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Original Research Article

Pulmonary Pneumocystis in HIV-Negative Patients: About 13 Cases

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Abstract

We present thirteen examples of pulmonary pneumocystis (PCP) in patients without HIV infection. Eight men and five women, average age 55, with one instance of breast neoplasia, two cases of DICV, one case of "Goodpasture's syndrome," one case of idiopathic fibrosing PINS treated with extended corticotherapy for two years, and the other patient without known immunosuppression. In 11 cases, there is persistent dyspnea and severe hypoxia. Lymphopenia (9 instances), with a 920.76 element/mm3 average rate. Except in two cases where examination of the bronchoalveolar lavage fluid was required, the diagnosis was established by the isolation of Pneumocystis jiroveci in the induced sputum. The evolution was positive in every case while receiving trimethoprine-sulfametaxazole and corticosteroid therapy.

Keywords: Pneumocytis jiroveci, immunosupression, lymphopenia, induced sputum, prophylaxis.

INTRODUCTION

Pneumocystis jiroveci (PCJ), a fungus, is the culprit behind the serious opportunistic illness known as pulmonary pneumocystis (PCP), which affects immunocompromised people. Since it still has a dismal prognosis and seems to be on the rise in HIV-negative patients, early detection and treatment are still necessary.

The purpose of our study is to analyze the clinical and paraclinical characteristics of individuals with PCP and to identify the immunodepressions (apart from HIV) most at risk for this infection.

MATERIALS AND METHODS

Patient Selection

This study was conducted retrospectively over a two-year period (from January 1, 2021, to December 31, 2022), using the computerized medical data of the pulmonology department of CHU Hassan II Fez. The study included only HIV-negative individuals, and HIV serology testing was done in every PCP episode.

Data Collection

Analysis of the clinical records involved gathering epidemiological information (age, sex, date of beginning), history (particularly immunosuppressive disease), and immunosuppressive therapies used. The PCP episode's clinical, biological, radiological, and microbiological data were gathered, together with information on the treatments used and how they changed over time.

RESULTS

Population Description

A total of 13 cases were gathered, with a sex ratio of 8 men to 5 women (1.6), and an average age of 55.23+/-15.44 [28-75 years]. PCP happened in the spring in 4 cases, the summer in 2, the fall in 6, and the winter in 1. A third of patients (30.76%) reported actively smoking.

The underlying conditions that caused the immunosuppression in each case were, respectively: a Goodpasture's syndrome in one case where the patient had already gotten five boluses of cyclophosphamide and had been on azathioprine for a year; and chronic hemodialysis. A common variable immunological deficit affected both patients. Chemotherapy for a left breast cancer in one patient lasted six months. A fifth patient was treated for two years with azathioprine and long-term corticosteroid therapy for idiopathic fibrosing

PINS. The median period from the onset of symptoms to the diagnosis of PCP was 23 days, with a range of 5 to 62 days. In 5 cases, the beginning was gradual, while in 8 cases, it was sudden.

Clinically, all of the patients were dyspneic at the time of management, with 11 of them experiencing respiratory distress. 85% of the patients also had productive coughs, and 77% of them were feverish.

In terms of biology, the mean circulating lymphocyte count was 920.76 cells/mm3. In any case, CD4+ cells weren't counted. The C-reactive protein level was 132 mg/l.

10 patients exhibited diffuse bilateral lung illness on chest CT, with ground glass in 6 cases, condensation in 4, atypical pleural collection in 2, and sequential bronchial dilatation in 1.

With the exception of two cases where examination of the bronchoalveolar lavage fluid was required, all diagnoses were based on the isolation of Pneumocystis jiroveci in the induced sputum. ECBC and BAL fluid analyses revealed no co-infections in any patients.

An average of 30 days passed between the onset of symptoms and the beginning of treatment.

TMP-SMX was administered orally to all individuals. One instance of cotrimoxazole intolerance was noted with the emergence of a fixed erythema pigmentosa, which prompted the drug's withdrawal to try tolerance induction before suggesting an alternate in the event of failure.

Corticosteroid medication was given to eight individuals (62%) who had PCP. The mean room air SaO2 for patients who received corticosteroid therapy was 65.62%. Five patients needed oxygen therapy for an extra month, one patient needed non-invasive ventilation for his underlying chronic lung condition, and four patients needed non-invasive ventilation. All of these patients were alive after being hospitalized. There were no reported fatalities.

18 days on average were spent in the hospital. 8 days was the shortest and 51 days was the longest timeframe.

Three cases received a prophylactic dose of TMP-SMX: one was receiving cyclophosphamide and long-term corticosteroid therapy for his anti-synthetase syndrome, which was identified concurrently with his PJ infection; another was receiving long-term azathioprine and chronic hemodialysis; and the third case had a variable common immune deficiency with PJC colonization.

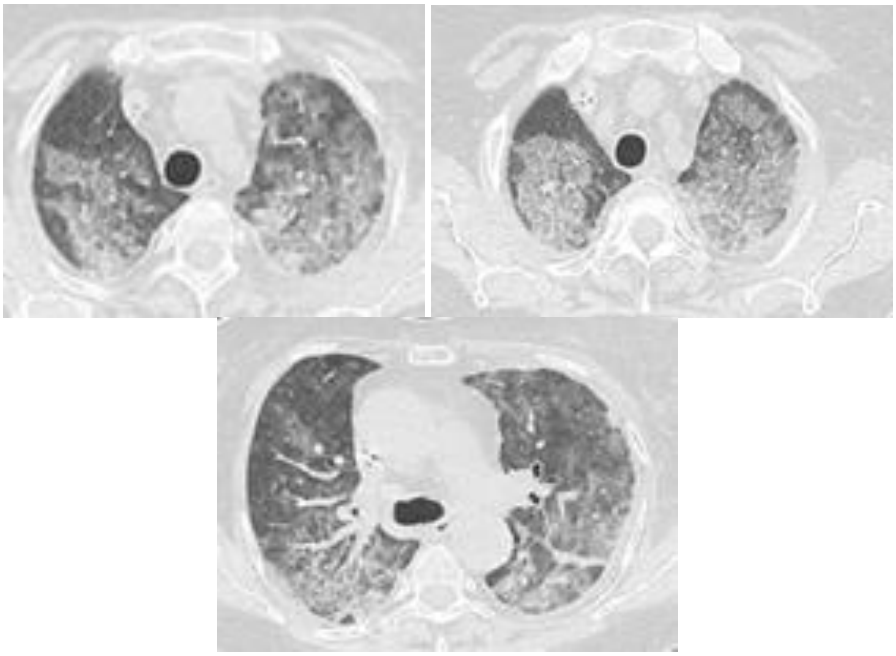

Figure 1: A 67-year-old female patient's CT scan reveals diffuse ground glass regions throughout the center and periphery of both lung hemifields

DISCUSSION

In the past, pulmonary pneumocystis was a rare pathology that exclusively affected kids with acute lymphocytic leukemia, severe malnutrition, congenital cellular immunity abnormalities, and organ transplant patients [1]. With the advancement of prophylaxis and antiretroviral treatment, the number of pneumocystis cases among HIV-infected patients has significantly decreased to reach a value of 0.3cas/100 persons/year by March 1998. In the 1980s, when AIDS first emerged, it was observed in 60-80% of HIV patients [2]. The bulk of pneumocystis cases currently reported

in developed nations include non-HIV infected patients who fall into other risk groups [3, 4].

Pneumocystis jiroveci is a ubiquitous fungus specific to the human species that is responsible for a primary infection most often asymptomatic in children [5, 6]. The corresponding antibodies are detected as early as four years of age [7].

The prevalence of PCP appears to be rising in patients without HIV infection [2, 8], especially in those with hematological malignancies, those receiving chemotherapy for cancer [2], those who have had a solid organ or marrow transplant, and anyone else receiving corticosteroid and/or immunosuppressive therapy. PCP appears to be caused more by Wegener's granulomatosis than other dysimmune illnesses. Two of the patients in our series had CVID, one had breast cancer, one had an autoimmune condition like Goodpasture's syndrome, and another was receiving prolonged corticosteroid therapy.

Between the fourth and fifth decade, pulmonary pneumocystis occurs often in HIV-negative people. The average age of the 28 patients in a study by Ficko [9] was 52.8 years, the three instances in a study by Battikh had an average age of 50 years, and the average age of our series was 55 years, with no clear sex preponderance [7]. It is distinguished by a more abrupt onset with an average delay of 5 to 6 days [3, 8], by more frequent and intense dyspnea (occurring in about 87% of cases in the literature), by more severe hypoxia necessitating more frequently mechanical breathing during this illness (in 60–70% of cases), and by other characteristics [10, 11]. The literature is therefore supported by our findings.

The median number of circulating lymphocytes in HIV-uninfected immunocompromised patients is 500/mm3 (278–880), compared to 802/mm3 (499–1200) in HIV-infected patients. The median in our series was 640mm3. The CD4 T cell count, which was 200 elements/mm3 in Roblot's series [12] but was not investigated in our investigation, appears to be less linked with PCP than in HIV patients [3]. In addition, the amount of C-reactive protein is greater, measuring 120 mg/l (60-210) as opposed to 48 mg/l (17-128) in HIV infection [8-13].

It might be challenging to make a positive PCP diagnosis in people who do not have HIV. In comparison to HIV infection, the pneumocytis burden in these patients is reduced [6].

Gomori-Grocott staining or immunofluorescence are used to detect the microorganism in induced sputum or BAL, but due to decreasing sensitivity and low fungal burden, new diagnostic tools such qPCR and B-D-glucan assay have been developed [13].

The sensitivity of PCR in BAL (84%) and induced sputum (almost 100%) is outstanding, with specificities calculated at 90 and 83%, respectively. As a result, PCR has a good negative predictive value, however as of 2015, it is not officially possible to distinguish between colonization and infection [14-15-16].

The measurement of serum levels of b-D-glucan, a component of the fungal wall and an indirect marker of fungal infection, can be used as an alternative to the diagnosis of pneumocystis. However, this test lacks Pneumocytis specificity and is unable to identify some fungi, including Zygomycetes and Blastomyces dermatitidis.

Three types of patterns can be identified when examining the radiological data of pneumocystis in non-HIV patients: diffuse ground glass, inhomogeneously distributed, without connection with secondary lobules and with respect for the subpleural zone, condensations along the bronchovascular axes, with distortion and thickening of the interlobular septa, or ground glass with clear demarcation by the interlobular septa of the normal lung [2].

Trimethoprim-sulfamethoxazole (TMP+SMX) is still the only curative treatment for pulmonary pneumocystis and is used as first-line therapy at the following doses: TMP 15-20 mg/kg and SMX 75-100 mg/kg were administered in three to four doses daily for 21 days, while some authors contend that 14 days may be adequate in light of the lower fungus load in individuals without HIV who had their alveoli treated. For hypoxemic patients (PaO2 70mmHg) with the following regimen: prednisone, 40 mg 2/d from d1 to d5, 40 mg/d from d6 to d10, and 20 mg/d from d11 to d21, adjuvant corticosteroid therapy should be combined [14, 13, 17]

The primary option, intravenous pentamidine, carries a high risk of significant side effects, including hypoglycemia, acute pancreatitis, and renal failure. Severe dosages of atovaquone or daily pentamidine sprays, which are less effective, shouldn't be prescribed.

Clinicians now advise preventative medication for select patient groups due to the primary prophylaxis's demonstrated effectiveness in the treatment of AIDS [18].

We were able to estimate the incidence of pneumocystis for the main risk diseases in a single-center observational study by Fillâtre *et al.*, [14], which included 154 cases of documented pneumocystis in non-HIV-infected patients. We did this by dividing the number of patients with pneumocystis for each disease by the total number of patients followed up for that disease during the study period. With the help of this research, we were able to rank the main

immunosuppressive illnesses and their therapies in terms of the risk of pneumocystis (Figure 2) [19, 20].

Steroids continue to be a PCP risk factor. In the trial by Yale *et al*., [21], doses of steroids equivalent to 16 mg of prednisone or higher provided for eight weeks were linked to a considerable chance of contracting pneumocystis. In the series by Roblot [12], 57 patients were receiving long-term corticosteroid therapy at a mean daily dose of 46.3 mg. In one of our cases, extended corticosteroid medication had been administered for two years.

First-line prophylaxis is based on TMP-SMX and uses either 400 mg SMX/80 mg TMP (Bactrim simple®) once a day or 800 mg SMX/160 mg TMP (Bactrim forte®), three times a week. With daily dose, one study hypothesized a marginally increased risk of adverse events [8, 22], but this has not been verified [7, 13].

In a side-by-side comparison study, 11% of patients receiving monthly pentamidine aerosols (300 mg) developed pneumocystis as opposed to none receiving TMP-SMX prophylaxis [23]. With incidences of pneumocystis assessed at 18.4 and 15.7 cases/100 patient-years, respectively, among the other oral prophylaxes that have been examined, dapsone (100 mg/day) and atovaquone (1500 mg/day) are expected to have equal efficacy [13]. However, atovaquone is more well tolerated.

In Godeau's series, 13 out of 23 patients with systemic disorders had received secondary prophylaxis, suggesting that it is not necessarily necessary. Patients receiving prophylaxis or not, no relapses were seen after 22 months [7]. In neither our series nor Niniin's [12] were any relapses reported, while Sepkowitz's [2] series documented two cases out of 254 patients.

For reasons that are not fully understood but may include diagnosis at a more advanced stage (more rapid progression of lesions, more difficult diagnosis), and difficulties in correcting the immune deficiency (more straightforward in the course of AIDS, since the advent of highly effective combined antiretroviral treatments), pulmonary pneumocystis remains serious in immunocompromised patients outside of HIV infection with a mortality ranging from 20 to 60% [10, 12]. In our study, no deaths were found, although severe respiratory distress was observed in 11 instances, 4 of which had benefited from non-invasive mechanical ventilation. There were 12 severe instances in Ficko's series, of which 9 received mechanical ventilation and resulted in 7 deaths; there were only 2 fatalities in Battikh's series.

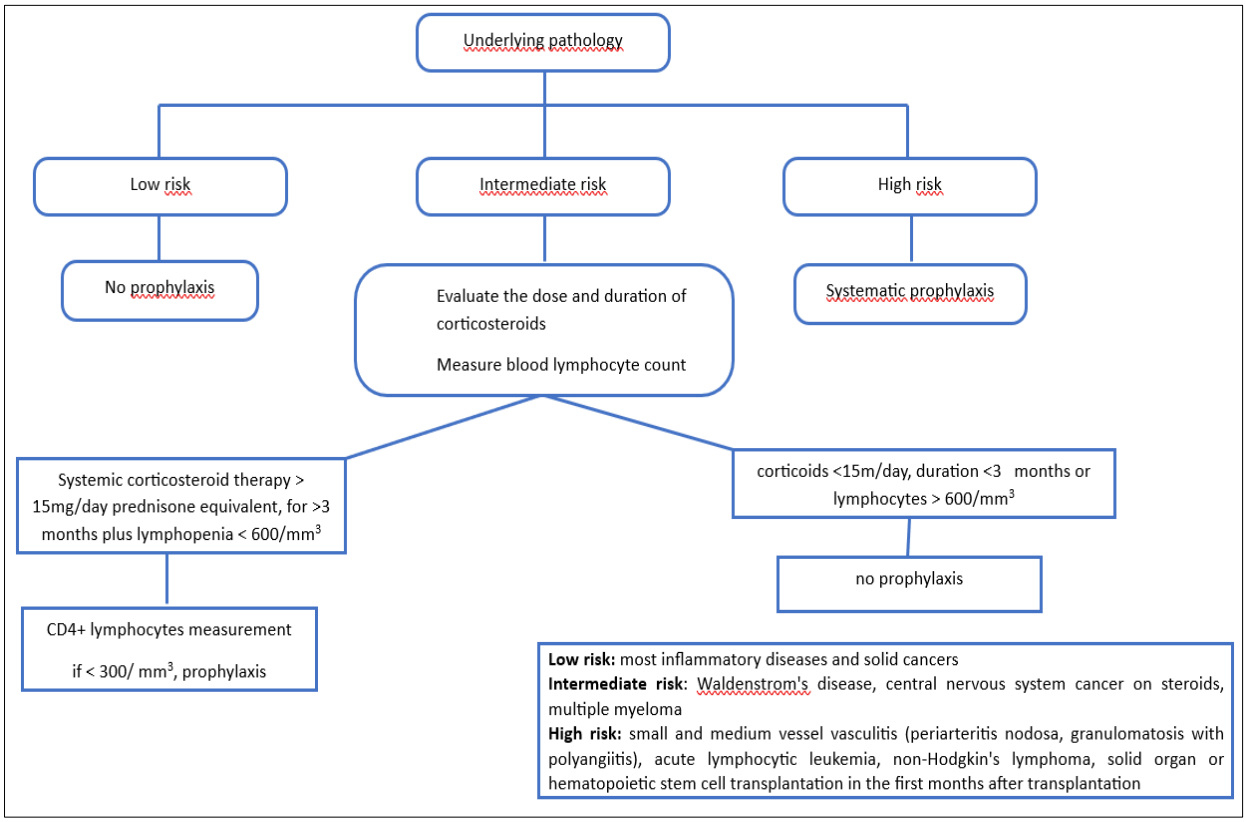

Figure 2: Decision support algorithm for pneumocystis prophylaxis in HIV-uninfected immunocompromised patients [8-18]

Table 1: Immunosuppressive illness frequency in PC patients without HIV

	Ficko (n=28)	**Peron** (n=321)	**Battikh** (n=3)	**Roblot** (n=103)	**Our series** (n=13)
Hematologic cancer	9 (marrow transplants)	74 (14 allograft, 11 autograft)	1 (lymphoma)	18	-
Vasculitis systemic	2	64	1(Wegener's granulomatosis)	27	-
Immune disorder	4				1 (Goodpasture's syndrome)
Cirrhosis	1				-
Organ transplantation		97		24	-
Solid cancer		38	1 (breast neoplasia)	18	1 (breast neoplasia)
Long-term corticosteroids	10 (at time of Dg) 23 cases of CO			57	1
Immunosuppressant or biotherapy	10 (At time of Dg) 10 cases (ATCD) 5 biotherapies	64	3 at the time of the Dg	22	3
Chemotherapy	1 (at the time) 5 (history of chemo)		2		1
Mortality	7		2		0

CONCLUSION

Pneumocystis is a serious illness with a rapid onset and a high fatality rate in patients who are not affected by HIV. TPM-SMX is still the first line of treatment, and corticosteroid therapy should only be used in hypoxemic patients. The course of treatment lasts for 21 days. It is necessary to include non-HIV immunosuppressed individuals in current education initiatives for HIV patients. Numerous premature deaths could be avoided if the same success is attained. Prophylaxis recommendations ought to be based on a number of factors, including the underlying illness, immunosuppressive medications taken, and total lymphocyte count.

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