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Xanthogranulomatous Appendicitis: an Unusual Pattern of Appendiceal Inflammation

Rana Shaker AL-Zaidi*
Consultant anatomic pathologist, King Faisal Hospital, Prince Majed Bin Abdulaziz Road, Al Maabda, Makkah, kingdom of Saudi Arabia

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***Corresponding author**
Rana Shaker AL-Zaidi

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Abstract: Xanthogranulomatous inflammation is an unusual destructive chronic inflammatory process that involves various organs & tissues particularly gallbladder (xanthogranulomatous cholecystitis) & kidney (xanthogranulomatous pyelonephritis). Xanthogranulomatous appendicitis (XA) is a rare form of appendiceal inflammation that has been regarded as an unusual healing pattern of appendicitis associated with delayed or interval appendectomy. It poses a significant diagnostic challenge because it can mimic clinically, radiologically, & even pathologically malignant tumors as well as other inflammatory processes of appendix. Little information has been written in the literature regarding this entity. In this review article, data have been collected from all the previously reported cases in the literature including my observation in a XA case I have diagnosed.

Keywords: xanthogranulomatous, inflammation, appendicitis, histiocytes, appendix.

INTRODUCTION

Xanthogranulomatous inflammation is a well– known form of chronic inflammation involving various organs and characterized histologically by collection of lipid‑laden macrophages admixed with lymphocytes, plasma cells, neutrophils, and often multinucleated giant cells with or without cholesterol clefts [1]. The inflammation often causes significant tissue destruction. It was first described in the kidney by Osterlind in 1944 [2]. Other organs in which xanthogranulomatous inflammation has been reported include gallbladder, stomach colon, anorectal area, endometrium, ovary, fallopian tubes, vagina, testis, prostate, epididymis, urinary bladder, bone, skin, appendix, thyroid, lung and adrenal glands [3, 4].

The involvement of appendix by xanthogranulomatous inflammation is a rare phenomenon with only 12 reported cases in the literature [5].

Clinical & radiological features

On the basis of a reported series, XA occurs in adults with a mean age of 47.9 year (83%, 21-78 years). It is rare in pediatric age group, with only three cases have been reported in the literature [5, 6]. There is no sex predilection. Clinical presentation of XA is quite variable. Most of the patients present with right iliac fossa abdominal pain, fever, nausea, and vomiting [7]. Birch *et al*., suggested an association of the xanthogranulomatous process with long-standing inflammation of the appendix and formation of the appendiceal mass [8]. In contrast, Munichor *et al*., and Omar *et al*., reported cases of xanthogranulomatous appendicitis with typical signs and symptoms of acute appendicitis [9, 10]. Due to the destructive nature of the disease, XA can occasionally present with a mass lesion which can mimic locally advanced cancer but it has a benign course and can be cured by surgical resection. Chuang *et al*. in 2005 reported a case of a 39-year-old man who was admitted with fever, lower abdominal pain, and a mass in the right iliac fossa. With a suspicion of cancer, right hemicolectomy was performed but on histopathological examination it turned out to be XA [7].

Radiological findings are non-specific; however consistent radiological features of XA could not be validated (Fig-1) [6]. CT scan may show the presence of appendiceal mass and that lack invasion to the surrounding tissues [11].

Pathological findings

XA is a pathologic entity with characteristic macroscopic and microscopic features. Grossly, the typical findings include bright yellow or golden yellow mass-like lesion associated with abscess cavities [1].

Microscopic examination of AX usually reveals a nodular or diffuse mucosal to transmural collection of macrophages including foamy histiocytes (xanthoma-type cells), intermixed with varying amounts

of other inflammatory cells, such as foreign body-type multinucleated giant cells, lymphocytes, plasma cells, neutrophils, and eosinophils (Fig-2 to 7). Occasionally, fibrosis, cholesterol clefts, granulation tissue, and necrotic debris are observed along with reactive lymphoid hyperplasia [12]. The adjacent non-inflammed mucosa may show hyperplastic epithelial changes (Fig-8). Xanthogranulomatous inflammation causes significant destruction and effacement of the normal architecture of the involved organ and could be misinterpreted as a locally invasive malignant lesion [13, 14].

The histiocytes in XA are immunoreactive for CD68, while negative for S100 protein and Cytokeratins (Fig-9, 10). They do not stain for periodic-acid-Schiff (PAS), iron stain (Perl's stain); and calcium stain (von Kossa).

Cytological evaluation of the touch imprint preparation for intraoperative diagnosis of XA has been discussed by R Kaushik *et al*., in 2017. Smears revealed benign glandular epithelial cell groups and sheets of xanthoma cells along with multinucleate histiocytic giant cells in the background of neutrophils and mononuclear inflammatory cells [15]. The intraoperative cytological evaluation of XA can play a rule in avoiding extended surgical resections since XA can resemble malignancy at surgery.

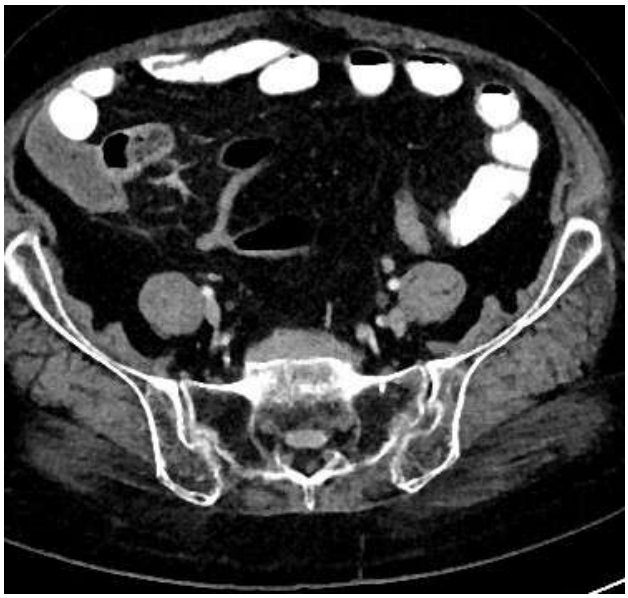

Fig-1: Axial computed tomography of abdomen with contrast. The appendix is distended with luminal diameter of 1.1cm & thickened enhancing wall.

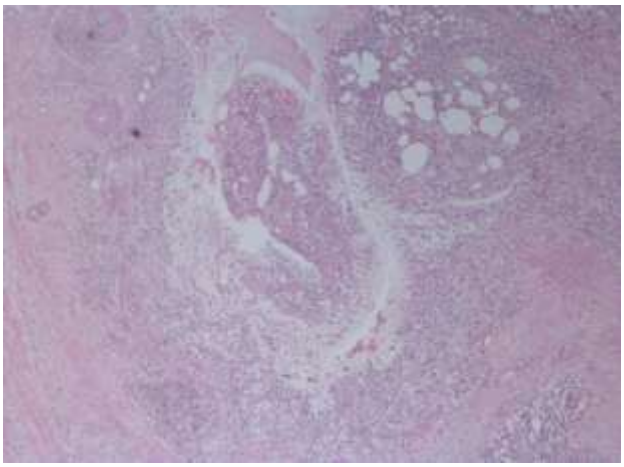

Fig-2: Xanthogranulomatous appendicitis. Dense transmural mixed inflammatory cells infiltrate including foamy histiocytes is noted in the partially destructed appendix wall. Note the completely ulcerated mucosal lining (empty space is the appendix lumen). (H&E, 40X original magnification).

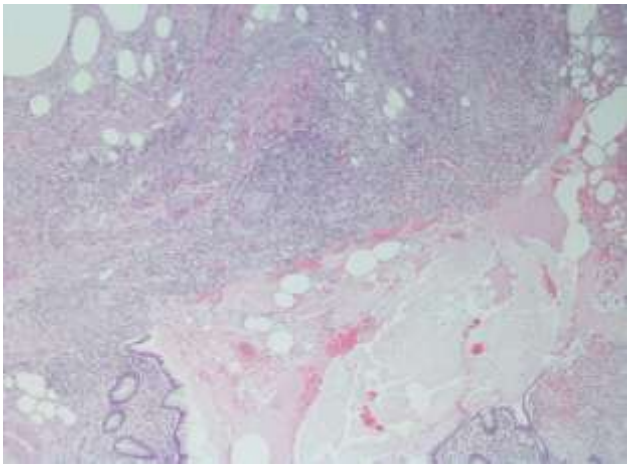

Fig-3: Xanthogranulomatous appendicitis. Focal mucosal ulceration & transmural dense mixed inflammatory cells infiltrate including foamy histiocytes are seen. (H&E, 40X original magnification).

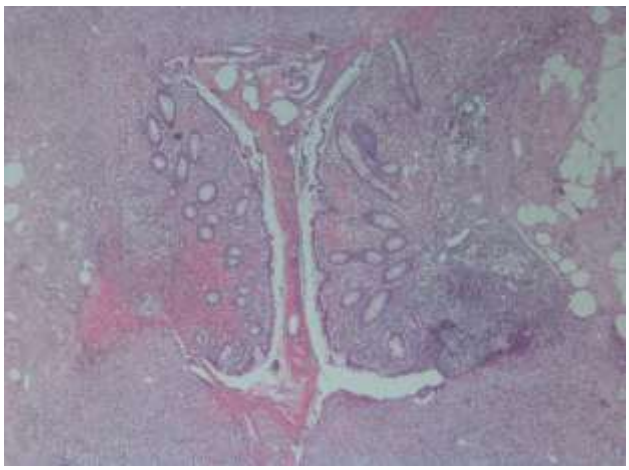

Fig-4: Xanthogranulomatous appendicitis. The mucosa is partially ulcerated. Dense transmural mixed inflammatory cells infiltrate including foamy histiocytes is seen infiltrating the appendix wall. (H&E, 40X original magnification).

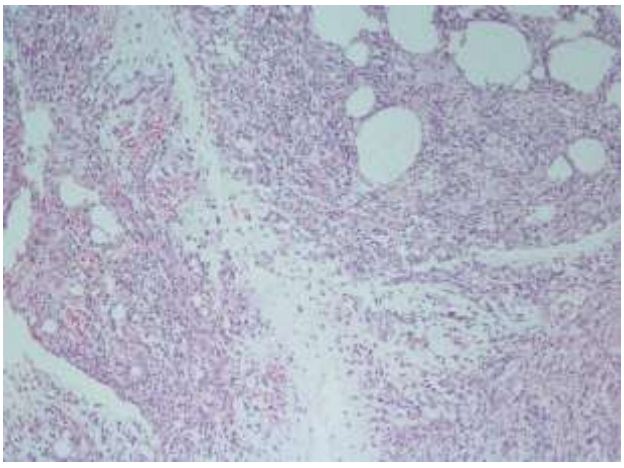

Fig-5: Xanthogranulomatous appendicitis. Foamy histiocytes (right upper corner) mixed with other inflammatory cells are noted in the wall. Note the completely ulcerated mucosal lining (empty space is the appendix lumen). (H&E, 100X original magnification).

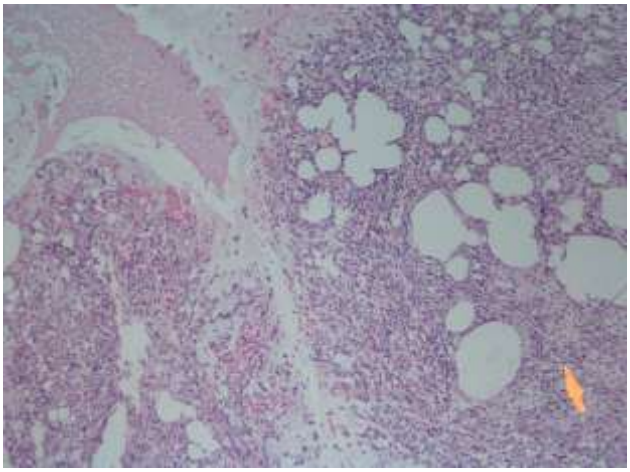

Fig-6: Xanthogranulomatous appendicitis. Foamy histiocytes (arrow head) mixed with other inflammatory cells are noted in the wall. Note the completely denuded mucosal lining (empty space is the appendix lumen). (H&E, 100X original magnification).

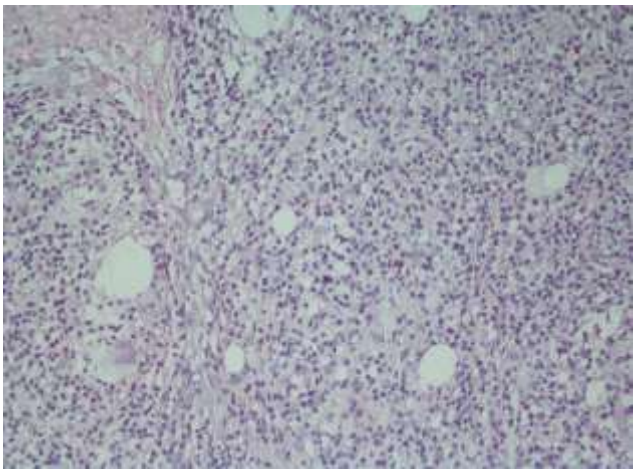

Fig-7: Xanthogranulomatous appendicitis. Foamy histiocytes mixed with other inflammatory cells including scattered foreign body-type multinucleated giant cells are noted in the wall. (H&E, 200X original magnification).

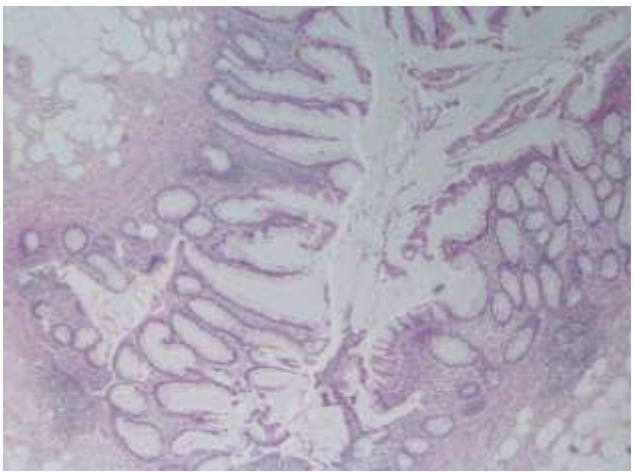

Fig-8: Xanthogranulomatous appendicitis. Hyperplastic epithelial changes are noted in the adjacent non-inflammed mucosa. (H&E, 40X original magnification).

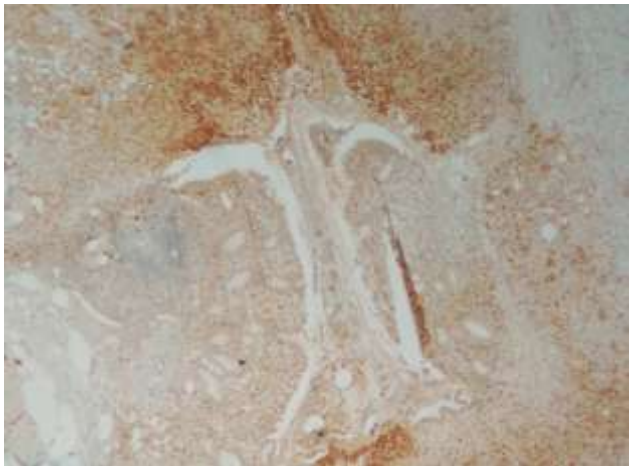

Fig-9: Xanthogranulomatous appendicitis. CD68 immunohistochemical stain highlights the dense histiocytic infiltrate in the appendix wall. (H&E, 40X original magnification).

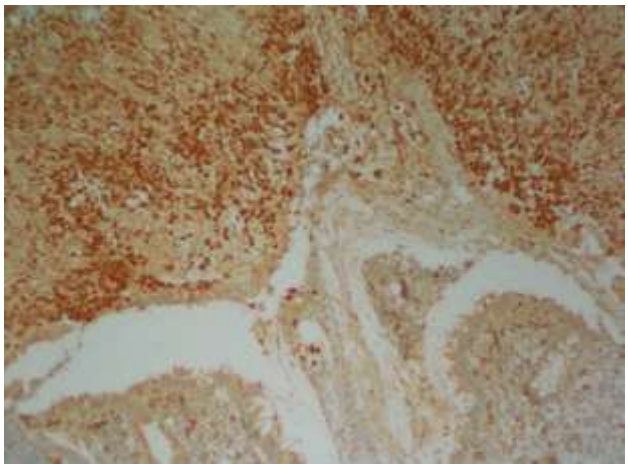

Fig-10: Xanthogranulomatous appendicitis. CD68 immunohistochemical stain highlights the dense histiocytic infiltrate in the appendix wall (strong cytoplasmic granular staining). (H&E, 100X original magnification).

Pathogenesis

The exact etiology of XA is still unknown. However, several theories and hypothesis have been proposed including defective lipid transport, immunologic disturbance of leukocyte and macrophage chemotaxis, lymphatic obstruction and infection by low-virulence organisms such as Proteus and Escherichia species [11, 12]. Some studies mentioned that XA probably represents a chronic inflammatory process leading to localized proliferation of macrophages containing large amounts of lipids and causing tissue destruction [16]. According to some authors, there are several factors that may precipitate XA including lumen obstruction, suppurative inflammation; hemorrhage and local tissue hypoxia. These authors concluded that no single pathophysiological factor can possibly cause XA as a spectrum of various morphological changes can be seen in XA [5].

It has been shown that XA can be associated with interval appendectomy according to Guo *et al*., in 2003 who concluded that delayed or interval appendectomy specimens often have a characteristic inflammatory pattern that Includes granulomas, xanthogranulomatous inflammation, mural fibrosis/thickening, and transmural chronic inflammation with lymphoid aggregates, and mucosal distortion [17, 18].

Differential diagnosis

Several inflammatory conditions should be considered in the differential diagnosis of XA. *Malakoplakia* is a rare inflammatory lesion that can affect the appendix and characterized by destructive inflammatory infiltrate rich in histiocytes that exhibit ample foamy to granular eosinophilic cytoplasm and the characteristic rounded, concentrically laminated intracytoplasmic inclusions known as Michaelis-Gutmann bodies. These basophilic inclusions stain positively for PAS, Perl's stain; and von Kossa stain. The histiocytes in XA and Malakoplakia are positive for CD68, while negative for Cytokeratin and S100 protein immunohistochemical stains. Both conditions lead to significant tissue destruction thus they both can be misdiagnosed radiologically as malignancy. Another differential diagnosis is *xanthoma* which is a localized collection of foamy histiocytes without other

inflammatory cells or parenchymal destruction, usually limited to the lamina propria. XA can cause transmural inflammation of the appendix, ulceration with granulation tissue formation, reactive lymphoid follicles, and fibrosis. These changes can mimic Crohn's disease involving the appendix but lacks epithelioid granulomas and should promote screening of the upper and lower gastrointestinal tract for features of inflammatory bowel disease [17].

Another important differential diagnosis is carcinoma, particularly on radiology and intraoperatively. Foam cells in XA can mimic signet ring cell carcinoma, however, they are almost always negative for Cytokeratin & mucin stains.

Nam S *et al*., in 2016 reported a case of XA mimicking residual Burkitt's lymphoma after chemotherapy [19].

Treatment & prognosis

Surgical resection is the treatment of choice, however, the extend of the resection depends on the intraoperative findings. Appendectomy is the usual treatment modality. Intraoperative evaluation of resected appendicular mass through frozen section or imprint cytological preparations can be performed to avoid extended surgical resections. XA can follow a fulminant clinical course as mentioned by Kochhar *et al*., who reported a case of complicated XA in an old aged man who succumbed to the disease process despite the aggressive management [20].

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