# Primary sclerosing cholangitis and sarcoidosis: An unusual combination. Case report and review of the literature

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**ABSTRACT:** A 43-year-old man with longstanding ulcerative colitis developed primary sclerosing cholangitis established by cholangiography and liver biopsy. Within one year of the diagnosis of primary sclerosing cholangitis, pulmonary sarcoidosis developed, proven by chest x-ray and transbronchial biopsy. The sarcoidosis initially presented with systemic systems rather than dyspnea. The relationship between primary sclerosing cholangitis, sarcoidosis and the symptomatology are discussed. Concomitant primary sclerosing cholangitis and sarcoidosis may be more common than previously anticipated and could be a further manifestation of disordered immune regulation. **Can J Gastroenterol 1990;4(8):489-494**

**Key Words:** *Sarcoidosis, Pancreatitis, Sclerosing cholangitis*

## Cholangite sclérosante primitive et sarcoïdose: Une combinaison inusitée. Observation et revue de la littérature

**RESUME:** Un homme de 45 ans atteint d'une colite ulcéreuse de longue date a développé une cholangite sclérosante primitive mise en évidence par une cholangiographie et une biopsie du foie. Au cours de l'année qui a suivi le diagnostic, une radiographie thoracique et une biopsie bronchique ont démontré qu'il était atteint d'une sarcoïdose pulmonaire. La sarcoïdose s'accompagnait initialement de symptômes généraux plutôt que de dyspnée. Le rapport existant entre la cholangite sclérosante primitive, la sarcoïdose et les symptômes est examiné. La cholangite sclérosante primitive et la sarcoïdose concomitantes pourraient bien être plus fréquentes qu'on ne le pense, témoignant plus avant d'un déficit de l'histo-immunité.

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IN AUGUST 1987, A 43-YEAR-OLD Caucasian male was referred for evaluation of persistently elevated aminotransferases and serum alkaline phosphatase. He had suffered from ulcerative colitis since 1970. The inflammatory bowel disease was controlled initially with sulphasalazine and recently with 5-aminosalicylic acid, and required only a single course of prednisone and no hospitalizations in the preceding 17 years.

Prior to investigation, he had complained of a 9 kg weight loss and malaise. Although his bowel movements were formed and nonbloody, prednisone had been prescribed and his symptoms abated. Colonoscopy and colonic biopsies had shown mild chronic inflammation consistent with ulcerative colitis, with no evidence of dysplasia or carcinoma. At the time of referral, he was taking 5-aminosalicylic acid 2.4 g daily and prednisone 20 mg per day; the latter medication was tapered over the next few months.

He had previously suffered three episodes of nephrolithiasis. All stones passed spontaneously and investigations revealed no specific underlying

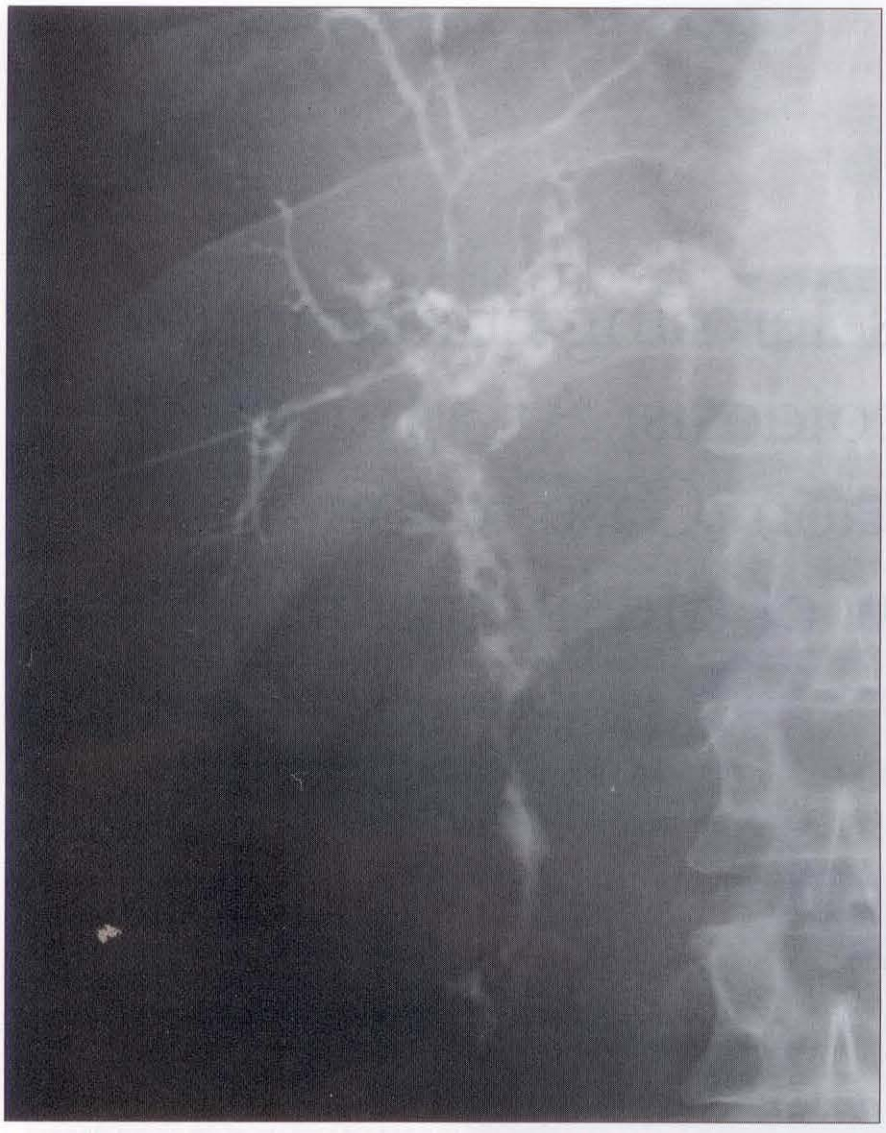

**Figure 1)** *Percutaneous transhepatic cholangiogram taken in July 1988 demonstrating multifocal intrahepatic and extrahepatic strictures and choledocholithiasis*

cause. He denied alcohol, tobacco or intravenous drug use and had not received blood or blood products. Employed in a mint, performing electrolysis using lead, tin and zinc, the patient had taken appropriate precautions against excessive exposure.

Physical examination was normal and revealed no signs of chronic liver or lung disease. The serum aspartate aminotransferase was 49 iu/L (normal 10 to 36), with an alanine aminotransferase of 128 iu/L (normal 10 to 40), and an alkaline phosphatase of 295 iu/L (normal 36 to 120). Routine hematological and biochemical tests including complete blood cell count, prothrombin time, bilirubin, calcium, albumin and total protein were normal. Ferritin, iron, iron-binding capacity and alpha-1-antitrypsin levels were normal. Hepatitis B surface antigen and antibody, antinuclear antibody and antimitochondrial antibody were negative. Anti-smooth muscle antibody, however, was present at a titre of 1 in 40. Human lymphocyte antigen (HLA) typing revealed that the patient was HLA-B8 and -DR3 positive.

Endoscopic retrograde cholangiopancreatography (ERCP) revealed strictures in the common bile duct and common hepatic duct, but nonfilling of the intrahepatic bile ducts. There was no evidence of choledocholithiasis and the pancreatic duct was normal. A computed tomography scan did not reveal a mass. Percutaneous transhepatic cholangiography visualized only the left intrahepatic ducts and showed multiple strictures. The extrahepatic ducts could not be opacified. Percutaneous liver biopsy demonstrated greatly expanded fibrotic portal areas with marked bile duct proliferation. The lobular architecture was preserved and there was no hepatitis or granulomas. Prednisone was tapered and the patient remained asymptomatic.

In March 1988 the patient was admitted to another hospital with acute pancreatitis, severe epigastric pain and a serum amylase greater than 1400 iu/L. The pain resolved completely in less than one week. He was not taking prednisone at that time. Several ultrasound examinations revealed gallbladder enlargement and hepatosplenomegaly but no cholelithiasis. Over the ensuing months he had recurrent episodes of epigastric pain lasting from hours to days, but the serum amylase remained normal during these episodes. However, the aminotransferase and alkaline phosphatase rose with these attacks and he became transiently jaundiced. Physical examination now demonstrated hyperpigmentation, hepatosplenomegaly with a liver span of 14 cm and a palpable spleen tip. There was tenderness over the liver, xanthelasmas about the eyes and intermittent scleral icterus. ERCP suggested common bile duct stones. The pancreatic duct was normal. Papillotomy and stent placement were not possible because of difficulty in deeply cannulating the common bile duct. A percutaneous transhepatic cholangiography outlined the intrahepatic and extrahepatic ducts, demonstrating multifocal strictures and choledocholithiasis (Figure 1).

In August 1988 he complained of marked malaise, nausea, an 8 kg weight loss, an aversion to strong smells, and mild exertional dyspnea. Chest examination was normal but a chest x-ray (normal in March) demonstrated diffuse interstitial disease with a reticulonodular pattern and hilar adenopathy (Figure 2). Pulmonary function tests showed a vital capacity of

3.06 L, 58% of predicted, and there was reduction of gas transfer; the diffusion capacity was 47% of the predicted value. Bronchoscopy was normal but a transbronchial biopsy showed multiple noncaseating granulomas consistent with sarcoidosis (Figure 3). Stains for fungi and acid-fast bacilli were negative. Bronchial washings showed normal cytology, no *Pneumocystis carinii* and negative bacterial cultures.

Prednisone 60 mg daily resulted in prompt resolution of malaise, nausea and dyspnea, and improvement in vital capacity and gas transfer. The patient's subsequent course was complicated by relapses of pulmonary symptoms with weaning of steroids. He developed steroid myopathy, candida pharyngitis and diabetes; the latter was controlled with diet and corticosteroid dose reduction.

Recurrent abdominal pain continued with episodes of cholestatic jaundice, chills and rigors. This has required chronic oral antibiotic administration, initially with cotrimoxazole and then norfloxacin. In June 1989 he had a second episode of acute epigastric pain, with a serum amylase of 1348 iu/L, associated transiently with increased jaundice. In July 1989 a biliary stent was placed endoscopically which markedly reduced the number of episodes of recurrent abdominal pain and cholangitis. In October 1989 he had an esophageal variceal bleed. A course of sclerotherapy was undertaken with no further bleeding. Albumin and prothrombin time remained normal, but the bilirubin level, while fluctuating, was consistently elevated. The patient has not yet returned to his former employment because of continuing pulmonary symptoms. Attempts to reduce his prednisone therapy below 20 mg per day have resulted in significant exacerbations of malaise and dyspnea.

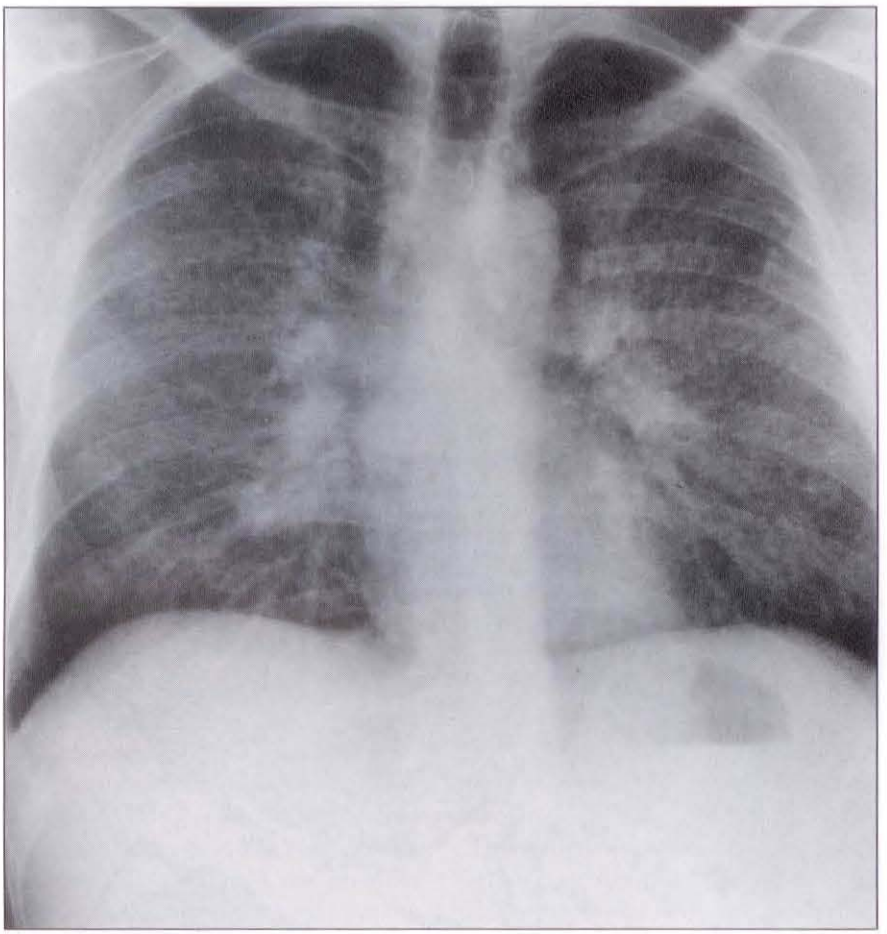

**Figure 2)** *Chest x-ray showing reticulonodular interstitial pattern and bilateral hilar adenopathy*

## DISCUSSION

Primary sclerosing cholangitis is characterized by inflammation and fibrosis of bile ducts and is of unknown etiology. The wide use of ERCP has shown that primary sclerosing cholangitis can occur in 5.7% of patients with longstanding ulcerative colitis, many being asymptomatic (1). Conversely, two-thirds of patients with primary sclerosing cholangitis have ulcerative colitis or subsequently develop it. If the prevalence of ulcerative colitis is between 40 and 100 per 100,000 (2), a prevalence of primary sclerosing cholangitis between one and eight per 100,000 is likely. The diagnosis of primary sclerosing cholangitis requires twofold or higher elevation of serum alkaline phosphatase, cholangiographically demonstrated multifocal strictures with tortuosity and irregularity of extrahepatic and intrahepatic bile ducts and compatible histopathology, and the absence of prior choledocholithiasis, biliary tract surgery other than simple cholecystectomy, and cholangiocarcinoma. Pathology, rarely diagnostic, reveals cholangitis, with periportal fibrosis or hepatitis, bridging necrosis or fibrosis and ultimately, biliary cirrhosis. Although the present patient had choledocholithiasis demonstrated in July 1988 (Figure 1), this was not evident on cholangiograms taken one year previously, and bilirubin choledocholithiasis is a recognized complication of biliary strictures, including primary sclerosing cholangitis (5). Cholangiocarcinoma can complicate primary sclerosing cholangitis (6), but the absence of progressive jaundice and the patient's prolonged survival make cholangiocarcinoma unlikely in this case.

A disorder mimicking primary sclerosing cholangitis can complicate immunosuppression, possibly due to biliary infection with cytomegalovirus (7) or cryptosporidiosis (8).

Although a test for antibodies to human immunodeficiency virus was not performed on the present patient, he had neither risk factors nor evidence of this infection.

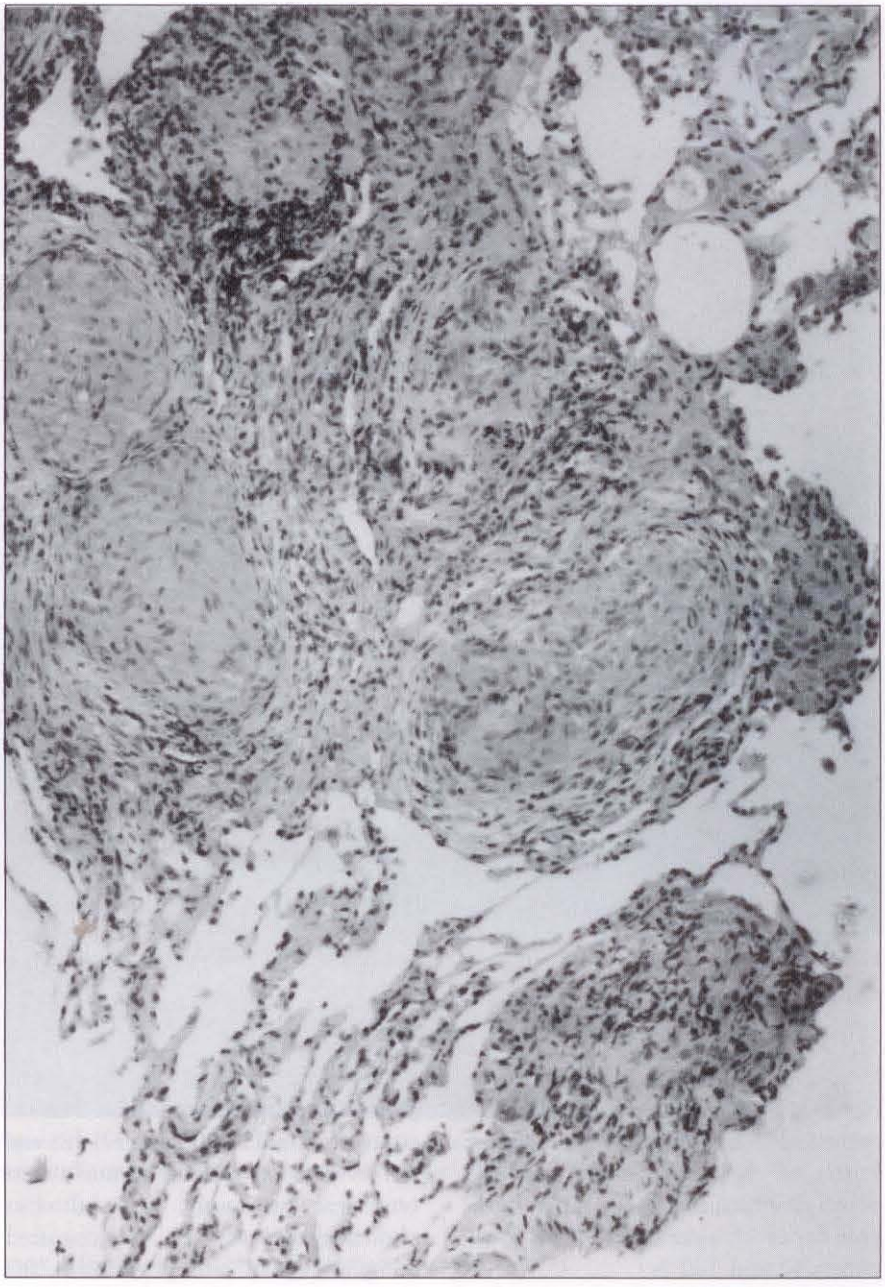

**Figure 3)** *Transbronchial biopsy revealing multiple noncaseating epithelioid granulomas*

Sarcoidosis is a variable, multisystem disorder of unknown etiology, characterized by the accumulation of T lymphocytes, mononuclear phagocytes and noncaseating epithelial granulomas in affected organs. The lung is most commonly affected. Skin, eye and lymph node involvement is also common, and virtually any organ may be affected. The prevalence of sarcoidosis is estimated at 10 to 40 per 100,000 in the United States and Europe (9). Although liver involvement is common, manifested by noncaseating granulomas on liver biopsy and less commonly by elevation of alkaline phosphatase, it is rarely of clinical importance. Occasionally, hepatic sarcoidosis causes cholestasis (10), portal hypertension (usually presinusoidal [11]), and a syndrome which may be impossible to differentiate from primary biliary cirrhosis (12,13).

Primary sclerosing cholangitis and sarcoidosis should occur in the same individual, by chance, approximately two to 32 times per one billion population. However, this association has been described in two individual reports (14,15) and was mentioned in two series (3,16). Thompson et al (16) found that one of 37 patients with primary sclerosing cholangitis had concurrent sarcoidosis. Of 70 patients with primary sclerosing cholangitis from the Mayo Clinic, 5% were said to have sarcoidosis (3). In case reports, sarcoid granulomas were noted in the liver, and in one patient sarcoidosis involved the lymph nodes in the hilum of the liver and mesentery, and cholangiocarcinoma was present (15). In 74 primary sclerosing cholangitis patients reported in two series from Europe, no sarcoidosis was noted (4,17).

Sarcoidosis and primary sclerosing cholangitis could occur together in a number of ways. Sarcoid granulomas in the hilar lymph nodes, as in one of the reported cases, could obstruct the extrahepatic ducts producing 'secondary' sclerosing cholangitis similar to that seen in chronic choledocholithiasis and Caroli's disease (15).

Multiple granulomas in the extrahepatic and intrahepatic ducts could theoretically simulate the cholangiographic appearance of primary sclerosing cholangitis. Local obstructive changes could result in secondary sclerosing cholangitis from recurrent episodes of bacterial cholangitis. Such a mechanism would require that sarcoidosis precede primary sclerosing cholangitis, which was not observed in the present patient.

The bile ducts are richly supplied by the hepatic artery, and interference with blood supply may be the basis of biliary strictures, which occasionally occur after biliary tract surgery (18). Hepatic arterial chemotherapy with 5-FUDR can lead to multifocal biliary strictures (19), and therapeutic hepatic arterial embolization has been complicated by bile duct necrosis (20). Although hepatic arterial involvement has not been described, clinically significant sarcoid vascular disease may involve pulmonary arteries (21) and veins (22), and hepatic veins (23). Thus, sarcoid-induced arterial involvement could lead to ischemia and multifocal stricturing of the bile ducts, but again, in the present patient the liver

disease preceded any evidence of pulmonary sarcoidosis.

The most likely explanation is that patients with primary sclerosing cholangitis, because of immunological abnormalities, are more susceptible to sarcoidosis. HLA-B8 and HLA-DR3 antigens are associated with an increased incidence of autoimmune diseases and are common in primary sclerosing cholangitis (24). Other immunological abnormalities in primary sclerosing cholangitis include elevated levels (25) and reduced clearance (26) of circulating immune complexes, inhibited leukocyte migration in response to biliary antigens (27), circulating autoantibodies against the colon and the portal tract (28), altered lymphocyte subset ratios (29) and increased complement metabolism (30). Besides its well known association with inflammatory bowel disease, primary sclerosing cholangitis has been described in association with a number of diseases which may be immunologically mediated, including sicca syndrome, mediastinal and retroperitoneal fibrosis, histiocytosis X, angioblastic lymphadenopathy and immune deficiency syndromes (5). Patients with sarcoidosis have no overall alteration in HLA antigen frequency, although the HLA-B8 antigen is associated with an increased incidence of erythema nodosum and arthritis (31), not observed the present patient. Sarcoidosis may be an autoimmune disease, but it more likely represents a response to an unknown antigen which may be infectious, chemical or other (32).

The present patient had two episodes of acute pancreatitis, probably due to choledocholithiasis. Epstein et al (33) found that 15% of patients with primary sclerosing cholangitis had changes suggesting chronic pancreatitis, eg, abnormal pancreatograms, and 36% had elevated isoamylase. The present patient did not have evidence of chronic pancreatitis on ERCP and the authors were unable to find any other reports of acute pancreatitis in primary sclerosing cholangitis. Interestingly, sarcoid involvement of the pancreas has been reported (34).

There is no effective therapy for primary sclerosing cholangitis. The use of mexthotrexate (35) or a combination of prednisone and colchicine (36) require further evaluation. Percutaneous dilation of extrahepatic duct strictures (37), nasobiliary drainage (38) or stent insertion have shown some promise. The present patient improved after the endoscopic insertion of a biliary endoprosthesis. Surgical approaches involve resection of extrahepatic ducts and use of a U tube through a hepaticojejunostomy (39) or stomatization of the afferent limb of the choledochojejunostomy-hepaticojejunostomy to allow later percutaneous access to the biliary tree. Bilateral hepaticojejunostomies with silastic transhepatic stents have helped some patients (41). These techniques and their impact on subsequent liver transplantation await full evaluation (42). They are contraindicated in cirrhosis (43). Controlled trials of corticosteroids in primary sclerosing cholangitis have not been reported, but corticosteroids are the main treatment in sarcoidosis. Although they improve symptoms secondary to inflammation, they may not prevent or reverse fibrosis. The present patient had mild dyspnea but marked constitutional symptoms which necessitated treatment. However, the complications which develop as a result of prednisone therapy greatly reduce the overall benefit. Unfortunately, controlled trials have not demonstrated superiority of any agent over corticosteroids in the therapy of sarcoidosis. Whether corticosteroid treatment will slow the progression of the present sclerosing cholangitis will be difficult to assess. This patient's combination of diseases and a review of the literature indicate that one should be aware of the occasional association between primary sclerosing cholangitis and sarcoidosis. Nonspecific symptoms such as malaise and weight loss as well as pulmonary complaints in patients with primary sclerosing cholangitis should prompt consideration of a possible diagnosis of sarcoidosis.

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