SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2006; 23; 135-140

Case studies to explore the pitfalls in the diagnosis of sarcoidosis

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Abstract. Sarcoidosis is a multisystemic disorder of unknown cause. Diagnosis is established when clinical and radiological findings are supported by histological evidence of noncaseating epitheloid cell granulomas. Exclusion of granulomas of known causes and sarcoidlike reactions is mandatory. A lot of infections may mimic a sarcoidlike granulomatous reaction. Even with well advanced pathological and microbiological examination, it could be hard to make the appropriate diagnosis. Moreover, sarcoidosis patients receiving corticosteroids are susceptible to opportunistic infections. The challenge is, however, making the right diagnosis because opportunistic infections can resemble sarcoidosis. The case reports presented in this paper are meant to stress the importance of excluding granulomatous infections in patients with (suspected) sarcoidosis. Appropriate diagnostic procedures are important to exclude an infectious condition mimicking sarcoidosis. Accordingly, appropriate treatment can start without further delay. ***(Sarcoidosis Vasc Diffuse Lung Dis 2006; 23: 135-140)***

Key Words. Sarcoidosis. Granulomatous infections. Whipple's disease. Lyme disease. Leishmania.

Introduction

Although the cause of sarcoidosis remains unknown, increasing numbers of studies support a putative role for biological agents including microbial agents. Diagnosis is established when clinical and radiological findings are supported by histological evidence of noncaseating epitheloid cell granulomas [1]. Granulomas of known causes and sarcoidlike reactions must be excluded. A lot of infections can mimic sarcoidosis, this may bias the confirmation of an appropriate diagnosis and may delay the initiation of the adequate therapy [2].

We report four patients highly suspected of sarcoidosis in whom a granulomatous infection was found. After the appropriate diagnosis was made, all cases responded well to antibiotics. The fifth case describes a patient suspected of an infection, in whom ultimately the diagnosis of sarcoidosis was more likely.

Case 1

A 33-year-old man was referred to the Sarcoidosis Management Center of University Hospital of Maastricht in Octo-

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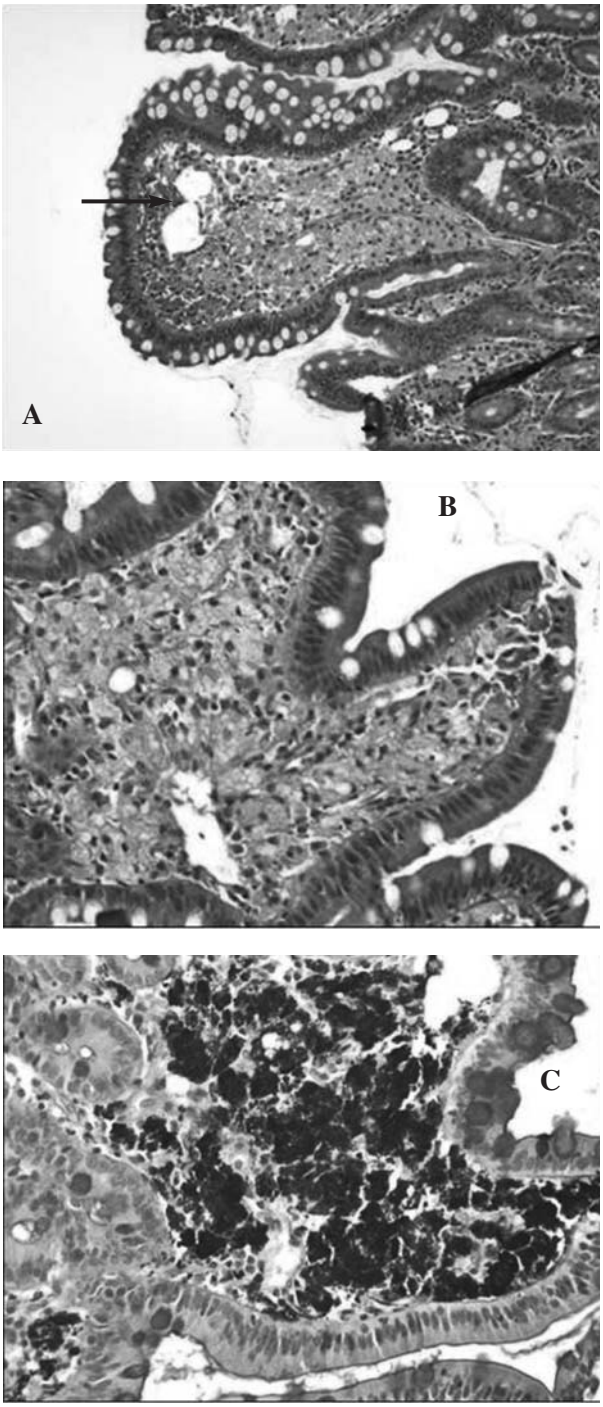

Fig. 1. (A) Small bowel biopsy with accumulation of foamy macrophages in the lamina propria obtained from a patient suffering from Whipple's disease. Note lymphatic dilatation (arrow). (B) Small bowel biopsy with accumulation of foamy macrophages in the lamina propria (high power) obtained from a patient suffering from Whipple's disease. (C) PAS staining showing the purple positive granules (lysosomes with partially digested bacilli) in the foamy macrophages

ber 2003 for a second opinion because of his sarcoidosis. A biopsy of the bronchus in March 2003 demonstrated a granulomatous reaction consistent with sarcoidosis. Culture of the biopsy was negative. Steroids were started and initially there was an improvement in the patient's condition. In September 2003 he suffered from diarrhoea and his complaints of coughing and dyspnea were still present despite the treatment with steroids. Additionally, a CT thorax showed small mediastinal lymphadenopathy, a large subcarinal lymphadenopathy and some fibrotic intrapulmonary lesions. Echocardiography revealed dilatation of the right ventricle, with tricuspid insufficiency 2/4 and pulmonary valve insufficiency. The vena cava did not collapse. These signs are indicative of an elevated pulmonary artery pressure. CT abdomen showed lymphadenopathy especially between the kidney and aortic bifurcation. In January 2004 a small bowel biopsy (*Fig. 1A, 1B*) was performed. The biopsy showed an accumulation of foamy macrophages in the lamina propria. Staining with PAS (*Fig. 1C*) showed the purple positive granules (lysosomes with partially digested bacilli) in the foamy macrophages. Accordingly, it was concluded that this patient was suffering from Whipple's disease. Antibiotic treatment with ceftriaxon during two weeks and cotrimoxazol for a period of one year was started with good response. Even the echocardiography was normalised.

Case 2

A 23-year-old male with intermittent, subsequently persistent hyperpyrexia, associated with profuse nocturnal sweating, weakness and lower limb pain unresponsive to different antibiotic therapies was referred to the Infectious Diseases Unit of the Department of Clinical Medicine and Immunology of Policlinico Le Scotte (Siena). Physical examination showed splenomegaly. Blood chemistry demonstrated an increase of transaminases and inflammation markers, elevated lymphocyte count and low blood iron with extremely high ferritin. Abdominal ultrasonography confirmed a slight splenomegaly. The chest X-ray was normal. ACE was elevated (91 U/l) and transaminases were rapidly increasing. Liver biopsy was performed and granulomatous hepatitis was found, compatible with sarcoidosis, no organisms were found. PCR for mycobacteria in tissue was negative. Bronchoscopy and biopsy of bronchial bifurcations were negative. Since fever persisted, steroid therapy was initiated. This revealed no clinical improvement. Accordingly, as the diagnosis of sarcoidosis was not convincing, bone marrow biopsy was performed and showed granuloma and parasite elements compatible with Leishmania. No signs of eosinophilic infiltration were found within the granulomas (*Fig. 2*). Infection was confirmed by PCR and serology was positive for Leishmania. Specific therapy with liposomal amphotericin B led to immediate improvement in clinical condition, progressive reduction of indices of liver cytolysis and cholestasis, and normalisation of liver function.

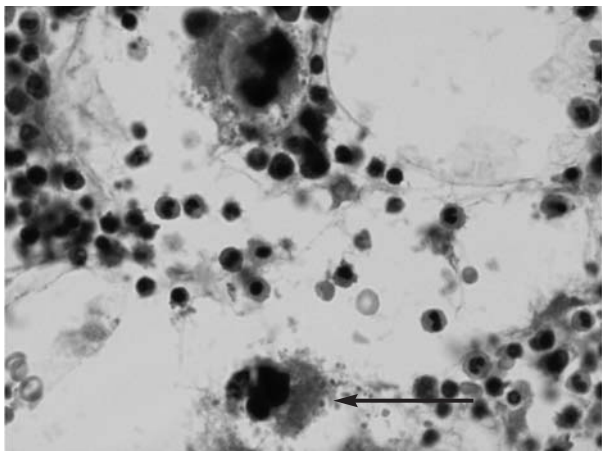

Fig. 2. Bone marrow biopsy obtained from a 23- year old male with suspected sarcoidosis. Giemsa staining showed Leishmania

Case 3

A 53-year-old man was known with sarcoidosis since 2001.The diagnosis was confirmed by a biopsy of the skin. He deteriorated in May 2002 and corticosteroids were started. At that time an elevated level of angiotensin converting enzyme (ACE 54 U/l: normal range 9-25 U/l) and soluble interleukin-2 Receptor (sIl-2R) 4315 kU/l (normal range: 241-846kU/l). In November 2002 he was admitted to hospital because of fever, cold chills and purulent sputum. At that time he was treated with prednisolone 20 mg orally daily. Laboratory examination showed no elevated level of ACE (10 U/l). A chest X-ray revealed infiltrative abnormalities in the right upper lobe. A bronchoscopy revealed endobronchial no abnormalities. Bronchial aspirate demonstrated a sporadic acid-fast branching, gram positive rod (*Fig. 3*) and culture revealed a Nocardia species, sensitive for cotrimoxazol. Cotrimoxazol as well as an aminoglycoside was started because of the immunosupressed condition of the patient. Thereafter, his clinical condition improved substantially.

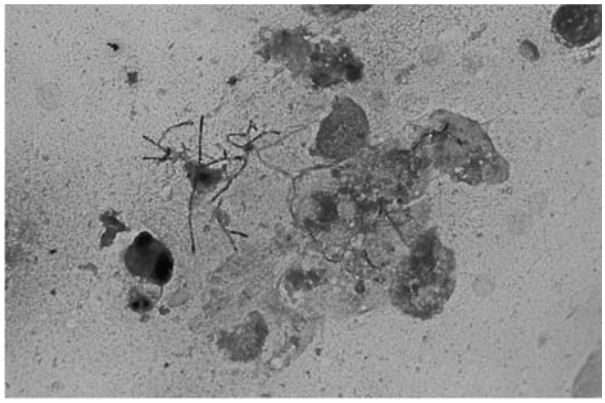

Fig. 3. Bronchial aspirate, obtained from a patient known with sarcoidosis. Gram staining showed grampositive rods, Nocardia spp

Case 4

A 53-year-old male with a diagnosis of sarcoidosis, established elsewhere in 2000 based on the presence of epithelioid granulomas consistent with sarcoidosis in transbronhial biopsy specimen, was referred to the Sarcoidosis center in Siena in 2001. He showed deterioration of clinical condition despite steroid therapy, he suffered from dyspnea, productive cough with mucopurulent sputum and evening fever (max. 37.8C°). Chest auscultation revealed absence of vesicular murmur in the left mediobasal field accompanied by plexal hypotympanism. The chest X-ray showed abundant left pleural effusion, and bilateral nodular opacities. Blood chemistry showed elevated indices of inflammation, serum ACE and lysozyme were normal. Lymphocyte phenotyping of peripheral blood was normal except for a reduction in CD19+ cells. Abundant yellow liquid was drained from the thoracic cavity. Biochemical analysis of the fluid revealed an exudate. Cytological examination of pleural liquid showed lymphocytes and occasional mesothelial cells. Cytofluorimetric phenotyping of lymphocytes showed CD4+ 16.8%, CD8+ 48%, CD19+ 19.3% and CD4/CD8 0.35. Culture and cytology of pleural liquid were negative. Subsequent chest CT scan showed extensive parenchymal opacity in the left lower lobe, organized pleural effusion on the left, localised hyperdensity in the lower left lobe and in the upper right lobe with traction bronchiectasis. Sporadic small nodules were present bilaterally in the upper lung regions. Hilar lymph nodes were not enlarged. Blood gas analysis was normal. Lung function tests showed moderate restrictive deficit. Diffusion capacity was altered. A bronchoscopy showed endobronchial no abnormalities. Bronchoalveolar lavage (BAL) contained 72% polymorphonuclear neutrophils, 22% alveolar macrophages and 6% lymphocytes. Tuberculin skin test was positive. Microbiological examination of bronchial aspirate and two consecutive expectorates was positive for *Mycobacterium tuberculosis*. The patient's clinical condition improved when appropriate therapy was started and he recovered rapidly.

Case 5

A 32-year-old man was admitted to a rheumatologist because of a monoartritis of the left ankle, diffuse arthralgia and general tiredness. Serology showed twice a positive IgM against Borrelia. Tetracyclines were started and the patients clinical condition improved.

A chest X-ray demonstrated signs of an enlargement of the right hilum. This was confirmed on CT thorax. Moreover, some small interstitial abnormalities were seen. Laboratory examination showed a slightly elevated ACE of 26 U/l (nor-

mal range 9-25 U/l). Because treatment was already started and the patient felt clinically better and he had a normal lung function, there it was decided not to perform additional tests, including BAL or biopsy. The first diagnosis which was suspected in this patient was a *Borrelia burgdorferi* infection with reactive artritis of the left ankle. Later on there were doubts of the diagnosis of an acute infection with *Borrelia burgdorferi*, because ankle arthritis is a late manifestation of Lyme disease and IgG against Borrelia was negative at first consultation and was still negative later by control [3]. Finally, it was concluded that the enlarged hilum seen on the X- ray and CT thorax together with the slightly elevated ACE were highly likely of the diagnosis sarcoidosis.

Discussion

The aetiology of sarcoidosis is not known and can affect any organ system, but pulmonary manifestations are the most common. It is a complex disease that appears to arise from the interaction of one or more triggers in an immunopathologically predisposed host.

The diagnosis of sarcoidosis is established when clinical and radiological findings are supported by histological evidence of granulomas [1]. The clinical course is heterogeneous, spontaneous remissions occur in nearly two-thirds of the patients, the disease becomes chronic in 10-30% of cases [4].

Nonproductive cough, dyspnea and chest pain are common features of pulmonary sarcoidosis. These features are non-specific and can also be seen in a lot of infectious diseases [5]. Laboratory signs are also non-specific in the diagnosis of sarcoidosis. Elevated levels of lysozym and ACE are a sign of activity of a granulomatous inflammation. These parameters should never be used in isolation to dictate therapeutic interventions [6]. More recently, Rothkrantz-Kos et al. found that serum levels of sIL-2R appeared to be more useful for monitoring disease severity in sarcoidosis [7]. Moreover, others have demonstrated that extrapulmonary manifestations of sarcoidosis are accompanied by increases in sIl-2R, suggesting that sIL2R may serve as a marker of disease activity [8].

Sarcoid granulomas exist of noncaseating epitheloid cell granuloma consisted of highly differentiated mononuclear phagocytes and lymphocytes. They are formed as a result of the persistence of non-degradable material, including (micro-)organisms.

Granulomatous infections are important in the differential diagnosis. They share several clinical and histopathological features which can cause problems by making the appropriate diagnosis. In this regard, microbiological and pathological studies are very important. Granulomatous infections have been conveniently classified into three categories (*Table I*) [2].

Microbes are also a likely trigger (but not as an infection) in a genetically predisposed individual and it is thought that this initial event culminates in the granulomatous response of sarcoidosis. Further research is necessary to confirm this hypothesis [9]. For example studies were performed to find out if there is a possibility that Borrelia may be involved in the pathogensis of sarcoidosis. Xu et al reported that *Borrelia burgdorferi* might not be the causative agent of sarcoidosis, the elevated titres of serum antibodies against *Borrelia*

Table I
Infectious granulomatous disorders

Granulomatous disorders with well-recognized causal agents	
Mycobacteria	Tuberculosis, Leprosy, Human Bovine TB, BCGiosis, Buruli ulcer, Fish tank granuloma
Bacteria	Brucellosis, Melioidosis, Actinomycosis, Nocardiosis, Granuloma inguinale, Tularaemia, Listeriosis
Fungi	Mycoses, Histoplasmosis, Cryptococcosis (European Blastomycosis), Coccidio-and paracoccidomycosis
Protozoa	Leishmaniasis, Toxoplasmosis, Amoeboma
Spirochaetes	Syphilis, Yaws, Pinta
Nematodes	Ascariasis, Toxocariasis
Trematodes	Schistosomiasis, Paragonimiasis, Fascioliasis, Opisthorciasis, Clonorchiasis
Cestodes	Echinococcosis, cysticerosis, sparganosis
Chlamydia	Lymphogranuloma venereum, Trachoma
Rickettsia	Q fever
Viral	Infectious mononucleosis, Cytomegalovirus (CMV) Infection, Measles, Mumps
Granulomatous disorders with recently recognized causal agents	
Bacteria	Cat-scratch disease Whipple's disease
Granulomatous disorders where causative agents suspected but not yet identified	
Measles virus	Crohn's disease
Mycobacterium	Primary biliary cirrhosis Sarcoidosis
Viral	Kikuchi's disease Chronic granulomatous disease of childhood Langerhans' granulomatosis

Adapted from: Granulomatous infections: an overview. The granulomatous disorders. Cambridge University Press. 1999

burgdorferi in patients with sarcoidosis was a non-specific response [10].

A biopsy in case five could have helped us by confirming the appropriate diagnosis. Pathological examination in Lyme disease reveals in the early stages a lot of neutrophils, later stages a mixture of neutrophils and mononuclear cells and in the chronic stages it is becoming more lymphoplasmacytic. Granulomas are not found [11].

Supplementary pathological and microbiological examinations seem very important in making the appropiate diagnosis. In case two the diagnosis of an infection with Leishmania was made. Leishmania is an organism which may cause a granulomatous infection. Leishmaniasis is an important cause of morbidity and mortality in Africa, the Middle East, South America and Asia [2]. Currently Leishmania is endemic in Italy, especially along the sea coasts it is diffused in dogs [12]. Leishmaniasis presents as a spectrum of clinical disease and is caused by several species of the protozoan *Leishmania* spp. There are three clinical forms: cutaneous, mucocutaneous and visceral [2].

Even with pathological and microbiological examination it could be hard to make the appropriate diagnosis, as shown in case one. The diagnosis of Whipple's disease was ultimately made by a biopsy of the small bowel. The biopsy of the bronchus showed an epitheloid granuloma and no micro-organisms were found in the biopsy. Pulmonary involvement is frequent. In 9% of the patients noncaseating epitheloid cell granuloma are found, especially in the lymph nodes and the liver. A pitfall in making the right diagnosis is that PAS staining of extra-intestinal inflamed tissue can be negative in patients with Whipple's disease [13]. Whipple's disease is a systemic infectious disorder affecting mostly middle-aged white males. Most common symptoms are weight loss, arthralgia, diarrhoea and abdominal pain. The disease is commonly diagnosed by a small-bowel biopsy. The finding of severe pulmonary hypertension in Whipple's disease is mentioned before [14-16]. Possible explanation of the pulmonary hypertension could be vascular infiltration by *Tropheryma whippelii* [16]. According to the other reports, after treatment with antibiotics the pulmonary hypertension resolved in our patient and his clinical situation dramatically improved.

It is known that patients receiving corticosteroids are susceptible to opportunistic infections. So it is not surprising that patients with sarcoidosis and receiving corticosteroids are also susceptible to opportunistic infections. The challenge is however making the right diagnosis because opportunistic infections can resemble sarcoidosis. For example, nocardiosis is a granulomatous disorder, but with a well recognized causal agent. Nocardiosis is an uncommon bacterial infection caused by aerobic actinomycetes in the genus Nocardia. Inhalation of *N. asteroides* usually does not cause disease in immunocompetent hosts, but disease is more seen in immunosuppressed hosts like pulmonary alveolar proteinosis, malignancy, organ transplantation, corticosteroid therapy, but rarely in sarcoidosis [17].

Case four was also an interesting case, because sarcoidosis combined with tuberculosis is a diagnostically puzzling. Mycobacterial infection and tuberculosis in the course of sarcoidosis does exist. However, there is paucibillary tuberculosis, which might be aggravated by corticosteroid treatment. In this case tuberculosis was ruled out in the first biopsy and reevaluation by PCR was negative too. These two cases underline again the relevant role of the clinician for the correct interpretation of the clinical, radiological and histological results.

In conclusion, the diagnosis of sarcoidosis needs a compatible clinical picture, histological demonstration of noncaseating granulomas and exclusion of other diseases capable of producing a similar histological or clinical picture according to the clinical guidelines [6].

In an effort to make an appropriate diagnosis in patients with (suspected) sarcoidosis, we stress that advanced microbiological and pathological tests are mandatory. Thereafter, appropriate treatment can be initiated without further delay.

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