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Esophageal Xanthogranulomatous Inflammation with Peripheral Eosinophilia in an Immunosuppressed Patient with Rheumatoid Arthritis: A Rare Case Report and Focused Literature Review

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Abstract

Background: Xanthogranulomatous inflammation of the esophagus is an exceedingly rare lesion characterized by extensive xanthogranulomatous tissue infiltration, often mimicking neoplasms. The association of esophageal xanthogranuloma with peripheral eosinophilia in immunosuppressed patients remains poorly understood, posing diagnostic challenges.

Objectives: This study aimed to present a rare case of esophageal xanthogranuloma with tissue eosinophilia in a patient with rheumatoid arthritis on multiple immunosuppressive agents. In addition, this study examined clinicopathological features, assessed potential pathogenic linkages, and revealed diagnostic considerations.

Methods: A 52-year-old man with a 17-year history of rheumatoid arthritis on immunosuppressants presented with progressive dysphagia and gastrointestinal bleeding. The diagnostic workup included contrast-enhanced CT, upper endoscopy, endoscopic ultrasound (EUS), and additional biopsies, all of which were inconclusive. Due to persistent symptoms and nondiagnostic minimally invasive procedures, a transhiatal esophagectomy was performed. Histopathological examination of the resected specimen was conducted, including routine hematoxylin and eosin (H&E) staining. Immunohistochemistry (IHC) was not performed owing to institutional limitations. Laboratory data included peripheral eosinophil counts, with emphasis on absolute eosinophil count. The literature review also included published cases of esophageal xanthogranulomas and eosinophil-associated esophageal lesions.

Results: Histology revealed a well-defined intramural esophageal mass demonstrating extensive xanthogranulomatous inflammation, rich in lipid-laden macrophages, multinucleated giant cells, and eosinophils, confirmed qualitatively. No evidence of malignancy or infectious granulomatous disease was identified. The patient recovered uneventfully post-surgery, with symptomatic improvement. Moreover, literature review demonstrated that esophageal xanthogranulomas are rare, with few cases reported, and their pathogenesis remains speculative, particularly regarding eosinophil involvement and immunosuppression.

Conclusion: This case revealed the importance of considering xanthogranulomatous inflammation in the differential diagnosis of esophageal intramural lesions in immunosuppressed patients with peripheral eosinophilia. Definitive diagnosis relies on histopathology, with surgical excision often necessary when less invasive methods are inconclusive. Further studies are warranted to elucidate the potential pathogenic links and the role of eosinophils in such lesions.

Keywords: Esophageal xanthogranuloma, Eosinophilia, Immunosuppression, Granulomatous inflammation, Benign esophageal lesion

1. Introduction

Esophageal xanthogranulomatous inflammation is an exceptionally rare benign inflammatory condition that may present as an esophageal mass and closely mimic malignant disease, creating substantial diagnostic and therapeutic challenges (1). Although xanthogranulomatous

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inflammation has been described in organs such as the gallbladder and kidney, involvement of the esophagus is exceedingly uncommon, and only a limited number of cases have been reported in the literature (2).

Consequently, the clinicopathological characteristics, optimal diagnostic approach, and management of this entity remain poorly defined (3). The rarity of esophageal xanthogranulomatous inflammation, combined with its nonspecific clinical and radiologic presentation, frequently makes preoperative diagnosis difficult, particularly when endoscopic biopsy or endoscopic ultrasound-guided tissue sampling fails to provide a definitive diagnosis. As a result, many patients undergo surgical resection because malignancy cannot be confidently excluded (4). Xanthogranulomatous inflammation is histologically characterized by aggregates of lipid-laden (foamy) macrophages, multinucleated giant cells, cholesterol clefts, and mixed chronic inflammatory infiltrates (5). In contrast, peripheral eosinophilia is a nonspecific laboratory finding associated with numerous allergic, infectious, inflammatory, autoimmune, and neoplastic disorders. In contrast, esophageal eosinophilic infiltration is classically associated with eosinophilic esophagitis (6). The coexistence of peripheral eosinophilia with esophageal xanthogranulomatous inflammation has rarely been described, and its clinical significance remains uncertain because of the paucity of reported cases (7).

At present, there is insufficient evidence to determine whether eosinophilia represents an incidental finding, a secondary inflammatory response, or a component of the underlying pathological process (8). Additionally, although patients receiving long-term immunosuppressive therapy may develop unusual inflammatory or infectious disorders, no causal relationship between immunosuppression and esophageal xanthogranulomatous inflammation has been established. Any association should be considered hypothesis-generating rather than conclusive (9). The available evidence regarding esophageal xanthogranulomatous inflammation consists almost exclusively of isolated case reports and small case series, precluding meaningful conclusions regarding its epidemiology, pathogenesis, clinicopathological spectrum, prognosis, or optimal management (10). Reports describing this entity in association with peripheral eosinophilia are even more limited, and cases occurring in patients receiving long-term immunosuppressive therapy for autoimmune diseases are exceptionally uncommon. Consequently, clinicians and pathologists may not readily consider this diagnosis when evaluating an esophageal mass with inconclusive biopsy findings (11). This knowledge gap underscores the importance of documenting well-characterized cases with detailed clinical, radiologic, surgical, and histopathologic findings to improve recognition of this rare entity and facilitate more accurate differential diagnosis in future patients.

To our knowledge, this case was among the first reported cases of esophageal xanthogranulomatous inflammation associated with peripheral eosinophilia in a patient with rheumatoid arthritis receiving multiple immunosuppressive medications. Rather than suggesting a causal relationship between immunosuppression and lesion development, this report presented a rare clinical case that broadens the current spectrum of reported cases and emphasizes an important diagnostic lesson. In immunosuppressed patients presenting with an esophageal mass and peripheral eosinophilia, esophageal xanthogranulomatous inflammation should be considered in the differential diagnosis, particularly when repeated endoscopic investigations are nondiagnostic. This case

also highlights the central role of histopathological examination in establishing the diagnosis. It discusses current evidence on diagnostic challenges, surgical management, and limitations of the existing literature.

2. Case Presentation

The objective was to document the clinical presentation, diagnostic evaluation, histopathological findings, surgical management, and short-term postoperative outcome of a patient with esophageal xanthogranulomatous inflammation associated with peripheral eosinophilia. Rather than investigating causality, this report aims to describe a rare clinical entity, highlight the diagnostic challenges encountered during evaluation, and compare the findings with previously published cases. The patient's hospitalization, diagnostic workup, surgical treatment, and pathological evaluation were performed at Razavi Hospital in Mashhad, Iran. The dates reported in the manuscript (March 10 to April 1, 2024) refer only to the period of hospitalization and definitive diagnostic management; the patient's symptoms had been present for approximately 2 years before admission, and postoperative follow-up continued after hospital discharge.

2.1. Clinical Assessment and Diagnostic Evaluation

A comprehensive clinical assessment was performed following admission. The patient's medical history included a 17-year history of rheumatoid arthritis treated with long-term immunosuppressive therapy, including hydroxychloroquine, sulfasalazine, methotrexate, leflunomide, azathioprine, prednisone, and rituximab. Particular attention was given to the duration of immunosuppressive therapy, gastrointestinal symptoms, constitutional manifestations, and previous medical history. The patient reported progressive dysphagia and dyspepsia for approximately two years, accompanied by recent weight loss and episodes of melena. A complete physical examination identified axillary lymphadenopathy, prompting further hematological evaluation. Laboratory investigations included routine hematological and biochemical analyses, inflammatory markers, and a complete blood count with differential. Peripheral eosinophilia was documented, and both the eosinophil percentage and the absolute eosinophil count were recorded in the clinical data. Because peripheral eosinophilia may occur in numerous inflammatory, infectious, allergic, autoimmune, and neoplastic conditions, its presence was interpreted within the broader clinical context rather than considered diagnostic of the final pathological process.

2.2. Radiological and Endoscopic Investigations

The radiological evaluation consisted of contrast-enhanced computed tomography of the thorax and abdomen to characterize the lesion and identify possible metastatic disease or other intra-abdominal pathology. Computed tomography demonstrated circumferential thickening of the distal esophageal wall extending from the level of the carina to the gastroesophageal junction without definitive radiological evidence of distant malignancy; an incidental hepatic hemangioma was also identified. Upper gastrointestinal endoscopy demonstrated an intramural mass involving the distal thoracic esophagus. To further characterize the lesion and guide tissue acquisition, endoscopic ultrasound (EUS) was subsequently performed. Based on the imaging characteristics, the principal differential diagnoses included gastrointestinal stromal tumor, leiomyoma, and other submucosal neoplasms. Multiple endoscopic tissue sampling procedures, including endoscopic biopsy and EUS-guided sampling, were undertaken but failed to establish a definitive diagnosis. These nondiagnostic findings, together with persistent concern for an

underlying malignancy, were central considerations in subsequent multidisciplinary management.

2.3. Histopathological Evaluation

Because minimally invasive diagnostic procedures were inconclusive and malignancy could not be confidently excluded, the patient underwent transhiatal esophagectomy for definitive diagnosis and treatment. The resected specimen was examined macroscopically and microscopically using routine hematoxylin and eosin (H&E) staining according to standard pathological protocols. Histopathological evaluation demonstrated features consistent with xanthogranulomatous inflammation, including aggregates of lipid-laden macrophages, chronic inflammatory infiltrates, and multinucleated giant cells where present. The pathological assessment was integrated with the clinical, laboratory, imaging, and operative findings to exclude more common malignant and inflammatory conditions. No histopathological evidence of malignancy or specific infection was identified. Immunohistochemical studies, including markers such as CD68, CD163, S-100, and CD1a, were not available at our institution and therefore were not performed. Furthermore, tissue eosinophil quantification was unavailable.

2.4. Multidisciplinary Management and Follow-up

Clinical decision-making was undertaken through multidisciplinary collaboration among gastroenterologists, thoracic surgeons, radiologists, pathologists, and hematologists. The diagnostic findings were also reviewed collectively after the nondiagnostic endoscopic and EUS-guided biopsies. The decision to proceed with transhiatal esophagectomy was based on the inability to exclude malignancy and the need to obtain an adequate specimen for definitive histopathological diagnosis. Postoperatively, the patient was monitored for surgical complications, nutritional recovery, and symptom recurrence. The follow-up evaluations included routine clinical assessment, and no immediate postoperative complications or evidence of disease recurrence were observed during the available follow-up period. Due to the relatively short follow-up period, long-term clinical outcomes could not be evaluated.

2.5. Literature Review

A focused literature review was undertaken to contextualize the present case within the existing evidence on esophageal xanthogranulomatous inflammation. The review emphasized previously reported esophageal xanthogranulomatous lesions, cases associated with eosinophilia, and inflammatory esophageal masses occurring in immunosuppressed patients. Reports describing xanthogranulomatous inflammation in unrelated organs or unrelated granulomatous disorders were excluded to maintain clinical relevance. The literature review was used to compare clinical presentation, diagnostic investigations, histopathological findings, treatment strategies, and outcomes with those observed in the present case.

2.6. Clinical Presentation

A 52-year-old man with a 17-year history of rheumatoid arthritis treated with multiple immunosuppressive agents, including hydroxychloroquine, sulfasalazine, azathioprine, prednisone, leflunomide, methotrexate, and rituximab, presented with progressive dysphagia and dyspeptic symptoms that had persisted for approximately two years. During the months preceding admission, he experienced unintentional weight loss and intermittent episodes of melena, prompting further investigation. The physical examination demonstrated palpable axillary lymphadenopathy without other remarkable findings. Laboratory evaluation revealed

peripheral eosinophilia, with an eosinophil percentage of 17% and an elevated absolute eosinophil count (reported in the laboratory findings). Because peripheral eosinophilia does not necessarily indicate eosinophilic tissue infiltration, histopathological evaluation of the resected lesion was subsequently used to assess tissue eosinophilia.

2.7. Radiological and Endoscopic Findings

The contrast-enhanced computed tomography of the thorax and abdomen demonstrated circumferential thickening of the esophageal wall extending from the level of the carina to the gastroesophageal junction, raising suspicion for an underlying neoplastic or submucosal process (Fig. 1). An incidental hepatic hemangioma was also identified and was considered unrelated to the patient's presenting symptoms. Upper gastrointestinal endoscopy demonstrated an intramural mass involving the distal thoracic esophagus with intact overlying mucosa, making superficial mucosal sampling diagnostically challenging. Endoscopic ultrasound further characterized the lesion as a submucosal mass arising within the esophageal wall, with imaging features favoring a gastrointestinal stromal tumor (GIST) or leiomyoma as the principal differential diagnoses (Fig. 2). These findings indicated that imaging alone was insufficient to establish a definitive diagnosis.

2.8. Diagnostic Evaluation and Surgical Management

Further diagnostic evaluation included the assessment of the axillary lymphadenopathy by fine-needle aspiration, which was nondiagnostic and demonstrated no evidence of malignancy or other specific pathological abnormalities. Endoscopic biopsy and endoscopic ultrasound-guided tissue sampling were also nondiagnostic, as they failed to yield sufficient representative tissue for definitive histopathological characterization of the intramural lesion. In view of the patient's persistent symptoms, ongoing gastrointestinal bleeding, and inconclusive minimally invasive investigations, a multidisciplinary team involving gastroenterologists, thoracic surgeons, radiologists, and pathologists recommended transhiatal esophagectomy. The decision was based on the need to establish a definitive diagnosis while simultaneously providing therapeutic resection of the symptomatic esophageal mass. The surgical exploration also confirmed a localized intramural thickening of the distal esophagus without gross evidence of metastatic disease or invasion into adjacent structures.

2.9. Histopathological Findings

The gross examination of the resected esophageal specimen demonstrated a well-defined intramural mass associated with marked thickening of the esophageal wall (Fig. 3). The histopathological examination of hematoxylin and eosin (H&E)-stained sections revealed extensive xanthogranulomatous inflammation characterized by numerous lipid-laden foamy macrophages (xanthoma cells), multinucleated giant cells, chronic inflammatory infiltrates, and associated fibrosis (Figs. 4 and 5). Eosinophils were identified within the inflammatory infiltrate, confirming tissue eosinophilia qualitatively on routine histopathological examination; however, tissue eosinophils were not formally quantified because standardized eosinophil counts were not available. Moreover, the careful pathological evaluation demonstrated no histological evidence of malignancy. Likewise, no morphologic features suggestive of infectious granulomatous diseases were identified on routine examination. Immunohistochemical studies, including macrophage and histiocytic markers such as CD68, CD163, S-100, or CD1a, were not performed because these tests were unavailable at our institution during the diagnostic workup. Accordingly,

the diagnosis was established based on characteristic histomorphological findings, with clinicopathological correlation, and the absence of immunohistochemistry is acknowledged as a limitation of the present report.

2.10. Postoperative Outcome

The patient recovered uneventfully following transhiatal esophagectomy, with gradual improvement in dysphagia and oral intake during the postoperative period. No immediate surgical complications were observed during hospitalization. The reported study period (March 10 to April 1, 2024) represents the hospitalization and diagnostic phase of management rather than the entire clinical course, as the patient's symptoms had been present for approximately two years before admission. The clinical follow-up demonstrated satisfactory postoperative recovery without the early evidence of recurrence; however, long-term surveillance data were unavailable at the time of manuscript preparation.

Figure 1. Contrast-enhanced computed tomography (CT) of the thorax demonstrating circumferential thickening of the esophageal wall (arrows) extending from the level of the carina to the gastroesophageal junction (GEJ), raising suspicion for an intramural esophageal neoplasm or submucosal lesion; an incidental hepatic hemangioma is also visible.

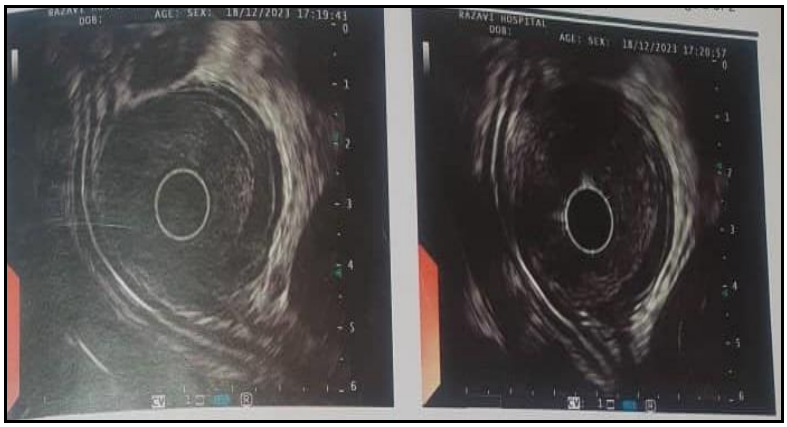

Figure 2. Endoscopic ultrasound (EUS) demonstrating a hypoechoic intramural/submucosal mass involving the distal thoracic esophagus with marked esophageal wall thickening; the imaging appearance favored a gastrointestinal stromal tumor (GIST) or leiomyoma as the principal differential diagnoses.

Figure 3. Gross and microscopic appearance of the resected esophageal lesion; left: Gross specimen showing a well-circumscribed intramural mass associated with marked thickening of the distal esophageal wall (arrow); right: Hematoxylin and eosin (H&E)-stained section (original magnification, ×40) demonstrating xanthogranulomatous inflammation composed of abundant lipid-laden (foamy) macrophages, multinucleated giant cells, chronic inflammatory infiltrates, and fibrosis.

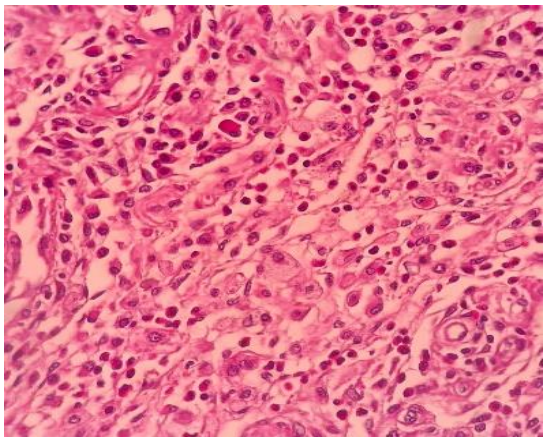

Figure 4. Histopathological features of esophageal xanthogranuloma. Hematoxylin and eosin (H&E) stain (original magnification, ×100) demonstrating sheets of foamy macrophages (xanthoma cells) admixed with multinucleated giant cells, chronic inflammatory infiltrates, and fibrosis; eosinophils are present within the inflammatory infiltrate (arrows), confirming qualitative tissue eosinophilia on routine histopathological examination.

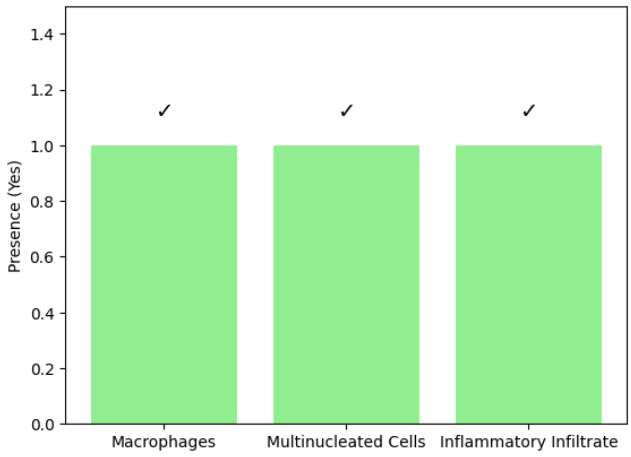

Figure 5. High-power photomicrograph of the esophageal xanthogranuloma. Hematoxylin and eosin (H&E) stain (original magnification, ×400) demonstrating characteristic lipid-laden foamy macrophages (arrowheads), multinucleated giant cells (arrows), chronic inflammatory cells including eosinophils, and associated fibrosis, consistent with xanthogranulomatous inflammation.

3. Discussion

This case demonstrated the diagnostic challenges posed by an uncommon esophageal xanthogranulomatous mass presenting with peripheral eosinophilia in a patient receiving long-term immunosuppressive therapy for rheumatoid arthritis. Despite comprehensive radiological assessment and multiple minimally invasive diagnostic procedures, a definitive diagnosis could not be established preoperatively, necessitating surgical resection for both diagnosis and treatment. The histopathological examination confirmed xanthogranulomatous inflammation with associated tissue eosinophilia while excluding malignancy on morphologic grounds. Although the coexistence of peripheral eosinophilia, tissue eosinophilia, and prolonged immunosuppressive therapy is noteworthy, this single case does not establish a causal relationship between these findings and the development of esophageal xanthogranulomatous inflammation. Rather, it revealed the importance of considering this rare entity in the differential diagnosis of esophageal masses when less invasive diagnostic approaches are inconclusive.

Esophageal xanthogranuloma is an exceptionally rare benign inflammatory lesion, with only a handful of published cases and no well-established diagnostic or therapeutic guidelines. Its rarity, coupled with nonspecific clinical, endoscopic, and radiological findings, makes preoperative diagnosis particularly difficult, and most patients are initially suspected to have neoplastic disease (12). Symptoms are generally related to luminal obstruction or mucosal irritation, including progressive dysphagia, dyspepsia, odynophagia, weight loss, or upper gastrointestinal bleeding. Cross-sectional imaging and endoscopic ultrasound frequently reveal intramural or submucosal masses that closely resemble gastrointestinal stromal tumors, leiomyomas, inflammatory pseudotumors, or other mesenchymal neoplasms (13). In the present patient, computed tomography demonstrated circumferential esophageal wall thickening. At the same time, upper endoscopy and endoscopic ultrasound identified a distal intramural esophageal mass highly suggestive of a gastrointestinal stromal tumor or leiomyoma. Despite repeated minimally invasive investigations, including endoscopic biopsy, endoscopic ultrasound-guided tissue sampling, and the fine-needle aspiration of an enlarged axillary lymph node, a definitive diagnosis could not be established. Due to persistent dysphagia, weight loss, melena, and the inability to confidently exclude malignancy, transhiatal esophagectomy was performed for both diagnostic and therapeutic purposes. Similar diagnostic uncertainty has also been emphasized by Keim and Peeraphatdit, who described esophageal granulomatous inflammation in a young woman in whom histopathological examination was ultimately required to establish the diagnosis after nonspecific clinical and endoscopic findings (14). Similarly, Nathoo et al. reported Crohn disease-associated granulomatous inflammation of the esophagus that required biopsy confirmation because clinical and endoscopic features alone were insufficient for diagnosis (15). Collectively, these reports, together with the present case, underscore that inflammatory esophageal lesions frequently mimic malignant or mesenchymal tumors and often require histopathological confirmation before appropriate management can be determined.

Histopathological examination remains the cornerstone of diagnosing esophageal xanthogranuloma, as neither imaging nor endoscopic appearance is sufficiently specific to establish the diagnosis (2, 7). In the present case, routine hematoxylin and eosin staining demonstrated characteristic xanthogranulomatous inflammation composed of abundant foamy macrophages

(xanthoma cells), multinucleated giant cells, and a mixed inflammatory infiltrate, without histological evidence of malignancy. Infectious and neoplastic processes were excluded on routine microscopic examination; however, immunohistochemical studies, including macrophage markers such as CD68 and CD163 or markers excluding Langerhans cell histiocytosis (S-100 and CD1a), were unavailable at our institution and therefore could not be performed. Similarly, although eosinophilic infiltration was identified microscopically, tissue eosinophils were not quantitatively assessed. These limitations reduce the completeness of pathological characterization and should be considered when interpreting the diagnosis.

Future reports should incorporate immunohistochemical confirmation, along with quantitative assessment of tissue eosinophilia whenever feasible, to strengthen diagnostic certainty and facilitate comparisons among published cases. The importance of histopathological confirmation is consistently reflected in the literature summarized in Table 1. Suarez-Zamora et al. demonstrated that esophageal pyogenic granuloma, another uncommon benign inflammatory lesion, was definitively diagnosed only after histopathological examination following endoscopic resection (16). Besides, Nojkov et al. and Shi et al. reported that esophageal granular cell tumors, despite their characteristic endoscopic appearance, still required histopathological evaluation for definitive diagnosis before successful endoscopic treatment. Although these lesions differ pathologically from xanthogranuloma, they illustrate the common diagnostic challenge posed by uncommon submucosal esophageal lesions and reinforce the indispensable role of tissue diagnosis (17, 18).

An additional noteworthy aspect of the present case was the coexistence of peripheral eosinophilia in a patient receiving long-term immunosuppressive therapy for rheumatoid arthritis. To improve the interpretation of this observation, the revised manuscript distinguishes peripheral eosinophilia from tissue eosinophilia. It reports the absolute peripheral eosinophil count in addition to the eosinophil percentage. Although eosinophilic infiltration was observed histologically, tissue eosinophils were not quantified, preventing meaningful correlation between peripheral and tissue eosinophilia. Peripheral eosinophilia has a broad differential diagnosis, including allergic disorders, parasitic infections, autoimmune diseases, medication reactions, and eosinophilic gastrointestinal disorders. While eosinophilic inflammation is well recognized in disorders such as eosinophilic esophagitis, its relationship with esophageal xanthogranuloma remains uncertain (19). Consequently, peripheral eosinophilia in the present patient should be regarded as an associated clinical observation rather than evidence supporting a pathogenic mechanism.

The studies summarized in Table 1 further emphasize the complex relationship between eosinophilic inflammation and esophageal pathology. Nojkov et al. (2017) described five patients with esophageal granular cell tumors associated with eosinophilic esophagitis, highlighting that eosinophilic inflammation may coexist with other esophageal lesions without necessarily representing a direct causal factor (17). Similarly, Shi et al. demonstrated favorable outcomes following endoscopic resection of esophageal granular cell tumors. However, they did not identify eosinophilic inflammation as a defining pathological feature. Together, these observations suggest that eosinophilic responses may accompany diverse esophageal conditions, although their contribution to xanthogranulomatous inflammation remains

speculative (18). Additional clinicopathological studies incorporating immunohistochemistry and eosinophil-specific markers, such as eosinophil cationic protein, are required to determine whether eosinophils participate directly in the pathogenesis of esophageal xanthogranuloma or merely represent a secondary inflammatory response (20).

The coexistence of longstanding rheumatoid arthritis and prolonged immunosuppressive therapy in the present patient also deserves consideration. Although chronic immunosuppression may modify inflammatory responses and predispose patients to atypical clinical presentations, current evidence is insufficient to establish a causal relationship between immunosuppressive therapy and the development of esophageal xanthogranuloma. Because this report represents a single observation without mechanistic investigations, any proposed association should be regarded as hypothesis-generating rather than causal (21). Nevertheless, this uncommon clinical setting expands the spectrum of reported presentations. It suggests that xanthogranulomatous inflammation should be considered in the differential diagnosis of esophageal masses occurring in immunocompromised patients when conventional investigations remain inconclusive (22).

Broader insight into xanthogranulomatous disorders is provided by Nelson et al., who analyzed 235 patients with necrobiotic xanthogranuloma, a systemic xanthogranulomatous disorder, and demonstrated favorable responses to immunomodulatory therapies, including intravenous immunoglobulin and corticosteroids. Although necrobiotic xanthogranuloma differs substantially from primary esophageal xanthogranuloma in both clinical behavior and pathogenesis, the study illustrates the heterogeneous biological spectrum of xanthogranulomatous diseases. It supports the concept that immune dysregulation may contribute to these disorders. However, whether similar immunological mechanisms operate in isolated esophageal xanthogranuloma remains unknown and warrants further investigation (23).

The differential diagnosis of an intramural esophageal mass remains broad. It includes gastrointestinal stromal tumor, leiomyoma, inflammatory pseudotumor, granulomatous inflammation, lymphoma, and primary esophageal carcinoma (20). Imaging modalities such as computed tomography and endoscopic ultrasound provide valuable information on lesion size, depth, and anatomical relationships but generally lack sufficient specificity to distinguish inflammatory lesions from neoplastic processes reliably. Furthermore, superficial endoscopic biopsies frequently fail to obtain representative tissue because these lesions are predominantly submucosal (24). The present case clearly illustrates these limitations, as multiple minimally invasive investigations remained nondiagnostic despite persistent symptoms and highly suggestive imaging findings. Under these circumstances, definitive surgical resection represented an appropriate management strategy because it simultaneously established the diagnosis, excluded malignancy, and relieved obstructive symptoms.

Similar observations emerge from the literature summarized in Table 1. Suarez-Zamora et al. achieved complete resolution of an esophageal pyogenic granuloma through endoscopic excision without recurrence, while Shi et al. demonstrated that endoscopic resection of esophageal granular cell tumors is both safe and highly effective with excellent long-term outcomes (16, 18). Conversely, Nathoo et al. reported

successful medical treatment with tofacitinib for Crohn disease-associated granulomatous esophagitis once the inflammatory etiology had been established histologically (15). These studies collectively indicate that management depends primarily on obtaining an accurate tissue diagnosis, with treatment ranging from conservative medical therapy to endoscopic or surgical resection, depending on lesion type, anatomical location, symptom severity, and the degree of concern for malignancy. In the present patient, extensive intramural involvement, persistent symptoms, nondiagnostic biopsies, and continued suspicion of malignancy justified esophagectomy rather than endoscopic resection.

Table 1. Summary of published reports relevant to esophageal xanthogranulomatous inflammation and eosinophil-associated esophageal lesions

Study/ Author	Patient Demographics	Relevant Condition	Diagnostic Approach	Management	Clinical Relevance/Outcome	Reference
Present case	Adult patient with rheumatoid arthritis receiving multiple immunosuppressive agents	Esophageal xanthogranuloma with peripheral eosinophilia	CT, EUS, endoscopic biopsy (nondiagnostic), transhiatal esophagectomy, histopathology (H&E); infection and malignancy excluded; immunohistochemistry not performed	Transhiatal esophagectomy	Definitive diagnosis established after surgery; favorable postoperative outcome	Present Study
Suarez-Zamora et al. (2018)	66-year-old male	Esophageal pyogenic granuloma	Upper endoscopy with histopathological examination	Endoscopic resection	Complete resolution without recurrence	(16)
Nojkov et al. (2017)	Five patients	Esophageal granular cell tumor associated with eosinophilic esophagitis	Endoscopy, endoscopic ultrasound, biopsy	Endoscopic resection; proton pump inhibitor therapy for eosinophilic esophagitis	Symptom improvement with no reported recurrence	(17)
Shi et al. (2021)	Twenty-two patients	Esophageal granular cell tumors	Endoscopy, endoscopic ultrasound, biopsy, histopathology	Endoscopic resection	Safe and effective treatment with excellent long-term outcomes	(18)
Keim and Peerapha tdit (2021)	22-year-old female	Esophageal granulomatous inflammation	Endoscopic biopsy and histopathology	Conservative management	Highlighted diagnostic difficulty and importance of histopathological confirmation	(14)
Nathoo et al. (2016)	67-year-old female	Esophageal Crohn-related granulomatous inflammation	Endoscopy with biopsy	Tofacitinib	Clinical and endoscopic improvement after medical therapy	(15)
Nelson et al. (2020)	235 patients (mean age 61.6 years)	Necrobiotic xanthogranuloma (systemic xanthogranulomatous disorder)	Clinical assessment and histopathology	Intravenous immunoglobulin, corticosteroids, immunomodulatory therapy	Demonstrated favorable responses in systemic disease; included for comparison with systemic xanthogranulomatous disorders rather than primary esophageal disease	(23)

Overall, the available literature remains limited to isolated case reports and small case series, reflecting the exceptional rarity of esophageal xanthogranulomatous inflammation. Despite differences in pathological diagnoses across previous studies, several consistent themes emerge. Histopathological examination remains the definitive diagnostic modality after inconclusive clinical, radiological, and endoscopic evaluation; uncommon inflammatory esophageal lesions frequently mimic neoplasms; and complete endoscopic or surgical excision generally provides favorable outcomes with low reported recurrence during available follow-up. The present case is consistent with these observations, as complete surgical excision established the diagnosis and resulted in an uneventful postoperative recovery with symptom resolution. Nevertheless, long-term follow-up data remain scarce, and the natural history, recurrence risk, and optimal surveillance strategy for esophageal xanthogranuloma remain poorly defined.

Further investigation is required to define better the clinical significance, pathogenesis, and optimal management of esophageal xanthogranuloma, particularly in patients with peripheral eosinophilia or underlying immunosuppressive conditions. Future studies should focus on multicenter case collections and longitudinal follow-up to clarify the natural history, recurrence risk, and outcomes of this rare entity. In addition, systematic evaluation of histopathological and molecular characteristics, including the potential role of immunohistochemical markers and inflammatory pathways, may improve diagnostic confidence and help distinguish xanthogranulomatous inflammation from malignant, infectious, or other eosinophil-associated esophageal disorders. The possible association between immunosuppressive therapy and the development of esophageal xanthogranuloma remains uncertain. It should be explored through larger observational studies rather than inferred from isolated cases. Comparative studies evaluating the diagnostic performance of endoscopic biopsy, endoscopic ultrasound-guided sampling, endoscopic resection, and surgical approaches may further assist clinicians in selecting appropriate management strategies. Given the rarity of this condition, the collaborative reporting of similar cases will be essential to establish evidence-based diagnostic and therapeutic recommendations.

This study has several limitations that should be considered when interpreting the findings. As a single-case report, the observations cannot establish a causal relationship between immunosuppressive therapy, peripheral eosinophilia, and the development of esophageal xanthogranuloma. In addition, immunohistochemical staining (e.g., CD68, CD163, S-100, or CD1a) and quantitative assessment of tissue eosinophil infiltration were unavailable, limiting further pathological characterization and confirmation of specific cellular components. Although infection and malignancy were evaluated through clinical, radiological, endoscopic, and histopathological assessments, the absence of additional molecular or immunohistochemical analyses represents a diagnostic limitation. Furthermore, the follow-up duration was limited, preventing the assessment of long-term recurrence risk or delayed complications. Considering the rarity of esophageal xanthogranuloma, larger multicenter studies with standardized pathological evaluation, longer follow-up, and comparative cohorts are needed to better define its pathogenesis, clinical course, and optimal management strategies, particularly in patients receiving immunosuppressive therapy.

4. Conclusion

This case demonstrated the diagnostic challenge of esophageal xanthogranuloma presenting as an esophageal mass in an immunosuppressed patient with rheumatoid arthritis and peripheral eosinophilia. However, the coexistence of immunosuppressive therapy and eosinophilia may suggest an association; a causal relationship cannot be established from a single case and requires further investigation. The diagnosis of this rare entity relies on careful histopathological evaluation, particularly when endoscopic biopsy or minimally invasive sampling is nondiagnostic. In immunosuppressed patients with an esophageal mass and peripheral eosinophilia, xanthogranuloma should be considered in the differential diagnosis, and definitive pathological assessment is essential to distinguish it from neoplastic, infectious, or other inflammatory conditions. Surgical resection may be required in selected cases when diagnostic uncertainty persists or when complete lesion removal is clinically indicated. Further studies with comprehensive pathological characterization and longer follow-up are needed to understand better the clinical behavior, potential associations, and optimal management strategies for esophageal xanthogranuloma.

Abbreviations

EUS: Endoscopic Ultrasound
GIST: Gastrointestinal Stromal Tumor
H&E: Hematoxylin and Eosin
GE: Gastroesophageal Junction
EGDs: Esophagogastroduodenoscopies (implied)
CD: Cluster of Differentiation (as in CD68, CD163, etc.)
S-100: S100 Protein
CD1a: Cluster of Differentiation 1a

Acknowledgements: Not applicable.

Consent for Publication: Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Availability of Data and Materials: The data supporting the findings of this study are available from the corresponding author upon reasonable request. The minimal dataset necessary to interpret, replicate, and build upon the findings is accessible, subject to privacy considerations.

Competing Interests: The authors declare no conflicts of interest, financial or non-financial.

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Ethics Approval and Consent to Participate: The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and institutional policies governing publication of clinical case reports. Written informed consent was also obtained from the patient for the publication of the clinical information and accompanying images. Besides, all identifying information was removed to preserve patient confidentiality.

Authors' Contributions: Sepehr Sadrizadeh conceptualized; Ali Sadrizadeh supervised and validated; Mohammad Hassan Jokar and Alireza Bary conducted the investigation and methodology; Reza Sahabi and Ali Reza Sharifian Attar drafted and edited the manuscript. All authors reviewed and approved the final version.

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