



## THE ENIGMA OF XANTHOGRANULOMATOUS APPENDICITIS

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**ABSTRACT** Xanthogranulomatous inflammation is a rare but a well - described type of chronic inflammation. It was first reported in the genitourinary tract. It can involve any organ, but kidney followed by the gallbladder are the most frequently involved. Histologically, it can be characterized by a collection of lipid - laden macrophages along with inflammatory infiltrate, with or without cholesterol clefts. This type of inflammation is extremely uncommon in the appendix. Due to its atypical presentation, it is usually detected post surgically. We present a case of XGA, detected post-operatively and on histopathology in a 44-year-old male and review the available literature on the same.

**KEYWORDS :** Appendix; Acute appendicitis; Appendectomy; Interval appendectomy; Xanthogranulomatous inflammation

**INTRODUCTION**

Xanthogranulomatous inflammation is an infrequent type of chronic inflammation that is still not fully understood, and its presence in the appendix has been rarely reported[1]. It is histologically characterised by a collection of lipid-laden macrophages admixed with lymphocytes, plasma cells, neutrophils, and often multinucleated giant cells with or without cholesterol clefts. It was first described by Schlagenhauser in 1916 in the kidneys. Since then, it has been widely reported in other organs, commonly involved being the kidney and gall bladder[2].

Xanthogranulomatous appendicitis (XGA) is extremely rare with a reported frequency of 0.22-0.64%[1]. The first case of XGA was described by Dymock and colleagues in 1977. Its clinical significance includes the diagnostic challenge it causes because it can clinically, radiologically, and even pathologically mimic neoplasia as well as other inflammatory processes of the appendix vermiformis. It is usually found retrospectively on surgical pathology and has no unique features on imaging studies, including abdominopelvic computed tomography[2]. Not much information is available in literature regarding this entity. Moreover, its clinical implications remain to be evaluated. In this review article, we present a case of XGA, and review data from all articles published on XGA.

**MATERIALS AND METHODS:**

The primary aim of this study is to review the English literature available on XGA. For the same purpose, a thorough search was done on PubMed, MEDLINE, Google Scholar, and Google databases using the following keywords: were "appendix," "appendectomy," "acute appendicitis," "chronic appendicitis" and "XGA." All documents published on XGA before April 2025 were reviewed. All articles without an accessible full-text version, those that did not provide adequate information in their abstracts, and those that did not include comprehensive information as that provided in other studies as well as articles available in languages other than English were excluded.

The secondary aim of this study was to present a 44-year-old male with XGA.

**RESULTS:****Review of literature:**

Although a total of 41 article titles matched as a result of the literature review conducted in accordance with the criteria specified in the methodology section, seven articles were excluded from the study due to the absence of demographic and clinical data of the patients. A total of 43 patients with XGA, were retrospectively analysed. Twenty-four (55.81%) of the 43 patients, aged 3 to 78 years (median: 36; IQR 31) were female, and the remaining 19 (44.18%) were male. Eighteen patients' WBC values were reported, and 15 (83.33%) of them had leucocytosis. Twenty-nine patients were diagnosed with acute

appendicitis, ruptured appendicitis, or subacute appendicitis, and the remaining 14 patients underwent surgery for tumoral lesions of the ileocecal region. Twenty-four of the patients underwent urgent or semi-urgent surgery, and the remaining 19 patients underwent interval appendectomy. Of the 34 articles, 32 were published in English, one in Japanese, and one in Spanish. The full text was obtained for 31 of the 32 articles, whereas only the abstract was available for one paper. The details of the demographic and clinical characteristics of the patients are given in Table 1.

**Case Presentation:**

A 44-year-old male reported to surgical OPD with a chief complaint of on and off pain in the right side of abdomen, which was progressively exacerbating since the past week. It was relieved intermittently on consumption of NSAIDs.

On examination, he presented with rebound tenderness in the right iliac fossa, clinically concluding an Acute Appendicitis. Preliminary laboratory investigations revealed moderate leukocytosis with a TLC of 12500 with neutrophilic predominance. However, peripheral blood findings did not reveal toxic changes within the polymorphs, excluding a likely perforation and rupture. Other biochemical parameters were within normal limits. He had no other significant co-morbidity. However, a CT scan revealed an inflamed tip of appendix with thickened edematous wall and periappendiceal fat stranding, associated with an inflamed caecum, where the inflamed base of appendix was adherent to the caecum, not clearly demarcable from each other, and appearing as a mass (Fig 1, Fig 2). Hence, the patient was taken up for elective laparoscopic surgical evaluation of the mass lesion the next day. Intra-operatively, he had a few adhesions surrounding his appendix, which could be easily removed. However, owing to the adhesions, the appendix had to be dissected piecemeal. No marked appendiceal enlargement or edema was noted. No mucinous transformation or discharge was noted. The patient recovered well post operatively.

The appendectomy specimen was sent for histopathological evaluation. The department of lab sciences received a fragmented specimen of appendix with the largest fragment measuring approximately 2cm in length and the smaller fragments aggregating to around 5ml in volume. Grossly, no mucin deposits or discharge was noted. No grossly necrotic areas were noted externally on the surface. On sectioning the largest fragment, necrotic debris was noted to be present within the lumen. No fecaliths or intraluminal parasites were seen. The complete specimen was processed.

Microscopic evaluation of the appendix revealed loss of normal architecture of the appendix with the mucosa exhibiting marked transmural congestion associated with a mixed inflammatory infiltrate along with presence of numerous scattered foamy macrophages, at

places forming clusters and occasional scattered giant cells. Mild surrounding fibrosis was also seen. No well-formed granulomas were noted (Fig 3). No atypical cells were visualized in the specimen. These microscopic findings connoted a diagnosis of Xanthogranulomatous Appendicitis.

Figure 1: CECT imaging of the Appendiceal pathology:



**Figure 1:** Inflamed tip of appendix (arrow) with thickened edematous walls and peri appendiceal fat stranding. Minimal peri appendiceal fluid is seen.

Figure 2: CECT imaging of the Appendiceal pathology:



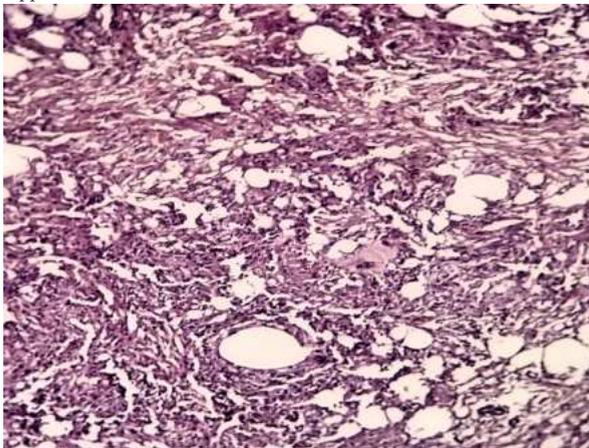
**Figure 2:** Inflamed caecum with thick edematous walls and partially collapsed lumen (arrow). The base of appendix is inflamed and adherent to the inflamed caecum, not clearly demarcable and appearing like an inflamed mass.

**Table 1: The Details Of The Demographic And Clinical Characteristics Of The Patients Of XGA Reported In Literature Till Date:**

No.	Ref.	Year	Country	Language	Article type	Article format	Pt Age	Pt Sex	Clinical presentation	WBC count
1.	Pitcher et al <sup>(3)</sup>	2024	USA	English	Case report	Full text	64	F	Recurrent appendicitis	NA
2.	Tanioka et al <sup>(4)</sup>	2024	Japan	English	Case report	Full text	78	F	Hilar cholangiocarcinoma – radical resection f/b irregular mass in the right lateral pelvis	6200/ul
3.	Ahsan et al <sup>(5)</sup>	2023	India	English	Case report	Full text	21	F	High grade fever Loss of appetite Abdominal pain Vomiting	NA
4.	Akbulut et al <sup>(2)</sup>	2021	Turkey	English	Systematic review	Full text	66	F	RLQ pain	12900
5.	Kumar et al <sup>(6)</sup>	2021	India	English	Case report	Full text	35	M	Pain in abdomen with vomiting and fever	NA
6.	Quadri et al <sup>(7)</sup>	2019	United States	English	Case series	Full text	64	M	RLQ pain + palpable mass	NA
7.	Adhikari et al <sup>(8)</sup>	2019	India	English	Case report	Full text	49	F	RLQ pain + fever	12200
8.	Yang et al <sup>(9)</sup>	2018	South Korea	English	Congress presentation	Full text	69	M	NA	NA
9.	Al-Zaidi et al <sup>(10)</sup>	2018	Kingdom of Saudi Arabia	English	Case report	Full text	48	M	RLQ pain	16000
10.	Kaushik et al <sup>(11)</sup>	2017	India	English	Case report	Full text	47	F	Abdominal pain vomiting Fever	14000
11.	Hoabam et al <sup>(12)</sup>	2017	India	English	Case report	Full text	56	F	RLQ pain	14000
12.	Mehrotra et al <sup>(13)</sup>	2017	India	English	Case report	Full text	30	F	RLQ pain	Normal
13.	Laiphrakpam et al <sup>(14)</sup>	2017	India	English	Case report	Full text	36	M	RLQ Pain	Normal
14.	Nam et al <sup>(15)</sup>	2016	South Korea	English	Case report	Full text	23	F	Low abdominal pain	NA
15.	Cavusoglu et al <sup>(16)</sup>	2016	Turkey	English	Case report	Full text	12	M	NA	NA
16.	Jusoh et al <sup>(17)</sup>	2016	Malaysia	English	Case report	Full text	11	M	NA	NA
17.	Jusoh et al <sup>(17)</sup>	2016	Malaysia	English	Case report	Full text	16	M	RLQ pain	NA
18.	Thapa et al <sup>(18)</sup>	2016	Nepal	English	Case report	Full text	19	F	RLQ pain	NA
19.	Singh et al <sup>(19)</sup>	2015	India	English	Case report	Full text	21	F	RLQ pain	NA
20.	Altay et al <sup>(20)</sup>	2015	Turkey	English	Case report	Full text	73	F	RLQ pain	Leukocytosis
21.	Chandanwale et al <sup>(21)</sup>	2015	India	English	Case report	Full text	40	F	RLQ pain	NA
22.	Montazer et al <sup>(22)</sup>	2014	Iran	English	Case report	Full text	29	F	RLQ pain	13000
23.	Kochhar et al <sup>(23)</sup>	2014	India	English	Case report	Full text	50	M	RLQ pain + fever	24000
24.	Al-Rawabdeh et al <sup>(24)</sup>	2013	United States	English	Case report	Full text	11	M	RLQ pain	4900
25.	Mado et al <sup>(25)</sup>	2013	Japan	English	Image in surgery	Full text	78	M	RLQ pain	NA

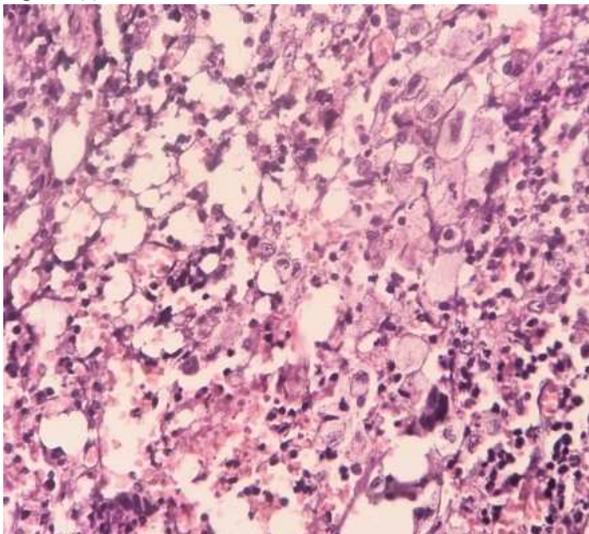
25.	Martinez-Garza et al <sup>(26)</sup>	2011	Spain	Spanish	Case report	Full text	30	F	RLQ pain	13700
26.	Omer et al <sup>(27)</sup>	2011	Sudan	English	Case report	Full text	49	M	RLQ pain	NA
27.	Omori et al <sup>(28)</sup>	2011	Japan	Japanese	Case report	Full text	57	F	RLQ pain	NA
28.	Young et al <sup>(29)</sup>	2009	United States	English	Case report	Full text	32	F	RLQ pain	22000
29.	Chuang et al <sup>(30)</sup>	2005	Taiwan	English	Case report	Abstract	39	M	RLQ pain	NA
30.	Guo et al <sup>(31)</sup>	2003	United States	English	Original article	Full text	4	F	NA	NA
							12	M	NA	NA
							13	M	NA	NA
1.							3	M	NA	NA
1.							9	M	NA	NA
1.							29	F	NA	NA
1.							29	F	NA	NA
1.							27	M	NA	NA
31.	Munichor et al <sup>(32)</sup>	2000	Israel	English	Case report	Full text	37	F	RLQ pain	12000
32.	McVey et al <sup>(33)</sup>	1994	United States	English	Letter	Full text	40	F	RLQ pain	12100
33.	Birch et al <sup>(34)</sup>	1993	United Kingdom	English	Brief Report	Full text	51	M	Perineal pain	NA
1.							66	F	Right flank pain	20000
34.	Rogers et al <sup>(35)</sup>	1992	United Kingdom	English	Case report	Full text	56	F	RLQ pain	NA

Abbreviations used: RLQ – Right Lower Quadrant; NA – Not mentioned in the article text; M – Male; F – Female Figure 3: Histopathological pictomicrographs of Xanthogranulomatous Appendicitis:



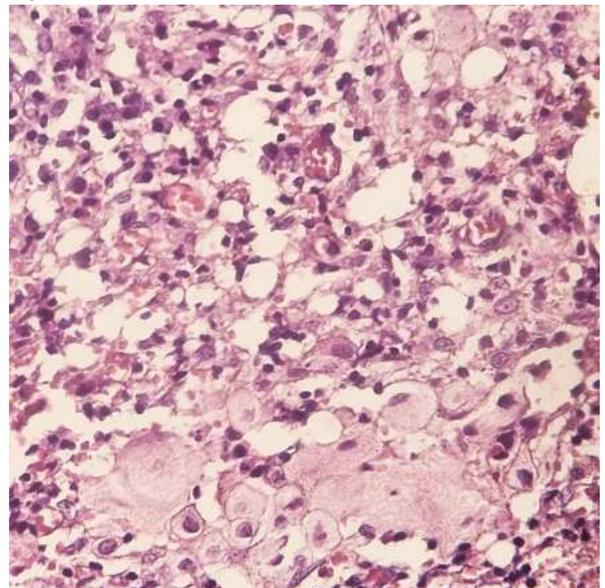
**Figure 3:** Low power (100x) view of H&E pictomicrograph of the appendix showing scattered macrophages and giant cells, at places forming macrophage clusters, in a background showing fibrosis within the thickened appendiceal wall.

Figure 4 (a):



**Figure 4(a):** High power (400x) view of H&E pictomicrographs of the appendix shows foamy macrophages scattered as well as forming clusters within the appendiceal wall amidst a background of chronic inflammatory cells

Figure 4 (b):



**Figure 4(b):** High power (400x) view of H&E pictomicrographs of the appendix shows foamy macrophages scattered as well as forming clusters within the appendiceal wall amidst a background of chronic inflammatory cells.

#### DISCUSSION:

Xanthogranulomatous inflammation is a type of chronic inflammation, macroscopically distinguished by mass forming golden yellow tumours and histopathologically characterised by accumulation and infiltration of foamy macrophages accompanied by presence of multinucleated giant cells with a minor component composed of chronic inflammatory cells, predominantly plasma cells and lymphocytes along with lipid deposition and fibrosis. At times, acute inflammatory cells, mainly neutrophils are also known to be associated with this entity[4,36]. It was first described by Schlagenhauser in 1916, who noted it in the kidneys[37]. Oberling in 1935, illustrated it as a phenomena presenting with a retroperitoneal mass in a series of three patients, all of whom reported with pain in abdomen and called it Retroperitoneal Xanthogranuloma[38].

Xanthogranulomatous inflammation involving the gastrointestinal tract is quite uncommon, as this inflammatory pathology is more commonly described within the kidneys and gall bladder. Among the GI tract, the involvement of the appendix is extremely unfamiliar. In 2017, a study undertaken by Kulkarni et al to determine the incidence of various neoplastic and non-neoplastic lesions of the appendix revealed the presence of Xanthogranulomatous appendicitis in only 0.22% cases[39]. Similarly, another 10-year study undertaken by Laishram et al revealed an incidence of 0.25% of XGA cases among the studied 4298 cases[40]. Additionally, Shaik et al, in a similar study,

noted the incidence of XGA to be 0.64%[41].

Overall, it can be safely concluded that xanthogranulomatous inflammation is a rare phenomenon affecting the appendix, with its overall incidence being less than 1%.

**Table 2: Surgical Procedures As Per The Clinical Diagnosis Of The Patients Mentioned In Table 1.**

Case	Pre-operative diagnosis	Surgical approach
1.	Acute perforated appendicitis	Interval appendicectomy
2.	Disseminated recurrence of hilar cholangiocarcinoma and newly emerged appendiceal carcinoma were suspected	Interval appendicectomy
3.	Acute appendicitis	Interval appendicectomy
4.	Recurrent appendicitis	Emergency appendicectomy
5.	Acute appendicitis	Emergency appendicectomy
6.	Right lower abdominal quadrant mass	Right hemicolectomy
7.	Acute perforated appendicitis	Interval appendicectomy
8.	Acute perforated appendicitis	Right hemicolectomy
9.	Acute appendicitis	Emergency appendicectomy
10.	?Neoplastic mass	Limited colon resection
11.	Acute appendicitis	Emergency appendicectomy
12.	Acute appendicitis	Emergency appendicectomy
13.	Acute appendicitis	Emergency appendicectomy
14.	Chronic appendicitis/Mucocoele	Emergency appendicectomy
15.	i. Appendicular mass ii. Acute appendicitis	Interval appendicectomy
1.		Interval appendicectomy
16.	Acute appendicitis	Interval appendicectomy
17.	Acute appendicitis	Interval appendicectomy
18.	Acute appendicitis	Emergency appendicectomy
19.	Appendicular mass	Emergency appendicectomy
20.	Right lower abdominal quadrant mass	Right hemicolectomy
21.	Acute appendicitis	Emergency appendicectomy
22.	Acute appendicitis	Right hemicolectomy + ileostomy
23.	Acute appendicitis	Emergency appendicectomy
24.	Mucocoele	Iliocaecal resection
25.	Acute appendicitis	Emergency appendicectomy
26.	Appendicular mass	Interval appendicectomy
27.	Appendicular mass	Right hemicolectomy + Right nephrectomy + oophorectomy
28.	Acute appendicitis	Interval appendicectomy
29.	Caecal colitis	Right hemicolectomy

30.	Acute appendicitis	Interval appendicectomy
1.	Acute appendicitis	Interval appendicectomy
1.	Acute appendicitis	Interval appendicectomy
1.	Acute appendicitis	Interval appendicectomy
1.	Acute appendicitis	Interval appendicectomy
1.	Acute appendicitis	Interval appendicectomy
1.	Acute appendicitis	Interval appendicectomy
1.	Sub-acute appendicitis	Interval appendicectomy
1.	Sub-acute appendicitis	Interval appendicectomy
31.	Acute appendicitis	Emergency appendicectomy
32.	Appendicular mass	Interval appendicectomy
33.	i. Acute appendicitis ii. Appendicular mass	Emergency Appendicectomy
34.	Fistula	Emergency Appendicectomy

Most XGA cases reported were in the adult age group, with the median age of presentation in this review being 36 years. The mean age (37.8 years) identified in this review was slightly higher than the previously reported mean age of 34 years<sup>[2]</sup>. Although there have been a few paediatric cases reported in literature, this disease remains more common in adults, with only 7 out of 43 patients in this review belonging to the paediatric age group (16.27%). The oldest patient diagnosed with XGA in this review are 78 years old, one of who presented with a mucocoele of the appendix while the other presented with a mass in right iliac fossa following a radical resection for hilar cholangiocarcinoma<sup>[4,25]</sup>, and the youngest affected patient was 3 years old, diagnosed at interval appendectomy<sup>[31]</sup>. No sex predilection was reported for XGA, however, in this review, there was a slight predilection for females in the number of cases reported between females (55.81%) and males (44.18%).

Although various theories have been proposed, the exact etiopathogenesis of XGA is not yet completely established. The different theories that have been suggested in the development of this entity include defective lipid transport, immunologic disturbances of leukocyte and macrophage chemotaxis, infection by low virulence organisms, and lymphatic obstruction<sup>[2]</sup>. It is generally believed that the localised proliferation of lipid laden foamy histiocytes represents a chronic suppurative inflammation secondary to interaction between the host and microorganisms. Examples of immunological disorders include disrupted chemotaxis of polymorphs and macrophages, which is a specific immune response to Proteus and Escherichia infections<sup>[36]</sup>. A case of xanthogranulomatous inflammation involving the terminal ileum reported in 2013 proposed a possible mechanism of perforation due to an ingested foreign body<sup>[42]</sup>. In another case report of xanthogranulomatous ileitis, infected laparotomy wound swab yielded E coli, while there were no symptoms to suggest pre-existing chronic suppurative inflammation. There was no evidence of a penetrating foreign body on history or gross examination of the pathological specimen<sup>[36]</sup>.

However, none of the above hypotheses have been able to fully explain the anatomical distribution of the condition, especially in the appendix where neither perforation due to ingested foreign bodies nor chronic suppurative inflammation is most often found. Cozzutto et al<sup>[43]</sup> performed an extensive review of all cases of xanthogranulomatous inflammation from various organs, and noted that the xanthogranulomatous process is usually associated with inflammation, haemorrhage, and necrosis. They suggested that haemorrhage may play a major role in the development of foamy macrophages, postulating that the ingested erythrocytes and platelets at the bleeding site overwhelm the lysosomal system of the macrophages, causing deposition of phospholipids, which results in a foamy appearance of the macrophages. Other possible postulations for the precipitation of XGA include lumen obstruction, suppurative inflammation, haemorrhage, and local tissue hypoxia, where the possibility of any of the above-mentioned entities singly being responsible for the pathophysiology of development of XGA is impractical<sup>[2]</sup>.

Xanthogranulomatous appendicitis usually presents with clinical symptoms similar to acute appendicitis, with right iliac fossa pain, fever, nausea, and vomiting. Rebound tenderness is usually seen. However, the clinical presentation of XGA is variable, which seems to vary with the spread of the disease. While some authors suggested an association of the xanthogranulomatous response with long-standing inflammation of the appendix and formation of the appendiceal mass(39), others have reported cases of XGA with typical signs and symptoms of acute appendicitis(44). In this review, 26 of the 43 reported cases were clinically diagnosed with acute appendicitis (60.46%), three of which were found to be perforated. Two cases presented with recurrent appendicitis and another case presented with an appendicular lump following radical cholecystectomy for hilar cholangiocarcinoma. Due to the destructive nature of the disease, XGA can also present with a mass lesion that can mimic locally advanced cancer, but it has a benign course and can be cured surgically.

XGA showed a higher incidence in interval appendectomies. Guo et al<sup>[31]</sup> reviewed the histopathology of all interval appendectomy specimens within a four-year period, and compared them with a control group of patients who had acute appendicitis and underwent routine acute appendectomy. The study revealed that xanthogranulomatous inflammation is common in interval appendectomy specimens. They represented 36% of the interval appendectomy cases in their series, but they did not occur in the emergency appendectomy group. Similarly, in our review, 19 of the 41 (46.34%) patients underwent interval appendectomy (Table 2).

The wavering exhibition of XGA connotes a differential diagnosis of acute appendicitis, an appendiceal mucinous epithelial neoplasm, an appendiceal non-mucinous epithelial neoplasm, and a variety of chronic infectious diseases. Other GI tract pathologies exhibiting granulomatous inflammation associated with foamy macrophages include Crohn's disease and malakoplakia. However, Crohn's disease presents with a transmural involvement by granulomas, along with its characteristic gross findings, which are not seen in xanthogranulomatous appendicitis; while malakoplakia distinctively exhibits Michaelis Gutmann bodies, which differentiates it from xanthogranulomatous inflammation. Additionally, atypical appendiceal pathologies ranging from neoplasms to inflammatory pathologies can imitate or even cause a superimposed acute inflammation, making them difficult to differentiate from the typical acute appendicitis. Furthermore, it can be quite challenging to differentiate XGA from a likely infiltrative malignancy as XGA may also commonly present as a mass lesion with extension of fibrosis and inflammation to the surrounding tissues. In such cases, contrast-enhanced computed tomography (CECT) is the yardstick and the most economical diagnostic test in non-pregnant adults presenting with right iliac fossa pain with or without rebound tenderness. However, radiological findings are broadly non-specific, and XGA is most commonly detected retrospectively on histopathological evaluation<sup>[21]</sup>.

## CONCLUSION:

Xanthogranulomatous inflammation is an unwonted, destructive and a chronic inflammatory pathology which can involve any organ at any point in life. Although it rarely affects the appendix vermiformis, it is associated with significant diagnostic and therapeutic predicaments. XGA is usually identified retrospectively on pathological examination of the appendiceal specimen, and has no unique features on imaging studies including contrast-enhanced computed tomography.

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