

Abdominal Sarcoidosis

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Abstract

Abdominal sarcoidosis is an uncommon form of sarcoidosis. The clinical presentation of esophageal, gastric, small bowel, colon, appendicular, spleen, pancreas, and abdominal aortic sarcoidosis are discussed in this review. The differential diagnosis of abdominal sarcoidosis is extensive. Other granulomatous diseases including tuberculosis, fungal infections, parasitic diseases, inflammatory bowel disease, and Whipple's disease should be excluded before making the diagnosis of

gastrointestinal sarcoidosis. Corticosteroid therapy is the mainstay of medical therapy in abdominal sarcoidosis. Second line agents such as methotrexate are also discussed. Surgical intervention may be necessary in patients with bowel obstruction, perforation, or massive hemorrhage. The authors also provide their experience regarding preoperative pulmonary evaluation of patients with pulmonary sarcoidosis undergoing surgery.

Key words: Gastrointestinal sarcoidosis, pancreatic sarcoidosis, splenic sarcoidosis, retroperitoneal lymphadenopathy, appendicitis, abdominal surgery, sarcoidosis

Introduction

Sarcoidosis is a systemic granulomatous disease of unknown etiology that is characterized by noncaseating granulomatous inflammation in different organs. Sarcoidosis commonly involves the mediastinal lymph nodes, lungs, liver, eyes, skin, and nervous system. Aside from liver involvement, abdominal sarcoidosis is a rare disease. Asymptomatic involvement of the gastrointestinal tract (GIT) is present in only 5% to 10% patients with systemic sarcoidosis [1-4]. Although rare, symptomatic GIT sarcoidosis may present with abdominal pain, bleeding, and obstruction. Involvement of the appendix,

pancreas, and abdominal aorta may result in acute and potentially life-threatening conditions that need surgical evaluation or intervention. Splenomegaly and retroperitoneal lymph node enlargement because of sarcoidosis are other manifestations of abdominal sarcoidosis that may need surgical intervention. We also provide our experience regarding preoperative pulmonary evaluation and medical management of patients with sarcoidosis undergoing surgery.

Gastrointestinal Tract Sarcoidosis

Sarcoidosis rarely involves the gastrointestinal tract (GIT). The incidence of subclinical GIT involvement in patients with systemic sarcoidosis is 5% to 10%. The incidence of symptomatic GIT sarcoidosis is only 0.6%. The esophagus, stomach, small and large intestine can be involved in sarcoidosis (**Table 1**). Symptoms of GIT sarcoidosis are nonspecific and may include dysphagia, epigastric pain, weight loss, nausea, vomiting, and diarrhea [1-7].

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Esophageal sarcoidosis can be divided into 3 different categories: mucosal involvement (grayish plaque-like lesions), myopathic involvement of the skeletal muscle portion of the esophagus, and extrinsic compression from mediastinal lymphadenopathy [8-17]. Gastric sarcoidosis is the most common form of GIT sarcoidosis. The clinical manifestations of gastric sarcoidosis are related to narrowing of the gastric or pyloric lumen or ulceration of the involved mucosa due to granulomatous inflammation and scarring. Gastric sarcoidosis can be divided into 4 different categories: subclinical, ulcerative, infiltrative and polypoid. Subclinical gastric sarcoidosis is the most common clinical category. Endoscopy may reveal normal or hyperemic mucosa and biopsies may incidentally reveal granulomatous gastritis. Ulcerative gastric sarcoidosis may cause epigastric pain or upper GI bleeding. Ulcers formed in the mucosa are related to the granulomatous inflammation. Infiltrative gastric sarcoidosis may be dominant in the distal part of the stomach, resulting in smooth coned-shaped antral narrowing and deformity. Diffuse infiltration of the gastric wall may lead to a linitis plastica-like stomach. This type of gastric sarcoidosis should be differentiated from gastric carcinoma. Lastly, single or multiple gastric polypoid lesions in sarcoidosis are extremely rare. Small bowel sarcoidosis is the least common form of GIT sarcoidosis. Granulomatous enteritis, protein-losing enteropathy, and duodenal obstruction have also been described. Subclinical colonic involvement has been found in grossly normal mucosa. Although rare, colonic sarcoidosis may present with proctocolitis, stricture, sigmoid ulcers and large bowel polypoid lesions [1-26].

The diagnosis of GIT sarcoidosis is challenging. The presence of granulomatous inflammation in GIT is a nonspecific finding and does not necessarily mean sarcoidosis is the culprit for the clinical presentation. On the other hand, other GIT diseases that are associated with granuloma formation should be excluded. The differential diagnosis of GIT sarcoidosis may include: tuberculosis, fungal infections, vasculitis, foreign body reactions, radiation injury, Crohn's disease, microscopic colitis, Whipple's disease, schistosomiasis, enterobiosis, lymphoma, and carcinoma [27].

Granulomatous Appendicitis

Involvement of the appendix in sarcoidosis is a rare clinical occurrence. Collins found one case of granulomatous appendicitis in a series of 50,000 appendectomy specimens. Patients with granulomatous appendicitis present with clinical manifestations similar to acute appendicitis. Histopathology of the affected appendix shows non-necrotizing granulomas without any acute inflammatory changes. Other causes of a granulomatous appendicitis (**Table 2**) are Crohn's disease, tuberculosis, Yersenia infection, parasites, and fungal infections. Isolated granulomatous appendicitis without evidence of systemic disease or infection is usually considered idiopathic disease [28-34].

Pancreatitis

Although pancreatic involvement is reported in 2.1% of patients with sarcoidosis, pancreatitis is rarely the presenting manifestation. The 3 major etiologies for pancreatic involvement in sarcoidosis: hypercalcemia, granulomatous infiltration of pancreas, or medications (**Table3**) [35-40].

Acute pancreatitis in sarcoidosis is most likely due to hypercalcemia. Hypercalcemia has been noted in 3% to 65% of patients with sarcoidosis. Hypercalcemia is the result of increased extrarenal synthesis of 1,25(OH)₂-D₃ (active form of vitamin D). Alveolar macrophages contain enzymes (1 α -hydroxylase) necessary to produce 1,25(OH)₂-D₃. When macrophages become activated within the granulomas by interleukin-2 and interferon- γ , they produce high levels of 1,25(OH)₂-D₃. Elevated levels of interleukin-2 and tumor necrosis factor- α may also increase the production of parathyroid hormone-related peptide. This peptide also may contribute to hypercalcemia in sarcoidosis. Prednisone is an effective therapy, and serum calcium usually declines within 3 to 5 days. Chloroquine and hydroxychloroquine 250 to 500 mg daily have been shown to normalize serum calcium in sarcoidosis. Ketoconazole 200 mg 4 times a day also may be used to treat hypercalcemia [35-40].

The clinical presentation of granulomatous infiltration of the pancreas may present as acute pancreatitis, recurrent pancreatitis, chronic pancreatitis, pancreatic mass, or incidental finding.

Pancreatic sarcoidosis may be found incidentally during an evaluation of nonspecific abdominal complaints. Symptoms include abdominal pain, weight loss, and obstructive jaundice. Retroperitoneal lymphadenopathy is common and is reported in 66% of patients. In rare cases, the pancreas can be replaced with granulomatous inflammation. The differentiation of pancreatic sarcoidosis from pancreatic cancer is difficult either radiographically or during laparotomy – a biopsy is usually needed. Tuberculosis and infectious granulomatous diseases should also be excluded with appropriate cultures and special stains of the biopsy. CT scan findings of pancreatic sarcoidosis are nonspecific and may include an ill-defined pancreatic mass (most commonly in head of pancreas), narrowing of distal common bile duct with proximal dilatation, pancreatic duct dilatation, and retroperitoneal lymph node enlargement. Treatment with corticosteroids and second-line agents may be needed in symptomatic patients. Surgical intervention is required in patients with obstructive jaundice that are unresponsive to medical therapy. Surgical biopsy or CT-guided biopsy is needed in most cases to establish the diagnosis [35-40].

Prednisone and methotrexate are commonly used in medical therapy of sarcoidosis. Pancreatitis has been rarely described in patients treated with these medications [41].

Hepatobiliary Sarcoidosis

Liver involvement in sarcoidosis is commonly asymptomatic. Hepatomegaly and elevated alkaline phosphatase and transaminases may be found on evaluation of these patients. Symptomatic hepatic sarcoidosis on the other hand is rare. Cholestasis, granulomatous hepatitis, cirrhosis, hepatic vein thrombosis, and portal hypertension are known sequelae of hepatic sarcoidosis. Methotrexate, commonly used as a second-line agent in the treatment of sarcoidosis, may also cause liver toxicity and should be considered in the differential diagnosis. Again, corticosteroids are the mainstay of therapy. In advanced cases, liver transplantation may be needed [42-43].

There are a few case reports in the literature describing gallbladder involvement in sarcoidosis where the presenting symptoms resembled acute

cholecystitis. The diagnoses were made after finding non-necrotizing granulomas in resected gallbladders [44-45].

Spleen Involvement

Splenic nodules secondary to sarcoidosis is relatively uncommon, occurring 15% of the time diagnosed by abdominal CT in a retrospective study by Warshauer et al in 1994 [46]. Sarcoidosis limited to the spleen is exceedingly rare with less than 10 reported cases in the literature [47]. Generally speaking, when a patient is found to have multiple splenic nodules, other diseases such as lymphoma and metastatic malignancy need to be considered. However, Britt *et al* [48] suggested that enlarged lymph nodes in lymphoma were larger in size when compared to sarcoidosis. Ultrasonography has been used as a modality in visualizing the spleen. Woszczyk *et al* [49] describe a case of asymptomatic splenomegaly which was eventually diagnosed as splenic sarcoidosis. The ultrasound revealed a heterogenic spleen with diffuse hypoechoic areas. Magnetic resonance (MR) imaging has also had a role in examining the spleen. Nodular sarcoidosis has been reported to “demonstrate low signal intensity with all MR imaging sequences and [in addition] the lesions are most conspicuous on T2-weighted fat-suppressed or early phase contrast-enhanced images.” [50]

Rarely, a patient may present with massive splenomegaly. Mohan *et al* [51] reported a case of a 39 year-old female in India who presented with joint swelling for 3 months, left upper abdominal pain for 2 months and constitutional-type symptoms for 6 months. The patient was found to have massive splenomegaly with significant nodularity. The patient was initially diagnosed with disseminated tuberculosis and was treated with the standard four drug regimen. Later, a skin biopsy was performed which showed noncaseating epithelioid granulomas. Not surprisingly, the patient had not improved, so based on the biopsy, a diagnosis of sarcoidosis was made. The patient was subsequently placed on oral prednisolone with significant clinical improvement. Of note, the repeat CT 4 months later revealed resolution of the splenic nodularity with a reduction in size of the spleen.

There may be times when splenic abnormalities

are seen but a diagnosis of sarcoidosis is not made until a splenectomy has been performed. In fact, a splenectomy may be indicated if a diagnosis cannot be made and/or if the patient has significant discomfort from the splenomegaly. Rodriguez-Garcia *et al* [52] describe a case of a 43 year-old woman with left upper quadrant abdominal pain who was found to have multiple bilateral lung nodules and mediastinal/hilar adenopathy. The patient had a nondiagnostic bronchoscopy and refused a mediastinoscopy so a splenectomy was performed to alleviate her symptoms as well as establish a diagnosis. A diagnosis of sarcoidosis was made based on histologic examination. Another case report by Zia *et al* [53] described a 47 year-old female with nausea and epigastric pain. The patient was initially found to have slightly elevated liver function tests and later developed left flank pain with an elevated white blood cell count. She was found to have splenic nodules by ultrasonography, which was confirmed with CT. A positron-emission tomography scan was performed which showed increased uptake in 5 focal areas in the parenchyma of the spleen. A laparoscopic splenectomy was performed to rule out a malignancy which revealed histology consistent with sarcoidosis. The patient's symptoms subsequently resolved after the surgical intervention.

Retroperitoneal Lymphadenopathy

Although retroperitoneal lymphadenopathy is commonly seen in sarcoidosis, it is usually asymptomatic. Unilateral or bilateral hydronephrosis and external compression of bile duct, uterus, pancreas, and lymphatics have been described. Other causes of retroperitoneal lymph node involvement are tuberculosis, testicular cancer, metastatic carcinoma, and lymphoma. Granuloma in a biopsy is a nonspecific finding and can also be seen in lymphoma and metastatic diseases (e.g. head and neck cancers, renal cell carcinoma, testicular cancer, etc). Careful evaluation of the patient is needed to exclude other causes of retroperitoneal lymphadenopathy [54-58].

Gastrointestinal Hemorrhage

Sarcoidosis may present with gastrointestinal (GI) hemorrhage. About 25% of patients with symptomatic gastric sarcoidosis present with

symptoms of upper GI bleeding. Hypersplenism leading to thrombocytopenia, portal hypertension and esophageal varices, and gastric ulcers associated with antral stasis are contributing factors to GI hemorrhage in sarcoidosis. Massive GI hemorrhage also has been reported in sarcoidosis of small intestine [13,19].

Gastrointestinal Obstruction

Gastric outlet obstruction may occur because of sarcoid pyloric ulcers, infiltrative gastric sarcoidosis. This results in a coned-shaped antral narrowing and deformity or diffuse infiltration of gastric mucosa leading to a linitis plastica-like appearance. Granulomatous enteritis may cause duodenal or small bowel obstructions. Sigmoid colon focal nodularity or segmental narrowing may also present as gastrointestinal obstruction. Rectal and large bowel polypoid lesions have also been described [6,7,16,17,22,23].

Abdominal Aorta Involvement

Aortic involvement in sarcoidosis leading to an aneurysm is extremely rare. Sarcoid aortitis has been described in the ascending, thoracic, and abdominal aorta. Several cases of the surgical repair of an abdominal aortic aneurysm have been reported. The diagnosis of sarcoidosis usually precedes the diagnosis of aortitis for several years. A high incidence of uveitis has been observed in these patients. The biopsy of lymph nodes adjacent to the involved aorta usually shows characteristic non-necrotizing granulomas. The aneurysmal wall usually contains atheromatous plaques with nonspecific lymphocytic infiltrates. Surgical repair of aneurysms can be difficult because of inflammation and friability of the aortic tissue. Preoperative systemic corticosteroid therapy has been suggested to decrease inflammation and tissue friability [59-63].

Deep Venous Thrombosis (DVT)

A relationship between sarcoidosis and venous thrombosis has been suggested in the literature. Thrombus formation has been described in a variety of organs, including retinal vein thrombosis in ocular sarcoidosis, dural sinus thrombosis in neurosarcoidosis,

Budd-Chiari syndrome, superior vena caval (SVC) obstruction, and mural thrombosis in myocardial sarcoidosis. Venous thromboses usually occur in close anatomical proximity with active sarcoidosis (i.e. mural thrombus in myocardial sarcoidosis, etc.). A local tissue thrombophilic state may explain this observation. Enhanced tissue factor pathway activity, increased tissue thromboplastin activity, diminished plasminogen activator activity, increased factor VII activity, decreased protein C activation, and increased thrombin-activatable fibrinolysis inhibitor have all been described in sarcoidosis. These alterations in pro-coagulation and fibrinolysis may favor thrombus formation in susceptible patients. Increased blood D-dimer levels in sarcoidosis patients also support the concept of coagulation activation and increased deposition of fibrin in tissues. In patients with active sarcoidosis, aggressive DVT prophylaxis and a high index of suspicion for the presence of DVT is warranted postoperatively [64-66].

Preoperative Pulmonary Evaluation

Although there are no guidelines or studies to stratify risk of postoperative pulmonary complications in sarcoidosis, in our experience they are at low-risk for postoperative pulmonary complications. Forced expiratory volume in the first second (FEV₁), forced vital capacity (FVC), and single-breath carbon monoxide diffusion capacity (DLCO) do not seem to correlate with the risk of postoperative pulmonary complications. The patient's general health, other co-morbid illnesses, functional status, presence of pulmonary arterial hypertension, and baseline oxygenation are likely better factors to be considered in the preoperative evaluation of these patients [67]. The following general statements may be helpful in the preoperative pulmonary evaluation of patients with sarcoidosis undergoing general anesthesia and surgery:

1. Patients with cardiac sarcoidosis and congestive heart failure: maximal medical therapy under the guide of a cardiologist is desirable before surgery.
2. Patients with sarcoidosis and a respiratory tract infection: the infection should be treated before an elective surgery.

3. Patients with end-stage lung disease with pulmonary fibrosis and baseline hypoxemia due to sarcoidosis have higher risk of postoperative pulmonary complication (respiratory failure).
4. Patients with pulmonary arterial hypertension due to sarcoidosis have an increased risk of postoperative pulmonary complications. Elective surgeries should probably be avoided if possible.
5. Patients with airway involvement and obstructive physiology on pulmonary function testing: bronchodilator therapy may be helpful.

Medical Management of Sarcoidosis

Systemic corticosteroids are the mainstay of therapy in sarcoidosis. Prednisone 40 to 60 mg daily is commonly used to treat active sarcoidosis. A gradual taper over several months (usually 6 months) is necessary to prevent reactivation of sarcoidosis. Some patients may need chronic prednisone therapy. Serial chest imaging and pulmonary function tests are used to follow the pulmonary disease. **Tables 4 and 5** summarize other agents used in treatment of sarcoidosis. Methotrexate and azathioprine are commonly used as steroid-sparing agents or in corticosteroid-refractory sarcoidosis.

Review of the literature revealed no studies that have addressed the effect of the corticosteroid and immunosuppressive therapy on postoperative complications in sarcoidosis. There is data available from rheumatoid arthritis patients undergoing orthopedic surgeries as well as patients with Crohn's disease undergoing abdominal surgeries. Since similar agents are used to treat rheumatoid arthritis and Crohn's disease, data from these studies may be helpful to guide the perioperative medical therapy of sarcoidosis [68-75]. Although the decision regarding continuation of medical therapy should be made on case by case bases, the following statements may be helpful:

1. Patients with life-threatening conditions should undergo surgery without delay. Cessation of all immunosuppressive therapy is probably safe. Stress-dose steroids should be administered if the patient has been on chronic corticosteroid therapy.
2. In elective surgeries, it is reasonable to attempt

to wean the patient off all immunosuppressive therapies preoperatively, if possible.

3. In patients undergoing orthopedic surgeries or simple abdominal surgeries, corticosteroids and immunosuppressive therapy can be continued. The risk of depressed wound healing and local infection do not increase with low-dose weekly methotrexate, low-dose azathioprine, or corticosteroid therapy.
4. In patients with malnutrition (low albumin), intra-abdominal infection/abscess, and undergoing complicated intra-abdominal surgeries, there is an increased risk of postoperative abdominal sepsis.
5. Methotrexate should be stopped in patients with postoperative renal failure due to risk of bone marrow suppression.

Table 1. GASTROINTESTINAL TRACT SARCOIDOSIS

Esophagus	Superficial mucosal ulcers
	Achalasia-like presentation
Stomach	Subclinical involvement
	Gastric ulcer
	Linitis plastica-like stomach
	Polypoid lesion
	Pyloric obstruction
	Upper gastrointestinal bleed
Small intestine	Duodenal obstruction
	Protein-losing enteropathy
	Granulomatous enteritis
	Bowel obstruction
	Gastrointestinal bleed
Large bowel	Subclinical involvement
	Polypoid lesions
	Proctocolitis
	Stricture

Table 2. ETIOLOGIES OF GRANULOMATOUS APPENDICITIS

1. Sarcoidosis
2. Crohn's disease
3. Mycobacterium tuberculosis
4. Bacterial infections (yersiniosis, actinomycosis, Brucella, Campylobacter)
5. Fungal infections (histoplasmosis, blastomycosis, candidiasis)
6. Appendicular schistosomiasis
7. Foreign bodies (fecalith)
8. Idiopathic granulomatous appendicitis

Table 3. PANCREATIC SARCOIDOSIS

Etiology	Clinical Manifestation
Hypercalcemia	Acute pancreatitis
Granulomatous inflammation	Acute pancreatitis
	Recurrent pancreatitis
	Chronic pancreatitis
	Pancreatic mass
	Obstructive jaundice
Medications (prednisone, methotrexate)	Acute pancreatitis

Table 4. SECOND-LINE AGENTS COMMONLY USED IN TREATMENT OF SARCOIDOSIS

Agent	Dose	Mechanism of Action
Methotrexate	Initial dose: 10 mg weekly	Inhibition of T-cell activation
	Titrated up to 15 to 20 mg weekly	Suppression of T-cell adhesion
Azathioprine	50 to 200 mg daily	Inhibition of lymphocyte proliferation

Table 5. THIRD-LINE AGENTS USED IN TREATMENT OF SARCOIDOSIS

Antimalarial	Chloroquine
	Hydroxychloroquine
Cytotoxic	Cyclophosphamide
	Cladribine
	Chlorambucil
Immunosuppressive	Cyclosporine
	Mycophenolate
	Thalidomide
TNF- α inhibitor	Infliximab

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