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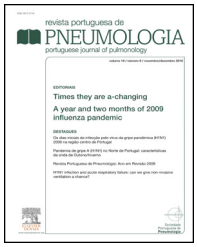

CASE REPORT

Unusual coexistence of opportunistic lung infections in a human immunodeficiency virus positive patient suffering from persistent *Pneumocystis jirovecii* pneumonia: A case report☆

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Abstract It is well-established that HIV patients are at high risk of opportunistic infections (OI), like the ones caused by *Pneumocystis jirovecii*, a worldwide pathogen implicated in interstitial pneumonia (PcP). We present a case of a newly diagnosed HIV-1 patient with multiple OI, including a persistent form of PcP, an invasive aspergillosis (IA), cytomegalovirus and *Mycobacterium xenopi* lung infection. We describe the combination of laboratorial screening, surgery and antimicrobial therapy which were crucial for patient recovery.

PALAVRAS-CHAVE
Vírus da imunodeficiência humana (VIH);
Pneumonia por *Pneumocystis jirovecii* (PPc);
Infeções oportunistas;
Pulmões

Coexistência de infeções oportunistas pulmonares num doente com infeção por vírus da imunodeficiência humana e uma forma persistente de pneumonia por *Pneumocystis jirovecii*: caso clínico

Resumo Como é sabido, nos doentes com infeção por vírus da imunodeficiência humana (VIH) existe um alto risco de ocorrência de infeções oportunistas (IO), tais como as infeções por *Pneumocystis jirovecii*, um agente patogénico com distribuição mundial, que provoca pneumonia intersticial (PPc). Apresentamos um caso de um doente recém-diagnosticado com infeção por VIH-1 e múltiplas IO pulmonares, incluindo uma forma persistente de PPc, aspergilose invasiva (AI), e infeções por citomegalovírus e por *Mycobacterium xenopi*. Descrevemos

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a combinação de fatores cruciais para a recuperação do doente, que incluíram a obtenção de dados laboratoriais, intervenção cirúrgica e múltipla terapêutica antimicrobiana.

Clinical case

A 59-year-old previously healthy man presented with a four-month history of progressive weakness, dysphagia, loss of appetite, weigh loss and occasional cough with purulent sputum. In November 2007 he was admitted with acute dyspnea. He was febrile (38.0 °C), exhibited an oropharyngeal trush, and had inspiratory crackles in both hemithoraxes. Blood analysis displayed a partial respiratory failure (pO_2 66 mmHg, pCO_2 34 mmHg); the chest radiography revealed a marked diffuse bilateral interstitial nodular infiltrate. Search for HIV antibodies (ELISA) was positive. A clinical diagnosis of PcP, oral and esophageal candidiasis were assumed. Cotrimoxazole (1960 mg q.i.d.), prednisolone (40 mg b.i.d. i.v.) and fluconazole (200 mg q.d. i.v.) were started.

Upper gastrointestinal endoscopy confirmed esophageal candidiasis. Fluconazole was stopped after two weeks of treatment, and cotrimoxazole dose was reduced to 960 mg q.d., after 21 days. Prednisolone was tapered to 10 mg q.d. The remaining analysis presented a peripheral blood $TCD4^+$ of 21 cell/μl (5%) and an HIV-1 viral load of 307,285 copies/ml.

Partial clinical improvement was observed with the above therapy, and the patient remained febrile. At the fourth week of hospitalization, a computed tomography (CT) of the thorax revealed a bilateral alveolar condensation and effusion, and a cavity with a *halo* sign in the left lung (Fig. 1). A broncoalveolar lavage (BAL 1) was collected during a bronchoscopy. A high burden of *P. jirovecii* cysts (4–30 cysts in one field at ×1000 magnification) was found using indirect immunofluorescence with monoclonal antibodies (IF) (MonoFluo kit *P. jirovecii*; Bio-Rad, France). The presence of *P. jirovecii* organisms was confirmed by amplification of the mitochondrial large-subunit rRNA (*mtLSU rRNA*) gene using nested-PCR. Likewise, *Aspergillus fumigatus* was revealed in BAL culture. Therapy was modified to clindamycin (600 mg q.i.d.), primaquine (30 mg q.d.) and voriconazole (200 mg b.i.d after a loading dose).

As the patient was febrile, we also searched for pp6 cytomegalovirus (CMV) antigenaemia that was positive (248 infected cells/50,000 leucocytes). Fundoscopy, cerebrospinal fluid analysis, upper and lower gastrointestinal endoscopy did not suggest CMV disease. However, DNA of CMV was found in PCR of BAL 1. Ganciclovir (325 mg b.i.d.) was started.

The patient finished the second anti-*Pneumocystis* treatment (26 days of clindamycin and primaquine) and ganciclovir (after 21 days). Prophylaxis with atovaquone (1500 mg q.d.), pyrimethamine (50 mg q.d.), and valganciclovir (900 mg q.d.) was begun, and voriconazol was maintained.

Eight weeks after admission, 57 days of anti-*Pneumocystis* treatment and 30 days of voriconazole, were provided. A new BAL fluid was collected (BAL 2), revealing the persistence of a high parasite burden of *P. jirovecii* (4–30 cysts in one field at ×1000 magnification) and *A. fumigatus*. CMV DNA was still positive in BAL 2. As the patient was apyretic and CMV antigenaemia became negative, we did not reinstitute anti-CMV therapy in full dose. However, the patient maintained significant cough and dyspnea. A new CT of the thorax still revealed alveolar condensation and the aspergilloma cavity with the previous dimensions. We opted to start a third course of PcP therapy (clindamycin and primaquine); and to add caspofungin (50 mg q.d. after a loading dose) to voriconazol. Meanwhile, the laboratory noticed the growth of *Mycobacterium xenopi* in BAL 1. Ethambutol (1200 mg q.d.), azithromycin (500 mg, q.d.) and levofloxacin (500 mg, q.d.) were started. Given the patient's profound immunosuppression, antiretroviral (ARV) therapy was also begun. After excluding HLA-B57 01, and to avoid interactions, we choose abacavir (ABC, 600 mg q.d.), lamivudine (3TC, 300 mg q.d.) and indinavir (IDV, 800 mg t.i.d.).

The two BALs collected during the episode were genetically characterized at five distinct *P. jirovecii* loci encoding the mitochondrial large-subunit rRNA (*mtLSU rRNA*), the cytochrome *b* (*CYB*), the superoxide dismutase (*SOD*), the dihydrofolate reductase (*DHFR*), and the dihydropteroate synthase (*DHPS*) using PCR with DNA sequencing analysis. Both samples revealed identical multiple genotypes combinations (Table 1).

One week later, the patient developed a left hydropneumothorax. He was submitted to thoracotomy, pleural decortication and aspergilloma removing (Fig. 1). In the removed tissue, *P. jirovecii* and *A. fumigatus* were identified. Two mutations were detected at codons 75 and 78 of the *DHPS* gene for the first time (GenBank: accession numbers GU479992, GU479993), in which a threonine was present instead of an isoleucine and a proline was present instead of a leucine, respectively. *P. jirovecii* genotyping results in the pleura tissue and in the aspergilloma sections are summarized in Table 1.

Since surgery, the patient has had a gradual and sustained improvement. He was discharged 16 weeks after admission. Overall, he completed 77 days of PcP therapy (21 days of cotrimoxazole and 56 days course of clindamycin and primaquine); 22 days of ganciclovir; 9 months of voriconazole (with 71 days of caspofungin); and 15 months of antibacillary treatment. ARV was later simplified, with indinavir substituted by efavirenze. Twenty months after discharge, the patient regained his lifestyle, had undetectable HIV-1 viral load and displayed 350 $TCD4^+$ lymphocytes/μl (11%).