Infectious cause of an interstitial lung disease

Cauză infecțioasă de boală interstițială pulmonară

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Abstract

We present a case of a previously healthy middle-age male patient, without personal history of other condition, who was admitted in our hospital presenting fever, weight loss, and signs and symptoms of acute respiratory distress. The chest computed tomography showed numerous cystic lesions, diffuse ground-glass opacities, honeycombing, and consolidation areas. An HIV infection was confirmed, and the diagnosis of Pneumocystis jirovecii pneumonia was made on induced sputum smear stain. After the initiation of oral treatment with trimethoprim-sulfamethoxazole, the clinical course was rapidly improved. It is important to consider that opportunistic infections such as Pneumocystis jirovecii pneumonia can occur not only in patients previously diagnosed with HIV-infection, but also in patients without a medical history of immunosuppressing disorders.

Keywords: ***HIV infection, Pneumocystis jirovecii, interstitial lung disease***

Rezumat

Prezentăm cazul unui pacient de sex masculin de vârstă medie, anterior sănătos, fără antecedente personale de alte boli, care a fost internat în spitalul nostru prezentând febră, scădere în greutate și semne și simptome de insuficiență respiratorie acută. Tomografia computerizată toracică a arătat numeroase leziuni chistice, opacități difuze tip sticlă mată, fagure de miere și zone de consolidare. O infecție cu HIV a fost confirmată, iar diagnosticul de pneumonie cu Pneumocystis jirovecii a fost făcută pe frotiul de spută indusă. După inițierea tratamentului oral cu trimetoprim-sulfametoxazol, evolutia clinică s-a îmbunătățit rapid. Este important să se ia în considerare faptul că infecțiile oportuniste, cum ar fi pneumonia cu Pneumocystis jirovecii, pot apărea nu numai la pacienții diagnosticați anterior cu infecție HIV, dar, de asemenea, și la pacienții fără un istoric medical de boli imunosupresoare.

Cuvinte-cheie: ***infecție HIV, Pneumocystis jirovecii, boală interstițială***

Background

Pneumocystis pneumonia (PCP) is the most common opportunistic infection among HIV-positive patients[(1)]. It is caused by *Pneumocystis jirovecii*, a worldwide pathogen that is classified as a unicellular fungus. Before the widespread use of anti-retroviral therapy (ART) and the anti-*Pneumocystis* prophylaxis, it represented a significant cause of mortality among individuals with profound immunosuppression (CD4 counts <100 cells/mm3)[(2)]. The highest mortality rate is directly correlated with a delayed diagnosis and delayed initiation of appropriate treatment. Because the clinical presentation is usually nonspecific, especially in HIV patients whose condition has recently progressed to AIDS status , the recognition of PCP can often be difficult. Specific therapy with trimethoprim-sulfamethoxazole can be initiated before establishing a definitive diagnosis because organisms persist in clinical specimens for days or weeks after the effective treatment is initiated[(3)]. This case report highlights the fact that a specific diagnosis of PCP should be sought in the presence of a severe respiratory disease occurring in patients with primary HIV infection.

Case report

A 47-year-old previously healthy man, smoker of 25 pack years, sailor, was admitted in our hospital with a 6-month history of fatigue, chest discomfort, non-productive cough and a poor appetite, 20 kg weight loss, and a 6-week history of progressive dyspnea and fever. For these symptoms, he initially went to his primary care physician, and was subsequently diagnosed with bronchitis and given antibiotics. At that time, the chest X-ray was normal (Figure 1a). The clinical response to the oral antibiotics was poor and, due to worsening of the clinical course, he required admission to hospital. The patient reported recent work related travel in different regions of Asia and Africa and possible close contact with sick people with flu-like symptoms. He denied any personal or family history of other conditions. A human immunodeficiency virus test was negative 5 years before the admission in our hospital.

On physical examination, the patient was febrile (37.8°C), underweight (BMI = 17.9 Kg/m^2), and presented signs of acute respiratory distress: central cyanosis, respiratory rate of 34 breaths/min, oxygen saturation of 72% in room air, blood pressure 125/65 mmHg, heart rate 123 beats/min and fine crackles bilaterally. The examination of other systems was normal. The chest radiograph revealed bilateral diffuse infiltrates in the mid and upper zones of the lungs (Figure 1b). The computed tomography (CT) of the chest showed numerous pulmonary cysts of varying shape, size, and wall thickness, which, practically, had replaced the normal lung parenchyma in the upper zones (Figure 2a). In the mid part of the lungs, the CT scan showed extensive ground-glass opacities with peripheral sparing, less frequent cystic lesions than in the upper part, honeycombing, and consolidation areas (Figure 2b). In the basal zones

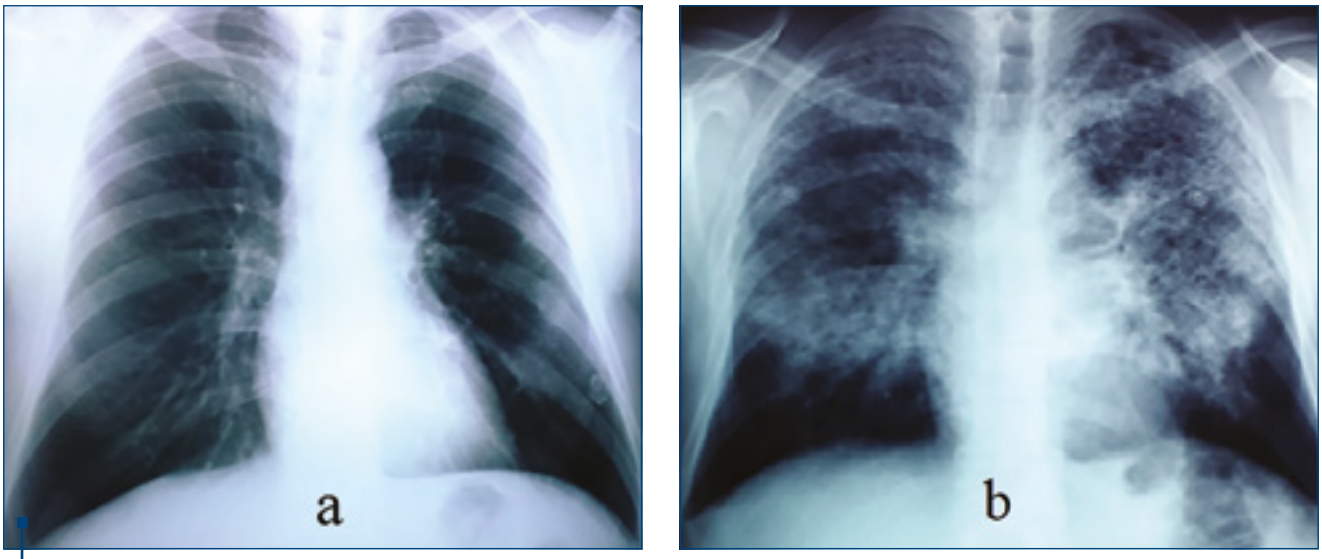

Figure 1. *Chest X-rays. (a) Before admission to hospital. (b) At hospital admission showing bilateral diffuse infiltrates and cysts in the mid and upper zones of both lungs.*

of the lungs there are fewer lesions and they are smaller in size.. The pulmonary function tests revealed mild restriction. The biological analyses were as follows: erythrocyte sedimentation rate of 84 mm/hour; haemoglobin 13.9 g/dL; white blood cells 5.500/µL (neutrophils, 71.6%; lymphocytes, 10.8%, eosinophils, 2.2%; basophils, 0.2%; monocytes, 15.2%), platelets 209.000/µL, PTT 36.7 seconds and INR 1.55. Serum chemistry showed normal results, including angiotensin converting enzyme (ACE). Beta-D-glucan analysis was not available in our laboratory. The basal arterial blood gas analysis revealed a pH of 7.44, PaO2 of 61mmHg and PaCO2 of 32.5mmHg. At that point, we took into consideration the possibility of an interstitial lung disease of different etiology: infectious, sarcoidosis, Langerhans cell histiocytosis, hypersensitivity pneumonitis (HP), lymphocytic interstitial pneumonia (LIP), or idiopathic pulmonary fibrosis (IPF). HIV antibody ELISA (third-generation assay) was found to be positive, and HIV infection was confirmed by Western Blot, with a viral load of 3.8 million copies/mL. CD4 cell count was 176/µL (15%). Apart from pulmonary infections such as pneumocystosis, cytomegalovirus disease, aspergillosis, mycobacterial infections, and viral infection syndromes including herpes simplex or respiratory syncytial virus, the other major differential diagnoses considered, included non-infectious pathology, such as lymphocytic interstitial pneumonia, Kaposi sarcoma, and IPF. Smear stains from induced sputum were negative for acid fast bacilli, fungi, and bacteria. Wright–Giemsa staining revealed trophic forms of *Pneumocystis jirovecii*, as shown in Figure 3 (×100). Polymerase chain reaction testing of the sputum was negative for *Mycobacterium tuberculosis* and IgM antibodies for cytomegalovirus were not detected.

The diagnosis of PCP was sustained by the epidemiology (the most common opportunistic infection among HIV-positive patients), clinical manifestation (progressive dyspnea, weight loss and fever), imagistic features (bilateral cystic lesions and diffuse ground-glass opacities), and microscopically examination (presence of *P. jirovecii* trophic forms on Wright–Giemsa stain). Treatment with oral trimethoprim/sulfamethoxazole (TMP-SMX) (960 mg twice a day) and corticosteroids (prednisone 80mg per day for five days, followed by 40mg per day for five days and 20mg per day for another five days) was started. The patient's symptoms resolved rapidly and he started antiretroviral therapy (ART) as an outpatient 3 weeks later. Follow-up evaluation in 6 months also revealed a marked improvement of the CT scan images (Figure 2 c,d).

Discussion

Pneumocystis pneumonia (PCP) diagnosis is usually suspected in known HIV-positive patients with CD4+ T-lymphocyte cell count less than 200 cells/µl, or in non-HIV severe immunosuppressed patients. In this case, our patient was previously healthy, without personal history of other medical conditions, and PCP was diagnosed simultaneously with HIV infection. The clinical presentation of PCP is generally not specific: non-productive cough, progressive dyspnea, hypoxemia, low-grade fever, and diffuse, bilateral, interstitial or alveolar infiltrates on chest radiography[5]. In the present case, the symptoms had been progressive, with a subacute course, but presenting a fast progression of severe dyspnea in the week before admission to our hospital. In HIV-infected patients with rapid and severe respiratory deterioration the diagnosis of PCP should be strongly suspected and rapidly confirmed, considering the fact that this clinical course is associated with a high mortality rate among these patients[6,7].

The usual CT appearance of PCP is characterized by extensive ground-glass attenuation associated with cystic lesions, which are considered to disappear after introducing adequate therapy[8], as observed in the pres-

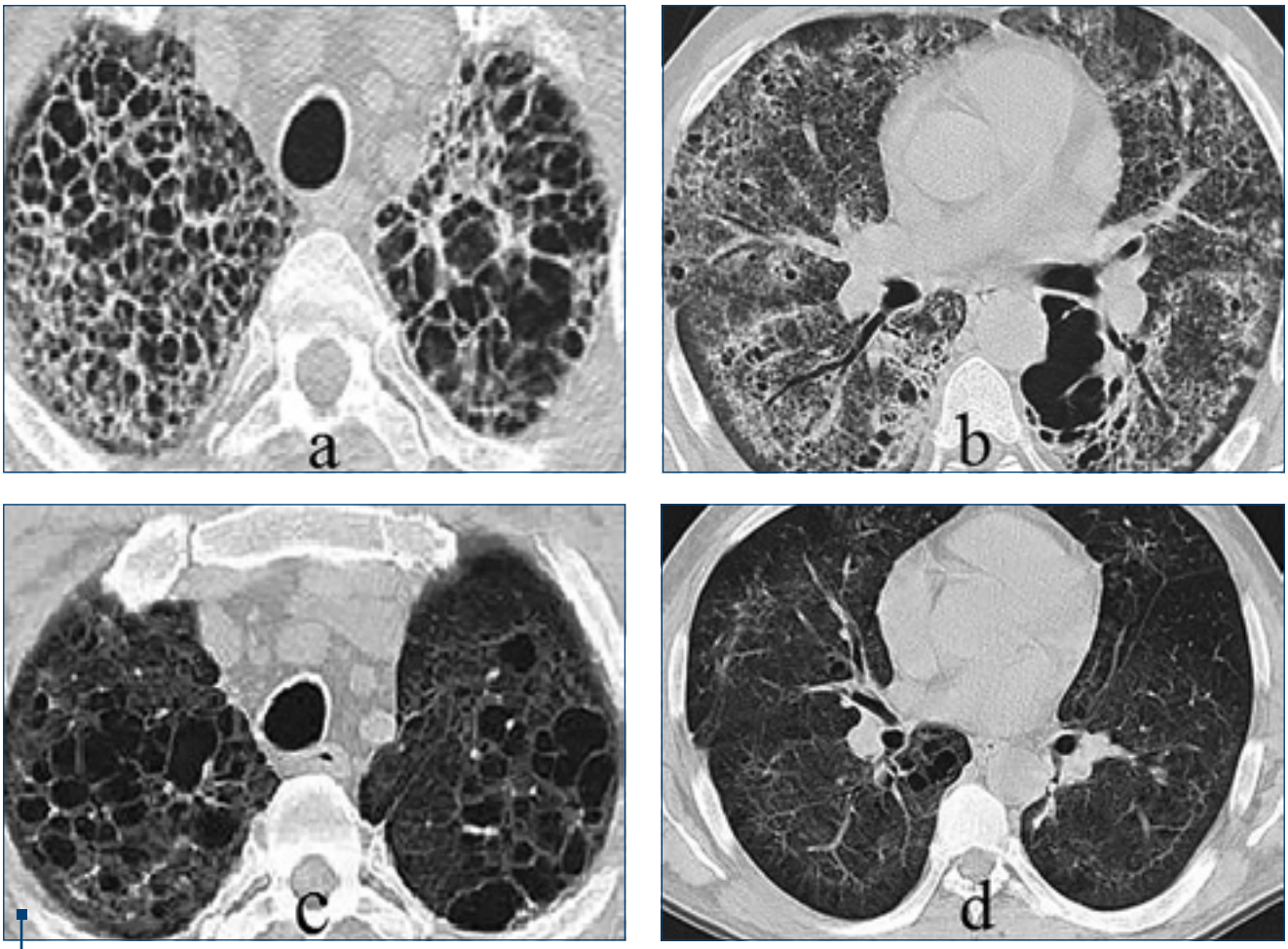

Figure 2. *Chest CT-scan (a) Initially showing cystic lesions in the upper lobes, (b) ground-glass opacities, and honeycombing. (c) Follow-up with decreased number and area of cystic lesions in the upper lobes, and (d) disappearance of ground-glass opacities and decreased honeycombing in the mid and lower lobes.*

ent case. In our case, the computed tomography examination showing numerous cystic lesions associated with extensive ground-glass attenuation, honeycombing and consolidation areas raised multiple issues regarding differential diagnosis. Before the confirmation of HIV infection, we considered the possibility of an interstitial lung disease (ILD) of different etiology: infectious, sarcoidosis, Langerhans cell histiocytosis, hypersensitivity pneumonitis (HP), lymphocytic interstitial pneumonia (LIP), or idiopathic pulmonary fibrosis (IPF). The arguments for an infectious cause consisted of the presence of persistent febrile syndrome associated with cough weight loss, dyspnea and chest pain, the normal aspect of the chest X-ray 6 months before the hospitalization, followed by the appearance of the bilateral infiltrates and the high level of ESR. Sarcoidosis was another possible diagnosis, given the fact that the patient was a middle age man, presenting a progressive dyspnea and non-productive cough, but with no enlarged mediastinal lymph nodes on imaging examination, and the ACE value being normal. The other possible diagnoses, including Langerhans cell histiocytosis, HP, LIP, or IPF were suspected based on the subacute indolent course occurring in a middle age man who smokes, with possible work related exposure, and an unusual association of different patterns present on the CT examination.

Once the HIV infection was confirmed, and considering the immunological status characterized by low CD4 counts and high HIV viral loads, we considered that a possible opportunistic infection could be the cause of the interstitial lung disease, since primary HIV infection can occur in 40–90% of individuals recently infected with HIV[9]. In order to facilitate the diagnostic process, timely induced sputum examination was considered, with a rapid analysis for bacteria, fungi, acid fast bacilli and *Pneumocystis jirovecii*. The definitive diagnosis of PCP requires the identification *Pneumocystis jirovecii*, on cystic or trophic forms, in appropriate specimens, such as induced sputum samples, bronchoalveolar lavage fluid and transbronchial or open lung biopsy[10]. Cystic and trophic forms can be detected using Giemsa, Diff-Quik, and Wright stains; the cyst wall can be stained with Gomori methenamine silver, Gram-Weigert, cresyl violet, or toluidine blue. In order to exclude other infection or co-infections, pathologic confirmation may be required[11,12]. In the present case, the presence of trophic forms of *Pneumocystis jirovecii* organisms was confirmed using Wright-Giemsa stain of sputum specimen. Data

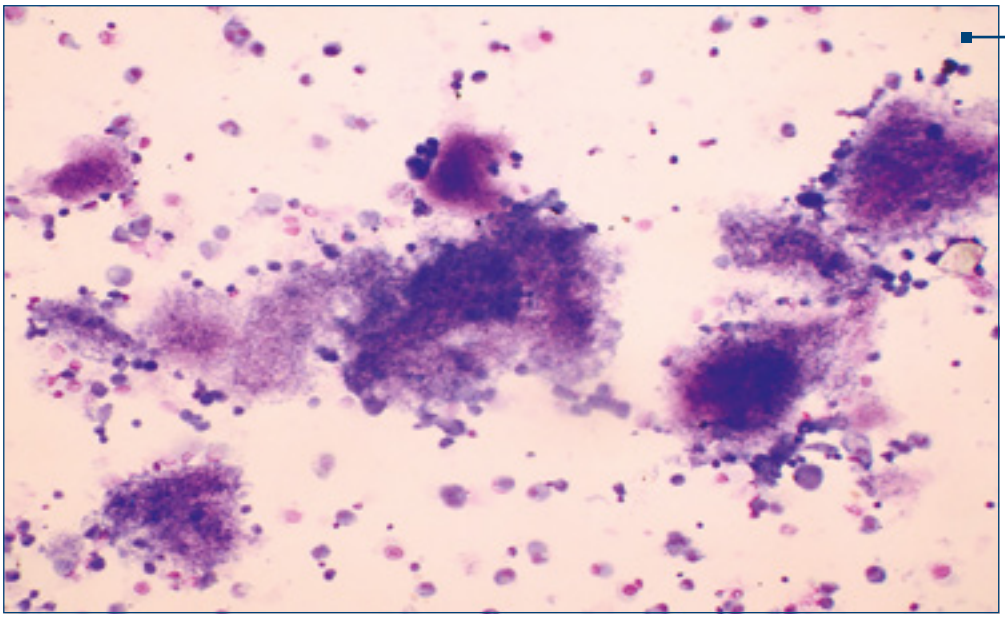

Figure 3. *Wright-Giemsa stain from induced sputum (×100) showing trophic forms of Pneumocystis jirovecii organisms*

from literature revealed a relative diagnostic sensitivity of induced sputum to be between between 50% and 90%, depending on the quality of the specimen, the pathogen load, and on the experience of the microbiologist or pathologist[13-15]. Specificity is high (99%-100%). This method may be less sensitive in HIV-negative patients, as the immunodeficiency caused by HIV infection typically leads to a greater alveolar load of Pneumocystis organisms[16].

Since TMP-SMX is the most effective drug used for treatment of pneumocystis pneumonia[3,17,18], a high-dose was orally administered, along with adjunct corticosteroids, and the patient's symptoms rapidly improved within several days. Corticosteroids are recommended in HIV-infected patients with PCP who have hypoxemia[9], as observed in the present case. Follow-up CT-scan showed spectacular regression of cystic lesions, ground glass, and also honeycombing.

Conclusions

The current case report indicates that PCP diagnosis should be considered and pursued not only in patients known with HIV-infection but also in patients without medical history of immunosuppressed diseases. The radiological findings in our patient's case raised important differential diagnosis issues, but the PCP diagnosis was rapidly confirmed using the induced sputum smear stained samples. Treatment was initiated with oral trimethoprim–sulfamethoxazole and corticosteroids, with good clinical outcome. ■

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