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Surgical Aspects of Abdominal Sarcoidosis

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Abstract: Abdominal sarcoidosis is an uncommon form of sarcoidosis. 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 Gastro-Intestinal Tract (GIT) is present in only 5 to 10% patients with systemic sarcoidosis (Ricker and Clark, 1949; Longcope and Freiman, 1952; Engle, 1953; Maylock *et al*., 1963). Although rare, symptomatic GIT sarcoidosis may present with abdominal pain, bleeding and obstruction. Involvement of 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). The symptoms of GIT sarcoidosis are nonspecific and may include dysphagia, epigastric pain, weight loss, nausea, vomiting and diarrhea (Ricker and Clark, 1949; Longcope and Freiman, 1952; Engle, 1953; Maylock *et al*., 1963; Palmer, 1958; Iwai *et al*., 1988; Israel and Sones, 1953).

Esophageal sarcoidosis can be divided in 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 (Lukens *et al*., 2002;

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 blled
Small intestine	Duodenal obstruction
	Protein-losing enteropathy
	Granulomatous enteritis
	Bowel obstruction
	Gastrointestinal bleed
Large bowel	Subclinical involvement
	Polypoid lesions
	Proctocolitis
	Stricture

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Levine *et al*., 1989; Siegel *et al*., 1961; Cook *et al*., 1970; Hardy *et al*., 1967; Cappell, 1995; Polachek and Matre, 1964; Wiesner *et al*., 1971; Dufrense *et al*., 1983; Boruchowicz *et al*., 1996). Gastric sarcoidosis is the most common from 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 to 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 is 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 (Gallagher *et al*., 1984; Chinitz *et al*., 1985; Ona, 1981; Kaneki *et al*., 2001; Roth *et al*., 1994; Kremer and William, 1970; Panella *et al*., 1988; Konda *et al*., 1980; Newton *et al*., 1998; Apell, 1951). Small bowel sarcoidosis is the least common form of GIT sarcoidosis. Granolumatous enteritis, protein-losing enteropathy and dodenal obstruction have also been described (Scott *et al*., 1953; MacRury *et al*., 1992; Fleming *et al*., 1994; Sprague *et al*., 1984; Bulger *et al*., 1988; Douglas *et al*., 1984; Lindgren *et al*., 1995; Godeau *et al*., 1992; Popovic *et al*., 1980; Stampfl *et al*., 1990; Noël *et al*., 1997). 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 (Tobi *et al*., 1982; Nchimi *et al*., 2003; Veitch and Badger, 2004; Zech *et al*., 1993).

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 (Sachar and Rochester, 2004).

Table 2: Etiology 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
1. Hypercalcemia	Acute pancreatitis
2. Granulomatous inflammation	Acute pancreatitis
	Recurrent pancreatitis
	Chronic pancreatitis
	Pancreatic mass
	Obstructive jaundice
3. Medications (Prednisone, Methotrexate)	Acute pancreatitis

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 (Cullinane *et al*., 1997; Clarke *et al*., 1983; Healy *et al*., 2003; Collins, 1955; Tinker *et al*., 1984; Macleod, 1965; Munt, 1974; Tucher *et al*., 2003).

Pancreatitis: Although pancreatic involvement is reported in 2.1% of the patients with sarcoidosis, pancreatitis is rarely the presenting manifestation. There 3 major etiologies for pancreatic involvement in sarcoidosis: Hypercalcemia, granulomatous infiltration of pancreas, or medications (Table 3) (Gupta *et al*., 2006; Gaur, 2001; Siavelis *et al*., 1999; McCormick *et al*., 1985; Limaye *et al*., 1997; Boruchowicz *et al*., 1996; O'Connor *et al*., 2003; Baroni *et al*., 2004; Trivedi and Pitchumoni, 2005).

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-ã, 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 to5 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 (Gupta *et al*., 2006; Gaur, 2001; Siavelis *et al*., 1999).

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 radiographically and during laparotomy-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 (Siavelis *et al*., 1999; McCormick *et al*., 1985; Limaye *et al*., 1997; Boruchowicz *et al*., 1996; O'Connor *et al*., 2003; Baroni *et al*., 2004).

Prednisone and methotrexate are commonly used in medical therapy of sarcoidosis. Pancreatitis has been rarely described in patients treated with these medications (Trivedi and Pitchumoni, 2005).

Hepatobiliary sarcoidosis: Liver involvement in sarcoidosis is commonly asymptomatic. Hepatomegaly and elevated alkaline phosphotase 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 (Karagiannidis *et al*., 2006; Moreno-Merlo *et al*., 1997).

There are a few case reports in the literature describing gallbladder involvement in sarcoidosis. Symptoms resembled acute cholecystitis. The diagnoses were made after finding of non-necrotizing granulomas in resected gallbladders (Mert and Avsar, 2004; Freed and Reiner, 1983).

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*. (1994). Sarcoidosis limited to the spleen is exceedingly rare with less than 10 reported cases in the literature (Payne *et al*., 2005). 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*. (1991) 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*. (2006) describe a case of asymptomatic splenomegaly which was eventually diagnosed as splenic sarcoidosis. The ultrasound revealed a heterogeneic spleen with diffuse hypoechogenic 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 (Elsayes *et al*., 2005).

Rarely, a patient may present with massive splenomegaly. Mohan *et al*. (2004) 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 as 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.* (2001) 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.* (2005) 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 granuloma formation 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 (Meranze *et al.*, 1985; Farman *et al.*, 1995; Miyazaki *et al.*, 1996; Al-Mofleh, 1992).

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 (Ona, 1981; Kaneki *et al.*, 2001; Roth *et al.*, 1994; Kremer and William, 1970; Panella *et al.*, 1988; Konda *et al.*, 1980; Newton *et al.*, 1998; Apell, 1951; Scott *et al.*, 1953; MacRury *et al.*, 1992; Fleming *et al.*, 1994).

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. Granolumatous 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 (Chinitz *et al.*, 1985; Apell, 1951; Stampfl *et al.*, 1990; Nchimi *et al.*, 2003; Veitch and Badger, 2004; Zech *et al.*, 1993).

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 (Numata *et al.*, 2005; Maeda *et al.*, 1983; Naraynsingh and Raju, 1987; Weiler *et al.*, 2000; Gasparovic *et al.*, 2004).

Deep Venous Thrombosis (DVT): Relation between sarcoidosis and venous thrombosis has been suggested in the literature (Vahid *et al.*, 2006; Mclaughlin, 2003; Van and Tuynman, 1991; Rowlan and McGibbon, 1985). 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 (Ohara *et al.*, 1995; Akova *et al.*, 1993; Russi *et al.*, 1986; Kinney *et al.*, 1980; Wynne *et al.*, 1979). Venous thromboses usually occur in close anatomical

proximity with active sarcoidosis i.e., mural thrombus in myocardial sarcoidosis, etc. 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 been described in sarcoidosis. These alterations in pro-coagulation and fibrinolysis may favor thrombus formation in susceptible patients. Increased D-dimer levels in the blood of sarcoidosis patients also support the concept of coagulation activation and increased deposition of fibrin in tissues (Gunther *et al*., 2000; Hasday *et al*., 1988; Chapman *et al*., 1985; Kobayashi *et al*., 1998; Fijimoto *et al*., 2003; Shorr and Hnatiuk, 2000; Perez *et al*., 1993). In patients with active sarcoidosis, aggressive DVT prophylaxis and high index of suspicion for presence of DVT is warranted postoperatively.

PREOPERATIVE PULMONARY EVALUATION

Although there are no guidelines or studies to stratify risk of postoperative pulmonary complications in sarcoidosis, in our experience they are 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 (Smetana, 1999; Lawrence *et al*., 1996; Wolters *et al*., 1996). The following general statements may be helpful in the preoperative pulmonary evaluation of patients with sarcoidosis undergoing general anesthesia and surgery:

- Patients with cardiac sarcoidosis and congestive heart failure: Maximal medical therapy under the guide of a cardiologist is desirable before surgery.
- Patients with sarcoidosis and a respiratory tract infection: The infection should be treated before an elective surgery.
- Patients with end-stage lung disease with pulmonary fibrosis and baseline hypoxemia due to sarcoidosis have higher risk of postoperative pulmonary complication (respiratory failure).
- Patients with pulmonary arterial hypertension due to sarcoidosis have an increased risk of postoperative pulmonary complications. Elective surgeries should probably be avoided if possible.
- 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. Table 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 (Vahid and Waibel, 2006; Newman *et al*., 1997).

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 treated rheumatoid arthritis and Crohn's disease, data from these studies may be helpful to guide the perioperative medical therapy of sarcoidosis (Bibbo and Goldberg, 2004; Kasdan and June, 1993; Sany *et al*., 1993; Grennan *et al*., 2001; Murata *et al*., 2006; Yamamoto *et al*., 2000; Mahadevan *et al*., 2002; Colombel *et al*., 2004). Although the decision regarding continuation of medical therapy should be made on case by case bases, the following statements may be helpful:

- Patients with life-threatening conditions should undergo surgery without delay. Cessation of all immunosuppressive therapy is probably safe. Stress-dose steroids should be administrated if the patient has been on chronic corticosteroid therapy.
- In elective surgeries, it is reasonable to attempt to wean the patient off all immunosuppressive therapies preoperatively, if possible.
- In patients undergoing orthopedic surgeries or simple abdominal surgeries, corticosteroids and immunosuppressive therapy could be continued. The risk of depressed wound healing and local infection do not increase with low-dose weekly methotrexate, low-dose azatioprine, or corticosteroid therapy.
- In patients with malnutrition (low albumin), intra-abdominal infection/abscess and the patients undergoing complicated intra-abdominal surgeries, there is an increased risk of postoperative abdominal sepsis.

Table 4: Second-line agents commonly used in treatment of sarcoidosis

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

Table 5: Third-line agents used in treatment of sarcoidosis

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

- Methotrexate should be stopped in patients with postoperative renal failure due to risk of bone marrow suppression.

REFERENCES

Akova, Y.A., T. Kansu and S. Duman, 1993. Pseudotumor cerebri secondary to dural thrombosis in neurosarcoidosis. J. Clin. Neuroophthalmol., 13:188-189.

Al-Mofleh, I.A., 1992. Ultrasound-guided fine needle aspiration of retroperitoneal, abdominal and pelvic lymph nodes. Diagnostic reliability. Acta. Ctol., 36:413-415.

Apell, A.A., 1951. Pyloric obstruction due to sarcoid of the stomach. Arch. Surg., 62: 140-144.

Baroni, R.H., I. Pedrosa, E. Tavernaraki *et al.*, 2004. Pancreatic sarcoidosis; MRI features. J. Magn. Reson. Imaging, 20: 889-893.

Bibbo, C. and J.W. Goldberg, 2004. Infectious and healing complications after elective orthopedic foot and ankle surgery during tumor necrosis factor-alpha inhibition therapy. Foot Ankle Int., 25: 331-335.

Boruchowicz, A., V. Canva-Celcambre, F. Guillemot *et al.*, 1996. Sarcoidosis and achalasia: A fortuitous association? Am. J. Gastroenterol., 91: 413-414.

Boruchowicz, A., E. Hachulla, A. Cortot *et al.*, 1996. Chronic pancreatitis: a complication of sarcoidosis? Eur. J. Gastroenterol. Hepatol., 8: 1125-1127.

Britt, A.R., I.R. Francis, G.M. Glazer *et al.*, 1991. Sarcoidosis: Abdominal manifestations at CT. Radiology, 178: 91-94.

Bulger, K., M. O'Riodaron, S. Purdy, M. O'Brien and J. Lennon, 1988. Gastrointestinal sarcoidosis resembling C rohn's disease. Am. J. Gastroenterol., 83: 1415-1417.

Cappell, M.S., 1995. Endoscopic, radiographic and manometric findings in dysphagia associated with sarcoid due to extrinsic esophageal compression from subcarinal lymphadenopathy. Am. J. Gastroenterol., 90: 489-492.

Chapman, H.A. Jr, C.L. Allen, O.L. Stone and D.S. Fair, 1985. Human alveolar macrophages synthesize factor VII *in vitro*. Possible role in interstitial lung disease. J. Clin. Invest., 75: 2030-2037.

Chinitz, M.A., L.J. Brandt, M.S. Frank, D. Frager and L. Sablay, 1985. Symptomatic sarcoidosis of the stomach. Dig. Dis. Sci., 30: 682-688.

Clarke, K., W. Pollett and S. Chittal *et al.*, 1983. Sarcoidosis with involvement of the appendix. Arch. Int. Med., 143: 1603-1604.

Collins, D.C.S., 1955. A study of 50,000 specimens of the human vermiform appendix. Surg. Gynecol. Obstet., 101: 437-445.

Colombel, J.F., E.V. Loftus and W.J. Jr, Tremaine *et al.* Early postoperative complications are not increased in patients with Crohn's disease treated perioperatively with infliximab or immunosuppressive therapy. Am. J. Gastroenterol., 99: 878-883.

Cook, D.M., D.E. Dines and D.S. Dycus, 1970. Sarcoidosis: Report of a case presenting as dysphagia. Chest, 57: 84-86.

Cullinane, D.C., S.C. Schultz and L. Zellos *et al.*, 1997. Sarcoidosis manifested as acute appendicitis: Report of a case. Dis. Colon Rectum, 40: 109-111.

Douglas, J.G., J. Gillon, R.F. Logan, I.W. Grant and G.K. Crompton, 1984. Sarcoidosis and celiac disease: An association? Lancet, 2: 13-15.

Dufrense, C.R., K. Jeyasingham and K.K. Baker, 1983. Achalasia of the cardia associated with pulmonary sarcoidosis. Surgery, 94: 32-35.

Elsayes, K.M., V.R. Narra and G. Mukundan *et al.*, 2005. MR Imaging of the spleen: Spectrum of abnormalities. Radiographics, 25: 967-982.

Engle, R.L. Jr., 1953. Sarcoid and sarcoid-like granulomas. A study of twenty-seven post-mortem examinations. Am. J. Pathol., 29: 53-69.

Farman, J., G. Ramirez and J. Brunetti *et al.*, 1995. Abdominal manifestations of sarcoidosis. CT appearances. Clin. Imaging, pp: 30-33.

Fijimoto, H., E.C. Gabazza and O. Hataji *et al.*, 2003. Thrombin-activatable Fibrinolysis Inhibitor and Protein C Inhibitor in Interstitial Lung Disease. Am. J. Respir Crit. Care Med., 167: 1687-1694.

Fleming, R.H., M. Nuzek and D.W. McFadden, 1994. Small intestinal sarcoidosis with massive hemorrhage: Report of a case. Surgery, 115: 127-131.

Freed, J.S. and M.A. Reiner, 1983. Acute cholecystitis sa a complication of sarcoidosis. Arch. Int. Med. 143: 2188-2189.

Gallagher, P., M. Harris, F.W. Turnbull and L.Turner, 1984. Gastric Sarcoidosis. J. Roy Soc. Med., 77:837-839.

Gasparovic, H., R. Bueno and F.J. Rybicki *et al.*, 2004. Sarcoidosis of the aortic root. J. Thorac. Cadiovasc Surg., 128: 761-762.

Gaur, S., 2001. Sarcoidosis manifested as hypercalcemic pancreatitis. South Med. J., 94: 939-940.

Godeau, B., J.P. Farcet, J.C. Delchier, D.H. Xuan, M.T. Chaumette and P. Gaulard, 1992. Protein-losing enteropathy in gastrointestinal sarcoidosis associated with malignant lymphoma. J. Clin. Gastroenterol., 14: 78-80.

Grennan, D.M., J. Gray and J. Loudon *et al.*, 2001. Methotrexate and early postoperative complications in patients with rheumatoid arthritis undergoing elective orthopedic surgery. Ann. Rheum. Dis., 60: 214-217.

Gunther, A., P. Mosavi and C. Ruppert *et al.*, 2000. Enhanced tissue factor pathway activity and fibrin turnover in the alveolar compartment of patients with interstitial lung disease. Thromb. Haemost., 83: 853-860.

Gupta, D., R. Agrawal and A. Singh *et al.* 2006. A respiratory cause of abdominal pain. Eur. Respir J. 27: 430-433.

Hardy, W.E., H. Tulgan and G. Haidak *et al.*, 1967. Sarcoidosis: A case presenting with dysphagia and dysphonia. Ann. Int. Med., 66: 353-357.

Hasday, J.D., P.R. Bachwich, J.P. Lynch and R.G. Sitrin, 1988. Procoagulant and plasminogen activator activities of bronchoalveolar fluid in patients with pulmonary sarcoidosis. Exp. Lung. Res., 14: 261-278.

Healy, V., M. Jeffers, F.B.V. Keane and O.N. Tucker, 2003. Granulomatous appendicitis. J. Roy. Coll. Surg. Edinb., 1: 286-289.

Israel, H.L. and M. Sones, 1953. Sarcoidosis: Clinical observation on one hundred sixty cases. Arch. Int. Med., 102: 766-776.

Iwai, K., T. Tachibana, Y. Hosoda and Y. Matsui, 1988. Sarcoidosis autopsies in Japan. Frequency and trend in the last 28 years. Sarcoidosis., 5: 60-65.

Kaneki, T., T. Kizumi, H. Yamamoto, S. Yamaguchi, T. Hachiya and K. Kubo *et al.*, 2001. Gastric sarcoidosis-a single polypoid appearance in the involvement. Hepatogastroenterol., 48: 1209-1210.

Karagiannidis, A., M. Karavalaki and A. Koulaouzidis, 2006. Hepatic sarcoidosis. Ann. Hepatol., 5: 251-256.

Kasdan, M.L. and L. June, 1993. Postoperative results of rheumatoid arthritis patients on methotrexate at the time of reconstruction surgery of the hand. Orthopedics, 16: 1233-1235.

Kinney, E.L., R. Murthy and G. Ascumce *et al.*, 1980. Sarcoidosis: Rare cause of superior vena caval obstruction. Pa Med., 83: 31.

Kobayashi, H., E.C. Gabazza and O. Taguchi *et al.* 1998. Protein C Anticoagulant System in Patients with Interstitial Lung Disease. Am. J. Respir Crit. Care Med., 157: 1850-1854.

Konda, J., M. Ruth, M. Sassaris and F.M. Hunter, 1980. Sarcoidosis of stomach and rectum. Am. J. Gastroenterol., 73: 516-518.

Kremer, R.M. and J.S. William, 1970. Gastric sarcoidosis: A difficult diagnosis. Am. Surg., 36: 686-690.

Lawrence, V.A., R. Dhanda and S.G. Hilsenbeck *et al.* 1996. Risk of pulmonary complications after elective abdominal surgery Chest, 110: 744-750.

Levine, M.S., O. Ekberg, S.E. Rubesin and R.A. Gatenby, 1989. Gastrointestinal sarcoidosis: Radiographic findings. Am. J. Roentgenol., 153: 293-295.

Limaye, A.P., D. Paauw and G. Raghu *et al.*, 1997. Sarcoidosis associated with recurrent pancreatitis. South Med. J., 90: 431-433.

Lindgren, A., C.P. Engstrom, O. Nilsson and H. Abrahamsson, 1995. Protein-losing enteropathy in an unusual form of sarcoidosis. Eut. J. Gastroenterol. Hepatol., 7: 1005-1007.

Longcope, W.T. and D.G. Freiman, 1952. A study of sarcoidosis. Medicine, 31: 1-132.

Lukens, F.J., V.I. Machicao, T.A. Woodward and K.R. DeVault, 2002. Esophageal Sarcoidosis: An Unusual Diagnosis. J. Clin. Gastroenterol., 34: 54-56.

Macleod, J.B., 1965. Sarcoidosis involving the vermiform appendix. J. Roy. Coll. Surg. Edinb., 10: 319-323.

MacRury, S.M., G. McQuaker, R. Morton and R. Hume, 1992. sarcoidosis: Association with small bowel disease and folate deficiency. J. Clin. Pathol., 45: 823-825.

Maeda, S., S. Murao and T. Sugiyama *et al.*, 1983. Generalized sarcoidosis with sarcoid aortitis. Acta. Pathol. JPN., 33: 183-188.

Mahadevan, U., E.V. Loftus and W.J. Tremaine *et al.*, 2002. Azathioprine or 6-mercaptopurine before colectomy for ulcerative colitis is not associated with increased postoperative complications. Inflam. Bowel. Dis., 8: 311-316.

Maylock, L.R., P. Bertrand, C.E. Morrison and J.H. Scott,, 1963. Manifestations of sarcoidosis. Am. J. Med., 35: 67-89.

McCormick, P.A., D. Malone and M.X. Fitzgerald *et al.*, 1985. Pancreatitis in sarcoidosis. BMJ., 290: 1472-1473.

Mclaughlin, A.M., McNicholas, 2003. Sarcoidosis presenting as upper extremity venous thrombosis. Thorax, 58: 552.

Meranze, S., B. Coleman and P. Arger *et al.*, 1985. Retroperitoneal manifestations of sarcoidosis on computed tomography. J. Comput. Assist. Tomogr., 9: 50-52.

Mert, A. and S. Avsar, 2004. Gall bladder involvement in sarcoidosis. J. Clin. Gastroenterol., 38: 612-613.

Miyazaki, E., T. Tsuda and A. Mochizuki *et al*., 1996. Sarcoidosis presenting as bilateral hydronephrosis. Int. Med., 35: 579-582.

Mohan, A., R. Sood and N. Shariff *et al*., 2004. Sarcoidosis manifesting as massive splenomegaly: A rare occurrence. Am. J. Med. Sci., 328: 170-172.

Moreno-Merlo, F., I.R. Wanless and K. Shimamatsu *et al*., 1997. The role of granulomatous phlebitis and thrombosis in the pathogenesis of cirrhosis and portal hypertension in sarcoidosis. Hepatol., 26: 554-60.

Munt, P.W., 1974. Sarcoidosis of the appendix presenting as appendiceal perforation and abscess. Chest, 66: 295-297.

Murata, K., T. Yasuda and H. Ito *et al*., 2006. Lack of increase in postoperative complications with low-dose methotrexate therapy in patients with rheumatoid arthritis undergoing elective orthopedic surgery. Mod. Rheumatol., 16 :14-19.

Naraynsingh, V. and G.C. Raju, 1987. Sarcoid aortic aneurysm: Surgical difficulties. J.R. Coll. Edinb., 32: 167-168.

Nchimi, A., N. Francotte, L. Rausin, J. Khamis and Ileocecal Sarcoidosis. Radiol., 228: 452-455.

Newman, L.S., C.S. Rose, L.A. Maier, 1997. Sarcoidosis. New Engl. J. Med., 336: 1224-1234.

Newton, C., L. Nochomovitz and J.M. Sackier 1998. Gastric adenocarcinoma associated with isolated granulomatous gastritis. Ann. Surg. Oncol., 5: 407-410.

Noël, J.M., I.M. Katona, V.M. Piñeiro-Carrero, 1997. Sarcoidosis Resulting in Duodenal Obstruction in an Adolescent. J. Ped. Gastroeterol. Nutr., 24: 594-598.

Numata, S., K. Kanda and T. Hatta *et al*., 2005. Sarcoidosis with double sacular abdominal aortic aneurysm. J. Vasc. Surg., 41: 1065.

O'Connor, A.S., F. Navab and M.J. Germain *et al*., 2003. Pancreatitis and Duodenitis from sarcoidosis: Successful therapy with mycophenolate mofetil. Dig. Dis. Sci., 48: 2191-2195.

Ohara, K., A. Okubo, H. Sasaki and K. Kamata, 1995. Branch retinal vein occlusion in a child with ocular sarcoidosis. Am. J. Ophthalmol., 119: 806-807.

Ona, F.V., 1981. Gastric sarcoid: Unusual cause of upper gastrointestinal hemorrhage, Am. J. Gastroenterol., 75: 286-288.

Palmer, C.D., 1958. Note on silent sarcoidosis of the gastric mucosa. J. Lab. Clin. Med., 52: 231-234.

Panella, V.S., S. Katz, E. Kahn and R. Ulberg, 1988. Isolated gastric sarcoidosis. Unique remnant of disseminated disease. J. Clin. Gastroenterol., 10: 327-331.

Payne, M.M., V. Kaimatchiev and M. Loriax, 2005. Pathologic quiz case: Multiple splenic nodules. Arch. Pathol. Lab. Med., 129: 419-420.

Perez, R.L., A. Duncan and R.L. Hunter *et al*., 1993. Elevated D dimer in the lungs and blood of patients with sarcoidosis. Chest, 103: 1100-1106.

Polachek, A.A. and W.J. Matre, 1964. Gastrointestinal sarcoidosis: Report of a case involving the esophagus. Am. J. Dig. Dis., 9: 429.

Popovic, O.S., S. Brkic, P. Bojic, V. Kenic, N. Jojic and N. Djuric *et al*., 1980. Sarcoidosis and protein-losing enteropathy. Gastroenetrol, 78: 119-125.

Ricker, W. and M. Clark, 1949. Sarcoidosis: A clinicopathologic review of three hundred cases, including 22 autopsies. J. Clin. Pathol., 19: 725-749.

Rodriguez-Garcia, J.L., J. Picazo and C. Mira C, *et al*., 2001. Systemic sarcoidosis with spleen involvement. Post Grad. Med. J., 77: 265.

Roth, D., B. West, J. Madison and D. Cooper, 1994.Gastric carcinoma in a patient with sarcoidosis of the gastrointestinal tract. Am. J. Gastroenterol., 89: 1589-1591.

Rowlan Payne, C.M. and D.H. McGibbon, 1985. Sarcoidosis presenting as widespread thrombophlebitis. Clin. Exp. Dermatol., 10: 592-594.

Russi, E.W., G. Bansky and M. Pfaltz *et al*., 1986. Budd-Chiari syndrome in sarcoidosis. Am. J. Gasteroentreol., 81: 71-75.

Sachar, D.B. and J. Rochester, 2004. The myth of gastrointestinal sarcoidosis: a case of guilt by association. Inflamm. Bowel. Dis., 10: 441-443.

Sany, J., J.M. Anaya and F. Canovas *et al*., 1993. Influence of methotrexate on the frequency of posto-perative infectious complications in patients with rheumatoid arthroitis. J. Rheumatol., 20:1129-1132.

Scott, N.M., V.M. Smith and P.A. Cox, 1953. Sarcoid and sarcoid-like lesions of the alimentary tract. Arch. Int. Med., 92: 741-749.

Shorr, A.F. and O.W. Hnatiuk, 2000. Circulating D Dimer in Patients With Sarcoidosis. Chest, 117: 1012-1016.

Siavelis, H.A., M.E. Herrman and G.V. Aranha *et al*., 1999. Sarcoidosis and the pancreas. Surgery., 125: 456-461.

Siegel, C.I., M. Honda and J. Salik *et al*., 1961. Dysphagia due to granulomatous myositis of the cricopharyngeus muscle: Physiological and cineradiographic studies prior to and following successful surgical therapy. Trans. Assoc. Am. Physicians., 74: 342-352.

Smetana, G.W., 1999. Preoperative pulmonary evaluation. New Engl J. Med., 340: 937-944.

Sprague, R., P. Harper, S. McClain, T. Trainer and W. Beeken, 1984. Disseminated gastrointestinal sarcoidosis. Case report and review of the literature. Gastroenterology, 87: 421-425.

Stampfl, D.A., I.S. Grim, D.J. Barbot, E.F. Rosato and S.J. Gordon, 1990. Sarcoidosis causing duodenal obstruction. Case report and review of gastrointestinal manifestations. Dig. Dis. Sci., 35: 526-532.

Tinker, M.A., B. Viswanathan, H. Laufer and I.B. Margolis, 1984. Acute appendicitis and pernicious anemia as complications of gastrointestinal sarcoidosis. Am. J. Gastroenterol., 79: 868-872.

Tobi, M., I. Kobrin and I. Ariel, 1982. Rectal involvement in sarcoidosis. Dis. Col. Rectum., 25: 491-493.

Trivedi, C.D. and C.S. Pitchumoni, 2005. Drug-induced pancreatitis: An update. J. Clin. Gastroenterol., 39: 709-716.

Tucher, O.N., V. Healy and M. Jeffers *et al*., 2003. Granulomatous appendicitis. Surgeon, 1: 286-289.

Vahid, B. and S. Waibel, 2006. Management of Corticosteroid-Refractory Neurosarcoidosis. Clin. Pulm. Med., 13: 328-331.

Vahid, B., B. Wildemore and P.E. Marik, 2006. Multiple venous thrombosis in a young man with sarcoidosis: Is there a relation between sarcoidosis and venous thrombosis? South Med. J., 99: 998-999.

Van den Heuvel, J.W. and F.H. Tuynman, 1991. Two unusual causes of venous obstruction of the arm. Neth. J. Surg., 43: 6-9.

Veitch, A.M. and I. Badger, 2004. Sarcoidosis presenting as colonic polyposis: Report of a case. Dis. Col. Rectum., 47: 937-939.

Warshauer, D., S. Dumbleton and P. Molina *et al*., 1994. Abdominal CT findings in sarcoidosis: radiologic and clinical correlation. Radiology, 192: 93-98.

Weiler, V., S. Redtenbacher and C. Bancher C, *et al*., 2000. Concurance of sarcoidosis and aortitis: case report and review of the literature. Ann. Rheum. Dis., 59:850-853

Wiesner, P.J., M.S. Kleinman and J.J. Condemi *et al*., 1971. Sarcoidosis of esophagus. Am. J. Dig Dis., 16: 943-951.

Wolters, U., T. Wolf and H. Stutzer *et al*., 1996. ASA classification and perioperative variables as predictors of postoperative outcome. Br. J. Anaesth., 77: 217-222.

Woszcyk, D., A. Kolodziej-Jaskula and J. Mykata-Ciesla *et al*., 2006. Focal lesions in the ultrasonographic examination of the spleen as a symptom of various disease statuses: Literature survey and case descriptions. Med. Sci. Monit., 12: 67-73.

Wynne, J.W., G.G. Ryerson and J. Dalovisio, 1979. Myocardial sarcoidosis complicated by mural thrombosis. Thorax, 34: 127-129.

Yamamoto, T., R.N. Allan and M.R. Keighley, 2000. Risk factors for intra-abdominal sepsis after surgery in Crohn's disease. Dis. Colon. Rectum., 43: 1141-1145.

Zech, J.R., E. Kroger, A.J. Bonnin and G.W. Richmond, 1993. Sarcoidosis: Unusual cause of a rectal mass. South Med. J., 86: 1054-1055.

Zia, H., H. Zemon and F. Brody, 2005. Case report: Laparoscopic splenectomy for isolated sarcoidosis of the spleen. J. Laparoendosc. Surg. Tech., 15: 160-162.