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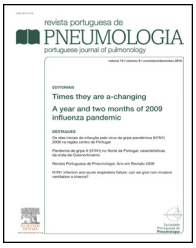

LETTER TO THE EDITOR

Pulmonary sarcoidosis in the context of a telaprevir-based triple therapy for hepatitis C

Dear Editor,

We would like to present the first case of a patient coinfected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV), diagnosed with pulmonary sarcoidosis in the context of a triple therapy with pegylated-interferon, ribavirin and telaprevir.

A 50-year-old man, diagnosed with HIV in 1993, stage A2, treated with antiretroviral therapy: tenofovir, emtricitabine and raltegravir. In 2004 was diagnosed with chronic hepatitis C, genotype 1a with F2 degree of liver fibrosis, and treated during 24 weeks with pegylated-interferon and ribavirin, presenting partial response.

In 2013, the patient was treated with telaprevir-based triple therapy according to the regimen: telaprevir 2250 mg/day for the first 12 weeks; pegylated-interferon 2a 180 mcg/week and ribavarin 1200/day for a total of 48-weeks. At the time of starting treatment, the patient had a F3 degree of fibrosis determined by Fibroscan® (9.9 kPa), a HCV VL of 5,810,000 IU/ml, CT IL28B polymorphism, a CD4 count of 544 cells/mm^3 (32%), HIV VL <20 copies/ml, ALT of 75 IU/L and AST of 62 IU/L, the rest of the analytical was normal. During the following weeks, he did not show relevant adverse events.

At week 43, the patient started having dyspnea and chest pain without fever, symptoms that worsened in the following weeks. The chest radiography showed bilateral diffuse interstitial lung disease, ground-glass opacities and mediastinal lymphadenopathy. Also, a lung scan was performed and no findings of acute pulmonary embolism were observed. The gas analysis showed: pCO_2: 31.2 mmHg, pO_2: 68.2 mmHg, O_2 saturation: 95.9% and pH: 7.47, and the biochemistry showed an angiotensin-converting enzyme value greater than 100.

Two weeks later, the patient presented clinical improvement (after drug treatment with antibiotics and bronchodilators) but with persistent injury in chest radiography, so a thoracic CT was performed, showing bilateral and diffuse ground-glass opacities, multiple centrilobular micronodules (Fig. 1) and mediastinal lymphadenopathy. Bronchoscopy was normal, and transbronchial biopsy showed the presence of non-necrotizing granulomas. Ziehl Neelsen, and Groccott staining were negative, as PCR and mycobacteria culture. After completing HCV treatment, the clinical course of the patient was favorable, showing the following thoracic CT gradual improvement in lung and lymph node involvement, and finally, a year later, the resolution of the disease (Fig. 2).

HCV VL values became undetectable at week 8 and remained undetectable 24 weeks after completion of HCV therapy, reaching sustained viral response (SVR). In addition, the liver function values normalized after 28 weeks of treatment (ALT 31 IU/L, AST: 35 IU/L), and remained within the normal range 24 weeks after completion of antiviral therapy.

Sarcoidosis is a granulomatous disease of unknown origin and multisystemic character, in which lung, liver, lymphoid system and skin are the most affected organs.[1] Although its etiology is unknown, probably an exaggerated response to various antigens as mycobacterias, environmental agents or autoantigens, produces an abnormal activation of CD4+ T cells, activating peripheral blood monocytes, and causing the formation of granulomas.[2]

Diagnosis of sarcoidosis is often a matter of exclusion, as in our case; there is no specific test for the condition. All the findings of our case raised the possibility of a differential diagnosis of granulomatous inflammation caused by infection or sarcoidosis. Findings on cultures for viral, fungal and mycobacterial organisms were negative. Radiological findings and clinical manifestations were consistent with an atypical pulmonary sarcoidosis. Similar clinical findings were reported in other cases of sarcoidosis associated with interferon.[1,3,4]

Interferon is a cytokine with immunomodulatory activity on T lymphocytes, which is successfully used in the treatment of hepatitis C. Several adverse effects have been described for interferon therapies, like hematologic symptoms, flu-like symptoms, and cutaneous events,[5] and although the exact mechanism of action is unknown, interferon is also associated with the occurrence of certain immunological diseases like hemolytic anemia, hypothyroidism, and sarcoidosis.[3,5] The majority of patients achieved spontaneous resolution of sarcoidosis after stopping treatment with interferon, and there is also evidence of remission in spite of continuing treatment, demonstrating that interferon may play a role in its appearance, but not

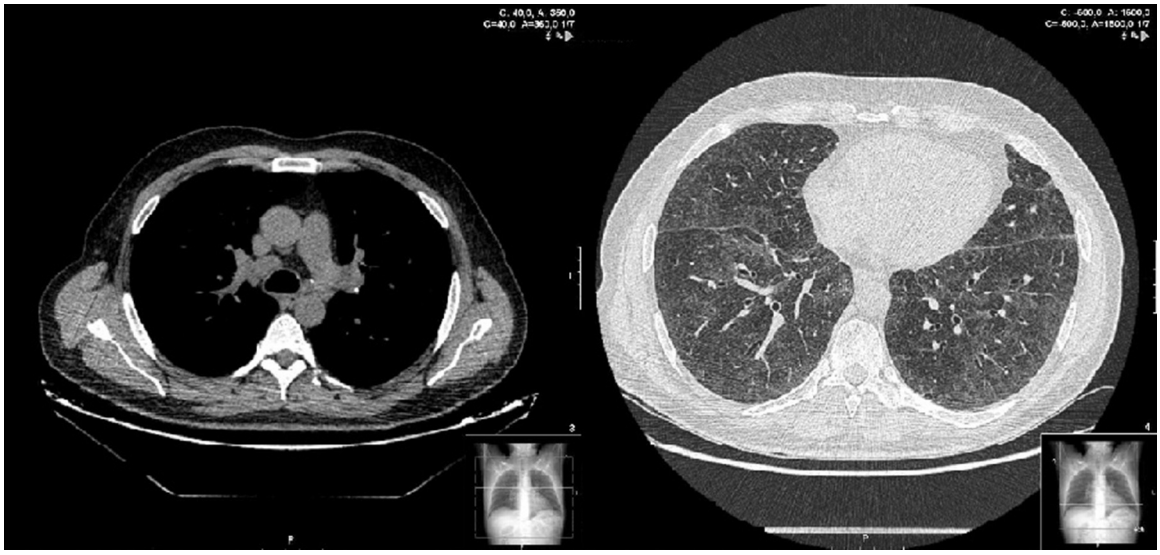

Figure 1 Sarcoidosis in 50 years-old man, coinfected with HIV and HCV, and treated with telaprevir-based triple therapy. Thin-section of thoracic CT shows bilateral and diffuse ground-glass opacities, and multiple centrilobular micronodules.

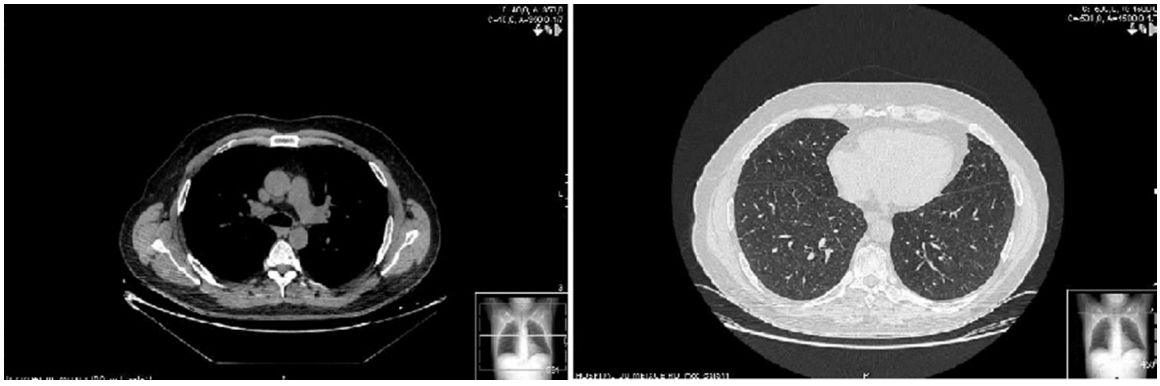

Figure 2 Sarcoidosis in 50 years-old man, coinfected with HIV and HCV, and treated with telaprevir-based triple therapy. Thin-section of thoracic CT shows sarcoidosis resolved a year after stopping HCV treatment. Small calcified micronodules are observed.

in the maintenance, so the decision to continue treatment should be assessed depending on the risk-benefit balance. In our case, the patient continued the treatment until completion, reaching SVR, and showing clinical and radiological improvement since the end of treatment.

The systemic manifestations of sarcoidosis are usually treated with oral steroids, but it often increases the hepatitis C viral load. In this case, it was not necessary to use corticosteroid treatment, and sarcoidosis was resolved after stopping HCV treatment, which may indicate the role of HCV treatment in his appearance.

Although there are several articles about the relationship between sarcoidosis and interferon, their relationship with ribavirin cannot be ruled, because it can activate the Th1 helper lymphocytes, or even with telaprevir, this occurred in another case of sarcoidosis in a patient treated with telaprevir, ribavirin and standard interferon 3 times per week.[4]

This case draws attention to this serious side effect that some patients may experience during the antiviral treatment, and it is essential that the diagnosis of sarcoidosis is considered in patients with compatible clinical findings.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Cardoso C, Freire R, Alves A, Oliveira A. Interferon-induced sarcoidosis. BMJ Case Rep. 2011:19.
2. Kataria YP, Holter JF. Immunology of sarcoidosis. Clin Chest Med. 1997;18:719–39.

3. Raanani P, Bassat Ben I. Immune-mediated complications during interferon therapy in hematological patients. Acta Hematol. 2002;107(3):133–44.
4. Trien R, Cooper CJ, Paez D, Colon E, Ajmal S, Salameh H. Interferon-alpha-induced sarcoidosis in a patient being treated for hepatitis C. Am J Case Rep. 2014;15:235–8.
5. Silva M, Poo J, Wagner F, Jackson M, Cutler D, Grace M, et al. A randomised trial to compare the pharmacokinetic, pharmacodynamic, and antiviral effects of peginterferon alfa-2b and peginterferon alfa-2a in patients with chronic hepatitis C (COMPARE). J Hepatol. 2006;45(2):204–13.

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Response to imatinib in patient with corticosteroid-unresponsive idiopatic hypereosinophilic syndrome

Dear Editor,

Hypereosinophilia (HE) is defined as peripheral blood eosinophils >1.5 eosinophils $\times 10^9$/L blood on 2 examinations and/or tissue HE defined by the following: (1) the percentage of eosinophils in the bone marrow section exceeds 20% of all nucleated cells and/or (2) the pathologist is of the opinion that tissue infiltration by eosinophils is extensive and/or (3) marked deposition of eosinophil granule proteins is found (in the absence or presence of major tissue infiltration by eosinophils). Hypereosinophilic syndrome (HES) is defined by the following: (1) criteria for peripheral blood hypereosiniphilia (HE) fulfilled and (2) organ damage and/or dysfunction attributable to tissue HE and (3) exclusion of other disorders or conditions as major reason for organ damage. HES subtypes have been defined; these include (1) idiopathic HES, (2) primary (neoplastic) HES, (3) secondary (reactive) HES.[1] We here report a case of idiopathic hypereosinophilic syndrome successfully treated with imatinib.

A forty-six-year-old male patient was admitted to our clinic with complaints of itching, cough, shortness of breath, and stomach pain. The symptoms had increased over the last six months. He had a history of chronic smoking (30 pack-years). There was no history of any drug use. Admission blood pressure: 110/80 mmHg; respiratory rate 20/min; pulse 95/min; saturation in room air was found to be 95%. Breath sounds were bilaterally decreased. Widely excoriated itchy lesions were present. There was tenderness in the epigastric region. Blood eosinophil rate was 55.4% (9880/mm^3). Parasite stool examination and serologic tests were negative. A mild obstructive pattern was present in the pulmonary function test. However, the patient did not benefit from treatment with high doses of inhaled corticosteroids/β2 agonists. Laboratory tests showed no significant alterations except increased vitamin B12: 1081 pg/ml (reference range: 111–663 pg/ml) and total IgE: 194 IU/ml (reference range: <100 IU/ml) autoimmunity work-up was negative. Troponin T and echocardiography were normal.

Centrilobular ground-glass nodules were found to be more prominent in the upper lobes of the lungs in thorax computed tomography (CT) (Fig. 1a). Abdominal CT and ultrasonography were found to be normal. Endoscopic biopsy for stomach pain was reported as eosinophilic gastritis. Eosinophilic infiltration was observed on transbronchial lung biopsy. Numerous eosinophilic granulocytes (40%) were observed in bone marrow biopsy without increased blast cells. A prominent mast cell population was not observed. There was no malignant infiltration. FIPLI-PDGFRα mutation, JAK-2 mutation and Philadelphia chromosome were also found to be negative.

In our case, differential diagnosis was performed for primary (hematopoietic neoplasms with HE) and secondary HES, (helminth infections, allergic reactions, atopic diseases, drug reactions (allergic or toxic), Hodgkin disease, B- or T-cell lymphoma/leukemia, Langerhans cell histiocytosis, indolent systemic mastocytosis, solid tumors/malignancy, allergic bronchopulmonary aspergillosis, chronic inflammatory disorders, autoimmune diseases and lymphoid variant of HES), organ-restricted conditions accompanied by HE (eosinophilic gastrointestinal disorders, eosinophilic pneumonia, dermatologic diseases, etc.) and specific syndromes accompanied by HE (Gleich syndrome, Churg-Strauss syndrome, eosinophilia myalgia syndrome, Hyper-IgE syndrome).[1–6] The patient was diagnosed with idiopatic HES after exclusion of all primary and secondary causes and exclusion of other conditions and syndromes. The patient was started on imatinib mesylate therapy with 400 mg/day because he did not respond to corticosteroids (CS) and hydroxyurea therapy. The treatment was reduced to a 100 mg in the third month of treatment due to normalization of eosinophil levels and disappearance of all complaints. The ground-glass nodules disappeared after 1 year of imatinib treatment (Fig. 1b).

CS have been used for decades in the treatment of HES, with the exception of PDGFR-α associated HES. A number of cytotoxic therapies have been used for the management of corticosteroid-refractory HES. Of these, hydroxyurea has been the most extensively studied. However, the utility of hydroxyurea monotherapy is limited in the treatment of HES. Imatinib mesylate is a tyrosine kinase inhibitor with activity against several receptor tyrosine kinases, including the fusion kinase FIP1L1/PDGFR-α, which is responsi-