

(CASE REPORT)



Recurrent *Pneumocystis jirovecii* pneumonia in an HIV-infected patient: A case report

Nina Dimitrova Tsvetkova ¹, Rumen Nenkov Harizanov ^{1,*}, Aleksandra Ivanova Ivanova ¹, Dimitar Todorov Strashimirov ², Rusina Stanislavova Grozdeva ² and Nina Stoyanova Yancheva-Petrova ³

¹ National Centre of Infectious and Parasitic Diseases, Department of Parasitology and Tropical Medicine, Sofia, 1504, Bulgaria.

² Specialized Hospital for Active Treatment of Infectious and Parasitic Diseases (SHATIPD, Department for AIDS, Sofia, 1431, Bulgaria.

³ Medical University-Sofia, Department for Infectious Diseases, Parasitology and Tropical Diseases, Sofia, 1431, Bulgaria.

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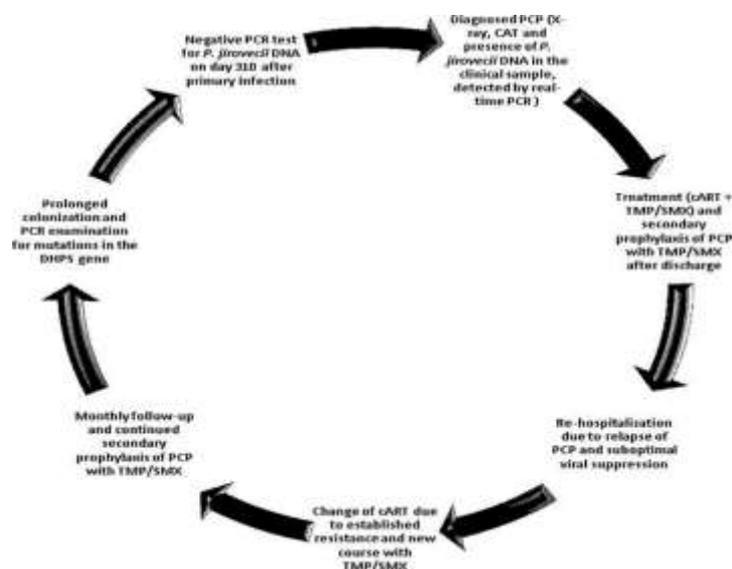
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Abstract

We present a case of *Pneumocystis* pneumonia (diagnosis was based on imaging X-ray and CAT examinations, and real-time PCR) in an HIV-infected patient with relapse four months later and long lasting colonization as detected by the positive real-time PCR results and lack of clinical symptoms during the follow up of the patient after second course of treatment with trimethoprim/sulfamethoxazole. The wild-type *P. jirovecii* DHPS genotype was identified in all patient samples tested.

Keywords: *Pneumocystis jirovecii*; *Pneumocystis* pneumonia (PCP); Real-time PCR; Colonization

Graphical abstract



* Corresponding author: Rumen Nenkov Harizanov; phone: +35929446999; ext. 360; e-mail: harizanov@ncipd.org
National Centre of Infectious and Parasitic Diseases, Department of Parasitology and Tropical Medicine, Sofia, 1504, Bulgaria.

1. Introduction

In humans, *Pneumocystis jirovecii* (formerly known as *Pneumocystis carinii*) [1] is mainly located in the pulmonary alveoli and is the causative agent of *Pneumocystis* pneumonia (PCP), a frequent and severe opportunistic infection in immunocompromised patients [2].

The relevance of studies on the *P. jirovecii* and the infection caused by the pathogen is determined by the vastly increasing contingent of immunocompromised individuals today, which forms the main risk group for the development of pneumocystosis. These are mostly persons with AIDS, cancer, and haematological malignancies, organ transplant patients with systemic connective tissue diseases, and premature infants [3, 4, 5].

Aim of this study is to present an unusual case of relapse of *Pneumocystis* pneumonia in an HIV-infected patient against the background of CD4 count greater than 200 cells/ μ L and trimethoprim/sulfamethoxazole prophylaxis. Long lasting colonization was detected by the positive real-time PCR results during the follow up of the patient after second course of treatment and lack of clinical symptoms.

2. Case Presentation

On February 10th (Day 0, D0) 2020, a Bulgarian male was diagnosed with HIV infection. The examination was performed on patient's request and the reason was protracted fever persisting about six months, cough that lasted for a month, and a significant weight reduction of about 30 kg. On the same day, he was hospitalized for the first time in the Department for AIDS, SHATIPD in Sofia due to progressive shortness of breath.

Imaging (X-ray, CAT) tests showed data for bilateral, caudally located areas of changes of the parenchyma with “frosted glass” type appearance and irregularly shaped centrilobular lesions forming “tree in bud” pattern of image. Immunological assays (D+1) had evidence of stage III of HIV infection (Table 1) and AIDS. The presence of *P. jirovecii* DNA in the clinical sample was detected by real-time PCR assays (RIDA®GENE *Pneumocystis jirovecii* real-time PCR Kit, R-biopharm AG) targeting mitochondrial large subunit rRNA (mtLSU rRNA) gene of *P. jirovecii*. Microscopic examination of Giemsa-stained smears of the same specimen did not prove the presence of trophozoites and/or cysts of the microorganism. The microbiological test results of sputum showed the presence of *Candida albicans* 10³, and a sterile blood culture (D+3). A treatment with trimethoprim/sulfamethoxazole (TMP/SMX), amikacin, cefoperazone, rifampicin, isoniazid, ethambutol and fluconazole in usual doses and regimens was started, as well as from the third day after hospitalization and combined antiretroviral therapy (cART) with dolutegravir/abacavir/lamivudine was initiated.

The patient was discharged at D+40 with improvement and recommendations for monthly follow-up and secondary prophylaxis of PCP with TMP/SMX (960 mg daily) after 30 days of a hospital stay.

The patient was re-hospitalized at D +123 in the same hospital ward due to intermittent subfebrility and nonproductive cough three months later. On the day of hospitalization, his CD4+ T-cells count was > 200 cells/ μ L, but the virological examination showed suboptimal viral suppression (Table 1). The real-time PCR assay of sputum showed the presence of *P. jirovecii* DNA. Quantitative real-time PCR (RIDA®GENE, R-biopharm AG) revealed increase in the copy number/mL to the level detected in the first sample tested (Table 1). In view of the relatively high levels of viral load and persistent colonization by *Pneumocystis*, determined in the monthly follow-up examinations after the first discharge (Table 1), a drug resistance test for the ART therapy with dolutegravir/abacavir/lamivudine was recommended. Due to the fact that such resistance was established (D+126), the medicinal product was replaced by darunavir/cobicistat/emtricitabine/tenofovir alafenamide. A repeat course of TMP/SMX was performed, after which at D+141 the patient was discharged with improved general condition and recommendations for continuation of the secondary prophylaxis with TMP/SMX.

Eight months later (D+249) he was hospitalized again for low-grade fever (37.3°C), cough, and chest pain. Radiography showed evidence of chronic bronchitis and pneumofibrotic changes paracardially, but no evidence of interstitial pneumonia. *P. jirovecii* real-time PCR of sputum was positive again. Serological testing for the presence of specific anti-COVID 19 IgM and IgG antibodies in the ELISA was negative. In addition to continuing ART, a course of antibiotic therapy with levofloxacin was prescribed, after which the complaints resolved and the patient remained permanently afebrile.

Discussion of the case lead to the conclusion that it referred to a patient with advanced HIV infection, episodes of recurrent PCP and persistent colonization by *Pneumocystis* (established by monthly real-time PCR tests of sputum specimens), resulting in the suboptimal immune response. Based on low viral load levels and sustained retention of

CD4+ T-cells above 200 cells/ μ L, prophylaxis with TMP/SMX was discontinued, and at D +310, control real-time PCR was negative. To date, patient had no episodes of new recurrent PCP.

Table 1 Data from the laboratory analyses of the patient during the follow up.

Day of the test	Real-time PCR (mt LSU rRNA)		DHPS genotype	Immunological and Virological Examinations			
	Qualitative Ct value	Quantitative copies/ml		CD-4 cells/ μ L	CD-8 cells/ μ L	CD-4/CD-8	VL / log ₁₀
D +1	20,72	5,035 x 10 ⁸	wild-type	35	436	0,08	420000 / 5,62
D +38	22,76	1,534 x 10 ⁷	wild-type	67	295	0,23	238 / 2,38
D +95	25,72	9,789 x 10 ⁵	wild-type	212	844	0,25	9470 / 3,98
D +123	19,74	5,245 x 10 ⁸	wild-type	221	655	0,34	5520 / 3,74
D +249	30,90	1,392 x 10 ⁴	wild-type	225	1054	0,21	225 / 2,35
D +310	negative	-	-	304	1605	0,19	<20

3. Discussion

Following active ART initiation for HIV infection, there has been a significant reduction in viral replication, an increase in the number of CD4+ T-cells, and a sharp decrease in the opportunistic infections incidence rate leading to death [6, 7]. Before Antiretroviral Therapy Era, lifelong secondary prophylaxis of PCP is required when CD4 lymphocyte level is below 200, or after first episode of the disease. Some subsequent studies conducted in a small group of patients and in a short-term follow-up observation indicated that secondary prophylaxis could be discontinued in the course of ART, and when the CD4 lymphocyte levels remain above 200 cells/ μ L for at least three months. However, other authors reported that in patients receiving combined ART, the incidence rate is approximately 2.5-fold higher after discontinuation of TMP/SMX prophylaxis, than before that, meaningless the number of CD4+ T-cells (above or below 200 cells/ μ L [8]).

In the presented case, four months after the primary infection, despite the ART and secondary prophylaxis with TMP/SMX, PCP recurrence was established, and subsequently a persistent colonization was detected. Recurrent PCP was demonstrated on the background of relatively optimal levels of CD4+ T-cells, high levels of viral load, and the increased copy number of the mtLSU rRNA gene of *P. jirovecii* on D +123 reaching the level in the first sample tested (Table 1). This led us to assume that the problem was caused either due to the resistance to the initially administered ART and the associated high levels of viral load found in the second hospitalization, or the pathogen's resistance to the ongoing TMP/SMX therapy. In this regard, we performed a retrospective study of isolated DNA samples of *P. jirovecii* for mutations in the DHPS gene, according to Calderón et al. [9]. However, no mutations were detected. This finding indicates that the main reason for the recurrence of PCP and subsequent persistent colonization by *Pneumocystis* is the high plasma HIV RNA level, taking into account the background of a gradually improving T-cell immune response. In this sense, our data differ from the findings of other authors [8], who reported that patients with CD4+ T-cell count increasing above 200 cells/ μ L while on cART are at low risk of recurrence of PCP, regardless of the plasma level of HIV RNA.

4. Conclusion

Given the possibility of recurrences of PCP we believe that molecular methods could play a significant role in detecting the pathogen and determining the therapeutic regimen in view of the possibility of mutations leading to resistance to TMP/SMX, and that CD4+ T-cell count do not always play a leading role in determining the risk of recurrence of the infection. We hope that the data presented in our study will be useful in terms of diagnostic approaches and management of PCP.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that they have no conflict of interest.

Statement of ethical approval

The study was reviewed and approved by the institutional review board (IRB) 00006384.

Statement of informed consent

Informed consent was obtained from all patients included in the study.

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