GI Tract Sarcoidosis: A Review

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Sarcoidosis of the GI tract is rare and usually causes no symptoms. The diagnosis of GI tract sarcoidosis is problematic as it needs to be distinguished from other granulomatous diseases of the GI tract. Treatment is usually indicated for symptomatic disease, which is rare. In this review, we discuss the diagnostic approach, clinical manifestations, and treatment approach to GI tract sarcoidosis.

INTRODUCTION

Sarcoidosis is a multisystem, granulomatous disease of unknown cause. It may affect any organ but rarely involves the gastrointestinal (GI) tract. The diagnosis of GI tract sarcoidosis is problematic in that it must be distinguished from alternative granulomatous GI tract diseases. This paper will review the clinical aspects of GI tract sarcoidosis, focusing on its manifestations, diagnosis, and treatment.

Diagnosis

The diagnosis of sarcoidosis usually follows the algorithm outlined in Figure 1. The need to exclude alternative causes of granulomatous inflammation implies that the diagnosis of sarcoidosis can never be established with complete confidence. Therefore, a diagnostic evaluation for sarcoidosis can never result in a definitive diagnosis, but rather a statistical likelihood of the disease. The criterion of documenting systemic involvement implies that the identification of granulomas confined to the GI tract is insufficient to make a diagnosis of sarcoidosis. For example, idiopathic granulomatous gastritis is considered a distinct entity from sarcoidosis unless extra-gastric granulomatous inflammation is detected. This is an area of controversy since some have proposed that granulomatous inflammation of an isolated portion of the GI tract always has an identifiable cause if a meticulous evaluation is performed.

The diagnosis of GI tract sarcoidosis is problematic, in part, because it is rare. Several alternative causes of granulomatous inflammation of the GI tract are statistically more likely than sarcoidosis. The clinician needs to be cautious of misdiagnosing granulomatous inflammation of the GI tract as sarcoidosis, since the treatment of infectious granulomatous GI tract diseases with corticosteroids or other anti-sarcoidosis therapies may have disastrous consequences.

GI tract sarcoidosis rarely causes symptoms. It is usually identified on endoscopy performed to evaluate a condition other than GI tract sarcoidosis. Therefore, the frequency of GI tract involvement in sarcoidosis is problematic to determine. Table 1 displays the differential diagnosis for granulomatous inflammation in the GI tract. Mycobacteria and fungi may involve any portion of the GI tract. Lymphoma, GI tract malignancies and Crohn’s disease may also cause granulomatous inflammation throughout the GI tract. It is particularly problematic to distinguish GI tract sarcoidosis from Crohn’s disease. An upcoming section of this manuscript is devoted to this topic.

The identification of GI tract granulomas is likely to represent sarcoidosis if the patient has previously been diagnosed with sarcoidosis or has evidence of granulomatous inflammation in another organ. If the GI tract is the only organ in which granulomatous inflammation has been identified, the diagnosis of sarcoidosis may be suspected but it is not confirmed (vide supra).
Esophagus

Esophageal sarcoidosis was first described in 1948, and presently, less than thirty cases have been published. Esophageal sarcoidosis can present at the time that systemic sarcoidosis is initially diagnosed or in previously diagnosed cases. In rare instances, esophageal sarcoidosis may cause symptoms related to esophageal dysmotility from involvement of the muscles involved with peristalsis, involvement of the esophageal lumen or esophageal compression from paraesophageal lymphadenopathy. Additional manifestations of esophageal sarcoidosis include an achalasia-related syndrome from granulomatous infiltration of nerve fibers innervating the esophagus, Barrett’s-like esophagitis, esophageal stricture from previous granulomatous inflammation and a pseudodiverticular secondary to granulomatous infiltration. Endoscopic findings of esophageal sarcoidosis are non-specific and can range from normal appearing mucosa to Barrett’s-like esophagitis, stricture or ulcers. Esophagus sarcoidosis almost always responds to corticosteroid treatment. On rare occasions, additional treatment is required such as botulism toxin injection with balloon dilation for achalasia related to esophageal sarcoidosis or surgical resection for severe, recalcitrant disease.

Sarcoidosis can also affect the esophagus indirectly. Paraesophageal lymphadenopathy from sarcoidosis may cause extrinsic luminal compression. Portal hypertension, which occurs in less than three percent of patients with hepatic sarcoidosis, may lead to the development of esophageal varices.

Stomach

Although sarcoidosis is rare in all portions of the alimentary tract, the stomach is probably the most common alimentary tract site involved. A study in 1958 demonstrated that 10% of male African American sarcoidosis patients had gastric granulomata when blind biopsies of normal gastric mucosa were performed. Clinically significant gastric sarcoidosis is much more rare. The most common presenting symptoms are...

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epigastric pain, weight loss, emesis with or without hematemesis and melena.\textsuperscript{22} Pernicious anemia\textsuperscript{23} and irritable bowel-like syndrome\textsuperscript{24} are unusual presentations.

Ulcerations can be an endoscopic manifestation of gastric sarcoidosis in symptomatic patients (Figure 2).\textsuperscript{22} Ulcerations can be single or multiple, can involve several regions of the stomach, and are macroscopically similar peptic ulcer disease lesions. On rare occasions, these lesions may cause life-threatening hemorrhage.\textsuperscript{25-30}

Gastric sarcoidosis may manifest as cone-shaped antral deformities, polyposis, single (Figure 3) or diffuse nodular lesions\textsuperscript{31-34} or a linitis plastica type lesion (vide infra).\textsuperscript{33,35,36} Other endoscopic abnormalities of gastric sarcoidosis include thickening of the gastric wall,\textsuperscript{37-40} “cobblestoning”\textsuperscript{31-34,41} and pyloric stenosis.\textsuperscript{42}

The linitis plastica-like presentation of gastric sarcoidosis is usually irreversible. In these cases, diffuse gastric wall thickening, rigidity, and distortion of mucosal folds develop. Surgical resection is indicated for refractory disease, obstruction, severe malabsorption and life threatening hemorrhage.\textsuperscript{43-46}

A diagnostic biopsy of the stomach should be performed when symptomatic gastric sarcoidosis is suspected. When a biopsy reveals granulomatous inflammation, alternative causes should be excluded including \textit{Helicobacter pylori}, Crohn’s Disease, tuberculosis, lymphoma and sarcoid-like reactions secondary to malignancy. Endoscopic ultrasound may be useful in detection of not only sarcoidosis involvement of the stomach, but also concurrent liver and spleen lesions and lymphadenopathy.\textsuperscript{40,47}

Symptomatic gastric sarcoidosis should be treated with a proton pump inhibitor and systemic corticosteroids.\textsuperscript{48} Endoscopic resection is an option for single lesions that cause bleeding or other symptoms.\textsuperscript{34} Gastric resection should be considered only in cases of refractory disease, obstruction, severe malabsorption, and life threatening hemorrhage.

**Small Intestine**

The clinical manifestations of small intestine sarcoidosis are non specific and may include dyspepsia, diarrhea, malabsorption, crampy periumbilical pain, constitutional symptoms (e.g., fever and weight loss), duodenal obstruction and intestinal hemorrhage.\textsuperscript{15,49-56}

Small intestine sarcoidosis may cause a protein-losing enteropathy.\textsuperscript{53,57,58} Other rare small intestine manifestations of sarcoidosis include mesenteric venous insufficiency caused by pressure from enlarged sarcoïd lymphadenopathy,\textsuperscript{59} and granulomatous infiltration of the terminal ileum causing megaloblastic anemia.\textsuperscript{55,60}

Endoscopic findings of small intestine sarcoidosis may vary from normal to marked inflammation of the mucosa.

**Colon**

Occasionally, colonic sarcoidosis may present as a colonic mass, polyposis or colitis.\textsuperscript{61,63} Colonic obstruction may occur because of diverticular disease that is accompanied by an exuberant sarcoïd granulomatous reaction.\textsuperscript{62,64} Endoscopic findings include friable mucosa, nodular hyperplasia (Figure 4,5), obstructing lesions mimicking carcinoma and polyposis.\textsuperscript{65}
Other GI tract Involvement

Appendix
Sarcoidosis may rarely involve the appendix (Figure 6). Collins found only four cases in a review of 71,000 (0.006 percent) appendectomy specimens. Symptomatic appendiceal sarcoidosis represents only a fraction of these cases. To date, only seven cases with symptomatic, biopsy-proven sarcoidosis of the appendix have been reported in the English literature. Appendiceal perforation from sarcoidosis was demonstrated in only one of these cases.

Rectum
We have identified eight cases of rectal sarcoidosis reported in the English literature. Usually, the lesions are found unexpectedly when a rectal biopsy is performed for another reason. Rarely, sarcoidosis may present as a rectal mass or polyp. Rectal sarcoidosis may cause a paralytic ileus resembling adult-onset Hirschsprung’s disease by involving Auerbach’s plexus and Meissner’s plexus.

Disseminated Gastrointestinal Sarcoidosis
Sarcoidosis may rarely involve multiple portions of the gastrointestinal tract. Two or more specific portions of the GI tract may be involved or a diffuse granulomatous enterocolitis resembling Crohn’s disease may occur.

Distinguishing GI Tract Sarcoidosis from Crohn’s Disease

GI Tract Manifestations
Sarcoidosis and Crohn’s disease are granulomatous disorders of unknown etiology with some overlapping features including impairment of cell-mediated immunity, anergy and clinical findings such as erythema nodosum, uveitis and arthritis. Distinguishing these two entities may be problematic and, at times, impossible.

The presenting symptoms of Crohn’s disease may vary from subtle to severe. Diarrhea is the most common presenting symptom of colonic disease, which correlates with the extent of colitis and severity of inflammation. The diarrhea related to Crohn’s disease might be bloody. Proctitis with perianal disease may be the initial presentation in some cases. Intestinal Crohn’s disease may cause subclinical inflammation leading to fibrostenosis, presenting with intermittent colicky pain, nausea and vomiting and even small bowel obstruction. Patients with active intestinal Crohn’s disease present with anorexia, loose or frequent stools, fever, night sweats and weight loss.

Upper gastrointestinal tract Crohn’s disease is uncommon in the absence of disease beyond the ligament of Treitz. Approximately one third of patients with proximal Crohn’s disease do not have evidence of distal Crohn’s disease at the time of diagnosis, but virtually all develop distal disease in time. Since gastrointestinal symptoms are unusual in GI tract sarcoidosis, Crohn’s is more likely in patients with significant diarrhea, bloody diarrhea or intestinal obstruction. Rectal lesions, perianal lesions and fistulas in any location would favor Crohn’s disease over sarcoidosis.

Estimates of the prevalence of granulomas in Crohn’s disease have varied greatly, ranging from 15% in endoscopic series to as high as 70% in surgical series. Although the granulomas of sarcoidosis are usually well formed, unlike those seen with Crohn’s disease, there is overlap concerning this characteristic so that the two diseases cannot be distinguished on this basis. The histologic findings of bowel granulomas that favor sarcoidosis over Crohn’s disease include the presence of IgA, IgM, IgG, IgD and Schaumann bodies. However, clinical utility of these features in separating the two diseases has not been established. When granulomata are seen, presence of crypt inflammation, aphthae and ulcers are more suggestive of Crohn’s disease. Conversely, absence of inflammatory

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changes in association with granulomas would favor sarcoidosis. Crohn’s disease may cause transmural inflammation with lymphoid aggregates in the bowel wall, whereas intestinal sarcoidosis usually involves only the mucosa.53

Extraintestinal Manifestations of Crohn’s Disease versus Sarcoidosis

Crohn’s disease and sarcoidosis are both associated with extraintestinal manifestations, and often these features are helpful in distinguishing the two diseases. Between 6% and 26% of all patients with Crohn’s disease have extraintestinal manifestations.83-85 More than 90% of sarcoidosis patients have pulmonary manifestations of the disease,86 and the skin and eye are the two most common extrapulmonary organs involved.86

The presence of pulmonary disease, especially with significant mediastinal adenopathy, strongly favors the diagnosis of sarcoidosis over Crohn’s disease. Although granulomatous pulmonary nodules may develop before, during and after the development of digestive symptoms of Crohn’s disease,87-89 lung involvement related to Crohn’s disease is rare. Pulmonary dysfunction and thoracic radiographic abnormalities including mediastinal adenopathy rarely occur in Crohn’s disease.90,91 However, these histologic and radiographic abnormalities may develop as the result of treatment (e.g. eosinophilic pneumonia from sulfasalazine and mesalamine)92 or concomitant illnesses such as tuberculosis.90,91 Subclinical lung involvement in Crohn’s disease may be more common than is appreciated, perhaps reflecting the commonality between bronchus-associated and gut-associated lymphoid tissue.93

Disorders of the bones and joints are the most common extraintestinal manifestations of Crohn’s disease. In most patients with Crohn’s disease, joint symptoms occur in the setting of active intestinal disease. Pauciarticular and polyarticular arthropathy may occur in both Crohn’s disease94 and sarcoidosis.95 Axial arthropathies such as spondylitis and sacroilitis may occur with Crohn’s disease, and these are very unusual with sarcoidosis. Osteopenia and osteoporosis are common with Crohn’s disease, occurring in 30% to 60% of patients.93 These disorders are also common in sarcoidosis, but almost always as a complication of corticosteroid use.

The most common skin lesions associated with Crohn’s disease are pyoderma gangrenosum and erythema nodosum (EN). Although pyoderma gangrenosum is not specific for Crohn’s disease, it is not associated with sarcoidosis and, therefore, suggests Crohn’s disease rather than sarcoidosis. EN occurs frequently with both Crohn’s disease and sarcoidosis. EN often manifests during exacerbations of intestinal Crohn’s disease and tends to improve with treatment. EN in sarcoidosis is usually an initial manifestation of acute disease and portends a good prognosis.96 The typical non-EN skin lesions seen in sarcoidosis are indurated with an apple-jelly color with diascopy (applying pressure on the lesion with a glass slide); such a lesion would suggest sarcoidosis rather than Crohn’s disease.97

Oral lesions are common among patients with Crohn’s disease, and usually these lesions do not demonstrate histologic evidence of Crohn’s disease (“nonspecific lesions”) such as angular cheilitis and aphthous ulcers.98 Such lesions are not found in (continued on page 34)
Sarcoidosis. Ocular manifestations of both diseases include episcleritis, scleritis, uveitis and keratopathy. Lacrimal gland disorders, including gland enlargement, favors sarcoidosis over Crohn’s disease. Optic neuritis is also much more common with sarcoidosis than with Crohn’s disease. Hepatobiliary complications occur in both diseases, although serum liver function test abnormalities are more common with sarcoidosis than with Crohn’s disease. Isolated elevations of alkaline phosphatase occur in approximately 30% of sarcoidosis patients but are rarely seen with Crohn’s disease.100

Table 2. Clinical Data Support the Possibility of Sarcoidosis Versus Crohn’s Disease

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Supports Sarcoidosis</th>
<th>Supports Crohn’s disease</th>
<th>Does Not Favor Either Diagnosis</th>
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<tbody>
<tr>
<td>Isolated GI tract disease</td>
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<tr>
<td>History of extra GI tract sarcoidosis</td>
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<td>GI symptoms</td>
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<td>Rectal / perianal lesions</td>
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<td>Disease isolated above the ligament of Trietz</td>
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<td><strong>Histology</strong></td>
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<tr>
<td>Granulomas</td>
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<td>Crypt inflammation</td>
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<td>Aphthae</td>
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<td>Ulceration</td>
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<tr>
<td><strong>Extra GI Tract Manifestations</strong></td>
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<tr>
<td>Erythema nodosum</td>
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<tr>
<td>Pyoderma gangrenosum</td>
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<td>Aphthous ulcers</td>
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<td>Cheilitis</td>
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<td>Uveitis</td>
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<td>Arthritis</td>
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<tr>
<td>Pulmonary nodules and/or thoracic adenopathy</td>
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<td>Spondylitis</td>
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<td>Uric acid nephrolithiasis</td>
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<tr>
<td>Calcium oxalate nephrolithias</td>
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<tr>
<td>Elevated 24 hour urine calcium or elevated serum 1,25 di-hydroxy vitamin D</td>
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</table>

+: supports diagnosis
++: strongly supports diagnosis
√: condition common in both disorders
Crohn’s disease may be associated with fatty liver or autoimmune hepatitis. Primary sclerosing cholangitis is also associated with Crohn’s disease, usually as a side effect of therapy. \textsuperscript{101} Nephrolithiasis secondary to calcium oxalate and uric acid stones can occur with Crohn’s disease. Calcium oxalate kidney stones also occur with sarcoidosis, \textsuperscript{102} especially in white patients. \textsuperscript{86} Because nephrolithiasis in sarcoidosis is the result of excessive 1,25-dihydroxy vitamin D production, the serum level of 1,25-dihydroxy vitamin D and the 24-hour urine calcium excretion should both be elevated, \textsuperscript{102} whereas both should be normal when calcium oxalate kidney stones occur in Crohn’s disease. Intrinsic renal disease can occur as a complication of both diseases; however, membranous nephropathy and glomerulonephritis are more common in Crohn’s disease than in sarcoidosis.

Clinically significant involvement of the heart and nervous system occurs in 5-10% of patients with sarcoidosis; such involvement is unusual, although reported, in patients with Crohn’s disease. \textsuperscript{89} Although an elevated serum angiotensin converting enzyme (ACE) level has a sensitivity as low as 57% for sarcoidosis, \textsuperscript{103} values are typically low or normal with Crohn’s disease \textsuperscript{104}; therefore an elevated ACE suggests the diagnosis of sarcoidosis rather than Crohn’s disease.

Table 2 outlines the distinguishing clinical features between Crohn’s disease and sarcoidosis. Although none of the findings in Table 2 definitively differentiate the two diseases, they may be used to favor one of these diseases over the other.

**Treatment**

There is no standardized treatment of GI tract sarcoidosis. In general, treatment is indicated only for symptomatic disease. Extrapolating from sarcoidosis treatment of other organ involvement, \textsuperscript{86} corticosteroids at a dose of 20 to 40 mg of daily prednisone equivalent is suggested as initial therapy. This corticosteroid dose is usually effective for GI tract sarcoidosis. \textsuperscript{13,19,23,35,48,61} A case has been reported of multisystem sarcoidosis including intestinal sarcoidosis causing a severe protein-losing enteropathy that was refractory to high-dose corticosteroid therapy and was successfully treated with infliximab. \textsuperscript{58} We believe that, if GI-tract sarcoidosis is refractory to corticosteroid therapy, antimetabolite agents such as methotrexate, azathioprine and leflunomide should be considered as corticosteroid sparing agents. Tumor necrosis factor alpha antagonists should be considered as third line agents behind the antimetabolites. In cases causing severe symptoms, tumor necrosis factor agents could be used as second line agents after corticosteroids.

**SUMMARY**

Sarcoidosis may affect any portion of the GI tract. GI tract sarcoidosis usually causes no symptoms, although this is not always the case. The diagnosis of GI tract sarcoidosis is problematic, as alternative causes of granulomatous inflammation must be excluded. When treatment is indicated, corticosteroids are the drug of choice.

**References**

GI Tract Sarcoidosis

INFLAMMATORY BOWEL DISEASE: A PRACTICAL APPROACH. SERIES #2


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