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Severe opportunistic infections in extrapulmonary sarcoidosis

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ABSTRACT

Introduction: Sarcoidosis is a chronic multisystemic disease of unknown etiology characterized by noncaseating granulomas that most frequently affect the lungs, but frequently has extrapulmonary manifestations. Treatment of symptomatic sarcoidosis, glucocorticoids and immunosuppressants, may be associated with an increased risk of infection. Case Report: We report a patient with extrapulmonary sarcoidosis on immunosuppressive therapy who had polymicrobial infection, including *Mycobacterium tuberculosis* and *Mycobacterium genavense* complicated by infected aortic aneurysm. Conclusion: In patients with sarcoidosis with persistent fever, a possible over-infection, including opportunistic agents should be evaluated. Infected tuberculous aneurysm is very unusual. This is the first case in the literature of tuberculous aneurysm associated with anti-TNF treatment.

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INTRODUCTION

Sarcoidosis is a multisystem disease of unknown cause that is characterised by the formation of noncaseating epithelioid-cell granulomas in the absence of organisms or particles [1–2]. Sarcoidosis typically affects the lungs, eyes or skin but any organ may be involved [3].

Opportunistic infections seem to be rare in the setting of sarcoidosis. Corticosteroids-induced immune suppression are often present in these cases of infection [4–7].

Infected aneurysm, also known as mycotis aneurysm, describes those rare aneurysms which occur secondary to destruction of artery wall [8]. *Mycobacterium tuberculosis* is a rare cause of infected aortic aneurysms [9–10].

We present a case of a 50-year-old man with extrapulmonary sarcoidosis in immunosuppressive therapy who presented fatal polymicrobial infection, including *Mycobacterium tuberculosis* and *Mycobacterium genavense* complicated with infected aortic aneurysm.

CASE REPORT

The patient is a 50-year-old man of Caucasian origin, a smoker with no other toxic habits who did not report previous illnesses. He had to undergo a laparotomy 30 years earlier due to a stab wound. In November 2015, he presented abdominal pain and jaundice, with a diagnosis of obstructive jaundice due to choledocholithiasis. Papillotomy and stone removal were treated by an endoscopic retrograde cholangiopancreatography (ERCP). In an abdominal CT scan he showed signs of acute cholecystitis, homogeneous splenomegaly and multiple inflammatory-type adenopathies of the pancreas and splenic hilum.

In recent months he had intermittent fever, sweating and had lost more than 20 kg of weight. A blood test 5 months earlier showed elevated gamma glutamyltranspeptidase (GGT) and alkaline phosphatase (ALP) levels that his doctor linked to alcohol consumption, but he refused.

As he again presented abdominal pain with signs of acute cholecystitis and dilation of the common bile duct, he underwent a new ERCP with sphincterotomy, removal of bile mud mold and lithiasis with insertion of plastic prosthesis. Subsequently, he underwent a cholecystectomy by open surgery with Kehr tube insertion.

Forty days after the operation, fever increased. Collections in subphrenic and vesicular bed were appreciated and percutaneous drainage was performed. Abdominal CT scan (Figure 1) also showed a 35 mm infrarenal saccular aneurysm with mural thrombus. As the fever persisted despite the antibiotics, new samples were taken for blood and urine cultures. A new ultrasound and cholangiogram, an echocardiogram and a Gallium scan did not show the cause of the fever. The study was extended by serology to *Brucella spp, Leishmania, Coxiellaburnetti, Chlamydias, Mycoplasma*, B and C viruses, HIV, cytomegalovirus viral load and Quantiferon TB-Gold, which were negative. Angiotensin converting enzyme (ACE) levels were elevated (68 U/L). A positron emission tomography-computed tomography (PET-TC) was performed and showed hepato-splenomegaly and mediastinal right paratracheal, retroperitoneal and external iliac adenopathy. A bone marrow biopsy was performed with the presence of non-necrotizing epithelioid granuloma, but without acid-fast bacilli (AFB) or parasites. The mycobacterial cultures were negative.

A cytometry at cd3 and cd20 showed no lymphoproliferative infiltration and, at cd34, no infiltration by blast cells. The reticulin technique did not show fibrosis. In addition, a liver biopsy (Figure 2) was performed and it showed multiple nonnecrotizing granuloma and giant cells without AFB or other microorganisms by the special techniques (PAS, fite, silver and CMV).

It was diagnosed as extrapulmonarysarcoidosis, he started a treatment with daily prednisone 60 mg and

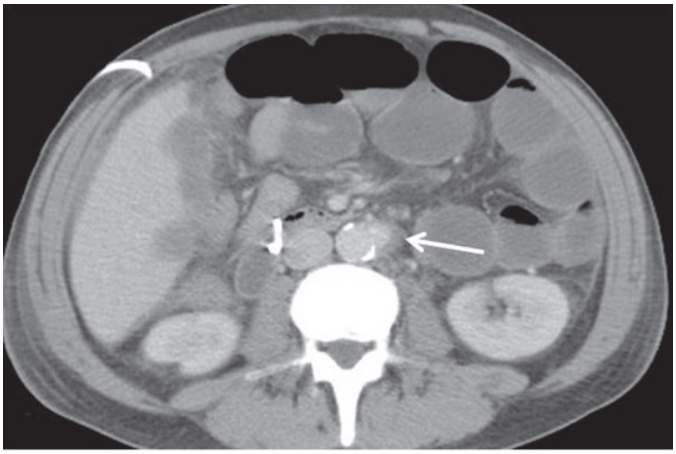

Figure 1: CT scan of the abdomen with contrast IV in portal phase and axial cut, identifying aortic wall calcifications and a left lateral wall saccular aneurysm of infrarenal abdominal aorta of 35 mm maximum axial diameter with mural thrombus, subhepatic hypodense collection and dilation of small intestine loops.

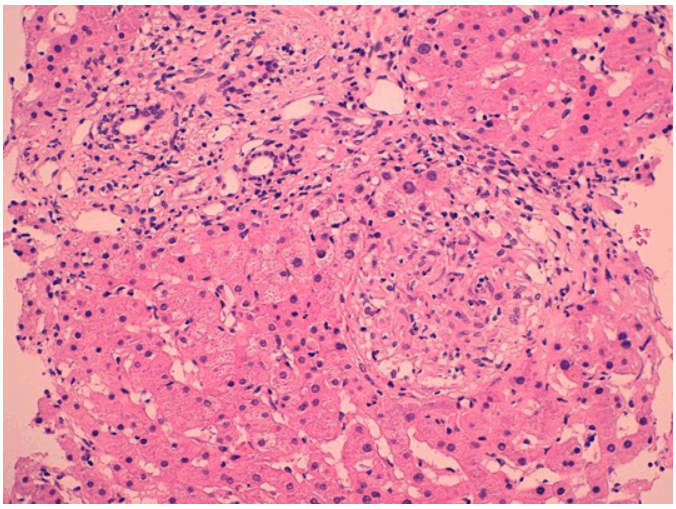

Figure 2: Discrete, non-necrotizing epithelioid granuloma in liver biopsy

became afebrile. After 4 weeks the dose of prednisone was tapered off and the fever reappeared when tried below 30 mg. At six months, lab tests showed normal blood count and hepatic biochemistry, 8 mm/1st hour ESR and CRP 17 mg/L. An abdominal ultrasound ruled out collection and the chest X-ray showed no infiltrates. It was advisable to reduce prednisone gradually to 15 mg by associating treatment with azathioprine (AZA).

In the following months it was not possible to reduce prednisone below 20 mg due to new flares of fever. He developed AZA-related pancytopenia. AZA was stopped and, when he recovered from pancytopenia, he was given methotrexate 20 mg per week. Two months later, after 18 months of follow-up, he developed a fever above 40 degrees Celsius with chills and sweating. In the physical examination, chest X-ray and abdominal ultrasound there were no relevant findings. In the blood testshowedleukocytes 4,240/mcL, hemoglobin 12.4 g/

dL, platelets 104,000, CRP 109 mg/L and procalcitonin 4.28 ng/mL (normal < 0,5) suggesting an infectious complication. Piperacillin and tazobactam was started and fever disappeared. Blood and urine cultures were negative. An echocardiogram showed no signs of vegetation. When steroid treatment was stopped, the patient had a daily fever again. A flow cytometry was performed, which showed no alteration. A new bone marrow biopsy was hypocellular, containing all three series and with the presence of histiocyte aggregates compatible with incomplete granulomas. The PCR for *Leishmania* was negative. PET-TC was repeated and laterocervical, mediastinal and abdominal adenopathies of high metabolic grade were observed, with high metabolic grade hepato-splenomegaly suggesting sarcoidosis or neoplasia. It was not considered to repeat Quantiferon or mycobacterial culture, which had previously been negative. After PET-TC was performed a 40 mg corticosteroid treatment was continued, leaving the patient afebrile and his general condition improved. This suggested again a combined treatment with MTX and antiTNF with infliximab and it was advisable to reduce steroids in the coming weeks.

After discharge, he had an intermittent fever, initially well tolerated. Instead of reducing prednisone, he decided himself to increase prednisone to 60 mg daily. Three months later, he went to the emergency room with a high fever, above 39º C. He also suffered from badly localized lumbar pain, which was not related to movements and did not disappear at rest. He denied coughing, expectoration or shortness of breath. His admission was decided for a study.

On examination, his temperature was 37.1ºC, the blood pressure 90/45 mm Hg, the pulse 81 beats per minute, the respiratory rate 18 breaths per minute and the oxygen saturation 94% while the patient was breathing ambient air. He seemed to be ill, with cushingoid signs, no palpable peripheral adenopathies. Heart sounds were rhythmic with no murmurs present. The vesicular murmur was preserved with the presence of scattered wheezing and hoarseness. Sensitive hepatosplenomegaly was palpated, with no edema of the peripheral limbs, and neurological examination was normal.

Blood tests showed pancytopenia, with leukocytes 3260/mcL, hemoglobin 10.3 g/dL, platelets 102000/mcL, impaired renal function with creatinine 1.96 mg/dL, and CRP 315.6 mg/L and procalcitonin 0.99 ng/mL. A chest X-ray revealed patched infiltrates in the upper lobes. A CT scan of the chest and abdomen (Figures 3 and 4) revealed pseudonodular opacities patched in ground glass in both upper and middle lobes; a solid 2.5 cm nodule surrounded by a small halo of ground glass in a newly formed lower left lobe, homogeneous spleen of 18.5 cm and a saccular aortic aneurysm of abdominal aorta of 48 mm maximum axial diameter and 35 mm sagittal diameter (already seen in the last cuts of the previous study of a year and a half before; however, it had grown from the initial maximum axial diameter of 35 mm). The October 2017 PET-CT scan was reviewed, which showed an aneurysm with a size of 45 mm (not reported at the time). Serial blood culture samples were obtained, also for mycobacteria, and a treatment with ceftriaxone and levofloxacin was

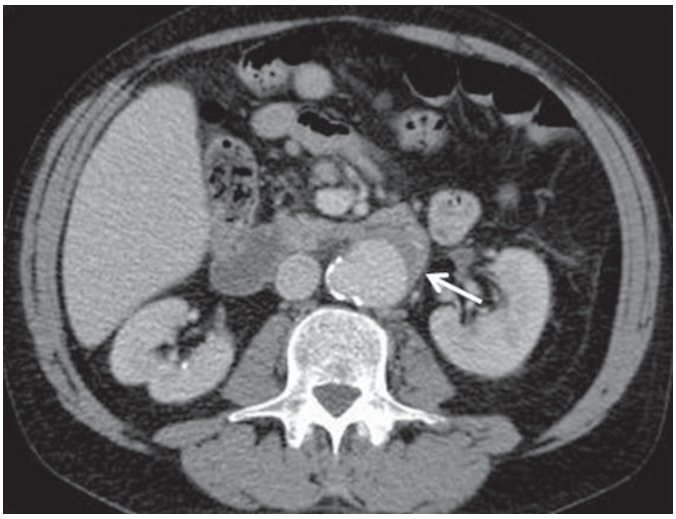

Figure 3: CT scan of abdomen with contrast IV portal phase and axial cut, where aortic wall calcifications and left lateral wall saccular aneurysm of infrarenal abdominal aorta of 48 mm maximum axial diameter are identified, which has grown since the previous study in 2016. The mural thrombus persists.

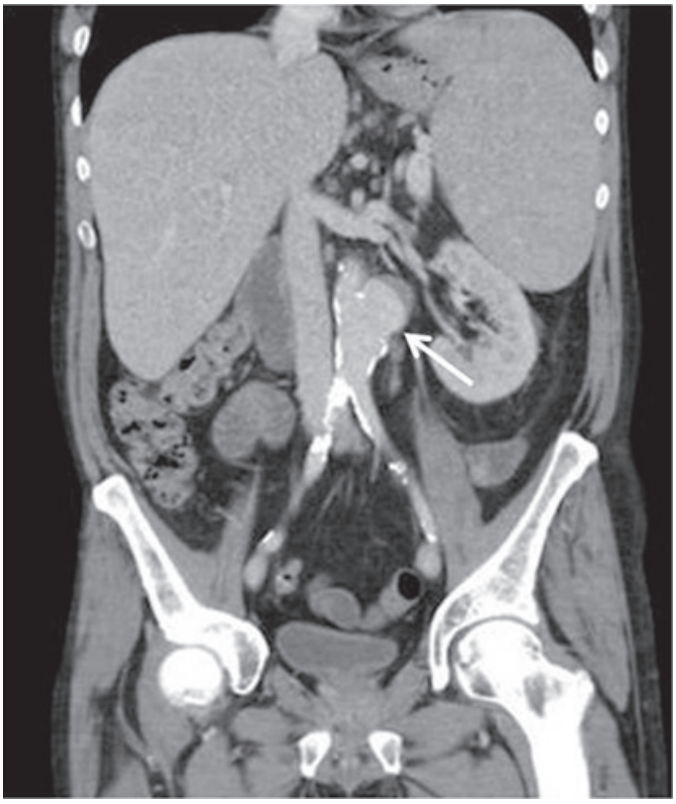

Figure 4: CT scan of abdomen with portal phase IV contrast and coronal cut, shows hepatosplenomegaly, multiple calcifications in vascular wall of aorta and iliac arteries, and left lateral wall saccular aneurysm of infrarenal abdominal aorta with mural thrombus.

initiated. The echocardiography did not show valvular vegetations. Bronchoaspiration was performed and smear microscopy, cytomegalovirus (CMV) and *Pneumocystis jirovecii* were positive. Antitubercular therapy (isoniazid, rifampin, pyrazinamide, and ethambutol), cotrimoxazole and ganciclovir was initiated. The patient became afebrile. By direct bronchoaspirate PCR techniques, the mycobacterium was identified as *Mycobacterium genavense* and treatment with clarithromycin, rifampicin and moxifloxacin was modified. Subsequently, blood cultures taken at admission detected growth of AFB, which were identified as Mycobacterium genavense and *Mycobacterium tuberculosis* complex. The bronchoaspirate culture showed growth after 15 days of incubation and was identified as *Mycobacterium genavense*. This confirmed the initial identification made in a direct sample. It was necessary to associate a treatment with fluconazole due to the presence of candidiasis of mucous membranes.

The treatment against CMV with ganciclovir was completed for three weeks. He was transferred to the Angiology and Vascular Surgery Service of the Virgen de la Victoria University Hospital for a mycotic aneurysm intervention. During the preoperative study, the patient again had a febrile ascent to 39 ºC, Samples were taken for serial blood cultures that were negative.

The aneurysm was resected with a 16 mm calibre, 110 mm long aorto-aortic corpse homograft implant and washed with rifampicin. The pathological study showed vascular wall and perivascular tissue with extensive granulomatous inflammation, abundant histiocytes, giant cells and foci of abscessification. The histochemical study for the detection of mycobacteria (Fite-Faraco) was positive.

In March, four days after the operation, the patient suffered extensive parenchymal cerebral hemorrhagewith a subarachnoid component and died. We suspectthe cause was rupture of another infected aneurysm. The patient's necropsy was not allowed. After 12 days of incubation, the biopsy of the fungal aneurysm showed growth of AFB, which after processing by molecular techniques were identified as *M. tuberculosis* complex. It was studied to determine its sensitivity profile and found resistance to isoniazid, a mutation in the katG gene, which was confirmed in the phenotypic antibiogram.

DISCUSSION

Sarcoidosis is a systemic disease of unknown cause that is diagnosed on the basis of compatible clinical and radiologic findings, due to the presence of non-caseifying epithelioid cell granulomas and the exclusion of other causes of granulomatous disease [1, 11]. Sarcoidosis may affect any organ, but most commonly involves the lung. Extrapulmonary organ involvement occurs in up to 50 % of patients, but only 5 to 9% of patients have extrapulmonary disease without pulmonary involvement [12].

Our patient had fever, weight loss, hypertransaminasemia with liver granulomas, splenomegaly and granulomatous infiltration of the bone marrow, which was ruled out as infectious at the time of diagnosis.

Nonspecific constitutional symptoms such as fever, malaise, and weight loss may occur in about one-third of patients with sarcoidosis [13]. Most patients with hepatic sarcoidosis are asymptomatic. Altered liver function tests appear in 35 %, with alkaline phosphatase elevation being the most common. Liver involvement is underestimated and liver granulomas are found in 50–80 % of patients who have undergone necropsy. Splenic involvement, usually asymptomatic, may result in fever and discomfort [3, 14]. Sarcoidosis is one of the main causes of granulomas in the bone marrow, and it rarely appears as an isolated extrapulmonary disease (it has been described as a cause of fever of unknown origin) [15].

Tuberculosis is closely related to sarcoidosis. Both are chronic multi-systemic granulomatous diseases with similar manifestations. The role of mycobacteria in the pathogenesis of tuberculosis has also been evaluated, so sarcoidosis would be an exaggerated immune response to partially degraded antigenic structures present in mycobacteria and propionibacteria [2, 4]. On the other hand, there is a possibility of tuberculosis in patients diagnosed with sarcoidosis. The risk of developing tuberculosis is currently exceptional and is mainly associated with patients taking glucocorticoids [4, 7, 16]. The involvement of other opportunistic mycobacteria is also exceptional [17].

Mycobacterium genavense is a fastidious microorganism that requires special conditions for its growth, such as acidification of the culture medium [18, 19]. It is a ubiquitous environmental microorganism that has been found in water and can also be isolated in birds and pets [20].

M. genavense predominantly has been reported among patients with advanced HIV infection. In non-HIV immunosuppressed patients the main cause is in transplant recipients, the main cause is in transplant recipients, with sarcoidosis being the second most commonly described cause. In a recent systematic review of Mahmood et al, only 44 cases of infection with *M. genavense* appear in non-HIV patients, presenting sarcoidosis in 6 of them, generally related to high doses of corticosteroids associated or not with immunosuppressants (14%) [21]. It has been postulated that the presence of *Mycobacterium genavense* was the cause of granulomatous disease, being an alternative to the diagnosis of sarcoidosis and not a concurrent disease due to immunosuppression [17]. There are no described cases of *M. genavense* in relation to anti-TNF therapy.

Its clinical presentation is usually related to bone marrow and gastrointestinal involvement with fever, abdominal pain and the presence of mesenteric lymphadenitis and splenomegaly [17, 21], which could be confused with the underlying disease. In HIV patients,

its appearance is closely related to a low CD4 lymphocyte count, but in non-HIV patients, although associated with a deficit in cellular immunity, this relationship is not clear [21], as in our patient.

Infected aneurysms, also known as mycotic aneurysms, are the damage to the wall of the arteries caused by infection that causes vascular dilation of saccular appearance. Infected aneurysms can be classified according to the pre-existing arterial status and the sources of infection [8]. An infected aneurysm may appear in a previously healthy or arteriosclerotic artery, in an arteriosclerotic aneurysm, or in an arterial prosthesis. The source of infection may be by (a) hematogenous spread of infectious microemboli inside the vasa vasorum from vegetations of endocarditis or other causes of bacteremia; (b) infection of a pre-existing intimal defect by circulating infectious agent; (c) direct extension of an adjacent site (e.g. infected valve in the endocarditis, or paravertebral abscess); and (d) direct inoculation of the vessel wall at the time of vascular trauma [22, 23]. Infected aneurysms related to endocarditis often have multiple locations. Infected aneurysms over atherosclerotic aneurysms are most commonly found in the abdominal aorta.

Tuberculous aneurysms are rare, particularly aneurysms of the aorta and great vessels [9]. They are not the only form of vascular involvement, as aortitis without aneurysm formation has also been described. Tuberculous aneurysms have the same pathogenesis as other microorganisms but are most often associated with a direct spread into an adjacent tuberculous focus, demonstrated in up to 75% of cases [24]. In cases of tuberculous aneurysm, the diagnosis of tuberculosis coincides with that of aneurysm in 63%. It appears as disseminated tuberculosis in up to 46%. The usual clinical presentation may be pain (chest, abdominal or lumbar pain), such as a pulsating mass, or it may be a radiological finding. Less frequently, it may occur with hemorrhagic complications with shock, which can be externalized in various ways (gastrointestinal, pulmonary, pleural, pericardial, peritoneal or retroperitoneal). The treatment must be medical and surgical, but still has a mortality rate of 50% of published cases [9].

In our patient there were several special circumstances such as (a) refractoriness of sarcoidosis requiring high doses of prednisone with poor response to immunosuppressants; (b) polymicrobial infectious complication including disseminated infection by *M. tuberculosis* and *M. genevense*; and (c) development of tuberculous aneurysm, that could be aggravated by the septic process derived from cholecystitis with extension of the infectious focus to the aorta.

Sarcoidosis is a diagnosis by exclusion and a possible infectious disease was evaluated from the outset. The initial study ruled out infectious causes (specific stains, cultures and serologies), as elevated levels of the angiotensin converting enzyme and non caseifying granulomas were found in liver and bone marrow biopsies. We reviewed the initial biopsies without the presence of AFB and proceeded to perform a PCR study for *M. genavense* and *M. tuberculosis* complex on the initial paraffinized samples that were negative. Even if an aneurysm is present at diagnosis, its growth was only detected in recent months after diagnosis of tuberculous infection, and its location in the abdominal aorta, along with other radiological signs of arteriosclerosis (atheromas in the abdominal aorta with calcification, which was evidenced during the surgical procedure) suggested that it was an infected atherosclerotic aneurysm. At admission, in October 2017, although bone marrow pathology and microbiology samples were repeated, it was not considered to repeat the studies for the diagnosis of tuberculous infection. It is only advisable to repeat screening if changes in clinical symptoms occur or after possible exposure to *M. Tuberculosis* [25]. The autopsy was not allowed but we suspect that the rupture of another cerebral mycotic aneurysm was the cause of the cerebral hemorrhage.

CONCLUSION

Opportunistic infections should be considered in patients with sarcoidosis under immunosuppressive treatment. Tuberculosis is a rare cause of infected aneurysms and may appear during anti-TNF treatment. In case of antiTNF treatment with negative study for tuberculous infection, the study should be repeated periodically.

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Josefa Andrea Aguilar-García – Acquisition of data, Drafting the article, Final approval of the version to be published
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Guarantor of Submission
The corresponding author is the guarantor of submission.

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Consent Statement
Written informed consent was obtained from the patient for publication of this case report.

Conflict of Interest
Authors declare no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.

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