAT, IgG and IgA), but also α -fetoprotein, albumin, transferrin, orosomucoid, haptoglobin, fibrinogen and IgM [32, 40, 45]. As previously reported in other tumors [46, 47], PAS with and without diastase digestion and Masson's trichrome stains highlight the thanatosomes seen in PIXJ.

The underlying pathogenetic mechanisms leading to the formation of PIXJ remain uncertain; both a reactive process and a benign neoplastic origin have been favored [1, 2]. It is well-established that secondary xanthomas of the bones associated with systemic lipid diseases have a distinct etiology. Local trauma and/or hemorrhage allow for lipid leakage from vessels which leads to recruitment of macrophages and subsequent accumulation of lipids within the cytoplasm of foamy histiocytes, whereas extracellular cholesterol crystallizes into clefts [13, 21]. However, the lipid leakage mechanism fails to explain the development of PIXJ which, as mentioned, are not related to systemic lipid disorders.

Dahlin [48] suggested that solitary bone xanthomas represent a senescent, degenerative or even reparative phenomenon to a pre-existing pathologic condition, such as fibrous dysplasia, simple bone cyst and central giant cell lesions. This theory linking PIXJ with tissue degeneration and/or repair appears plausible based on the following observations: (a) traumatic bone cysts of the jaws and benign fibro-osseous lesions occasionally exhibit varying presence of xanthoma cells [1, 5] and (b) tissue trauma and subsequent reparative events may cause aggregations of lipid-laden histiocytes as it occurs, for example, in xanthomatous post-traumatic fibro-osseous lesions of the ribs [49]. Proper documentation of trauma history may be challenging in PIXJ. One of the patients in the present cohort reported previous orthodontic treatment, as it has been the case for other PIXJ [11, 12].

The overall biologic behavior of PIXJ is inconspicuous and surgical excision with curettage is adequate treatment [1–4, 10–17]. No recurrences have been reported for PIXJ in a follow-up period ranging between 6 and 60 months post-surgery [10–14, 16, 19].

Conclusions

PIXJ represent infrequent, solitary, predominantly mandibular lesions with a strong predilection for the second and third decade of life. In pure PIXJ the xanthoma cells comprise the largest portion of the lesion. A panel of ancillary immunohistochemical markers, e.g. CD68, CD163, CD1 α , CD207 and S100, may aid in the exclusion of other histiocytic lesions involving the gnathic bones. Herein, we report for the first time the marked presence of thanatosomes in PIXJ, a finding strongly related to cell injury, apoptosis and tissue

degeneration. PIXJ demonstrate, overall, indolent biologic behavior and excellent prognosis following curettage.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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