

Xanthogranulomatus inflammatory lesion mimicker of malignancy: A clinicopathological study from rural India

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ABSTRACT

OBJECTIVE: Xanthogranulomatus inflammation is an uncommon variant of chronic inflammation and a well-established pathological entity involving various organs and systems. It may be associated with infection and obstruction, defective lipid transport, immunological disturbances, and often confused as a malignant neoplasm. The confirmatory diagnosis is made on histopathology.

METHODS: This is a retrospective study conducted from January 2008 to April 2020 on histopathologically diagnosed xanthogranulomatus lesions. All the relevant available data regarding age, sex, and organ involvement were collected from histopathology lab records. The macroscopic and microscopic evaluation of cases was also done. This study was aimed to determine the significance of histopathology in the diagnosis of xanthogranulomatus lesions, revealing pathological changes, and clinicopathological correlation.

RESULTS: In the current study, there were 93 cases of xanthogranulomatus inflammatory lesion. Gall bladder was frequently involved 70 (75.27%), followed by 5 (5.37%) kidney, gastrointestinal Tract 6 (3 [3.23%] cases in colon and 3 [3.23%] in appendix, respectively), and others. The maximum number of cases was in the age group of 31–40 years with 24 (25.80%) cases. The female to male sex ratio was 2.3:1.

CONCLUSION: Awareness and knowledge of xanthogranulomatus inflammatory lesion is significant to the pathologist and surgeon to prevent extensive surgery. This lesion often mimics as malignancy and confirmatory diagnosis is made on histopathology. Thus, every excised specimen must be examined histopathologically to diagnose and rule out differential.

Keywords: Histopathology; lipid-laden macrophages; malignancy; Touton giant cell; xanthogranulomatus inflammation.

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Xanthogranulomatus inflammation (XGI) is a distinct uncommon type of chronic inflammation and a well-established pathological entity involving various organs and systems. It is characterized by xanthogranuloma which is composed of lipid laden foamy macrophages, lymphocytes, plasma cells with variable number of foreign body giant cells that leads to destruction of tissue of the affected organ [1].

The exact etiopathogenesis of xanthogranuloma remains uncertain but it may be associated with infection and obstruction, defective lipid transport, and immunological disturbances. A combination of factors may be responsible in some cases. The normal structures in the involved organ may undergo destruction and effacement that may be occasionally confused as malignant neoplasm. On the imaging studies, it appears as a locally invasive malignant lesion [2].



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XGI was first reported in the genitourinary tract [3]. It can involve various organ, such as bronchi, lung, endometrium, vagina, fallopian tubes (FTs), ovary, testis, epididymis, stomach, colon, ileum, appendix, pancreas, bone, lymph nodes, bladder, prostate, adrenal gland, abdomen, breast, urachus, and branchial cleft cyst [4–6]. However, the most common sites are kidney and gallbladder [7, 8]. Researchers also suggested that a wide array of entities characterized by a large content of histiocytes and foamy macrophages could be traced back at least in part to a XGI. Typical gross findings includes bright yellow or golden yellow mass-like lesions or streaks and macroscopic examination is associated with abscess cavities, micro-abscesses, and large numbers of lipid-laden macrophages as well as minor component of chronic and acute inflammatory cells, foreign body-type and touton-type giant cells, cholesterol clefts and hemosiderin deposits are additional findings and varying proportions of fibrous tissue [9]. This study was planned with aim to determine the significance of histopathology in the diagnosis of xanthogranulomatus lesions revealing pathological changes occurring during xanthogranulomatus process and performing clinico-pathological correlation including its variable such as age, sex, site, and presenting complaints.

MATERIALS AND METHODS

This is a retrospective study conducted on histopathologically diagnosed xanthogranulomatus lesions reported in the department of pathology from January 2008 to April 2020. All the cases reported as xanthogranulomatus lesions on histopathology were included in the study.

The received specimens were fixed in 10% formal saline, sectioned at 4 μ , processed by routine methods, stained with Hematoxylin and Eosin (H&E) stain. Along with that periodic acid-Schiff (PAS) and acid-fast bacilli stains were also applied where ever required to rule out differential. Additional sections if required were also taken. All the relevant available data regarding age, sex, and organ involvement were also collected from histopathology lab records. The macroscopic and microscopic evaluation of specimens was done and the results were analyzed.

Ethical approval was taken from UPUMS Institutional ethical Committee on 27.2.19 with reference no. 231/18.

Highlight key points

- Xanthogranuloma is a distinct chronic inflammatory lesion.
- It involves various organs but gall bladder and kidney were the common organs found involved.
- Its often mimics malignancy on clinical and radiological examination.
- Knowledge and awareness of this inflammatory lesion are mandatory to surgeons and pathologist to reduce radical surgeries.
- Xanthogranuloma confirmatory diagnosis is made on histopathology examination, so every excised specimen must be examined histopathologically for the diagnosis and to rule out differential.

TABLE 1. Organs distribution of XGI

Specimen	Number	XGI	Percentage of total cases	Organ wise incidence (%) of XGI
GB	7783	70	75.27	0.89
Kidney	113	5	5.37	4.42
Fallopian tube	2471	2	2.15	0.08
Ovary	1040	2	2.15	0.19
Endometrium	2961	1	1.08	0.03
Testis+Spermatic cord	90	2	2.15	2.22
Colon	220	3	3.23	1.36
Appendix	594	3	3.23	0.51
Thyroid	137	1	1.08	0.73
Thyroglossal cyst	15	1	1.08	6.66
Tendon	18	1	1.08	5.56
Eye	180	1	1.08	0.56
Bone	138	1	1.08	0.73
Total	15760	93	100	

XGI: Xanthogranulomatus inflammation. Gall bladder was the most common organ involved with XGI.

RESULTS

A total of 93 cases of xanthogranulomatus inflammatory lesion were diagnosed by histopathology, out of which gall bladder constituted 70 (75.27%) cases followed by kidney having 5 (5.37%) cases, six cases in gastrointestinal tract (3 [3.23%] cases in colon and 3 [3.23%] in appendix, respectively), five cases in female genital tract

TABLE 2. Age distribution in Xanthogranulomatus lesion

Organ	0–10 yrs	11–20 yrs	21–30 yrs	31–40 yrs	41–50 yrs	51–60 yrs	61–70 yrs	71–80 yrs	81–90 yrs	Total
GB			12	18	16	16	7		1	70
kidney	1		2	1	1					05
FT		1	1							02
Ovary and FT				1	1					02
Endometrium						1				01
Testis					1					01
Spermatic cord				1						01
Colon				2	1					03
Appendix			2				1			03
Thyroid			1							01
Thyroglossal cyst	1									01
Eye					1					01
Tendon				1						01
Bone					1					01
Total (%)	2.15	1.08	19.3	25.80	23.66	18.28	8.60		1.08	93

FT: Fallopian tube. (31–40) years was the frequent age group involved with Xanthogranulomatus inflammation.

(2 [2.15%] cases in FTs, 2 [2.15%] cases in ovary and 1 [1.08%] case in endometrium), and three cases in head and neck (1 [1.08%] case each in thyroid, thyroglossal cyst and eye), similarly there was one (1.08%) case in bone and 1 (1.08%) case in tendon (Table 1).

The maximum number of cases was in the age group of 24 (31–40) years aggregating (25.80%) followed by 22 cases in the age group of (41–50) years constituting (23.66%) (Table 2).

The female to male sex ratio was 2.3:1. XGI was found common in females, while in colon, appendix, thyroid, thyroglossal cyst, tendon, and bone, results were found opposite (Table 3).

Among the gall bladder cases minimum, maximum and mean age in our study was 21, 90, and 46.5 years, respectively, with female preponderance (F:M ratio 3.12:1) (Table 4).

All the histopathologically diagnosed xanthogranulomatus cholecystitis was associated with cholelithiasis. Perforation was present in one case (90 years female) whereas adhesion was found in four cases and even one case of xanthogranuloma cholecystitis was found associated with adenocarcinoma of gall bladder. In most of the cases on gross examination, gall bladder wall was found

TABLE 3. Sex distribution for XGI in various organs

Organs	Male	Female	Total
Gall bladder	17	53	70
Kidney	1	4	5
Colon	2	1	3
Appendix	2	1	3
Thyroglossal cyst	1	0	1
Thyroid	1	0	1
Tendon	1	0	1
Eye	0	1	1
Genital tract	2	5	7
Bone	1	0	1
Total	28	65	93

XGI: Xanthogranulomatous inflammation. The frequency of XGI was found more among females.

irregularly thickened with yellow deposit, while on microscopy showed xanthoma cells with other inflammatory cells and giant cell reaction (Fig. 1A).

Kidney was the 2nd most common organ involved with xanthogranuloma in current study (5 cases).

TABLE 4. Age and sex distribution in xanthogranulomatous cholecystitis

Age	Male	Female	Percentage
21–30	0	12	17.14
31–40	6	12	25.71
41–50	4	12	22.86
51–60	4	12	22.86
61–70	3	4	10
71–80	0	0	0
81–90	0	1	1.43
Total	17	53	100

31–40 years age group was more diseased with XGI cholecystitis.

Among these patients, four were females which were of young age group, while one male was also there, who was 6 years old. There was preponderance of involvement of the left kidney. Grossly, in maximum cases yellow deposit seen and in few cases most parts of the kidney were replaced by fibrofatty tissue. In 40% cases (i.e., in two cases, 24 years female and 6 years male) staghorn calculi was identified. In one another case, there was renal lipoma along with xanthogranulomatous pyelonephritis. Among all the cases one case was suspected as malignant clinically but it was diagnosed as xanthogranulomatous lesion on microscopic examination. All the five cases were of chronic pyelonephritis, out of which two were having focal xanthogranulomatous changes while three cases were having extensive xanthogranulomatous pyelonephritis (Fig. 1B).

FT, ovary, and testis with spermatid cord were next common organs involved with XGI in present study (two cases in each, respectively). On histopathological examination of FT, expansion of tubal plica by infiltration of foamy histiocytes, few lymphocytes, and plasma cells were seen favoring xanthogranulomatous salpingitis. Ovary also presented as tuboovarian mass which was mimicking as malignancy. In gross of this testis areas of yellow deposits were also seen which on histopathology showed foamy histiocytes in the stroma of testis with other inflammatory cells (Fig. 2).

Colon and appendix were the next organs involved with XGI in our study (three cases in each). Grossly, there was colon stricture in one case and growth in the lumen in another case and one more case of colon was excised due to suspicion of tuberculosis of colon.

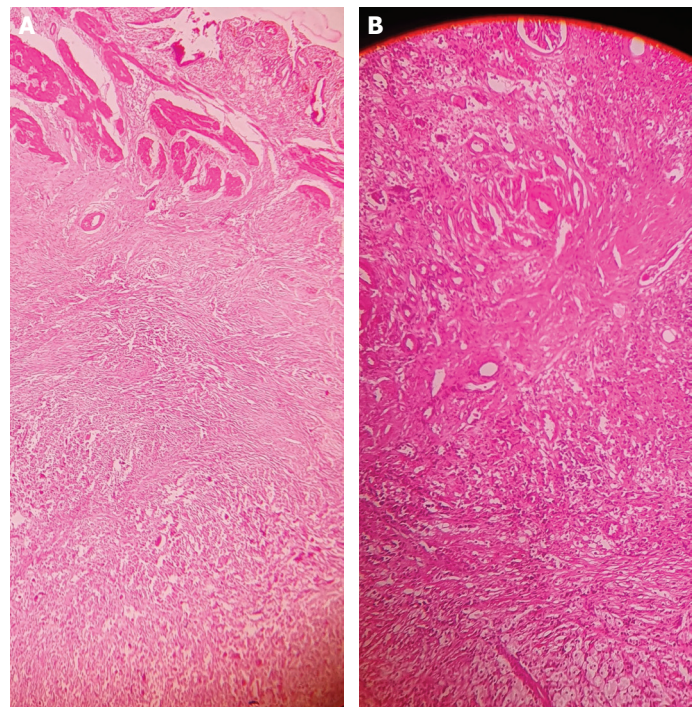


FIGURE 1. (A) H&E ($\times 10$) stained section of Xanthogranulomatous lesion gall bladder. (B) H&E ($\times 10$) stained section of Xanthogranulomatous lesion kidney.

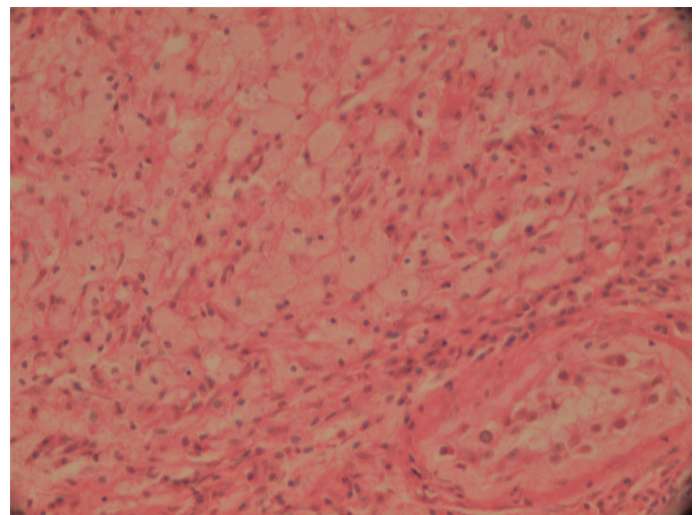


FIGURE 2. H&E ($\times 40$) stained section of Xanthogranulomatous lesion testis.

All the cases of appendix were excised for appendicitis. None of them found malignant on histopathology.

Along with the above-mentioned organs single case of XGI was found in endometrium, thyroid, thyroglossal cyst eye, bone, and tendon, respectively. All of these cases were belonging to young age group, with age rang-

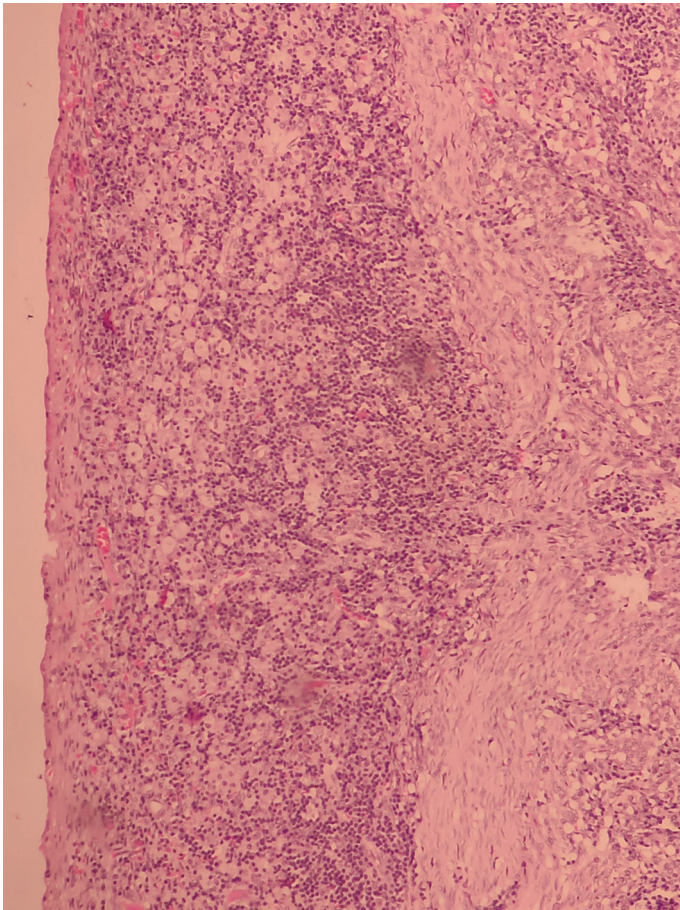


FIGURE 3. H&E ($\times 40$) stained section of Xanthogranulomatus lesion endometrium.

ing from 10 to 45 years. In thyroglossal cyst, ZN and PAS were also applied to rule out any other pathology if present. In endometrium, XGI was an incidental finding (Fig. 3), which is a rare presentation. Clinically granuloma was suspected in eye and similarly, the bone case was diagnosed as giant cell lesion on fine needle aspiration (clinically it was having diffuse swelling raising suspicion for malignancy). On histopathology bone case was diagnosed as xanthogranulomatus osteomyelitis. Tendoachillies tendon case on microscopic examination showed cholesterol clefts surrounded by collagenous fibrous stroma which was infiltrated by multinucleated giant cells, histiocytes and mixed inflammatory cells. In thyroid mass, hashimoto thyroiditis with xanthogranulomatus change was seen histopathologically

Statistical Analysis

In the current study, statistical analysis was done by percentage.

DISCUSSION

XGI is a pathological entity with unique characteristic macroscopic and microscopic features. It presents as destructive tumor-like masses with variable extension into adjacent fat and connective tissue, often mimic as malignancy [10].

Under microscope, XGI includes cellular components such as neutrophils, lymphocytes, plasma cells, erythrocytes, hemosiderin-laden macrophages, and foamy histiocytes. The latter are interspersed among other cells but often they cluster in a compacted mosaic-like pattern. The large lipid-laden macrophages display an eosinophilic or clear cytoplasm with a granular and vacuolated quality but can also have a spindle shape. Foreign body-type and touton-type giant cells, calcospherites, cholesterol clefts, and hemosiderin deposits are additional findings. Hemorrhage, suppuration, and necrosis are therefore, the initial conditions leading to the xanthogranulomatus response. Plasma cells and fibrosis increases in later stages with the former being numerous and prominent. The presence of calculi or biliary tree obstruction may play an important role in pathogenesis of xanthogranulomatus cholecystitis, analogous to xanthogranulomatus pyelonephritis [11].

Its importance lies in the fact that clinically and radiologically, it can be confused with carcinoma.

In our study, gall bladder was the most common organ involved by XGI (Table 1). In a review of 53 cases of gall bladder adenocarcinoma by Lopez et al. [12], five cases were associated with diffuse XGI including close admixture of inflammatory and neoplastic components in three cases making a prompt diagnosis difficult.

Xanthogranulomatus cholecystitis may presents as growth with adjacent organ invasion like a malignant neoplasm but also is infrequently associated with gall bladder carcinoma [12, 13, 14]. It was pragmatic that there was a direct relationship between gallbladder wall thickness and the degree of inflammation; therefore, the degree of gallbladder inflammation was severe with thicker gallbladder wall, and this pointed to the existence of a thick, dysfunctional, and inflamed gallbladder with impaired contractility which makes the diagnosis suspicious for malignancy clinically. It has been reported that gall bladder carcinoma can be seen as a coexistent lesion with xanthogranulomatus cholecystitis in 2–35.4% of the cases. In current study one case of xanthogranulomatus cholecystitis was found associated with malignancy, similar in the study done by Laishram et al. [13].

The incidence of xanthogranulomatus cholecystitis varied from 0.7% to 10% in different studies [13–15]. Similarly, in the current study, the incidence was 0.89%. In our study, all cases of xanthogranulomatus cholecystitis were associated with cholelithiasis. All these findings were in accordance to study done by Laishram et al. [13]. In their study, xanthogranulomatus cholecystitis constituted 1.5% of the total cholecystectomy specimens, 86.4% cases were associated with calculi [13]. This justify that the stone could be initiating factor for the genesis of XGI.

The mean age at presentation for xanthogranulomatus cholecystitis varies in different studies ranging from 44 to 63 years, which was in accordance with our study in which mean age was 46.5 years. There was female preponderance in our study (M:F ratio 2.3:1). Similarly, results were found from other researchers [13, 15].

In our study, xanthogranulomatus pyelonephritis constituted 5.37% of the total xanthogranulomatus (5/93 cases) and the incidence was third highest with 4.42% (5/113) of the total nephrectomy specimens. These findings were in accordance with the study done by Laishram et al. [13], in which xanthogranulomatus pyelonephritis constituted 5.1% of the total XGI (5/98) but the incidence was highest with 12.19% (5/41) of the total nephrectomy specimens.

In our study, among the cases of xanthogranulomatus pyelonephritis most of patients were young females, out of which 40% cases were associated with staghorn calculi. Left kidney was more affected in comparison to right kidney. Similarly, in the study done by Chuang et al. [16] xanthogranulomatus pyelonephritis usually affects middle aged females. The most instances of diffuse xanthogranuloma develop in the setting of obstruction due to infected renal calculi. Similar to our study, in study by Korkes et al. [17], about 34% of the affected individuals had a staghorn calculus and according to them, usually there is a massive destruction of renal parenchyma that occurs due to the presence of chronic obstruction and suppuration. However, in study done by Laishram et al., Kundu et al., and Nawaz et al., the higher incidence of calculi was observed, which was 90.2%, 90%, and 100%, respectively [13, 18, 19]. This difference might be because of difference in study population.

In our study, grossly there was colon stricture in one case, growth in lumen in another one and the last case was excised due to suspicion of tuberculosis of colon. All these patients were of middle age, so according to the age the chances of malignancy was less, but the ir-

regular growth in radiological findings raised suspicion of malignancy. Similarly, in a case reported by Kapoor et al. [20], in a 65-year-old woman, right hemi-colectomy was performed because of contrast enhanced computed tomography of abdomen revealed a solid irregular mass in the ascending colon with large necrotic areas and surrounding enlarged nodes suggestive of malignancy arising from the right colon but histopathology of the surgical specimen showed florid inflammatory infiltrate with collection of histiocytes, lymphocytes, and polymorphs. Further on the immunohistochemistry CD68 and CD45 were found to be positive and pan-cytokeratin was negative. Similar incident also happened in a colon case reported by Dhawan et al. [21].

In the current study, all the cases of appendix were excised for appendicitis. XGI was an incidental finding in them. Incidence of involvement of appendix was 0.51%, which was in accordance to the study done by Laishram et al. [13]. In their study, incidence in appendix xanthogranuloma inflammation was lowest with 0.25% of the total appendectomy specimens [13]. Guo and Greenson [22] compared histopathology of all interval appendectomy specimens with a control group of patients who had acute appendicitis and underwent appendectomy, 36.4% of the interval appendectomy cases had XGI compared to none in the acute appendicitis group ($p < 0.0001$).

There were five cases of XGI found in female genital tract in our study. One case was of xanthogranulomatus endometritis in 55 years female presented with prolapse. The age of the patient was in accordance with previously reported cases of xanthogranulomatus endometritis. The age at onset ranges from 59 to 88 years, with an average age of 72 years. Xanthogranulomatus endometritis was also named as histiocytic endometritis. XGI of the female genital tract is an unusual lesion, and clinically forms mass-like lesion in the pelvic cavity that invades the surrounding tissues, which may mimic the tumor clinically and on imaging. There are two groups of xanthogranulomatus endometritis; one is pure XGI, the other is xanthogranulomatus endometritis accompanied with endometrial cancer [23].

Among the 15 reported cases of xanthogranulomatus endometritis in literature; nine cases are accompanied with endometrial cancer. The histological changes are similar to those in FTs. Nevertheless, the affected endometrial glands may disappear completely and disintegrate, occasionally be necrotic. There is usually exudation

covering the endometrial serosal surface. The concomitant cancer mainly is endometrioid carcinoma.

In our study, there were two cases of xanthogranulomatus oophoritis and xanthogranulomatus salpingitis each, respectively. XGI of female genital tract is a rare and special type of chronic inflammation with destruction of the tissues of affected organs. Only 13 cases of XGI of ovary and FT have been reported in the literature till date [24]. Actinomycosis, tuberculosis, and XGI of ovary are rare but are specific causes of transovarian abscess, sometimes these can be misdiagnosed as ovarian neoplasms due to their unusual appearances on sonography, computed tomography, and even on magnetic resonance imaging [25].

There were two cases of XGI in testis with spermatid cord. It is also a rare presentation. In literature only 12 cases of xanthogranulomatus orchiepidymitis had been reported [26]. In most of the reported cases testicles and spermatid cord both were involved. Similarly, in our cases both the testicles and spermatid cord were involved.

In the current study, we found three cases in head and neck region, one case each in thyroid, thyroglossal cyst and eye, respectively. The head and neck region is also an uncommon site for XGI. This type of inflammatory reaction has been defined in branchial cleft cyst, salivary gland tumors following fine-needle aspiration biopsies, Rathke's cleft cyst in the pituitary gland, and colloid cyst in the 3rd ventricle [27]. Thyroglossal cyst characterized by an infiltrative subcutaneous central neck lesion, clinically mimicking a thyroid carcinoma. Patients may present with radiologic findings mimicking an invasive malignant tumor, and should be taken into account during the differential diagnosis with cystic squamous cell carcinoma.

Histopathologically, adult orbital xanthogranulomatus is characterized by infiltration of foamy histiocytes and Touton-type giant cells, they are often negative for S100 and CD1a and positive for CD 68. This infiltration, along with accompanying lymphocytes, can replace the normal lacrimal gland architecture, causing mass effects, and loss of tear production [28].

Xanthogranulomatus osteomyelitis is also a rare finding, mimicking malignancy of bone. Its pathogenesis is still not very clear but according to the Borjian et al. [29] delayed-type hypersensitivity reaction of cell mediated immunity may be implicated in its pathogenesis.

Xanthogranuloma of Achilles tendon is also a rare variety, one case of which was found in our study. It may

occur due to familial hypercholesterolemia, type 2 and 3 hypoproteinemias and cerebrotendinous xanthomatosis. It should be differentiated from tophaceous gout, chronic tendon degeneration (e.g. mucoid), tendinosis, partial-thickness tears, and giant cell tumor of the tendon sheath [30].

The coexistence of cancer and XGI is rare but also described in the literature [31]. Pathologically, other lesions containing foam cells should be distinguished from XGI. Differentials may include malakoplakia or pseudoxanthomatous inflammation. Poorly differentiated carcinomas or diffusely infiltrating histiocytic lymphomas can be differentiated with the help of immunohistochemistry.

Conclusion

Awareness of this inflammatory lesion is important to the pathologist and treating surgeon to prevent extensive surgery and also over diagnosis as malignancy. Although a correct diagnosis is chiefly made through histopathology, a suggestive preoperative and intraoperative diagnosis of XGI could lead to less radical surgery.

Ethics Committee Approval: The UPUMS University Clinical Research Ethics Committee granted approval for this study (date: 27.02.19, number: 231/18).

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