SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2017; 34; 272-275 DOI: 10.36141/svdld.v34i3.6593

Risk of death in patients with progressive pulmonary sarcoidosis

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Abbreviations:
high resolution computed tomography(HRCT), arterial blood gas (ABG) analysis,lung function tests (LFT), interstitial lung diseases (ILD), bronchoalveolar lavage (BAL), transbronchial needle aspiration (TBNA), diffusion lung capacity for CO (DLCO).

Dear Editor,

few months ago the Mayo Clinic collegues published an interesting document about the causes of death in patients with sarcoidosis. These authors reported 44 consecutive patients who underwent an autopsy (35 patients) or died in their hospital in a 20 years period of observation. This study underlined that in sarcoidosis patients the cause of death is unrelated to the granulomatous lung disease in the majority of cases; in one third of them the diagnosis of sarcoidosis was performed after death (1). Sarcoidosis-related causes of death included cardiac localization, opportunistic infections and progressive pulmonary sarcoidosis. Sarcoidosis is a multi-system, granulomatous disorder of unknown etiology. In 80% of the cases, the acute onset is associated with pulmonary manifestations, and in the majority of patients clears up spontaneously with no sequelae. The chronic form is characterized by the development of multiple pulmonary granulomas and progressive fibrosis. Although most patients enter remission and have good long-term outcomes, up to 20% develop fibrotic lung disease, whereby granulomatous inflammation evolves to irreversibile pulmonary fibrosis. The development of pulmonary fibrosis is associated with significant morbidity and can be fatal. Complications of fibrotic pulmonary sarcoidosis include pulmonary hypertension (consequent to capillary obliteration) and chronic aspergillus disease with hemoptysis, a common and potentially life-threatening manifestation (2-3). Lung transplantation should be considered for patients with severe end-stage fibrotic pulmonary sarcoidosis (4). Thus, the disease is associated with a variable prognosis and few and conflicting data is available about sarcoidosis exacerbation causing death in patients with sarcoidosis (5-11).

Here we report the clinical case of a young woman who developed a severe and fatal acute respiratory failure as clinical onset of pulmonary sarcoidosis. The complex management of this patient during her hospitalization was discussed ad compared with the literature data in order to contribute to the description of rare sarcoidosis-related causes of death secondary to pulmonary sarcoidosis.

A 44-years-old North African never smoking woman, was admitted to the Respiratory Medicine Section of our Hospital for productive cough, hyperpyrexia, fatigue, acute onset dyspnea with exertion and seven kilograms weight loss over the last eight weeks. Patient's past clinical history revealed pulmonary tuberculosis at the age of 20 years old. At the admission, she had dyspnoea for minor activities

Received: 7 July 2017
Accepted after revision: 4 September 2017
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(modified Medical Research Council - mMRC=3), increased respiratory rate (22 breaths/min) and, fine bibasal crackles. Low arterial oxygen partial pressure in room air (58 mmHg) was evident at blood gas analysis and the hypossia (Pa02 65 mmHg) was corrected by oxygen support(4L/min). Chest x-ray was performed revealing widespread thickening of peribroncovasal interstitium with multiple, shaded parenchymal consolidations tending to a wide confluence. High resolution computed tomography of the chest (HRCT) showed diffuse bilateral parenchymal consolidations, with widespread bilateral bronchiectasis, bronchioloectasis, periscissural nodules and enlarged confluent mediastinal and hilar lymphoadenopathies (fig. 1). The echography of the abdomen was normal. The Positron Emission Tomography (PET) reveled bilateral multiple areas of hyper-metabolism in the mediastinal lymphonodes and bilaterally in lung parenchymes in correspondence with the underlined lung consolidations. No other areas of ipercapation were found. The cardiological evaluation was negative and transthoracic echocardiography reveled left normal size and wall thickness ventricle without alteration on kinetic segmental. Ejection fraction was preserved (EF 60%). No alteration on hearts valves and right section were detected. Anti-nuclear antibodies, anti-extractable nuclear antigen, cANCA, pANCA autoantibodies, rheumatoid factor, serology for HIV, HCV, HBV, were all normal. To exclude any underlying infection, we performed serology for Chlamydia pneumoniae, Legionella pneumophila, Mycoplasma pneumoniae, nasopharyngeal swab for influenza viruses, urino and coproculture examinations that were all negative. The routine inflammatory markers such as c-reactive protein, erythrosedimentation velocity, hemocromo with leukocyte formula, L-lactate dehydrogenase were not elevated. Also serum levels of beta 2 microglobulin and alpha 1 anti-trypsine were normal.

Therefore, bronchoscopy with bronchoalveolar lavage was performed after the informed consent of the patient. Sub-samples were cultured for

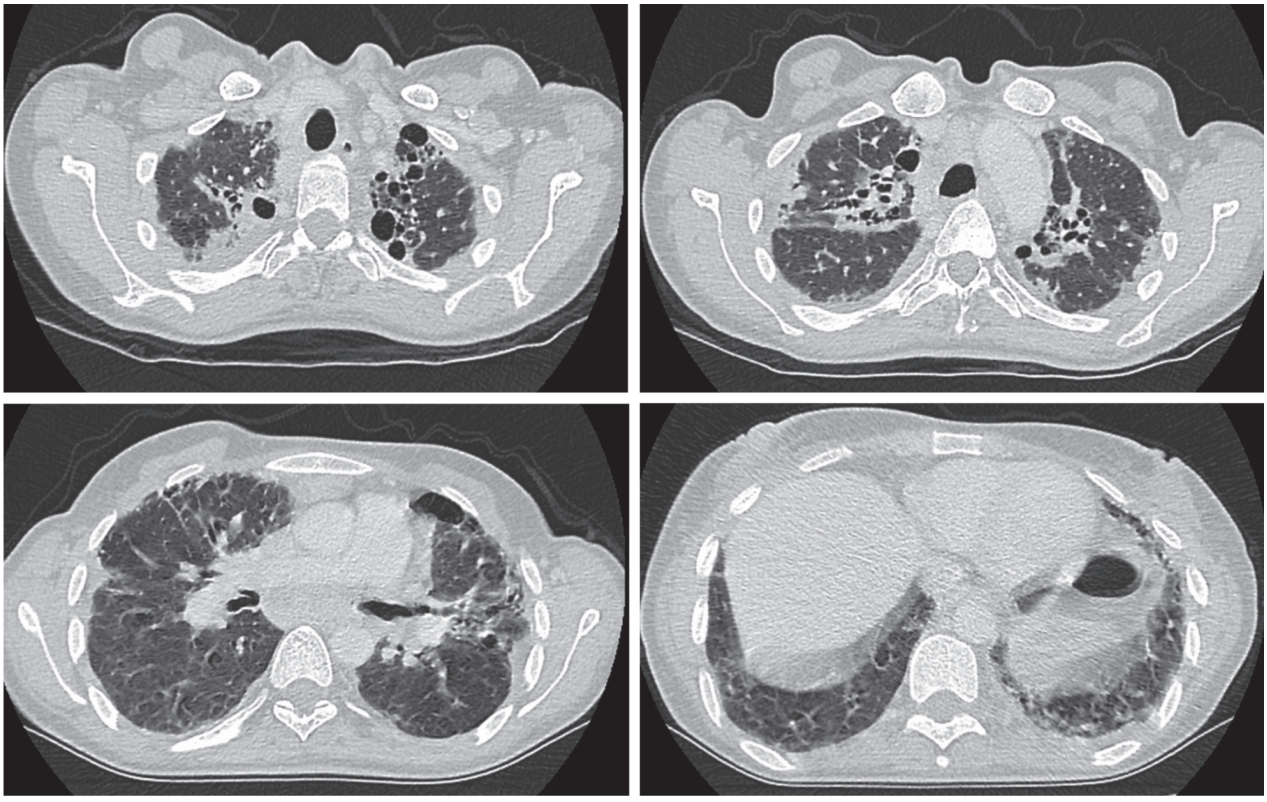

Fig. 1. a-d) The pulmonary aspects of fibrocystic changes (cysts, bullae, honeycombing) most evident in the upper lobes but diffusely present in the lungs with diffuse areas of traction and consolidation

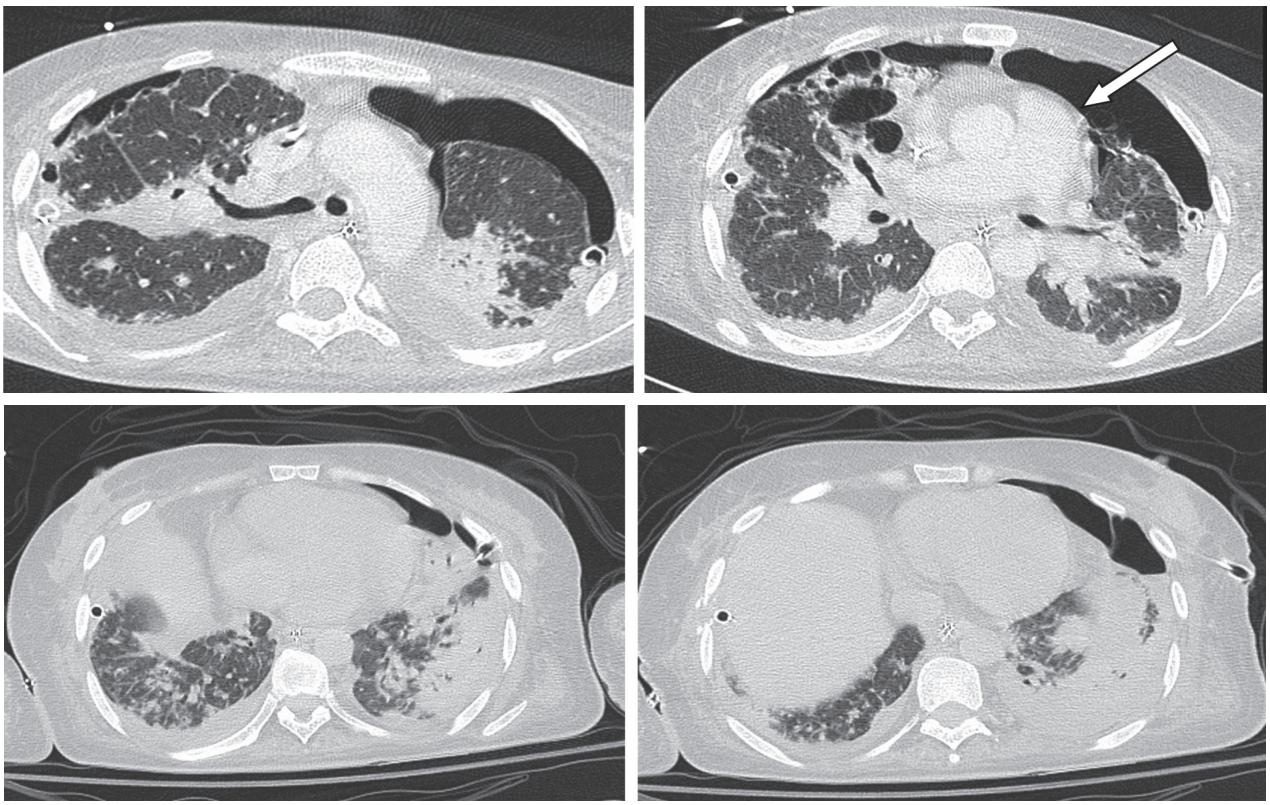

Fig. 2. a) Diffuse fibrocystic changes (cysts, bullae) are associated with confluent opacities corresponding with airspace consolidation. b) Bilateral pneumothorax (larger on the left lung) caused by the rupture of lung cysts (white arrow). c, d) Bilateral diffuse confluent consolidation areas

microbes, fungi, Mycobacteria (typical and atypical TB) and viruses to excluded infections. Differential cells count was done demonstrating lymphocytosis (58%) with increased CD4/CD8 ratio (11.4). Subsequently the patient underwent mediastinoscopy with mediastinal lymphonode biopsy and histological sections showed non-caseating, non-necrotizing granulomas in fibro-sclerotic evolution indicative for sarcoidosis. Immunohistochemistry for CD68 was positive, while CD1a and protein S 100 were negative. Mycobacteria research was negative in all cultures (tissue as well as in BAL and sputum). No signs or symptoms of other organ involvement were found, particularly no dermatologial lesions, heart, eyes, spleen or liver involvement were documented. The patient, treated with high dose of steroids (starting with intravenous administration of 80 mg methylprednisolone and slowly tapering every 5 days), empirics antiobiotics therapy and high flow oxigen therapy experienced a progressive worsening. Bilateral pneumothorax caused by the rupture of honeycomb cysts was treated by a bilateral chest tube, with a partial re-expation of lungs. Chest HRTC showed evolution of prior documented radiological findings, in particularly we observed diffuse fibrocystic changes (cysts, bullae, honeycombing) associated with confluent opacities corresponding with airspace consolidations. Subsequently she developed a refractory respiratory failure that needed orotracheal intubation and therefore a tracheostomy was performed. Despite that, she died in intensive care unit. Patient's family denied the autopsy consent.

In this case report we described a North African female with a severe sarcoidosis onset and acute respiratory failure determining death in few days. The diagnostic algorithm was complicated as the patient had a previous history of TB, a severe and rapid deterioration. She may have a severe infection, a TB relapse or she may be affected by an oncological disease as lymphoproliferative disorder determining weight

loss and enlarged lymphonodes with bilateral severe consolidations. We excluded TB reactivation as well as the presence of lymphoproliferative malignant disease. Thus, we treated the patient with high dose of steroids but the deterioration was incredibly rapid as never observed before in sarcoidosis.

In the majority of patients with sarcoidosis the cause of death is unrelated to the interstitial granulomatous disorder (1-4). Cardiac involvement is the most common cause of sarcoidosis-related (6). Mortality rates are low among patients with sarcoidosis, however is higher in patients with pulmonary fibrosis (stage four) (5). In a recent retrospective study performed in France, a 10-year mortality rate of 16% was reported in patients with fibrotic sarcoidosis and it was significantly higher than the rate established for the general population of a similar age (6). The extent and stability of fibrosis and the development of secondary complications are likely important determinants of survival in fibrotic sarcoidosis. Once patients are sick enough to be listed for lung transplant, mortality rates are high and similar to those for patients listed for IPF (7). There are few published data on the natural history of fibrotic sarcoidosis, including rates of exacerbations. Exacerbations of sarcoidosis are due to an acute-on-chronic increase in disease activity or to the recurrence of disease in patients previously in remission or with stable end-stage disease. In a recent review, it was noted that exacerbations of sarcoidosis are not uncommon; however, for long-standing fibrotic disease in particular, exacerbation rates remain largely undefined (8). Probably no data is available about increased risk of sarcoidosis exacerbations in those patients with fibrothorax secondary to TB or increate risk according to different race. Although two years ago an interesting paper reported that the age-adjusted mortality rate for African Americans affected by sarcoidosis was 12 times higher than for Caucasians (12). In conclusion acute pulmonary sarcoidosis exacerbations are rare and fatal events that require further studies in large population.

References

1. Hu X, Carmona EM, Yi ES, et al. Causes of death in patients with chronic sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2016 Oct 7; 33(3): 275-80.
2. Grutters JC, Van den Bosch JM. Corticosteroid treatment in sarcoidosis. Eur Respir J 2006; 28: 627-36.
3. Paramothayan S, Jones PW. Corticosteroid therapy in pulmonary sarcoidosis: a systematic review. JAMA 2002; 287: 1301-7.
4. Patterson KC, Strek ME. Pulmonary fibrosis in sarcoidosis. Clinical features and outcomes. Ann Am Thorac Soc 2013 Aug; 10(4): 362-70.
5. Nardi A, Brillet PY, Letoumelin P, Girard F, Brauner M, Uzunhan Y, Naccache JM, Valeyre D, Nunes H. Stage IV sarcoidosis: comparison of survival with the general population and causes of death. Eur Respir J 2011 Dec; 38(6): 1368-73.
6. Shorr AF, Davies DB, Nathan SD. Outcomes for patients with sarcoidosis awaiting lung transplantation. Chest 2002; 122: 233-8.
7. Panselinas E, Judson MA. Acute pulmonary exacerbations of sarcoidosis. Chest 2012; 142: 827-36.
8. Bub E. Heart failure, skin manifestations, enlarged hilar lymph nodes. Is it sarcoidosis? MMW Fortschr Med 2003 Oct 9; 145(41): 36-8.
9. Ginelliová A, Farkaš D, Farkašová Iannaccone S, et al. Sudden unexpected death due to severe pulmonary and cardiac sarcoidosis. Forensic Sci Med Pathol 2016 Sep; 12(3): 319-23.
10. Birnie D, Ha AC, Gula LJ, Chakrabarti S, Beanlands RS, Nery P. Cardiac Sarcoidosis. Clin Chest Med 2015 Dec; 36(4): 657-68.
11. Valeyre D, Bernaudin JF, Jeny F, et al. Pulmonary Sarcoidosis. Clin Chest Med 2015 Dec; 36(4): 631-41.
12. Mirsaeidi M, Machado RF, Schraufnagel D, Sweiss NJ, Baughman RP. Racial difference in sarcoidosis mortality in the United States. Chest 2015 Feb; 147(2): 438-49.