BENIGN FIBROHISTIOCYTIC GNATHIC LESIONS: A 48 YEAR CLINICOPATHOLOGIC AND IMMUNOHISTOCHEMICAL ANALYSIS AND REVIEW OF THE LITERATURE

by

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ABSTRACT

"BENIGN FIBROHISTIOCYTIC GNATHIC LESIONS: A 48 YEAR CLINICOPATHOLOGIC AND IMMUNOHISTOCHEMICAL ANALYSIS AND REVIEW OF THE LITERATURE"

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Introduction: Intra-osseous fibrohistiocytic lesions of the jaws are rare entities variably described in the literature. It is postulated they represent a heterogenous group of both reactive and neoplastic processes. **Purpose**: This case series categorized clinical, radiographic and morphologic features of gnathic fibrohistiocytic lesions. **Materials and Methods**: A search of archival material at the NPDS, WRNMMC and the Joint Pathology Center (including the Armed Forces Institute of Pathology) was conducted (1970-2017). Diagnosis was confirmed via histologic evaluation. Adjunct immunohistochemical staining was performed as required. Demographic, radiographic, clinical and follow-up data were recorded if available. **Results**: The 50 cases meeting inclusion criteria consisted of 29 males and 21 females. Ages ranged from 11-70 years (mean 29). The majority of lesions (82%) were found in the 2nd through 4th decades. Most were identified incidentally or presented with mild expansion in the posterior body/ramus of the mandible (84%). Although radiographic presentation varied, a distinctive sclerosing and punctate pattern was identified. Approximately 80% of the cases demonstrated characteristic morphologic features, while a minority demonstrated a predominant xanthomatous component. Immunohistochemical staining revealed strong, positive CD68 and CD163 expression with

variable smooth muscle actin staining. Preoperative radiographic and/or follow-up data was available in 21 cases. Ages ranged from 6 months to 34 years (mean 85 months). The vast majority (92%) of cases were treated conservatively. Lesional stability was demonstrated with serial radiographs; only two cases recurred. **Conclusions**: This is the largest case series to date and demonstrates distinctive radiographic and histologic findings, along with characteristic clinical and immunophenotypic features. The follow-up data suggests that these are benign neoplasms with reactive features and limited potential for recurrence, and are generally amenable to conservative treatment.

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I. INTRODUCTION

Fibrohistiocytic and fibroxanthomatous lesions of bone encompass a broad spectrum of morphologic and radiographic presentations. Understandably, a plethora of descriptors have been used to classify these lesions. The rare gnathic forms are likewise subject to numerous taxonomic groupings and provide an additional challenge for definitive characterization. The World Health Organization (WHO) classifies fibrohistiocytic tumors of bone as one of three entities with different presentations: fibrous cortical defects (FCD), non-ossifying fibroma (NOF) or benign fibrous histiocytoma (BFH).[1]

The entity now known as the NOF was first recognized in 1941 and formally identified the following year as long bone metaphyseal lesions in young, skeletally immature individuals.[2,3] They have distinct clinico-radiologic features, typically undergoing spontaneous resolution.[1,4-6] Multiple NOF have been identified in Neurofibromatosis 1 and in patients with Jaffe-Campanacci syndrome.[7-9] The FCD is considered essentially identical to the NOF by the WHO, but is confined to the cortex and tends to be smaller (<3 cm).[1,5] Based on these specific features, the NOF and FCD terminology is not applicable to jaw lesions. True BFH of bone are rare entities, with less than 100 reported in the literature.[1,6,10,11] They are histologically identical to NOF, but are distinguished by their non-metaphyseal location.[1] Approximately 50% of BFH are found outside the long bones, with a predilection for the vertebrae, a slight male predominance, an older age, >20 years, and pain upon presentation.[1,5,6,12] Clarke et al. noted recurrence in three out of eight (37.5%) intra-bony BFH in their case series.[13]

Since they were first described in 1951 by Agazzi and Belloni,[14] authors have used varied terminology to characterize gnathic fibrohistiocytic lesions (Table I), though current classification systems should preclude the use of NOF for jaw lesions. Gnathic BFH are

uncommon with only 18 published cases specifically utilizing this descriptor.[16,24,25,28,35,37,38,42,43,47,49,50] They often presented as well-defined multilocular or unilocular radiolucencies with sclerotic borders with or without clinically evident swelling. However, both ground glass[25] and mixed radiographic appearances with poorly defined borders[49] have been reported.

Regardless of nomenclature, benign intra-bony fibrohistiocytic lesions consist of bland, spindle shaped fibroblastic cells arranged in a storiform pattern. The plump or slender nuclei lack atypical features and scattered osteoclastic giant cells are found. Varying numbers of histiocytes and foamy cells are distributed throughout the fibroblastic tissue.[1,6] The histiocytic or xanthomatous component may be a dominant feature in an intra-bony BFH and differing terminology such as solitary xanthogranuloma, xanthoma, xanthofibroma or fibrous xanthoma of bone has been applied to such lesions.[6] Cystic change may be present, along with typical mitotic figures.[1,5,6] In 2015, a new descriptor, central xanthoma of the jaws (CXJ), was proposed.[45] Five new cases were presented and an additional 12 cases from the literature were considered to meet the criteria of CXJ. Unlike typical BFH, CXJ is dominated by xanthoma cells and lacks a dominant, storiform proliferation of fibrous tissue.[45] CXJ was utilized as diagnostic terminology again, two years later, in a 10 case series, which found an equal sex predilection and higher incidence in the second and third decades.[51]

II. MATERIALS AND METHODS

A retrospective case study utilizing files from the Department of Oral Pathology at the Naval Postgraduate Dental School, located at the Walter Reed National Military Medical Center (WRNMMC) and the Joint Pathology Center (JPC), including archival Armed Forces Institute of Pathology cases, was conducted. This study protocol (WRNMMC-2018-0125) is in compliance with the Declaration of Helsinki and was reviewed and granted ethics approval by the WRNMMC Institutional Review Board. A diagnosis and comment search utilizing CoPath/CoPath Plus at WRNMMC and the Joint Pathology Information Management System (JPIMS) at the JPC was conducted for intra-bony histiocytic lesions from the mandible and maxilla between January 1, 1970 and December 31, 2017. Search terms included "fibrohistiocytic", "fibroxanthomatous", "central xanthoma", "non-ossifying fibroma", "fibrous cortical defect", and "benign fibrous histiocytoma".

Tissue specimens were evaluated based on existing hematoxylin and eosin (H&E) and immunohistochemical (IHC) stained microscopic slides. If existing tissue sections were unavailable or unable to be clearly assessed, new H&E and select IHC slides were produced from archived formalin-fixed, paraffin embedded tissue blocks. Routine IHC studies for CD68, CD163, S100 and smooth muscle actin (SMA) were performed, as required, on a Roche Ventana Benchmark Ultra automated slide-stainer. Cases were reviewed and confirmed for study inclusion by two board-certified oral and maxillofacial pathologists (RDF, BEJ) and the principal investigator (PM) utilizing histologic sections, radiographic, clinical and surgical data. Inclusion criteria included positive finding of a fibrohistiocytic lesion in either a mandibular or maxillary intra-osseous location. Cases demonstrating morphologic, clinical or radiographic evidence of malignancy were excluded from this review. Additionally, cases with evidence of odontogenic

inflammatory origin or association with a non-vital tooth were omitted. Follow-up data was obtained, when available, via review of accessible medical and dental databases.

III. RESULTS

Clinical

Fifty cases meeting inclusion criteria were identified (Table II) with patient ages ranging from 11 to 70 years, with a mean of 29 years. A marked predilection (82%) for the 2nd-4th decades was noted, with nearly half of cases presenting in the 3rd decade (Figure 1). There were 29 male and 21 female patients, resulting in male predominance of 1.4:1 M:F. Only one case presented in each of the 7th and 8th decades and both were in female patients. The mandible, particularly the posterior region, including body, angle and ramus, was by far the most common location (92%), with only four cases occurring in the maxilla. Four cases involved the anterior mandible. Interestingly an almost 2:1 L:R bias was noted for the 41 mandibular lesions with designated laterality.

Nearly all lesions presented as incidental findings on panoramic radiographs or as mild expansion prompting further evaluation. Pain or discomfort was only reported in two cases (cases 15 and 45). Perforation of cortical bone was also identified in two separate cases (cases 24 and 44). Two cases showed radiographic or clinical evidence of concomitant cemento-osseous dysplasia (cases 24 and 45). None of the patients had a known history of a glycogen storage disorder, Erdheim-Chester, Gaucher or Niemann-Pick disease at the time of diagnosis. Interestingly, a single case occurred in an 18 year old male patient with Marfan Syndrome (case 34).

Radiographic Findings

Radiographic information was available for 42 cases. The presentation varied widely, but a few consistent patterns emerged. Six cases, designated as Type 1 (T1), presented as multilocular radiolucencies, with a distinctive mottled, punched-out and sclerotic appearance

(cases 22, 31, 34, 36, 38, 42, 46) (Figure 3, A-F). A predilection for the ramus was noted. Type 2 (T2) consisted of larger, predominantly radiolucent lesions (cases 18, 24, 26, 27, 32, 39, 40, 47) (Figure 3, G). Most presented with ragged or poorly defined borders, though some were corticated. Smaller, occasionally multiple, lytic unilocular radiolucencies, often located in tooth-bearing areas, were identified and designated as Type 3 (T3) (cases 2, 3, 21, 23, 33, 50) (Figure 3, H). Mixed density lesions mimicking benign fibro-osseous lesions (BFOL) were common and designated as Type 4 (T4) (cases 4, 8, 9, 12, 15, 19, 35, 41, 45, 48, 49) (Figure 3, I). Remaining cases did not fit any of the four categories (cases 10, 11, 13, 14, 20, 25, 28, 43, 44).

Pathologic Features

On routine histologic staining, all cases demonstrated at least limited evidence of a classic intra-bony BFH including a spindled, storiform cellular component with focal histiocytic and foamy xanthomatous cells (Figure 4, A-B). Approximately 20% of cases (9/50) demonstrated a predominant xanthomatous component (Figure 4, C-D). Occasional cementum-like droplets in the spindled, fibrous connective tissue areas were noted in eight cases (Figure 4, E-F). Reactive, vital bone and scattered focal to moderate chronic inflammation was variably seen. Prominent cholesterol clefts were rarely noted (case 19) and mitotic figures were uncommon.

Immunohistochemical staining on select cases (Table 4) revealed 100% strong, scattered to diffuse reactivity with CD68 and CD 163 in the histiocytic elements (Figure 5, A-B). One case subjected to excessive decalcification demonstrated focal CD163 staining, but strong, generalized CD68 reactivity (case 45). In 83% if cases, SMA was moderately to focally positive in the spindled cellular components surrounding or rimming the xanthomatous histiocytes

(Figure 5, C). S100 was broadly negative with few cases demonstrating rare staining of dendritic cells.

Follow-up

Conservative treatment, to include biopsy, excisional biopsy and curettage was the treatment of choice in 92% of all cases (Table 3). When including preoperative serial radiographic observation, additional clinical data was available in 21 cases ranging from 6 months to 34 years (85 months mean). Documented radiographic follow-up data was specifically available in 19 cases (6 months to 34 years, mean 85 months). Cases treated by curettage or excisional biopsy mostly demonstrated resolution, except for two cases that recurred at 24 months each (cases 2, 29). Cases treated by biopsy and observation demonstrated no further change, though in two cases, which both showed T4, BFOL-like, features on initial radiographic evaluation, increased sclerosis was seen (cases 35, 41). Resection, including en-bloc, was conducted in four cases and no evidence of disease was noted in those with available follow-up. Malignant transformation was not identified.

IV. DISCUSSION

Our English language literature search revealed 39 series or case reports of fibrohistiocytic gnathic lesions with various descriptors (Table I). In fact, the first reports of this entity in the jaw bones used NOF[14] and xanthogranuloma[15] respectively. However, as previously noted in the introduction, the NOF terminology is only applicable to metaphyseal lesions in children. BFH was first used in 1970 for a gnathic lesion[16] and is our favored diagnostic term as it also encompasses lesions with prominent xanthomatous components.[6]

Our review revealed a posterior mandibular body, angle or ramus preference for gnathic BFH, of all described types, with only one lesion[25] noted in the anterior mandible. Six lesions involved in the maxilla.[28,32,45,51,52] Six reports noted multiple lesions on presentation.[8,25,32] Patient ages ranged from 6 to 80 years with a mean of 30 years. There was a slight female predominance with a M:F ratio of 1:1.2. A wide range of radiographic findings were noted, with the majority of lesions being multilocular or unilocular radiolucencies and treated with biopsy and observation, curettage, enucleation or resection. Clinical follow-up ranged from 4 months to 18 years, with an average of 34 months. No evidence of disease or recurrence was noted in most treated cases. Mild continued expansion was identified on some cases that were observed or partially curetted[25]. Additionally, a few cases demonstrated increased sclerosis, radio-opacification or bony consolidation.[25,44] In one case, regression was noted.[46]

The closest malignant counterpart to benign histiocytic bone lesions is the undifferentiated high-grade pleomorphic sarcoma (UPS).[53] Previously termed malignant fibrous histiocytoma (MFH)[54], it was incorrectly believed to be a malignant tumor of the fibroblastic lineage due to culture studies.[6] The modern classification of UPS, utilizing molecular and new differentiation markers, indicates a primary, high-grade, pleomorphic sarcoma of bone that

demonstrates no specific line of differentiation.[1,5,6,53] UPS is a rare neoplasm that represents less than 2% of bone lesions. The gnathic bones, specifically the mandible, are only involved in 3% of this subset.[1,55] Malignant transformation of BFH to MFH or UPS is a rare, less than one percent, occurrence.[54] We identified a singular case involving an 80 year old male who received an initial diagnosis of a mandibular BFH that underwent malignant transformation. The patient reportedly died of "severe cerebral infarct" six months after excisional biopsy; a post-mortem diagnosis of MFH was made on a recurrent mandibular mass.[42]

We identified numerous unique and characteristic findings in our 50-case study, while others were similar to existing literature. Many of our cases presented as incidental findings, with some demonstrating expansion. A majority of cases (82%) were identified in the 2nd-4th decades with few cases presenting outside this age range (Fig 1). A 1.4:1 M:F predominance was noted; military and Veterans Affairs sourced cases may lead to a male selection bias. However, approximately half of the cases were civilian consultations. Most cases demonstrated resolution or no change on follow up, with recurrence only observed in two cases at 24 months each (cases 2 and 29). Both recurring cases were initially treated with curettage. No malignant transformation was observed. Our findings support an excellent prognosis for these lesions. An extremely varied radiographic appearance was observed in our cases, though the multilocular, mottled and punctate variant (T1) is very distinctive and has few, if any radiographic mimics.

Morphologically, our nine xanthomatous-predominant cases may relate to Daley et al.'s premise of the CXJ. Our cases demonstrated sheet-like, foamy histiocytes, but also had small-intermediate sized collections of storiform, spindled cells. The CXJ classification supports the limited presence of these classic histologic features, but the dominant, storiform pattern should not be noted.[45,51] Additionally, multinucleated giant cells were found with some regularity in our

specimens and should not be present unless associated with cholesterol clefts in the CXJ. Additionally, CXJ tends to persist, with a slow progression that requires surgical intervention, but does not appear to recur.[45,51] Despite these differences, we believe the xanthomatous-predominant pattern illustrated in our study is simply a variant of the classic, intra-bony BFH pattern. Though the specific reporting terminology may be different, both Czerniak and the WHO support a xanthomatous variant of BFH.[1,6] Numerous cases in our study demonstrated BFOL-like features, mostly consisting of ossifying fibroma-like cementoid droplets or trabecular-type bone located in the surrounding spindled, fibrous tissue (Fig 4). This occasionally, but not always corresponded with cases presenting with our T4, BFOL-like, radiographic pattern.

Limited immunophenotypic analysis was conducted in previous studies, with all authors utilizing different staining patterns and procedures. As an increasingly important adjunct, IHC studies were first noted on case reports starting in 2004 (Table III). All reviewed reports utilized CD68, with a positive result, to preferentially identify histiocytes, while vimentin, S100 and SMA were also commonly used by authors. Universally, findings of CD68 positivity with negative or scattered S100 reactivity were noted. The CD68 antigen is most often recognized by KP1 and PG-M1 antibodies in IHC studies, but is not specific for monocyte-macrophage cells as CD68 is also found on lysosomes, phagosomes, and neutrophil primary granules.[56] CD163, a glycoprotein in the cysteine-rich scavenger receptor superfamily, has been demonstrated to be a highly specific marker for the monocyte macrophage lineage.[56] We present the first thorough immunohistochemical panel for gnathic BFH (Table IV); the cases demonstrate a universal positivity for histiocytic markers, CD68 and CD163, rare to negative S100 staining and common staining of myofibroblasts and spindled areas with SMA. SMA was preferentially reactive

immediately adjacent to and interspersed among some large groups of foamy histiocytes. The SMA staining pattern may be explained by duplicitous immunophenotypic exhibition or switching between histiocytic and myofibroblastic cellular differentiations.

The differential diagnosis of gnathic BFH may be broad and can typically be broken up into clinical and histologic categories. While most lesions appear radiographically as incidental findings the varied presentation can be difficult to interpret. Further complicating the differential diagnosis is the occasional presence of mild expansion and pain can be seen. Besides our reported unique, multilocular, punctate, sclerotic and ramus-preferring, T1 radiographic presentation, other cases may include those that are large, ill-defined and worrisome for the clinician (T2). They may encompass more than half of the mandible and can mimic malignancies, including metastatic disease, as well as classic odontogenic neoplasms and cysts including ameloblastoma, odontogenic keratocyst and myxoma; however, these are easily distinguished on histologic evaluation. Gnathic BFH may also present as single or multiple lucent, well-defined lesions (T3) in tooth bearing areas mimicking peri-radicular inflammatory lesions or inflammatory collateral cysts. Those unilocular, radiolucent lesions located inferior to the inferior alveolar canal may clinically mimic a Stafne bone defect, also known as a lingual mandibular salivary gland depression. A final radiographic mimic includes the category of benign fibro-osseous lesions (T4). A number of our cases demonstrated mixed lesions that on first glance look remarkably similar to focal cemento-osseous dysplasia or ossifying fibroma. Even on histologic examination, we noted BFOL-like features on some cases, but the storiform, spindled cellular pattern common to intra-osseous BFH was prominent. Two cases in this radiographic category demonstrated increased sclerosis, but otherwise no change on follow-up.

Morphologic mimics included both familiar and rarer, more obscure entities. Multinucleated giant cells, extravasated erythrocytes and mild-moderate inflammation were often found, but secondary to classic BFH features. As a result, the differential expands to include other entities that demonstrate giant cells in an inflamed fibroblastic background, including central giant cell granuloma or Brown tumor of hyperparathyroidism. Some giant cell tumors with a prominent fibrohistiocytic reaction may demonstrate a similar, histologically indistinguishable, appearance to BFH.[6] Central giant cell lesions are oft associated with other odontogenic cysts and tumors, such as central odontogenic fibroma.

Langerhans cell histiocytosis (LCH) is a clonal disease process of antigen-presenting dendritic histiocytes that may be a unifocal, multifocal or a multisystem disease. The disease process commonly occurs in the head and neck region and radiographically presents with punched out, well-demarcated radiolucencies. The Langerhans cells often demonstrate grooved, kidney-bean shaped nuclei, are set in a sea of prominent eosinophils, display diffusely positive S100, CD1a and CD207 immunophenotypes and demonstrate Birbeck granules by electron microscopy.[57,58] Erdheim-Chester disease (ECD), or polyostotic sclerosing histiocytosis, is a multisystem, non-Langerhans cell histiocytosis that demonstrates prominent foamy cells, stains with CD68 and CD163 and is typically diffusely sclerotic on imaging with possible punched out lytic lesions in the craniofacial bones. While it is typically negative with S100, ECD is multifocal and often presents with bone pain[57], features seen rarely in our case series. ECD is reported to harbor the BRAF V600E mutation 100% of the time.[59]

Additionally, Rosai-Dorfman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy, is a rare proliferative histiocytic disorder that can affect extranodal sites and may be confused with a xanthomatous variant of BFH of bone. Though emperipolesis

is an important diagnostic clue, it may be less prevalent on extranodal sites. The histiocytic cells are nonetheless positive for S100 and negative for CD1a, ruling out BFH and LCH.[57] Lipid reticuloendotheliosies, a subset of lysosomal storage diseases, include Gaucher's and Niemann-Pick diseases. These diseases can demonstrate large quantities of lipid-laden foamy or xanthomatous macrophages, containing accumulated lipid product. However, like RDD, these diseases are multifocal and multisystem with soft tissue and multiple potential intra-bony sites.[60]

The postulated origin of fibrohistiocytic gnathic tumors varies. It has been suggested that BFH of jaw bones may be the result of either neoplastic or reactive processes.[25,30,41] Reactive features, such as chronic inflammatory infiltrate, reactive bone and multinucleated giant cells are not uncommon findings, while the spontaneous growth without regression and expansion or bony destruction suggest a neoplastic etiology. Intriguingly, in our series we saw lesional stability with most cases, something that would be difficult to accept when thinking of a classic neoplastic process. Moreover, the WHO classifies intra-bony BFH as a "fibrohistiocytic tumor" and "lesion" in its own separate chapter, thus supporting the classification as a neoplasm, but also one that has excellent prognosis and does not need to be treated if asymptomatic.[1]

V. CONCLUSION

Benign fibrohistiocytic gnathic lesions are rare variants of intra-osseous BFH and may present with a prominent xanthomatous component. Similar to other intra-bony BFH, these lesions demonstrate some features of a benign, slow-growing or self-limiting neoplasm and features of a reactive process. While one case report of malignant transformation has been noted in the literature, it is evident that a conservative approach, including simple observation, will generally result in an excellent prognosis. Typically presenting as incidental findings, BFH of the jaw is an unusual entity that typically presents in the 2nd-4th decades, occasionally with a distinctive radiographic appearance. At times, the lesion may present with expansion, an extremely concerning radiographic appearance and may be under-recognized by the reviewing pathologist. Universal positivity for CD68, 163, focal positivity for SMA and universal negativity for S100 support the diagnosis. Future evaluation of molecular studies in conjunction with gnathic BFH may further help with classification and etiology. As a final aside, the oft-cited number of literature reports involving non-gnathic intra-bony BFH is less than 100.[1,6,10,11] Our 50-case series and literature review brings the total number of reported gnathic BFH alone to 68 and that number increases to over 100 if all similarly described lesions are included. This may indicate that this entity, along with long bone BFH, may not be as scarce as alleged.

VI. TABLES

Table I. Literature summary of benign fibrohistiocytic gnathic lesions

Authors	Year	Diagnosis	Age / Gender	Laterality / Site #	Radiographic findings	Treatment	Follow-up (mos)	Clinical Follow-up
Agazzi and Belloni[14]	1951	NOF	22 F	R / Body, ramus	Multilocular	Curettage	-	-
Rudy and Scheingold[15]	1964	XAN	49 F	R / Body, ramus	Multilocular	Curettage	10	NED
Quinn et al.[16]	1970	BFH	21 F	Angle	Unilocular	Curettage	34	NED
Liaw et al.[17]	1979	NOF	17 F	L / Angle, ramus	Unilocular, ovoid, well-demarcated bony defect	Resection	7	NED
Makek[18]	1980	NOF	20 M	L / Condyle	Multilocular	Resection	12	NED
Ide et al.[19]	1982	NOF	37 F	R / Body	Multilocular	Curettage	48	NED
Mirra et al.[8] @	1982	NOF	12 F	L& R / Body	Unilocular and Multilocular, multiple @	Curettage	36-48	NED, post-operative grafting to prevent pathologic fracture
Park et al.[20]	1982	NOF	21 F	L / Body	Unilocular	Curettage	4	NED
Mosby et al.[21-22]	1983	XAN	28 M	L / Body	Multilocular, mixed	Curettage	-	-
Elzay et al.[23]	1984	NOF	11 M	L / Ramus	Multilocular	Curettage	36	NED
		NOF	11 M	L / Angle, ramus	Multilocular	Curettage	36	NED
Remagen et al.[24]	1986	BFH / NOF	17 M	L / Body, ramus	Multilocular	-	4	-
Harsanyi and Larsson[25]	1988	XAN / BFH	16 F	R / Body, ramus, condyle	Multilocular, multiple	Partial enucleation	216	Continued slow growth
			23 M	L / Angle	Unilocular, mixed	Partial biopsy curettage	126	Somewhat enlarged
			27 F	R / Angle, ramus	Multilocular, multiple	Biopsy curettage	66	Subtle, progressive enlargement
			13 F	R / Body	Ground glass radiopacity	Biopsy	54	No change
			12 F	Anterior mandible	Multilocular, multiple	Biopsy	24	Distal progression and slight buccal-lingual expansion

			15 F	L / Body	Ground glass radiopacity	Biopsy	24	Increased radiopacity
			72 F	L / Angle, ramus	Radiopacity, Unilocular, multiple	Partial excision	10	NED
White and Makar[26]	1986	XAN	29 F	L / Body, ramus	Unilocular	Excision	24	NED
Aldred et al.[27]	1989	NOF	18 F	R / Condyle	Multilocular	Resection	-	-
Cale et al.[28]	1989	BFH	13 M	L / posterior maxilla	Unilocular, ill-defined	Excision	-	-
Roche et al.[29]	1993	NOF	26 F	L / Angle, body	Unilocular	Curettage	24	NED
Slootweg et al.[30]	1993	XAN	49 M	L / Angle	Radiopacity, ill-defined	Curettage	-	-
Mizukawa et al.[31]	1998	NOF	7 M	L / Body	Unilocular	Enucleation	14	NED
Uçkan et al.[32]	1999	NOF	16 F	L & R / Mandible and maxilla	Multilocular, multiple	Curettage	36	NED
Bailey et al.[33]	2001	NOF	6 F	R / Angle	Multilocular	Enucleation	-	-
Hudson et al.[34]	2003	NOF	13 M	R / Condyle	Unilocular	Curettage	18	NED
Heo et al.[35]	2004	BFH	42 M	L / Body, ramus, condyle, coronoid process	Multilocular	Resection	12	NED
Marqués Mateo et al.[36]	2004	XAN	11 M	L / Body	Multilocular	Curettage	60	NED
Kishino et al.[37]	2005	BFH	49 F	L / Condyle, ramus	Multilocular	Excision	35	NED
Katagiri et al.[38]	2007	BFH	48 M	R / Condyle, ramus	Unilocular	Curettage	12	NED
Abdelsayed et al.[39]	2010	NOF	14 F	R / Ramus	Multilocular, well-demarcated, scalloped sclerotic borders	Curettage	12	NED
			27 M	R / Ramus	Multilocular, honeycomb	Curettage	24	NED
Chrcanovic et al.[40]	2010	NOF	15 M	L / Angle	Unilocular	Curettage	60	NED
de Moraes Ramos-Perez et al.[41]	2011	XAN	25 M	L / Angle, ramus	Unilocular	Curettage	24	NED

Tanaka et al.[42]	2011	BFH	80 M	R / Body, ramus	Multilocular	Excisional biopsy	6	Recurrence, malignant transformation noted on autopsy
Wagner et al.[43]	2011	BFH	41 M	R/ Body	Multilocular	En-bloc resection	6	NED
Bowers et al.[44]	2013	NOF	22 F	R / Ramus	Multilocular, well-demarcated, sclerotic border	Curettage	12	On-going bony consolidation
Daley et al.[45]	2015	XAN	56 M	L / Body	Unilocular, scalloped	Curettage	24	NED
			24 M	L / Body	Radiolucency, corticated	Curettage	72	NED
			47 M	L / Posterior mandible	Radiolucency	Curettage	66	NED
			48 M	Anterior maxilla	Radiolucency	Curettage	-	-
			22 M	R / Body	Radiolucency	Curettage	12	NED
de Araujo et al.[46]	2015	XAN	14 F	L / Body	Unilocular	Curettage	12	Regression, decrease in size
Shoor et al.[47]	2015	BFH	30 F	L / posterior	Multilocular	Resection	24	NED
Morel et al.[48]	2016	XAN	40 F	L / Body	Multilocular, mixed	Biopsy	6	No change in size
Pattamparambath et al.[49]	2016	BFH	51 F	R / Angle, ramus	Multilocular, mixed, poorly defined	Resection	-	-
Vyloppilli et al.[50]	2016	BFH	46 F	L / Body, ramus	Multilocular	Resection	-	-
Rawal et al.[51] *****	2017	XAN	22 F	R	Unilocular	Curettage	*	NED
			25 M	L	Multilocular	Curettage	*	NED
			15 M	R	Unilocular	Curettage	*	NED
			12 F	R	Unilocular	Curettage	*	NED
			58 F	Anterior maxilla	Unilocular	Curettage	*	NED
			49 F	L	Unilocular	Curettage	*	NED
			36 M	R	Unilocular	Curettage	*	NED
			35 M	L	Unilocular	Curettage	*	NED
			53 F	L maxilla	Unilocular	Curettage	*	NED
			63 F	L	Unilocular	Curettage	*	NED

Cunha et al.[52]	2018	XAN	35 F	R maxilla	Unilocular, mixed	Excisional biopsy	18	NED

NOF, Nonosteogenic fibroma, Nonossifying fibroma or Fibrous cortical defect; *XAN*, xanthomatous lesion, central xanthoma of the jaws, intraosseous primary xanthoma or xanthogranuloma; *BFH*, benign fibrous histiocytoma, histiocytic lesion; *NED*, no evidence of disease

Mandible unless otherwise specified

- Not available / specified

@ Primary case report of Jaffe-Campanacci syndrome. Patient demonstrated multiple NOF (gnathic and long bones) and café au lait spots.

* Group follow-up reported as less than 12 to 144 months, individual follow-up not specified

Table II. Case summary

Case	Predominant xanthomatous component	BFOL-like features	Age (yrs) / Gender	Laterality / Site !	Radiographic appearance	Clinical presentation	Treatment	Follow-up (months)	Clinical follow-up
1			- F	L / body	-	-	Biopsy	-	-
2	+		18 F	L / angle, body	T3	-	Curettage	24	Recurrence at 24 mos
3			18 F	L / body	T3	Incidental, family history of mandibuloacral dysplasia	Biopsy	-	-
4			25 M	- / posterior	T4	-	Biopsy	144*	NC at 72 mos after biopsy
5			38 M	L / -	-	Expansile (2 months)	Curettage	-	-
6			21 M	Maxilla, L / premolar	-	Incidental	Curettage	408	NED
7			13 F	Maxilla - / anterior	-	-	Biopsy	-	-
8			19 M	L / posterior	T4	Incidental	Curettage	-	-
9	+	+	25 M	L / body	T4	-	Curettage	-	-
10			11 F	L / posterior	UC, multilocular	Incidental	Curettage	-	-
11			40 M	L / body	UC, unilocular	Incidental	Biopsy	-	-
12			59 M	Maxilla, L / -	T4	Incidental	Biopsy	-	-
13	+		11 M	R / posterior	UC, unilocular	-	Biopsy	-	-
14			29 M	L / body	UC, unilocular	Incidental	Biopsy	-	-
15			21 F	R / ramus	T4	Expansile, “discomfort”	Resection	-	-
16			23 M	R / angle, body	-	-	Biopsy	-	-
17	+		19 F	L & R / anterior and posterior	T3	-	Biopsy	-	-

18	+		31 F	L / body, ramus	T2	Expansile (7 years)	Biopsy	84*	-
19	+		29 M	L / body, anterior	T4	-	Curettage	204	NED
20			63 F	Maxilla / anterior	UC, multilocular	Expansile	Curettage	-	-
21			30 F	R / posterior	T3	-	Biopsy	-	-
22			27 F	R / ramus	T1	-	Curettage	-	-
23			29 M	R / body	T3	-	Curettage	110	NED
24			53 F	R / posterior	T2	Expansile (10 years), lingual perforation, periapical cemento-osseous dysplasia	Biopsy	120*	-
25			22 M	L / anterior body	UC, unilocular	Incidental	En-bloc resection	7	NED, defect consistent with procedure
26	+		25 F	R / body, ramus	T2	Mild expansion, asymptomatic	Biopsy	96	NC
27			43 M	L / body, ramus	T2	Expansile (5 years)	Biopsy	-	-
28			20 F	R / Ramus	UC, unilocular	-	Biopsy	-	-
29			40 M	L / posterior	-	-	Curettage	24	Recurrence at 24 mos
30			43 F	L / posterior	-	-	Curettage	-	-
31			34 F	R / angle, body	T1	-	Resection	-	-
32			22 F	L / ramus	T2	Incidental	Biopsy	-	-
33			70 F	R / ramus	T3	-	Curettage	-	-
34			18 M	L / ramus, angle	T1	Incidental, Marfan’s disease	Biopsy	108	NC
35			35 M	L / body, angle	T4	-	Biopsy	46	NC, increased

									sclerosis at site
36			18 F	L / ramus, angle	T1	Expansile	Biopsy	-	-
37		+	37 M	- / body	-	-	Biopsy	-	-
38			20 M	L / posterior body	T1	-	Curettage	-	-
39			51 M	L / Body, ramus	T2	-	Biopsy	-	-
40		+	21 M	L / ramus	T2	-	Excisional biopsy	6	Defect consistent with procedure, “healing noted”
41		+	25 M	L / body	T4	-	Biopsy	25	NC, increased sclerosis at site
42			20 M	R / body, ramus	T1	Mild expansion	Biopsy	12	NC
43			22 M	R / posterior	UC, unilocular	Incidental	Curettage	44	NED
44			26 M	Anterior mandible	UC, multilocular	Lingual and buccal cortical perforation	Resection	88	NED
45		+	31 F	R / body	T4	2/10 pain, periapical cemento-osseous dysplasia	Curettage	72*	NC
46		+	22 M	L / ramus	T1	-	Biopsy	72*	NC
47		+	33 M	L / body	T2	Mild expansion	Biopsy	45	NC
48	+		31 F	L / body, ramus	T4	Incidental	Curettage	-	-
49	+	+	25 M	L / ramus	T4	-	Curettage	-	-
50			29 M	L / ramus	T3	-	Curettage	36	NED

NED, No evidence of disease; *NC*, No change in size; *UC* Uncategorized; *T1* Type 1 Multilocular radiolucency with unique punctate and sclerotic appearance; *T2* Type 2 Predominantly radiolucent with large, often poorly defined appearance; *T3* Type 3 Lytic single or multiple unilocular radiolucencies; *T4* Type 4 Mixed density lesions mimicking BFOLs

- Not available / specified

! Mandible unless otherwise specified

* Includes pre-operative radiographic evidence

Table III. Literature summary of immunohistochemical stains performed

Author	Year	CD68	S100	SMA	Other
Cunha et al.[52]	2018	+	-		- CD34, AE1/AE3, desmin
Rawal et al.[51] *	2015	+			*, +163
Pattamparambath et al.[49]	2016	+ focal	-		+ vimentin
Morel et al.[48]	2016	+	-		- CD1a
Shoor et al.[47]	2015	+			
de Araujo et al.[46]	2015	+	-	-	+ vimentin, - CD1a, CD34, desmin, AE1/AE3
Daley et al.[45]	2015	+	+ scattered		+ CD1a, HLADR, - CD34
		+	+ scattered		+ HLADR, - CD1a, CD34
		+	+ scattered		+ HLADR, - CD1a, CD34
		+	+ scattered		+ HLADR, - CD1a, CD34
		+			+ HLADR, - CD1a, CD34
Wagner et al.[43]	2011	+	-	-	+ vimentin, - desmin, cytokeratin, CD56
Tanaka et al.[42]	2011	+	-	-	+ vimentin, a-1-antitrypsin, a-1-antichymotrypsin, - HLADR, CD34, AE1/AE3, EMA
de Moraes Ramos-Perez et al.[41]	2011	+			
Katagiri et al.[38]	2007	+	-	-	+ vimentin, - cytokeratin, CD34
Kishino et al.[37]	2005	+ partial	-	-	+ vimentin, a-1-antitrypsin, a-1-antichymotrypsin, - AE1/AE3, desmin, CD34
Heo et al.[35]	2004	+	-	-	+ vimentin
Marqués Mateo et al.[36]	2004	+			+ vimentin

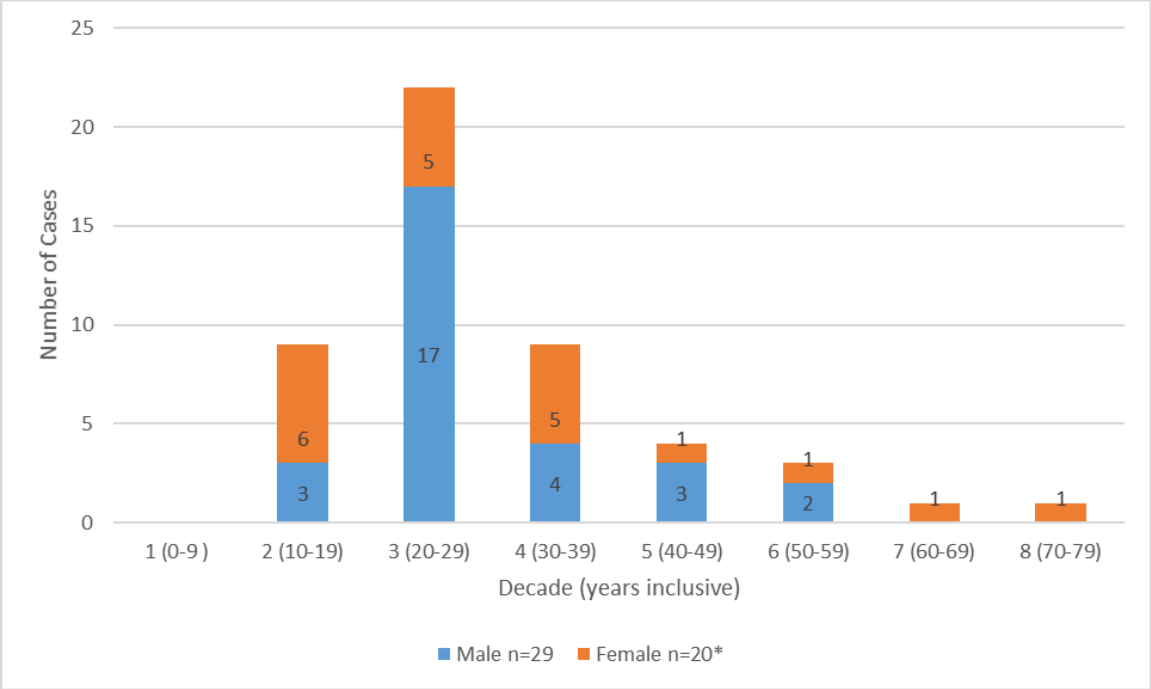
* 10 case study, stated “xanthoma cells…were uniformly, strongly positive for CD68 or CD163…All cases had either CD68 or CD163 to confirm the histiocytic/macrophage lineage of the cells. Some cases had additional immunohistochemical markers to exclude other potential histiocyte containing lesions.” [51]

Table IV. Immunohistochemical staining summary

IHC	Total cases positive (%)
68	22/22 (100%)
163	19/19 (100%)
SMA	15/18 (83%)
S100	0/18 (0%)

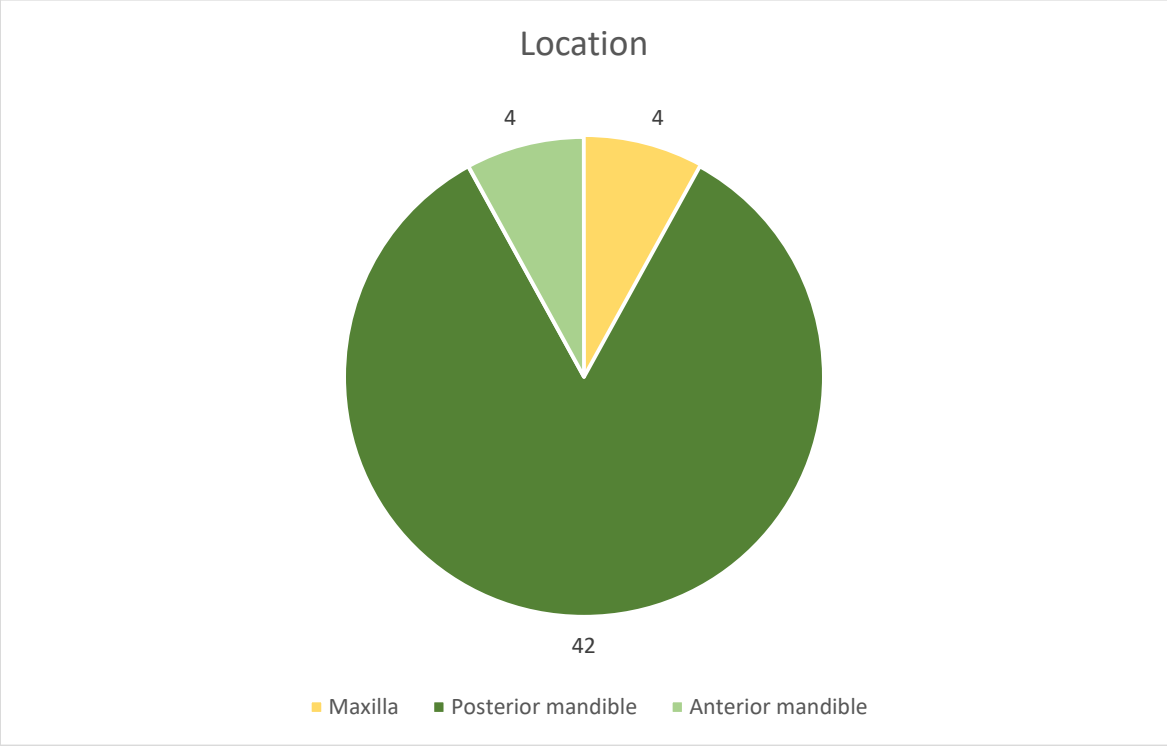
VII. FIGURES

Fig. 1. Age distribution with gender separation.



* One female case did not specify age.

Fig. 2. Presenting location.



* Anterior mandible includes two cases presenting in both anterior and posterior mandible.

Fig. 3. Radiographic findings. **A, B, C,** Panoramic radiographs demonstrating Type 1 – Punctate, sclerotic variant (Cases 22, 34, 42 respectively). **D, E, F,** CT Type 1 (Case 42, sagittal, axial, coronal views). **G** Panoramic radiographs demonstrating Type 2 – large, ill-defined, primarily radiolucent (Case 47). **H,** Type 3 – Lytic, unilocular radiolucencies (Case 23). **I,** Type 4 – BFOL-like mimic (Case 35).

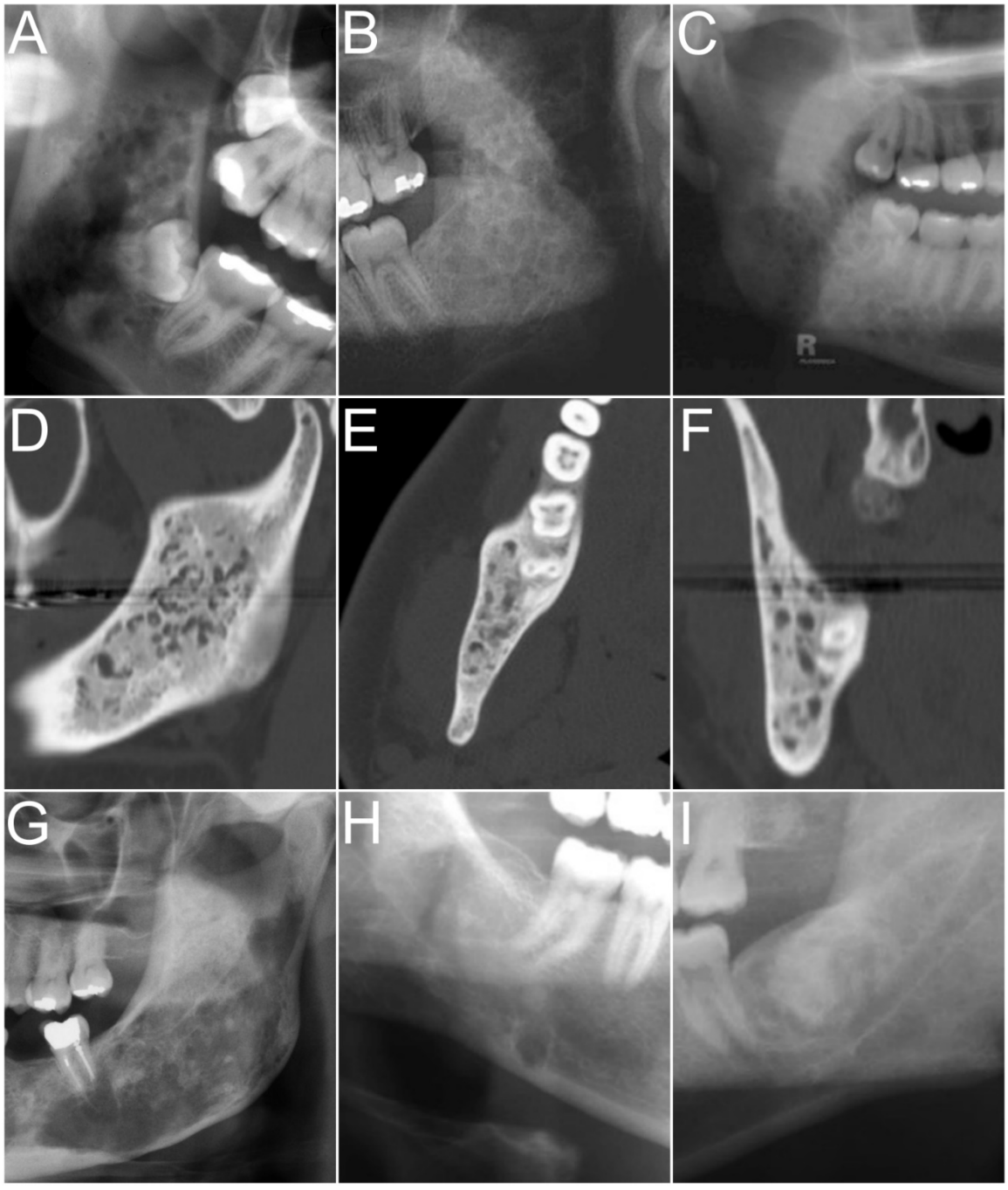


Fig. 4. Histomorphologic findings (H&E staining). **A, B,** Classic presentation demonstrating a cellular, spindled, storiform proliferation with focal foamy, xanthomatous histiocytes and multinucleated giant cells (Case 25, x100, x200 respectively). **C, D,** Xanthomatous predominant variant with numerous foamy, xanthomatous histiocytes with limited storiform, spindled component (Case 9, x100, x200 respectively). **E,** BFOL-like reactive bone with mildly increased xanthoma cells (Case 41, x100). **F,** Ossifying fibroma-like cementum droplet (Case 46, x100).

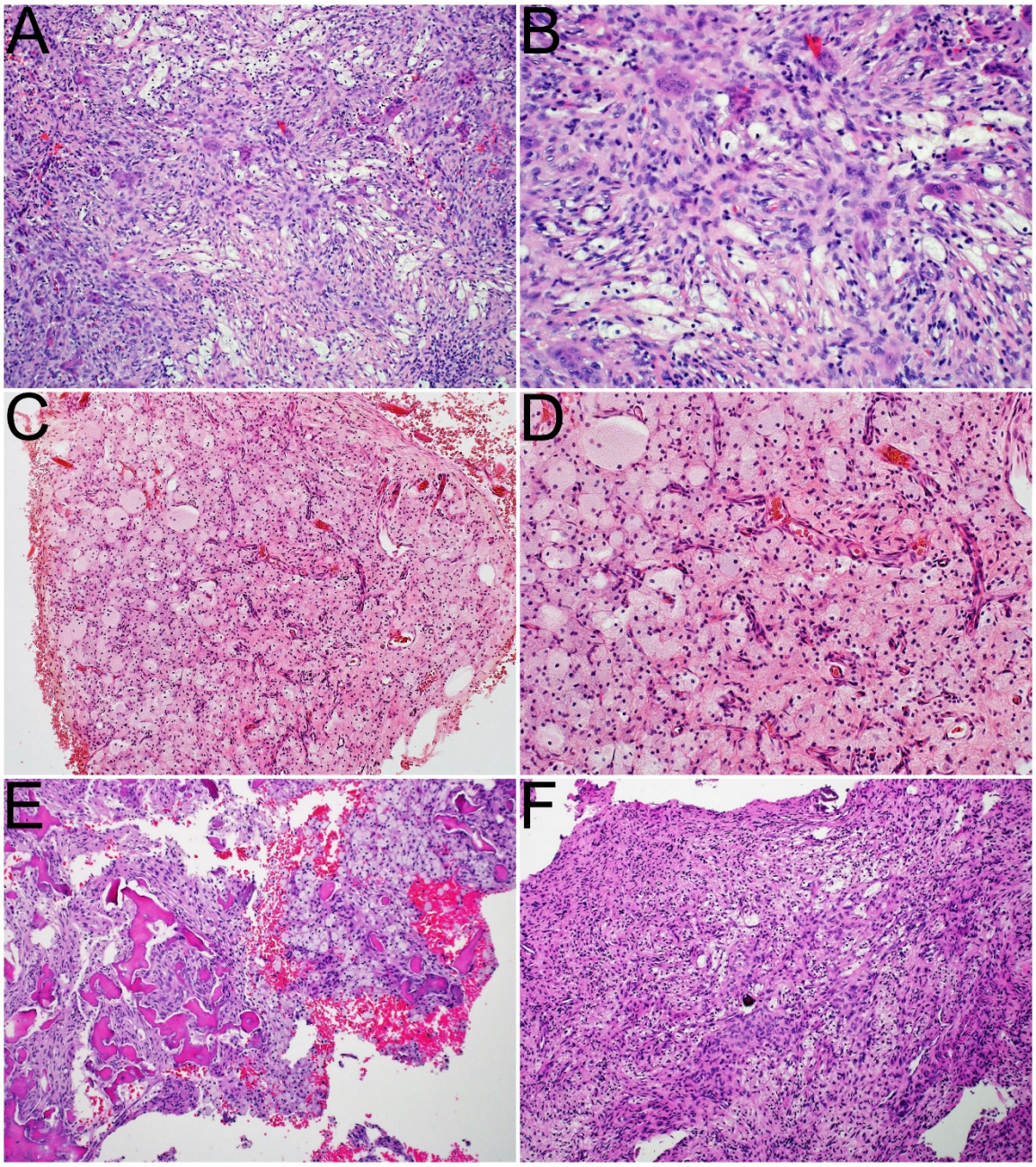
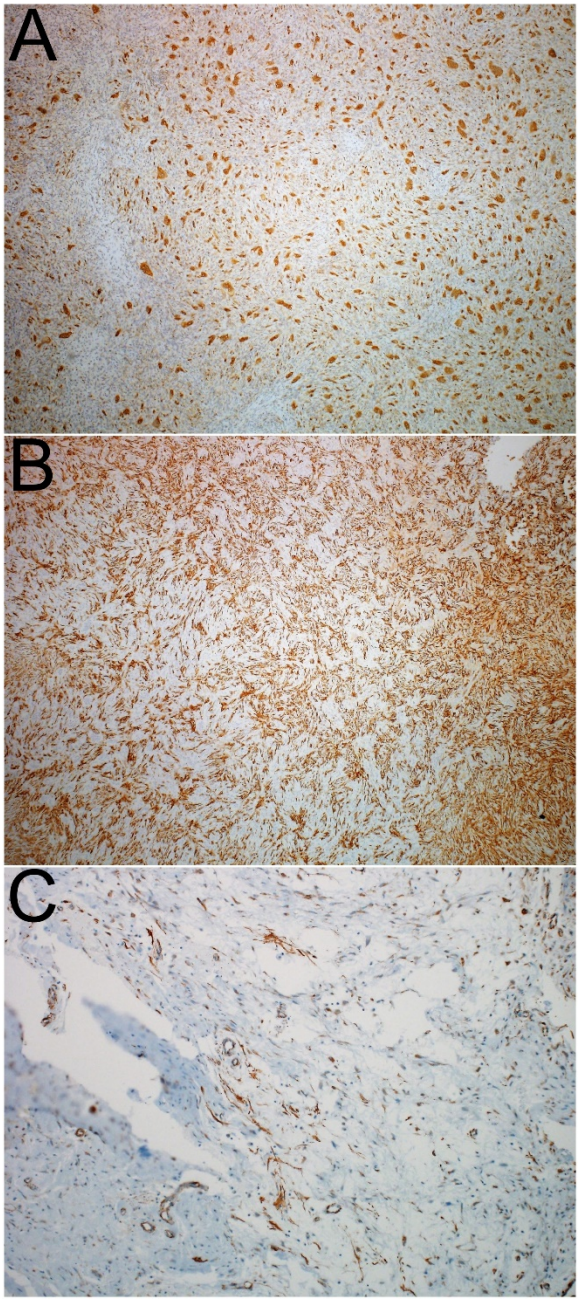

A
B
C
D
E
F

Fig. 5. Immunohistochemical findings. **A,** CD68 demonstrating strong, positive reactivity with histiocytes and moderate reactivity with spindle cell component (Case 25, x100). **B,** CD163 demonstrating strong, positive reactivity with histiocytes and spindle cell component (Case 25, x100). **C,** SMA demonstrating focal reactivity with spindled components interspersed amongst foamy histiocytes and vascular structures (Case 47, x100).



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