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ORIGINAL ARTICLE

Granulomas in the gastrointestinal tract: deciphering the Pandora's box

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Abstract Granulomas are organised collection of activated histiocytes induced by a persistent antigen stimulus. A wide variety of antigens encountered by the gastrointestinal tract are of this nature and hence the resulting granulomatous inflammation represents a tissue reaction pattern. The potential causes can be broadly classified as infections or non-infectious immune reactions. There is also a group where a cause is never identified. Granulomas may be of varying morphological appearance, most commonly epithelioid, foreign body type, suppurative and necrotizing. This may provide a clue as to the aetiology; however, in most cases, the cause requires further inquiry. Pathologists may need to cut deeper levels to look for foreign material and apply special stains to look for microorganisms. Pathologists also need to be certain that the process is a true granuloma and not a mimic. The site of occurrence in the gastrointestinal tract and the clinical setting is often paramount in establishing the aetiology. For instance, infections are more likely the cause in developing countries or when there is immunosuppression. Similarly, granulomas in the stomach are usually due to Crohn's disease; however, it is only rarely the cause of granulomas isolated to the appendix.

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Introduction

A granuloma is an organised collection of activated macrophages (or histiocytes), the result of a unique chronic inflammatory process to an antigen (or autoantigen) that is persistent or difficult to remove [1]. Many antigens encountered by the luminal gastrointestinal tract have these qualities, and hence granulomas are not infrequently encountered in this organ. The histiocytes in a granuloma are organised as a circumscribed collection with defined boundaries. Two main types of granulomatous reactions are recognised: (1) foreign body type, formed in an attempt to phagocytose relatively inert foreign material (e.g. suture material) and not involving activation of the T cell-mediated immune response, and (2) immune granulomata, developing as a result of a persistent T cell-mediated immune response and activation of both innate and adaptive immune pathways [1, 2]. The exact pathways and relative effect of mediating cytokines vary depending on the inciting antigen and this produces varied morphology. Lymphocytes are a common accompaniment of the histiocytes in a granuloma. Occasionally, other inflammatory cells such as neutrophils and eosinophils are also present, again dependant on the inciting antigen and consequent immune pathway.

Granulomatous inflammation is best viewed as an inflammatory reaction pattern with the defining morphological marker being an organised arrangement of histiocytes—a 'granuloma'. Granulomas may exhibit a variety of patterns which broadly reflect the underlying aetiology. General types include *foreign body type*, characterised by multinucleate cells with eccentrically or haphazardly arranged nuclei; *epithelioid*, characterised by

single or multinucleate collections of histiocytes with abundant eosinophilic cytoplasm and 'foot print'-like nuclei; *xanthogranulomatous*, characterised by collections of lipid laden macrophages and multinucleate cells; *suppurative*, with a central zone of neutrophils; and *necrotising*, with central necrosis that may retain the structure of the underlying necrotic tissue or in the case of tuberculosis related caseous necrosis will be devoid of any structure. Two important subtypes of epithelioid granulomas are also recognised. Sarcoidal granulomas are a form largely devoid of other inflammatory cells and often containing calcified bodies (Schaumann bodies and/or asteroid bodies). Microgranulomas are smaller than usual granulomas with the number of histiocytes averaging 7–18 as against 25–90 [3].

The inciting antigens are best considered for practical purposes under two headings, infectious and non-infectious. In some cases, despite extensive investigation, an identifiable cause may not be found and the term idiopathic granulomatous inflammation is appropriate. Table 1 lists the major aetiologies of granulomas in the gastrointestinal tract.

Approach to granulomas in the gastrointestinal tract

The first issue when presented with a 'granuloma' in the gastrointestinal tract is to confirm that the process is indeed a true granuloma. Many normal structures can mimic a granuloma under certain circumstances. for instance the sclerotic germinal centre of a reactive lymphoid follicle and cross-cutting of the pericryptal fibroblast sheath. Inflammation may also alter normal structures such that they might resemble a granuloma. Examples include ganglion cells which undergo hypertrophy and become translocated to the mucosa. Similarly, the muscularis mucosae might be disrupted and appear as a rounded collection of smooth muscle cells (Fig. 1a), and endothelial cells may enlarge and appear clustered. In addition, lesions such as Schwann cell hamartoma (Fig. 1b), perineurioma and elastofibroma can all resemble granuloma in their early development. Pathologists should be vigilant to the possibility of these mimics.

Once confirmed, the next step is to determine the likely cause of the granuloma and therefore the clinical significance. The clinical setting might already indicate the aetiology and no further inquiry is required, for example in follow-up biopsies of established Crohn's disease or a patient known to have chronic granulomatous disease. The morphology of the granuloma and presence, pattern and type of background inflammation are important to aid identification when the cause is unknown. Table 2 summarises this morphology-based method.

In all cases where the cause is not known, the following approach is recommended. Firstly, look for an inciting cause in the tissue sections. This might be a foreign material (polarise the slide, also consider pneumatosis) (Fig. 2a), a parasite (ensure sufficient levels are cut) (Fig. 2b) or crypt rupture (look for a crypt that is at the edge of the granuloma with mucin extravasation and neutrophil and eosinophil infiltration) (Fig. 2c). Secondly, look for any additional clues, for instance the brown pigment laden macrophages in the non-inflamed bowel of chronic granulomatous disease (Fig. 3b). Thirdly, all cases for which an aetiology remains uncertain should have organism stains ('bug stains') performed, at a minimum PAS, ZN and Wade-Fite. If infection is favoured clinically and organisms are not identified by special stains, additional polymerase chain reaction (PCR) studies on paraffin-embedded formalin fixed tissue can be performed for tuberculosis, fungi and *Yersinia*. Clinical investigations such as stool culture or serology are also potentially helpful.

Finally, and often most importantly, the clinical setting might provide the answer as to the aetiology, and great value is often obtained by discussing the case with the referring clinician. Significant clinical factors that aid in the diagnosis are summarised in Table 3.

Depending of the aetiology, granulomas may be localised to a particular site in the gastrointestinal tract or may occur at several sites.

Table 1 General aetiological considerations

Infectious
Systemic (tuberculosis, histoplasmosis, Whipple disease)
GI specific infections (S*almonella*, *Yersinia*, *Campylobacter*, *Helicobacter*)
Parasites (schistosoma, enterobius)
Venereal infections (syphilis, lymphogranuloma venereum)
Non-infectious
Crohn's disease
Drugs (non-steroidal anti-inflammatory drugs—diclofenac, biologics)
Foreign material (talc, starch, barium, faecal material including pulse granuloma, pneumatosis)
Crypt/gland rupture associated granuloma
Sarcoidosis
Inherited disorders (chronic granulomatous disease, Hermansky-Pudlak syndrome, Blau syndrome)
Autoinflammatory granulomatous diseases
Diverticular colitis
Malignancy/neoplasm related
Vasculitis (granulomatosis with polyangitis, Churg-Strauss syndrome, Behcet's disease, giant cell arteritis)
Common variable immunodeficiency
Cord colitis syndrome
Idiopathic

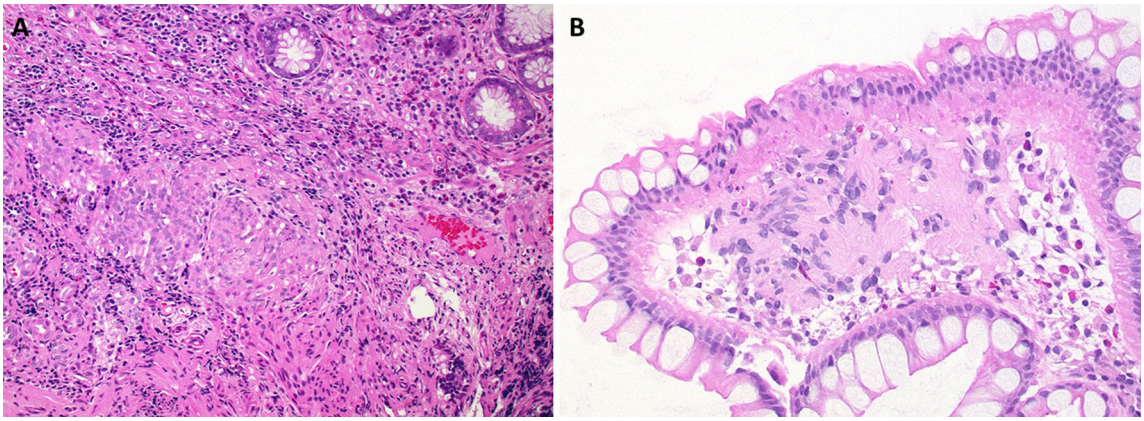

Fig. 1 **a** Disrupted muscularis mucosae in a chronic ulceroinflammatory process. **b** Small focus of Schwann cell hamartoma (tactile body-like appearance)

Specific aetiologies and diseases

Crohn's disease

Although considered to be a hallmark of this disease, the reported frequency of granulomas in Crohn's disease varies from only 15 to 60%, with an average detection of 45% [4, 5]. Granulomas are present in 25–40% of Crohn's disease biopsies at first presentation [6, 7]. Detection is higher in children than adults [7, 8], and the likelihood of finding granulomas increases with the more biopsies taken [4, 6]. Granulomas are more commonly found in resection specimens than mucosal biopsies [4]. It is also recognised that granulomas are more likely to be detected as the length of disease increases [6]. Granulomas developing in Crohn's disease are in a constant state of development and resolution [8, 9] depending on the immunological state. The findings of a recent meta-analysis conclude that the presence of granulomas in Crohn's disease is associated with a higher number of recurrences and reoperations and a shorter time to recurrence and reoperation compared to Crohn's disease without granulomas [5]. However, not all studies have found granulomatous Crohn's disease to be prognostically significant [8].

Granulomas in Crohn's disease may occur in all layers of the gastrointestinal tract wall. They may become intimately associated with the mural vasculature [10, 11]. Similarly, they may reside within the muscularis mucosae. A wide variety of patterns including microgranulomas (with limited numbers of histiocytes) [3], sarcoidal type epithelioid granulomas without associated inflammation and sometimes exhibiting Schaumann bodies (Fig. 4a) [12] and epithelioid type with prominent multinucleate histiocytes may be seen. Rarely, there may be focal necrosis or suppuration (see Fig. 4b).

Tuberculosis

Infection by mycobacterium tuberculosis (tuberculosis) remains an important treatable aetiology of granulomatous disease of the gastrointestinal tract with the combined impact of immigration from high risk areas, HIV infection, bacterial multidrug resistance [13] and increasing use of immunomodulators [14] altering the epidemiology. Clinically, radiologically,

Table 2 Histological pattern and potential aetiology

Granuloma type	Potential aetiology
Epithelioid granuloma with background active chronic inflammation	Crohn's disease, crypt rupture-associated granuloma in ulcerative colitis
Epithelioid granuloma, no inflammation	Sarcoidosis, inactive Crohn's disease, medication
Granuloma with background eosinophils	Parasites, Churg-Strauss vasculitis, pneumatosis, resolving Crohn's disease
Granuloma with background necrosis	Polyangitis granulomatosis, intravascular fungal infection
Granuloma with background vasculitis	Behcet's, polyangitis, Churg-Strauss, rarely Crohn's disease
Necrotising granuloma	Tuberculosis, *Yersinia*, fungal infection
Foreign body type granuloma	Foreign material, parasites
Xanthogranulomatous	Chronic infection

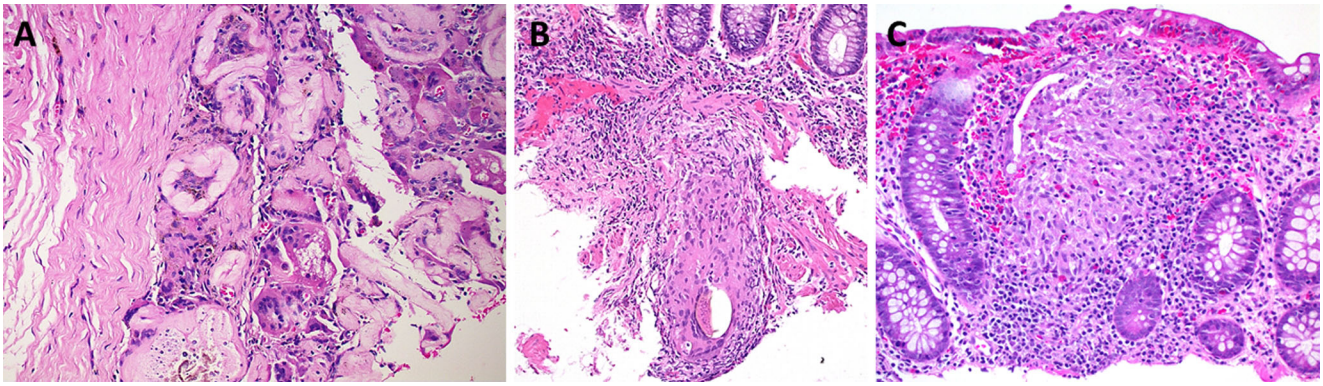

Fig. 2 **a** Pulse granuloma. Foreign body giant cells associated with hyaline ribbons and rings and dystrophic calcification. **b** Schistosomiasis parasite with surrounding granulomatous inflammation. The parasite was only apparent in deeper levels. **c** Crypt rupture-associated granuloma. Note the close association to the ruptured crypt

endoscopically and histologically, this infection may closely resemble Crohn's disease [15]. Histological features that serve as clues to the possibility of tuberculosis include large coalescing granulomas, the presence of caseous necrosis and tendency for the inflammation to be focal and have submucosal accentuation [16–18]. Basal plasmacytosis and presence of microgranuloma are more typical of Crohn's disease cases [16, 17]. In general, granulomata of tuberculosis are more readily found compared to Crohn's disease [16]. Unfortunately, while caseous necrosis is quite specific for gastrointestinal tract tuberculosis, it is found in a minority of cases on biopsy and only about half of cases overall [2, 16, 18]. Furthermore, the sensitivity of Ziehl-Neelsen stain is only approximately 20.5% [19] and formal culture is notoriously slow to yield a result when oftentimes diagnosis and treatment need to be established quickly. PCR performed on paraffin material to confirm the mycobacterium tuberculosis organism is more rapid and has a reported sensitivity of 64.1% [19]. The most useful investigation is serological examination for specific interferon gamma release (QuantiFERON tuberculosis) [20].

Inherited disorders

Several inherited conditions produce granulomas in the gastrointestinal tract. The most common of these is chronic granulomatous disease which can be inherited in both X-linked and autosomal recessive fashion [21]. The former is more common and hence males are more likely affected. Granulomas develop from defective neutrophil function resulting from dysfunction of NADPH oxidase required for the generation of superoxide essential to kill ingested bacterial organisms [21]. The condition typically presents within the first two decades of life and 55–61% of patients with chronic granulomatous disease have granulomas in the gastrointestinal tract [22, 23]. These are often associated with focal inflammation and this occurs

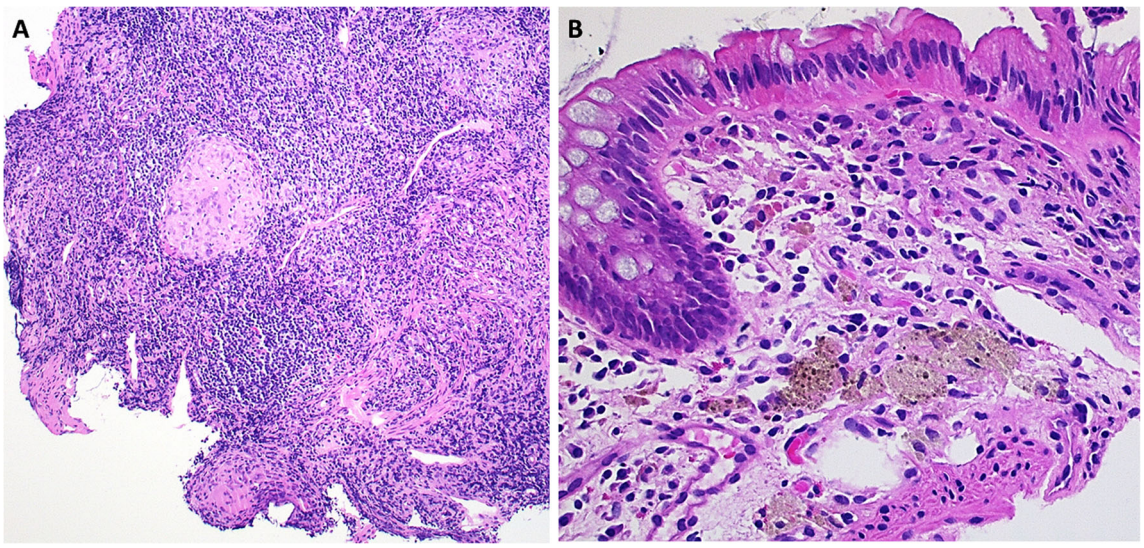

Fig. 3 **a** Granulomatous and chronic inflammatory process typical of chronic granulomatous disease. **b** Characteristic brown pigment laden macrophages in the non-inflamed mucosa

Table 3 Clinical setting and potential aetiology

Clinical finding	Potential aetiology
Significant past history	Crohn's disease, chronic granulomatous disease, common variable immunodeficiency, vasculitis
Extraintestinal granulomas	Crohn's disease, tuberculosis, sarcoidosis, Blau syndrome, chronic granulomatous disease
History of immunosuppression	Infectious causes
Travel history/geographic location	Potential exposure to parasitic infection, tuberculosis
Medication history	Recent introduction of a new medication
Sexual practices	Anal intercourse and the risk of lymphogranuloma venereum
Patient's age	Young patients—considered an inherited condition

throughout the gas intestinal tract but is more commonly seen in the colorectum (Fig. 3a) [22, 23]. The histological pattern may be strikingly similar to Crohn's disease [23]. A very useful diagnostic pointer is the presence of pigmented macrophages in the mucosa which is seen in up to 75% of patients (Fig. 3b) [22].

Other rare inherited conditions include Hermansky-Pudlak syndrome, an autosomal recessive condition characterised by albinism, skin hyperpigmentation and platelet deficiency. Fewer than 10% of patients develop colonic inflammation; however, this may closely resemble Crohn's disease by the presence of granulomas and/or fistulas [24]. Similar to chronic granulomatous disease, pigment laden (ceroid) macrophage may be seen in the adjacent mucosa [24]. Blau syndrome is an autosomal dominant condition with multiorgan granuloma formation. Similar to some forms of Crohn's disease, the immunopathogenesis is via mutation in NOD2 gene, although gastrointestinal tract involvement is relatively uncommon [25].

Sarcoidosis

This common cause of systemic granulomatosis only affects the luminal gastrointestinal tract in 0.1–1.6% of cases [26]. The stomach, in particular the antrum, is most commonly affected with 96% of all digestive tract sarcoidosis involving this site [26, 27]. This is followed by the colon which is involved in approximately in one third of cases [26]. Endoscopic features include ulceration, polyp formation and occasionally stricturing [26, 27]. The granulomas are tight non-necrotising collections of histiocytes typically with minimal or no inflammation (Fig. 5b) unless there is accompanying ulceration. Calcified structures (Schaumann bodies) may be seen within the granulomas and represent a minor clue to diagnosis; however,

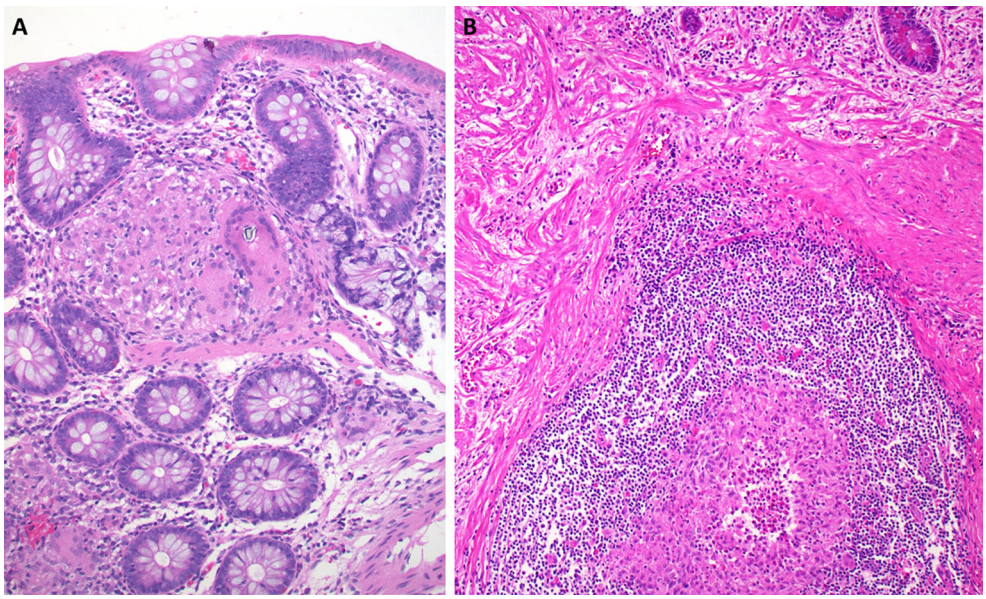

Fig. 4 **a** Crohn's disease with Schaumann-like body. **b** Crohn's disease resection with a focus of suppurative inflammation in one granuloma

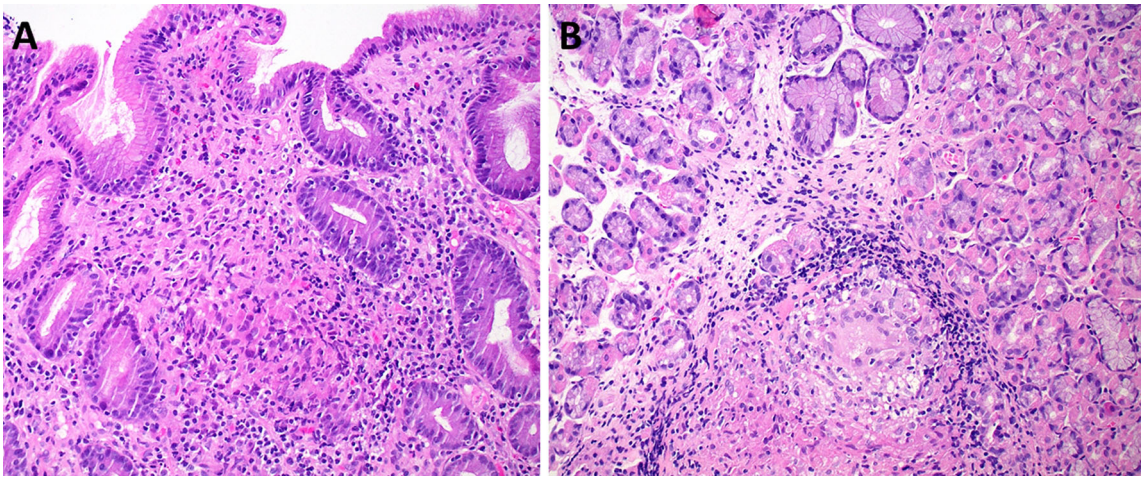

Fig. 5 **a** Crohn's disease of the stomach. The granulomas are epithelioid and often indistinct. Background focal inflammation is typical. **b** Sarcoidosis of the stomach. A large epithelioid granuloma with minimal associated inflammation

this feature is not specific (see Crohn's disease above). Foreign material may also mimic the calcific bodies. The diagnosis of sarcoidosis is usually established by identification of thoracic or other extraintestinal disease and by elevated level of angiotensin-converting enzyme.

Foreign material

The gastrointestinal tract encounters large number foreign bodies both via ingestion and by iatrogenic means (i.e. post-surgical). A characteristic feature is the foreign body giant cell reaction containing multinucleate giant cells with nuclei that are randomly distributed through eosinophilic cytoplasm. The inciting foreign material may be evident in the H&E stain, sometimes after cutting multiple deeper levels, or may become apparent upon polarisation. Well-described foreign materials encountered in the gastrointestinal tract include talc and starch (often in the subserosal region in a post-operative setting) [28], barium [29], suture material [30] and faecal material. A particular form of the latter is the pulse granuloma, most often encountered in the rectum and sometimes forming a mass ('pseudotumour') [31]. Histological features include foreign body giant cells with variable amounts of hyaline ribbons and rings, inflammation, calcifications and food particles (see Fig. 2a) [32]. A foreign body giant cell reaction often surrounds parasites and their eggs that invade the stomach or intestinal wall. Most commonly encountered are schistosomiasis [33], enterobius [34] and strongyloides [35] (see Fig. 2b). All may be accompanied by an intense eosinophil reaction sometimes masking the causative organism; hence, multiple deeper levels are always recommended when granulomas and focal eosinophil infiltration are encountered. Parasite-related granulomatous inflammation may be so marked as to cause a polyp or mass lesion [33]. This is often in the rectum with enterobius and schistosomiasis. Serological testing is available to assist in the diagnosis of strongyloides and schistosomiasis [33].

A foreign body giant cell reaction may occur around the gas pockets of pneumatosis in the gastrointestinal tract. In mucosal biopsies, this often occurs in the deep aspect of the specimen, where the inciting gas pocket may not be appreciated. Variable inflammation and crypt disarray can produce a resemblance to Crohn's disease [36]. Eosinophils can be prominent and further confuse the diagnosis but serve as a clue when the pathologist is cognisant of this condition.

Medications

A medication reaction producing granulomatous inflammation is surprisingly infrequently reported in the luminal gastrointestinal tract in contrast to examples in the liver, skin and lung. There exist sparse case reports [36]; however, our personal experience is that medications are responsible for some cases of either localised or diffuse gastrointestinal tract granulomatosis. In particular, we have seen cases associated with several new immune modulatory drugs (see Fig. 6a, b), although it is unclear whether the granulomas result from an aberrant immune reaction, florid crypt destruction or an infection due to the induced immunodeficiency. Recent reports have affirmed this impression with colonic granulomas being associated with PD1 inhibitor-induced colitis [37].

Vasculitis

Four forms of vasculitis affecting the gastrointestinal tract can be associated with granulomata. Eosinophilic granulomatosis with polyangiitis (Churg Strauss syndrome) is a triad of asthma, hypereosinophilia and vasculitis which involves the gastrointestinal tract in approximately one third to one half of patients [2, 38]. The associated vasculitis and eosinophilic infiltrate are a clue to the diagnosis; however, it is the clinical background that establishes the diagnosis. Despite the name granulomata are infrequent [38]. Granulomatosis with

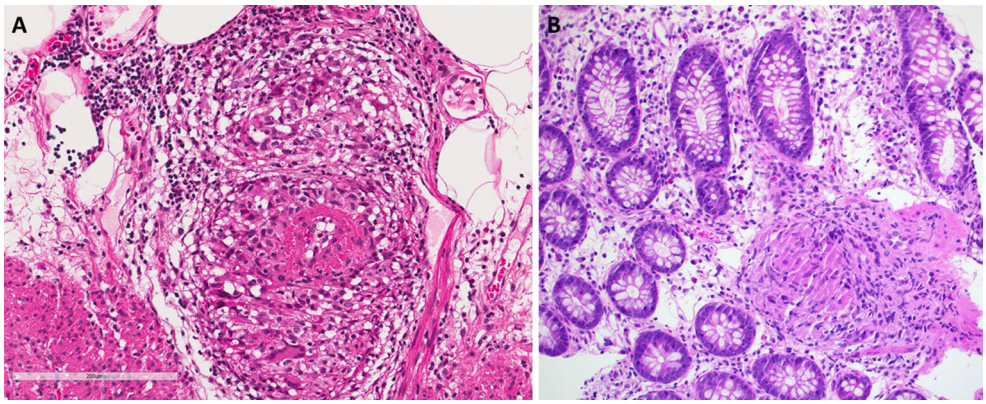

Fig. 6 **a** Granulomatous vasculitis in the intestinal wall in a patient taking a PD1 inhibitor drug. **b** Diffuse granulomatous colitis in a patient taking an anti-CD20 medication for multiple sclerosis

polyangitis (Wegener's granulomatosis) most commonly affects the respiratory tract. Unusually, there is involvement of the gastrointestinal tract. Granulomatous inflammation, vasculitis, extensive ulceration and necrosis are the main histological findings [2, 39]. Behcet's disease is a multiorgan inflammatory process of presumed immune aetiology that is characterised by recurrent oral and genital ulcerations and manifestations of vasculitis. Intestinal involvement is seen in between 3 and 60% of patients depending on geographic location [40]. The ileocaecal valve is the most involved site and punched out ulcers that appear aphthoid or round are present. Histologically, there is relatively non-specific active chronic inflammation. Characteristic vasculitis is not often identified on mucosal biopsies. Epithelioid granulomata are only rarely encountered, but when seen, the already difficult separation from Crohn's disease is further exacerbated. Finally, giant cell arteritis may very rarely involve the gastrointestinal tract. The intimate association of the giant cells with a medium-sized muscular artery helps with the diagnosis, although Crohn's disease is a far more common cause of this pattern in the gastrointestinal tract [41].

Miscellaneous

A small subset of common variable immunodeficiency presents an endoscopic and histological pattern identical to Crohn's disease with focal inflammation and granulomas [42]. The clinical association of recurrent infections and abnormality in gamma globulin is helpful in establishing the diagnosis. Cord colitis syndrome develops in recipients of umbilical cord blood transplant and is reported to show diffuse gastrointestinal tract granulomata [43]. A variety of neoplasms of the gastrointestinal tract may be associated with granulomatous inflammation generally as an immune reaction to the tumour. A commonly encountered example of this occurs in microsatellite instability—high colorectal carcinoma. Granuloma formation may occur when crypts or glands rupture as a result of any inflammatory process. The best characterised situation is in ulcerative colitis. The main clue to this process is the finding of the granuloma centred on the residual crypt or gland and the presence of some extravasated mucin admixed with neutrophils and eosinophils associated with the granuloma [8, 44, 45]. Deeper levels are very useful in documenting the association with a ruptured crypt [46].

Finally, there is an expanding interest in so-called autoinflammatory granulomatous diseases, which result from dysfunction, often inherited, of genes involved in certain inflammatory pathways, the end result being granulomatous inflammation [47]. Blau syndrome (discussed above) and early onset sarcoidosis are examples, with mutations existing in the NOD2 gene.

Idiopathic

Despite the investigation, some cases of gastrointestinal tract granulomatosis defy explanation. Infection for which the organism cannot be identified is often blamed. Immune dysregulation syndromes such as common variable immunodeficiency should always be considered, because other clinical manifestations may be underappreciated. In some cases, only long-term follow-up can exclude Crohn's disease.

Specific sites

Granulomatous gastritis

Aetiology common to granulomatous gastritis

- Crohn's disease
- Sarcoidosis
- *Helicobacter pylori*
- Non-*H. pylori* infections
- Neoplasm-related gastric adenocarcinomas and mucosa-associated lymphoid tissue (MALT) lymphomas
- Idiopathic

Granulomatous gastritis is the term given for the presence of granulomas occurring in the stomach. Most cases are associated with chronic inflammation, but the term is still applicable without it. This finding is uncommon, with a reported incidence between 0.08 and 0.35% in gastric biopsies [48–50]. Granulomas may be numerous and dominate the histological pattern. However, more often than not, granulomas are accompanied by other patterns of inflammation, commonly active chronic inflammation, that appear to be the major abnormality.

Granulomatous gastritis is a reaction pattern that has both infective and non-infective causes. The aetiology varies according to geography and ethnicity. For instance in developed countries, the majority of cases are of non-infectious aetiology with the most common cause being Crohn's disease [49, 50]. This is almost always the cause in children [51]. Meanwhile, worldwide, the most common aetiology of granulomatous gastritis is infection, of which tuberculosis is the most important cause to consider [52].

Crohn's disease is associated with granulomatous inflammation in the stomach in between 8 and 75% of patients [53, 54]. Up to half of all cases of granulomatous gastritis in developed countries are related to Crohn's disease [48]. The prevalence appears to be higher in the paediatric age group [51]. Within the stomach, a sub-pattern of focally enhanced gastritis may provide a clue to the diagnosis (Fig. 5a); however, a diffuse pattern with granulomas is occasionally encountered in limited biopsies [7]. Gastric Crohn's disease is often accompanied by involvement of the other sites of the GI tract; therefore, an important step is to correlate with the finding of biopsies of other sites [7].

Granulomas are found in a variable percentage of *H. pylori*-infected stomachs. In one study, which accords with our experience, they were identified in 1.1% of *H. pylori*-containing gastric biopsies [55]. This is in contrast to a Korean study where *H. pylori* were present in 78% of cases [49]. The granulomas were single and located in the antrum [49]. It is unclear whether *H. pylori* can be regarded as the aetiology or an incidental finding; however, eradication of *H. pylori* has been associated with regression of the granulomas [56, 57]. Practically, if a patient has ileal or ileocolonic Crohn's disease, then any granulomatous gastritis can be regarded as evidence of upper gastrointestinal tract Crohn's disease regardless of the presence of *Helicobacter* infection.

In addition to mycobacteria and *Helicobacter* infection, other infections have been associated with gastric granuloma formation but are quite rare. These include syphilis (tertiary form 'gumma'), Whipple disease, parasitic infections, such as anisakiasis, schistosomiasis and taeniasis, and invasive fungal infections [58, 59].

Rare causes of granulomas gastritis include sarcoidosis (discussed above; Fig. 5b), medications, e.g. carbimazole [60], and foreign body granulomas due to food or antacids that become impacted in an ulcer or due to suture material [59]. Granulomatous inflammation has been reported in association with several tumours including gastric adenocarcinomas, Langerhans cell histiocytosis and MALT lymphomas [59].

Finally, gastric granulomas develop without obvious aetiology in up to 25% of cases. The term idiopathic granulomatous gastritis is appropriate for these cases that remain of uncertain cause after extensive investigation both clinically and pathologically. Long-term follow-up is important as idiopathic granulomatous gastritis may precede the full spectrum of a specific disease, sarcoidosis or Crohn's disease in particular, sometimes by many years [59]. Therefore, an initial 'diagnosis' of idiopathic granulomatous gastritis should not be regarded as a distinct entity.

Granulomatous ileitis

Aetiology common to granulomatous ileitis

Infectious
- Tuberculosis
- *Yersinia*

Non-infectious
- Crohn's disease
- Vasculitis—Behcet's
- Neoplasm related—lymphoma, adenocarcinoma, neuroendocrine tumour

Crohn's disease is by far the most common cause of granulomas in the ileum in developed countries, whereas in underdeveloped countries, the main cause is tuberculosis. The ileum is a preferential site for intestinal tuberculosis because of the high densities of lymphoid aggregates, neutral pH environment and ready absorption of the organisms at this site [61]. Approximately 90% of all intestinal tuberculosis involves the ileum [62]. Distinction from Crohn's disease is extremely problematic in regions where tuberculosis is endemic. Features that favour Crohn's disease include the presence of anorectal disease, a longitudinal pattern of ulceration and a cobblestone appearance to the mucosa [13, 15, 18, 62]. Histologically large confluent granuloma and necrosis within the granulomas are rare for Crohn's disease and should always prompt investigation for tuberculosis. PCR from paraffin-embedded material can aid in the diagnosis.

Yersinia infection is a common mimic of both Crohn's disease and tuberculosis in the ileum. *Yersinia enterocolitica* and *Yersinia pseudotuberculosis* are the most commonly

encountered species. They are gram-negative coccobacilli acquired by ingestion of contaminated food. Infection is often self-limited but chronic infections can develop [62]. Infection risk is increased in patients with iron overload disorders. Table 4 provides helpful diagnostic clues.

Granulomatous colitis

Aetiology common to granulomatous colitis

Infectious
- Systemic forms (tuberculosis, histoplasmosis)
- GI infections (*Salmonella*, *Yersinia*, *Campylobacter*, parasites)
- Venereal infections in rectum (syphilis, lymphogranuloma venereum)

Non-infectious
- Crohn's disease
- Ulcerative colitis (mucin granuloma)
- Diverticular colitis (syn. diverticular disease-associated colitis)
- Pneumatosis coli
- Malignancy related—e.g. granulomatous reaction to microsatellite instability high colorectal carcinoma

The large intestine is the most common site in which granulomas are identified within the gastrointestinal tract. Crohn's disease is the most common aetiology. However, a high index of suspicion of other possibilities should always be maintained before making this diagnosis, particularly if the inflammatory changes and granulomata are limited to the large intestine. In particular, granuloma limited to the sigmoid colon can represent an idiosyncratic reaction to the diverticular disease [63]. Furthermore, granulomata limited to the distal rectum, while common in Crohn's disease, can also be seen with venereal infections in particular syphilis and lymphogranuloma venereum [64]. Patchy active chronic inflammation with granulomata, sometimes numerous, may represent resolving stage ulcerative colitis. Attention should be paid to the association of granulomas to crypts [45].

Foreign body type granulomata occurring at the base of the mucosa in biopsy specimens may represent pneumatosis coli. Associated gas pockets and eosinophil infiltrate are helpful clues for the latter [65]. Bacterial infection by *Salmonella* or *Campylobacter* may very rarely produce scattered microgranulomata typically in the setting of an acute inflammatory process with marked cryptitis, crypt abscess formation and mucosal oedema [66].

Granulomatous appendicitis

Aetiological common to granulomatous appendicitis

Infectious
- Tuberculosis, *Yersinia*, parasites (enterobius, schistosomiasis)

Non-infectious
- Interval appendicitis
- Crohn's disease
- Idiopathic

Granulomatous appendicitis is an uncommon finding identified in 0.1 to 2.0% of appendicectomy specimens [67, 68]. Cases may present with symptoms and signs of acute appendicitis or the process may be asymptomatic and identified in the appendix removed for other reasons. Granulomatous appendicitis was originally believed, at least in developed countries, to represent an isolated organ manifestation of Crohn's disease; however, it is now recognised that Crohn's disease accounts for only about 5–10% of granulomatous appendicitis [68] and that Crohn's disease involving only the appendix is exceptional.

While previously a common diagnosis, idiopathic (primary) granulomatous appendicitis is in fact rare. Two aetiologies now account for the majority of these cases, namely, *Yersinia* infection and interval appendicectomy-related inflammation (see Fig. 7a, b) [68–70]. The relative contribution of interval appendectomy depends upon local surgical management but may represent more than half of all granulomas appendicitis cases encountered [70]. Other infections, mainly tuberculosis and parasitic infestations, are more commonly the cause of granulomatous appendicitis in tropical and subtropical countries. In a recent review of 13 cases drawn mainly from underdeveloped countries, infectious and non-infectious causes were responsible for 62 and 38% of granulomatous appendicitis, respectively [67]. Parasites were responsible for 38.5% of the cases [67]. Infrequent causes include sarcoidosis, fungal infection and foreign body reaction to impacted faeces [68].

The appendix can be normal sized or enlarged. An important histological feature is the number of granulomas which are more numerous with both idiopathic granulomatous appendicitis and infection, than with Crohn's disease [71]. The latter may even be devoid of granulomas. The presence of necrosis in the granulomata should always suggest an infectious aetiology, while fistula or fissure formation is more common with Crohn's disease [71, 72].

Table 4 Distinguishing features between TB, *Yersinia* and Crohn's disease

Feature	Crohn's disease	*Yersinia*	Tuberculosis
Clinical/gross			
Predisposition	Family history −/+	Iron overload disorder	High prevalence area
Ulcers	Linear (longitudinal) and aphthoid	Linear and aphthoid	Tend to be in transverse axis or circumferential
Oedema	+	+	+
Pseudopolyps	+	+	+
Fistulae	+	+/−	+
Transverse fissures	+	−	+
Cobble stoning	+	−/+	−/+
Strictures	Generally long	+/−	Usually <3 cm
Anal lesions	Frequent	No	Rare
Serology	−	Yersinia specific	QuantiFERON tuberculosis
Stool culture	−	Often positive	30% positive
Specific PCR on paraffin material	−	+	+
Microscopy			
Granulomas			
Number	Multiple	Few	Many and may be confluent
Size	Small (<200 μm)	Large	Large (90% over 200 μm)
Nature	Compact sarcoid-like Poorly organised, discrete or isolated	Epithelioid granulomas without foreign body giant cells with central necrosis and prominent lymphoid cuffing; stellate abscesses	Epithelioid granulomas with Langhans giant cells and central caseation
Location	Mucosal location more common than in other sites. Granulomas may be associated with lymphatics	Mucosa but also submucosa and deeper in bowel wall	Granulomas in submucosa (if present in biopsy) or in granulation tissue favours tuberculosis
Microgranulomas/histiocytic aggregates	+	−/+	−/+
Crypt-centred inflammation/pericryptal granuloma	+	−/+	−/+

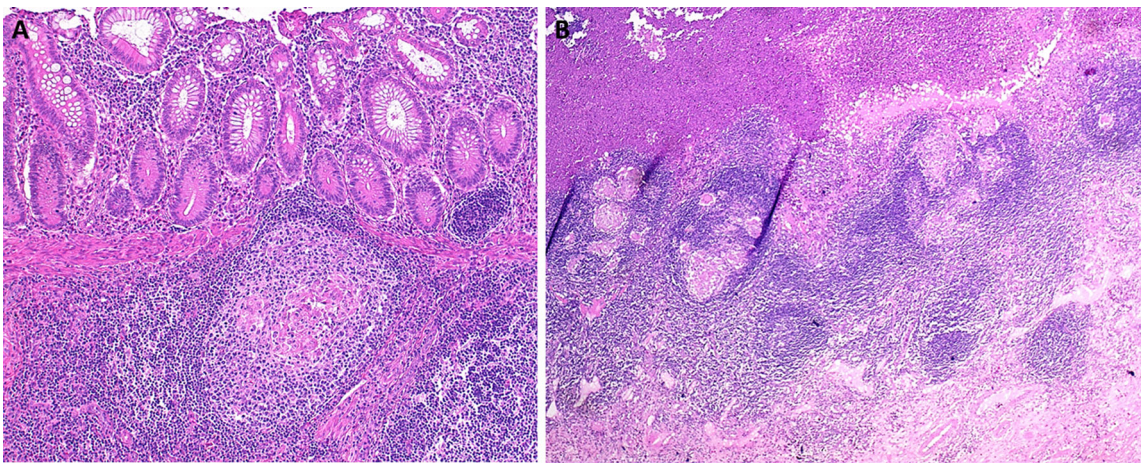

Fig. 7 **a** Granulomatous appendicitis in confirmed *Yersinia* infection. **b** Granulomatous appendicitis in interval appendicectomy with numerous granulomas evident

Other sites

Granulomata are uncommonly identified within the oesophagus. Partly, this is due to the fact mucosal biopsies do not include much submucosa. Crohn's disease is the most common association in developed countries with the granulomata sitting just beneath the epithelium typically associated with a heavy chronic inflammatory cell infiltrate and lymphocytic oesophagitis pattern [7]. In our experience, an oesophageal biopsy that shows sub-epithelial chronic inflammation in a patient with high clinical suspicion of Crohn's disease should be levelled even until the block is exhausted to identify a confirmatory granuloma. In countries with high prevalence of tuberculosis, this infection needs to be excluded since oesophageal involvement could represent either local infection or direct spread from the thoracic cavity.

Causes of granulomas in duodenum are similar to other sites in the intestine. The finding of ulceration, focal active chronic inflammation and granuloma formation is quite typical for Crohn's disease in our experience [7]. These findings will almost universally be associated with other inflammatory change in the upper gastrointestinal tract particularly within the stomach.

Conclusion

Granulomata represent an occasionally identified inflammatory process within the gastrointestinal tract. Histopathologists play an important role in identifying the aetiology or providing clinical guidance as to the likely cause. In most cases, clinicopathological correlation is required to establish the final diagnosis.

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