SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2022; 39 (4); e2022041 DOI: 10.36141/svdld.v39i4.11350

A case of hepatic and bone marrow sarcoidosis with progressive renal failure: diagnostic and therapeutic challenges

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Abstract. Sarcoidosis is a systemic granulomatous disease, sometimes characterized by an extrapulmonary localization in 30 – 50% of cases. We describe a 60-year-old Italian man with an unexplained history of fatigue, ascitis and progressive renal function impairment. Diagnosis of hepatic and bone marrow sarcoidosis was established by histology, and fast improvement of renal function was obtained after starting corticosteroid therapy. Atypical presentation and simultaneous involvement of liver, bone marrow and kidneys make diagnosis of extrapulmonary sarcoidosis still a diagnostic challenge. Delayed diagnosis could lead to serious organ damage like a progressive severe kidney failure.

Key words: sarcoidosis; extra-pulmonary; granulomatous diseases

Introduction

Sarcoidosis is a rare systemic disease characterized by a chronic granulomatous inflammation, and its aetiology remains yet to be discovered (1). The disease affects mostly women and young adults between 20 and 40 years of age, being predominantly observed in African-Americans and in people from Scandinavian countries (2). Every body organ could be affected by sarcoidosis, but lungs and mediastinal lymph nodes are the more common involved sites. The reported prevalence of extrapulmonary localizations is around 30 – 50% (1). Environmental exposures to musty odours, insecticides, or to metal-processing industries, predisposing human leukocytes antigen (HLA), and other genetic factors all are contributors (1).

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When considering the variety of stages at which sarcoidosis is diagnosed, and the multi-organ involvement in nearly 50% of patients (3), it is not surprising an atypical presentation that could delay a correct diagnosis. We describe an unusual case of sarcoidosis with acute renal failure, biopsy-proven liver and bone marrow involvement, in the absence of typical lung lesions.

Case report

An 60-old years man was admitted to Medicine Department on October 2017 because of dyspnoea, fatigue and abdominal tenderness.

The patient had always been healthy, but the family medical history was relevant since his father died because of hepatic failure of unknown origin.

Laboratory findings showed normal leucocytes (5310/mmc), haemoglobin (12.7 g/dL). Liver enzymes showed normal alanine transaminase (20 U/L), aspartate transaminase (28 U/L), and total bilirubin (0.8 mg/dL), but altered gamma-glutamil-transpeptidase (GGT 143 U/L; normal range 1-55) and alkaline phosphatase (ALP 209 U/L; normal range 30-120). There was a mild hypocalcemia (8.2 mg/dL) and a

markedly impaired renal function with creatinine 3.18 mg/dL, and estimated glomerular filtration rate (eGFR) of 20 mL/minute per 1.73 m^2. This finding was confirmed by a renal scintigraphy that estimated a creatinine clearance of 32 mL/minute.

Left pleural and large abdominal effusion were detected by chest-X-rays and abdominal echography respectively. A computed tomography of the abdomen showed an enlarged parenchimal liver with irregular borders, and splenomegaly, suggestive of hepatic cirrhosis.

A paracentesis was performed and chemical analysis of abdominal fluid showed 370 leucocytes/mmc, with predominance of lymphocytes. Culture from abdominal fluid was negative, and cytological analysis did not detect malignant cells.

Serology for hepatotropic viruses (HCV, HBV, CMV, EBV), human immunodeficiency virus (HIV), interferon-gamma release assay (IGRA) for latent tuberculosis infection, and biochemical markers for auto-immune diseases (anti-nuclear-antibodies; anti-DNA-antibodies; anti-liver and kidneys antibodies; anti-myeloperoxidase and antiproteinase 3 antibody, p-antineutrophil cytoplasmic antibody, ANCA and c-ANCA, and C3 and C4 fraction of complement) were all negative. Other blood investigations included iron, ferritin and serum immunoglobulin G, A and M, that were unremarkable.

The patient was treated with diuretic drugs obtaining a significant reduction of abdominal effusion, and he was discharged with diagnosis of hepatic cirrhosis of unknown origin on stage B9 according to Child-Pugh classification.

At the end of December 2017 the patient came back to the hospital because of fatigue, worsening of renal function and swollen legs. Haematological studies showed a low serum albumin (2.8 g/dL), and high values of serum urea (252 mg/dL), uric acid (9.4 mg/dL), and Beta-2-microglobulin (51.83 mg/L).

Chest CT-scan showed emphysematous lesions on both the upper lungs, and some enlarged mediastinal lymph nodes. The whole-body Positron Emission Tomography (PET) did not reveal pathological increased 18-F-fluoro-deoxyglucose (FDG) uptake.

With the suspicion of an haematological disease, a bone marrow sample for cytology was collected, but it did not show malignant cells.

We also performed a bone marrow, a liver biopsy and the patient was discharged, before we were noticed of histological results, on January 2018, with the advice to continue at home diuretic therapy and allopurinole treatment for hyperuricemia.

Ten days later the patient presented at our Outpatient Service with olyguria and legs oedema. Laboratory tests revealed a severe renal impairment with creatinine 6.91 mg/dL, and eGFR <15 mL/minute per 1.73 m2. There were also hyperkalemia (K 6.1 mmol/L), hypocalcemia (6.1mg/dL), metabolic acidosis (pH 7.27; bicarbonate 13.3 mmol/L; base excess -12.3 mmol/L), while 24-hours urine collection showed proteinuria (2.58 g/dL), hypocalciuria and hypernatriuria. The patient received one course of hemodialysis and aggressive diuretic treatment. Since histological pattern of both liver and bone marrow showed non-caseating granulomatous lesions (Figure 1 and 2), we suspected an unusual extra-pulmonary presentation of sarcoidosis. Three

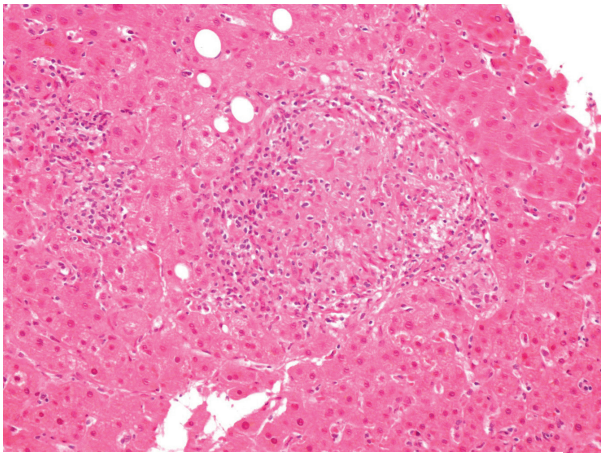

Figure 1.

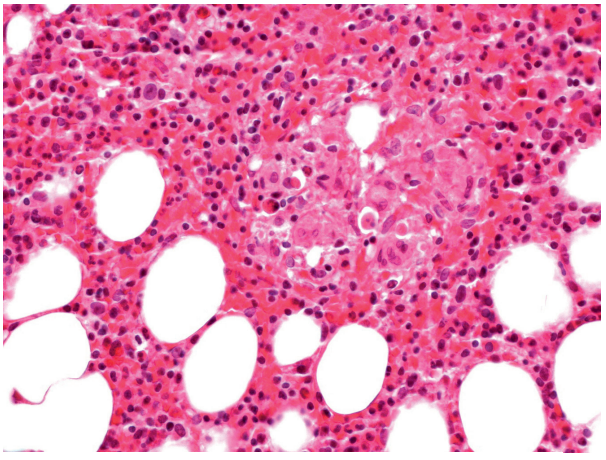

Figure 2.

weeks later serum laboratory tests showed hypercalcemia (11 mg/dL), while parathormon (PTH) level was low (12 ng/L) and Angiotensin Converting Enzyme (ACE) serum level was high (82 U/L; normal range of values <52 U/L). There were also a low level of vitamin D (12.3 nmol/L; normal range of values 75 – 250 nmol/L), hyperphosphoremia (7.6 mg/dL; normal range of values 2.5 – 4.5 mg/dL), hypoalbuminemia (2.25 g/dL), and higher levels of GGT (172 U/L) and ALP (267 U/L). We started steroid treatment with metyl-predisolone i.v, which lead to a fast improvement of renal function and disappearance of legs oedema. The patient was discharged on steroid maintenance therapy. After 18 months since the diagnosis, treatment with mycophenolate mophetil was added to corticosteroids, and at two-year follow-up the patient was in good clinical conditions, with a renal impairment on stage 3 according to the chronic kidney disease score (4) (Fig. 3).

Discussion

Sarcoidosis often mimics other diseases and diagnosis rely mainly on histopathological findings. In more than 90% of cases sarcoidosis involves the respiratory tract (5), but our patient presented with an unexplained abdominal ascitis without the typical biochemical markers and risk factors for hepatic cirrhosis.

Serology for common hepatotropic viruses and markers of auto-immune diseases were negative, and there was not a clear history of past alcohol consumption. For this reason liver biopsy was performed and granulomatous lesions suggestive of hepatic sarcoidosis were described. This diagnosis was at first unexpected since there were not respiratory symptoms and neither chest-X-rays nor thoracic CT scan did not evidence the typical hallmark of sarcoidosis. PET-CT is now recognized as an important diagnostic tool for an early diagnosis of pulmonary sarcoidosis with a reported sensitivity of 97% (6 – 8). However in our case PET-CT failed to detect suspected features of an inflammatory lung condition such as sarcoidosis.

Hepatic disease is one of the most represented extra-pulmonary sites of sarcoidosis, and it is described in about 20 to 30% of cases (9). In biopsy and autopsy studies liver involvement is even higher, reaching up to 80% of cases (10). In hepatic sarcoidosis mild liver test function abnormalities are common, whereas cirrhosis with ascitis and portal hypertension are rare (11). Our case depicts the typical multisystem and protean manifestation of sarcoidosis since granulomatous lesions were detected also in the bone marrow whereas PET-CT failed to detect significant lung abnormalities.

Bone marrow (BM) involvement is very uncommon in sarcoidosis. In a cohort study following 640 patients with sarcoidosis over 40 years, and in the ACCESS (A Case Control Etiologic Study of Sarcoidosis) study enrolling 736 patients, the prevalence of BM localization was 0.3 and 3.9% respectively (3, 12). The frequency of BM involvement may vary depending on age, gender and ethnicity.

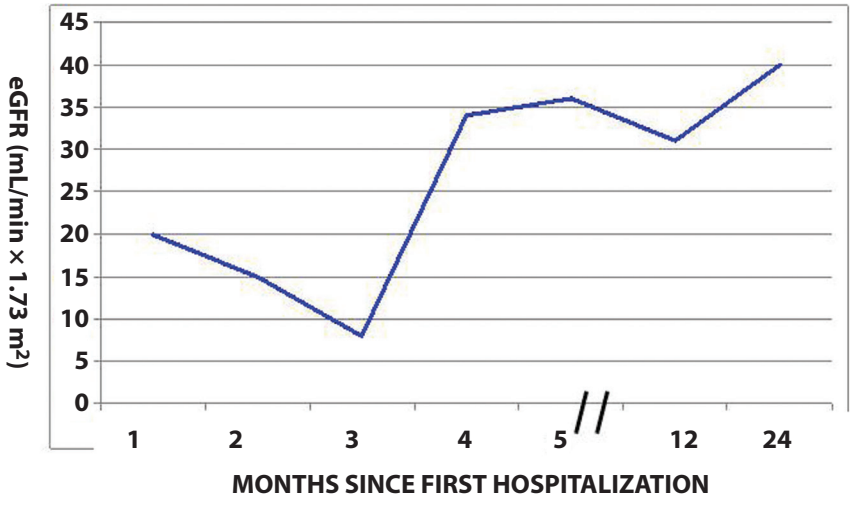

Figure 3.

Unexplained cytopenia, although nonspecific, may be a solitary finding of BM sarcoidosis, and clinicians should keep an high index of suspicion (13). Another extra-pulmonary site of sarcoidosis is the kidney, and autoptic renal granulomatous lesions were described in up to 13% of patients with sarcoidosis (14). Renal manifestations include abnormal calcium metabolism, nephrocalcinosis, and nephrolithiasis. Acute renal failure due to tubulo-interstitial nephritis commonly ranges from 0.7 to 4.3% of patients in published cases series (15).

It is worth of mentioning a paper of Bear RA, et al. who 40 years ago described six patients with renal sarcoidosis presenting with acute renal failure. Serum creatinine at the time of diagnosis ranged from 3 to 15.6 mg/dL, and four patients had metabolic acidosis. It is surprising that in this case series, as in our case, four patients had a normal chest-X-rays and detection of granulomatous lesions on liver biopsy. All six patients underwent kidney biopsy that revealed interstitial nephritis as a common pathological change. Long-term supervision in these patients is required, particularly following tapering or discontinuation of steroid treatment because of the risk of relapse of renal sarcoidosis (16). As in our patient, some degree of persistent renal failure is frequent in patients with renal sarcoidosis. This is well predicted from both histological fibrotic renal score and clinical response obtained at one month after the start of treatment (15). To avoid side effects of long-term steroid use, some corticosteroid-sparing agents such as methotrexate, azathioprine and mycophenolate mofetil could be useful in selected patients, but they need to be tested in prospective trials. In a double-blind randomized controlled trial patients receiving methotrexate needed a significantly lower dose of corticosteroids over a 12 months of follow-up (17). However, because this drug has a delayed effect, it has to be use with corticosteroids when a rapid effect is required for sarcoidosis that aggressively affects vital organs (1).

Conclusions

Extrapulmonary sarcoidosis still poses a serious diagnostic challenge for clinicians. This condition could be characterized by simultaneous multi-organ involvement, such as liver and bone marrow. Renal sarcoidosis should be also readily suspected in a patient with unexplained renal failure. Response to steroid treatment is generally favourable, but incomplete renal function recovery is frequently observed despite long-term steroid and other immunosuppressive therapies.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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