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Pneumocystis Pneumonia with Atypical Presentation in an HIV Seronegative Patient with Systemic Lupus Erythematosus during Steroid Therapy

Steroid Tedavisi Alan HIV Seronegatif Sistemik Lupus Eritematozisli bir Hastada Atipik Görünümlü Pnömosistis Pnömonisi

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Abstract

Pneumocystis pneumonia (PCP) is common among HIV patients, but it is rare in patients with autoimmune diseases such as systemic lupus erythematosus (SLE). Some of the risk factors related to PCP in SLE patients include a high steroid dose, greater disease activity, renal involvement, and lower lymphocyte and CD4+ counts. Described herein is the case of a 23-year-old female with SLE who was treated with high-dose steroid therapy. She was admitted to the clinic with a dry cough and a prolonged fever persisting since the tapering of the steroid dose. High-resolution computed tomography of the thorax revealed intraseptal thickening, subpleural nodules, and enlargement of the 4L, 6, and 7 lymph nodes. A laboratory examination of an induced sputum sample using polymerase chain reaction was positive for *Pneumocystis jirovecii*. Trimethoprim / sulfamethoxazole was administered for 14 days and clinical improvement was observed.

Key words: *CD4 lymphocyte, pneumocystis pneumonia, systemic lupus erythematosus.*

Özet

Pnömosistis pnömonisi (PP) HIV'li hastalarda sık görülürken sistemik lupus eritematozisli (SLE) gibi otoimmün hastalığı olanlarda nadirdir. Yüksek doz steriod kullanımı, ağır hastalık, böbrek tutulumu, lenfosit ve CD4+sayısında düşüklük gibi bazı nedenler SLE hastalarında PP için risk oluşturabilmektedir. Burada, yüksek doz steroid tedavi alan SLE'li 23 yaşındaki kadın olgu sunulmuştur. Steroid dozu azaltıldığı sırada kuru öksürük ve devam eden ateş yakınmaları ile kliniğe yatırıldı. Yüksek çözünürlüklü toraks tomografisinde, intraseptal kalınlaşmalar, subplevral nodüller ve 4L, 6 ve 7 nolu lenf nodlarında büyüme saptandı. İndükte balgam örneğinin PCR ile yapılan incelemesinde *Pneumocystis jirovecii* pozitif bulundu. Trimetoprim / Sülfametaksazol tedavisi 14 gün uygulandı ve klinik iyileşme gözlendi.

Anahtar Sözcükler: *CD lenfosit, pnömositis pnömonisi, sistemik lupus eritematozis.*

Pneumocystis pneumonia (PCP) is defined as an opportunistic infection caused by *Pneumocystis jirovecii* (formerly known as *Pneumocystis carinii*). PCP is common among HIV patients, but the incidence in non-HIV immunocompromised patients, including those with connective tissue disease, is increasing (1,2). Chen et al. (3) found 69 (26.1%) patients with autoimmune diseases who were diagnosed with PCP over a 10-year period. PCP infection in systemic lupus erythematosus (SLE)

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patients is uncommon, but it may be fatal (4). The incidence of PCP in SLE was reported as 0.58% in Taiwan and 2.4% in Thailand (5,6). Risk factors such as greater disease activity, a high steroid dose, renal involvement, and lower lymphocyte and CD4+ counts are related to PCP in SLE (7). Presently described is a case of PCP with atypical presentation in a patient with SLE that developed during steroid therapy.

CASE

A 23-year-old female presented at the pulmonary infection clinic of the hospital with a prolonged fever and nonproductive cough. Three months earlier, she had been hospitalized with the manifestations of acute decompensated heart failure accompanied by pleural effusion, nephritis, arthritis, and anemia. Laboratory results included a positive anti-nuclear antibody (9.0) and ds-DNA (>200 U/mL) test result. The level of C4 was low (5.2; normal: 15-57 mg/dL) and the level of C3 was normal (100; normal: 83-193 mg/dL). She had been diagnosed with a severe flare-up of SLE. She was hospitalized for a month and stayed in the intensive cardiovascular care unit for 2 weeks. She was initially treated with an intravenous corticosteroid, which was later replaced with an oral steroid. She was still taking the tapering dose of the oral steroid at the time of presentation to the clinic. There was no history of pulmonary tuberculosis (TB) treatment. She had never smoked and there was no exposure to occupational hazards.

A physical examination revealed moderately good general condition, including vital signs of a blood pressure of 100/70 mmHg on an anti-hypertension drug, a heart rate of 87/minute, a respiratory rate of 20/minute, and oxygen saturation of 98% in room air. Moon face was present; however, there was no enlargement of the neck or supraclavicular lymph nodes. Enlargement of the cardiac border was observed on chest percussion; but a pulmonary examination was normal.

A blood hemogram revealed leukocytosis (17.150/µL) with 15.9% lymphocytes. An HIV test was negative. The acid fast bacilli culture testing for *Mycobacterium tuberculosis* and a GeneXpert MTB/RIF assay (Cephaid, Sunnyvale, CA, USA) of sputum was negative. The sputum culture was negative for microorganisms. High-resolution computed tomography (HRCT) of the thorax was performed and indicated intraseptal thickening (Figure 1), subpleural nodules (Figure 2), and enlargement of the 4L, 6, and 7 lymph nodes. A polymerase chain reaction (PCR) test of induced sputum was positive for *Pneumocystis jirovecii*. The patient was diagnosed with PCP and treated with trimethoprim/sulfamethoxazole (TMP-SMX) for 14 days. After treatment, a marked improvement in clinical features was observed.

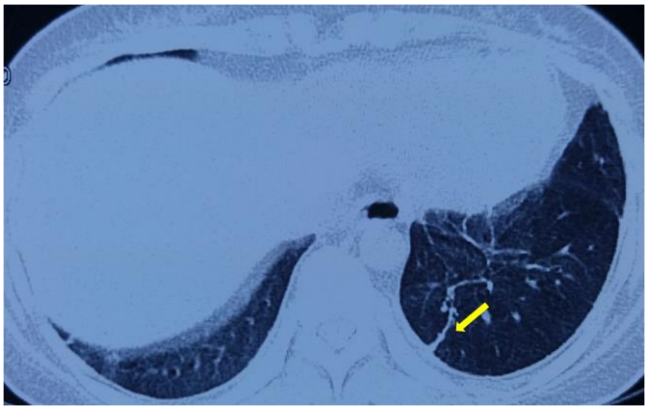

Figure 1: *High-resolution computed tomography of the thorax showed intraseptal thickening (arrow)*

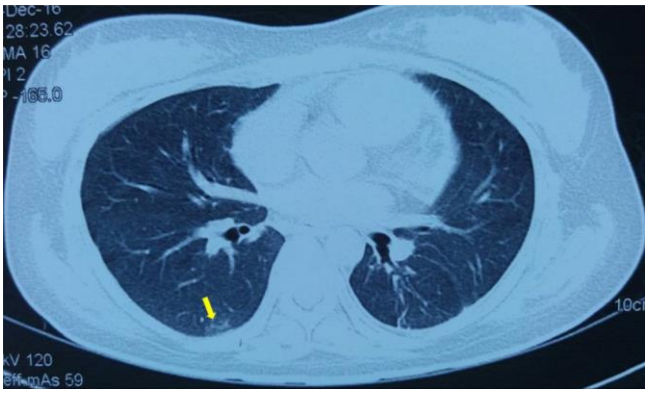

Figure 2: *High-resolution computed tomography of the thorax revealed subpleural nodules (arrow)*

DISCUSSION

Pneumocystis jirovecii is an atypical fungus exhibiting pulmonary tropism, though it is an alveolar pathogen, and only disseminates very rarely. It is also a host-specific organism, which means that *P. jirovecii* only infects humans and cannot infect other mammalians (1,2). The sources of PCP infection are the environment, an asymptomatic carrier, and active PCP patients. It may be transmitted via an airborne route, either in the general population or in a hospital environment (1,8,9). In our case, the patient had been hospitalized for a month before she was diagnosed with PCP, so that may be the potential source of PCP transmission in this case.

The use of high-dose steroids and immunosuppressive therapy are included as risk factors for PCP infection in SLE patients (4,7,8). Corticosteroids may decrease CD4+ counts, thus it may play a role in the development of PCP even when used in low or moderate doses. When the dose of steroid was tapered or it was discontinued sud-

denly, it led to immune reconstitution inflammatory syndrome (IRIS). In this condition, an excessive inflammatory response against *P. jirovecii* may injure the lung, causing the appearance of clinical symptoms. It also explains why PCP often occurs in cases of rheumatic disease when the CD4+ count has improved (>200/μL) (2,9). Our patient had consumed a high dose of oral steroid and the manifestations of PCP occurred after the steroid dose had been tapered for several days.

The clinical features of PCP in non-HIV immune-suppressed patients, such as connective tissue disease, are mild and non-specific in the early stages. Oxygen saturation measured by pulse oximeter may be normal at rest and chest X-ray findings may be almost normal. However, PCP in HIV-negative patients may cause fulminant respiratory failure with a high mortality index (8). HRCT of the thorax can help in PCP diagnosis. Ground glass opacity is a typical finding of PCP on HRCT, particularly in the upper lobes. Nevertheless, an atypical presentation, including asymmetrical infiltrates, subpleural nodules, cavitation, lymphadenopathy, cyst, pleural effusion, or pneumothorax may be seen on HRCT images of PCP patients (2,10). Roux et al. (11) found atypical HRCT patterns in 14% cases of PCP in HIV-negative patients in France.

Several laboratory examinations may be used to detect *P. jirovecii*, such as microscopic and molecular tests of induced sputum, bronchoalveolar lavage fluids (BALF), or a lung tissue specimen. Microscopic examination using light microscopy can detect this parasite, and especially mature cysts, with staining methods such as toluidine blue O, methanol-Giemsa, or Gomori-Grocott's methenamine silver nitrate. These staining methods have a high sensitivity, but a low specificity for the detection of *P. jirovecii* in BALF smears. Molecular detection using both conventional and real-time PCR was developed for the diagnosis of PCP. This method has a high sensitivity and specificity for the detection of *P. jirovecii* in most specimen sources, including induced sputum, BALF, nasopharyngeal aspirate, oropharyngeal wash, and lung biopsy. A PCR assay is also recommended for a diagnosis of PCP in an HIV-negative patient. In fact, a positive result from a PCR test may be seen in PCP patients or a Pneumocystis colonization, but it may be distinguished by clinical, radiological, and laboratory assessment (1,2). In our patient, mild, non-specific symptoms appeared in the early stage. Since our country has a high incidence of pulmonary TB, TB diagnostic procedures were performed. The result of these tests was negative, so we could exclude TB infection in this patient. The PCP diagnosis was established based on the use of a steroid as a risk factor for PCP, the HRCT scan features, and the positive *P. jirovecii* result in the induced sputum sample using the PCR method.

The recommended drug of choice and first-line therapy treatment for PCP is TMP-SMX. Alternative regimens, such as atovaquone, clindamycin plus primaquine, intravenous pentamidine, or TMP plus dapsone may be administered if there is a contraindication or the patient cannot tolerate TMP-SMX (Table 1). The clinician may also choose the drugs used to treat PCP based on the severity of the disease. The duration of PCP treatment in HIV-positive patients is 21 days. In contrast, in patients without HIV infection, the duration of treatment is 14 days (2). SLE patients who undergo a TMP-SMX regimen should have close monitoring, since it may trigger a lupus flare (12). Sulfa drugs may also provoke an allergic reaction in SLE patients and the frequency is higher in this group than in the normal population (13). Our patient had been administered a TMP-SMX regimen for 2 weeks. She had experienced nausea, but tolerated this adverse reaction.

Unlike the guidelines for PCP prophylaxis among HIV-positive patients, there is no published guideline for chemoprophylaxis of PCP in HIV-negative patients who are treated with immunosuppressive therapy (14). Chemoprophylaxis may be suggested in a patient who receives at least 20 mg of prednisone per day for at least 1 month, but it may expose the patient to an adverse reaction to these drugs. A CD4+ cell count of less than 200 cells/mm^3 after 1 month of immunosuppressive therapy is another alternative indication to provide PCP prophylaxis in this group. The CD4+ cell count should be monitored in patients who receive more than 15 mg prednisolone or equivalent per day, a corticosteroid for more than 3 months, or with a total lymphocyte count of less than 600 cell/mm^3 (2,14). The timing of the start of prophylaxis therapy as well as the duration and the timing of the discontinuation of therapy may need further investigation in this group. Some case reports have revealed that PCP infection still occurred in autoimmune patients after the immunosuppressive agents were discontinued though they had PCP prophylaxis during treatment with immunosuppressive drugs. Furthermore, the incidence of PCP among patients with rheumatic diseases is dissimilar. PCP in SLE patients is rare, but its incidence is high at dermatomyositis patient. This evidence is also another consider-

ation in the administration of chemoprophylaxis to patients with rheumatic disease (12).

In summary, PCP in SLE patients who receive long -term steroid therapy is unusual. The symptoms may be mild in the early stages, but it may be potentially life-threatening with severe infection. Diagnostic procedures, such as radiological and laboratory investigations, should be performed in cases of suspected PCP infection. The treatment for PCP infection may be selected based on the severity of disease and patient's tolerance. The clinician should be aware of the co-incidence of PCP in patients with rheumatic disease who receive immunosuppressive therapy, since the incidence is increasing and it is more fatal than PCP in HIV-positive patients.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - G.A., D.K.S.; Planning and Design - G.A., D.K.S.; Supervision - G.A., D.K.S.; Funding - ; Materials - ; Data Collection and/or Processing - D.K.S., G.A.; Analysis and/or Interpretation - D.K.S.; Literature Review - G.A., D.K.S.; Writing - G.A.; Critical Review - D.K.S.

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