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Respiratory Diseases

Pneumocystis in the Pulmonary Department: About 20 Cases

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Abstract **Original Research Article**

Pneumocystosis is an opportunistic infection responsible for severe infiltrative pneumonia and death in immunocompromised patients. However, few studies have been carried out to identify the epidemiological aspects of this pneumonia in our context. Its frequency at Morocco in not well known Our work is a descriptive, analytical and retrospective study of 20 cases collected from January 2008 to December 2021 in the respiratory diseases department of the IBN ROCHD in Casablanca. The goal is to give a better characterization of the specificities of this pathology in our context and thus to contribute to better management. We identified 12 men and 8 women, aged 28 to 45 with an average age of 37. Dyspnea (100%), hyperthermia (90%) and dry cough (30%) were the symptoms indicative of the infection. Pneumocystis jirovecii was isolated from bronchial aspiration fluid in 5 cases. The diagnosis was therefore radio-clinical in 75% of the cases. The LDH level was increased in 18 patients with an average value of 1379.3 UI/l. Curative treatment with the Triméthoprim-Sulfaméthoxazole combination has been initiated in all our patients. Fifty-five percent of patients adjuvant corticosteroid therapy and only 50% were on oxygen therapy. Prophylaxis remains the best treatment for combating this scourge.

Keywords: Pneumocystosis, Pneumocystis jirovecii, immunodepression, opportunistic mycosis.

INTRODUCTION

Pneumocystis (PCP) is an opportunistic infection caused by a newly classified fungus, Pneumocystis jirovecii classified as a fungus, Pneumocystis jirovecii (formerly Pneumocystis carinii). This eukaryotic and ubiquitous pathogen is responsible for severe interstitial lung disease and death in immunocompromised individuals in the absence of treatment [1].

Pneumocystis pneumonia was nevertheless considered rare until the onset of the AIDS epidemic in the early 1980s, when it emerged as the leading opportunistic infection and rapidly became the leading cause of death in AIDS patients. However, the successive introduction of prophylaxis and potent antiretroviral treatments has decreased its incidence [2, 3].

In contrast to this decrease, an increase in the number of cases has been reported in immunocompromised patients outside of HIV. Subjects at risk include patients with hematologic malignancies, those receiving chemotherapy, those who have undergone marrow or solid organ transplantation, and any patient on corticosteroids or other immunosuppressive therapy [3]. It is a severe infection in the absence of adequate management [4].

The aim of our study is to describe the epidemiological, clinical, paraclinical, therapeutic and evolutionary aspects of patients with pneumocystis followed up in the respiratory diseases department of the Ibn Rochd University Hospital in Casablanca.

METHODS

This is a descriptive, analytical and retrospective study, covering a period of 14 years from January 2008 to December 2021, targeting 20 patients with Pneumocystis pneumonia, hospitalized in the Pneumology Department of Ibn Rochd Hospital in Casablanca.

RESULTS

The average age of our patients was 37 years with extremes ranging from 28 to 45 years and a male predominance (12 men and 8 women). Fifty-five percent of patients were single. For sexual risk behavior, 15 (75%) of the patients reported having had unprotected sex with multiple partners at some time in their lives.

No patient was known to be immunocompromised at the time of admission. A history of treated tuberculosis was noted in three (15%) cases. Smoking was noted in eight (20%) cases. The average length of hospitalization was 38 days with extremes ranging from 5 days to 3 months. The onset of symptoms was progressive in 16 (80%) cases, with the exception of 4 (20%) whose onset was acute. This was dominated by dyspnea of progressive aggravation in all cases, dry cough in 6 (30%) cases, mucous bronchial syndrome in 12 (60%) cases, chest pain in 9 (45%) cases, hemoptysis in 3 (15%) cases and chronic watery diarrhea in 5 (20%) cases (Figure 1). Alteration of the general condition was noted in all our patients with asthenia, anorexia and uncounted weight loss. Feverish feelings were noted in 19 (95%) cases.

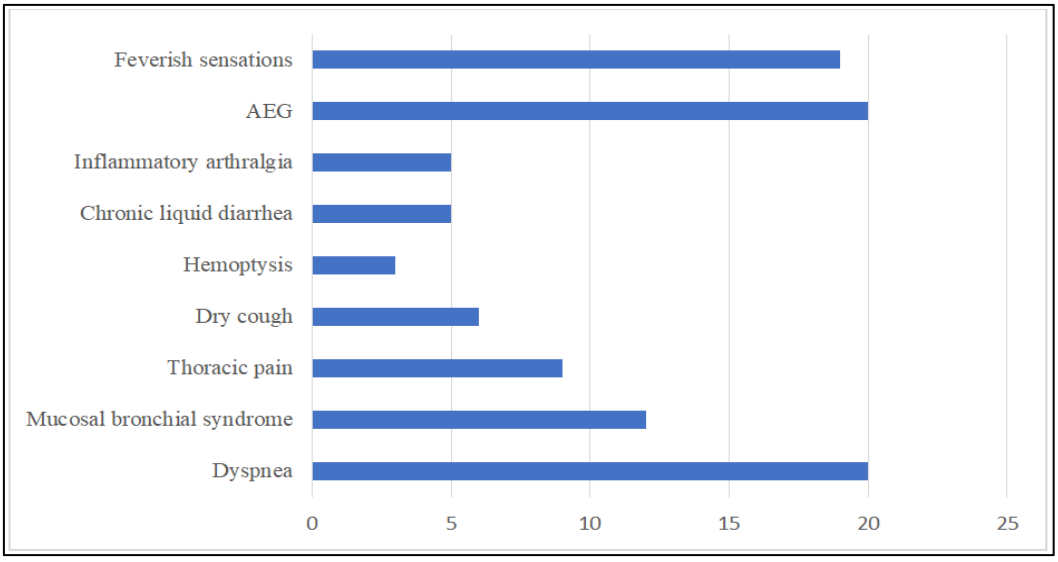

Figure 1: Distribution of patients according to functional signs

The general condition of the patients was judged by the WHO performance status (PS). The average PS was 3 with extremes between 2 and 4. A fever greater than 38.5°C was found in 18 (90%) cases. All patients were polyenic on admission, of which 9 (45%) were tachycardic and showed signs of respiratory struggle and cyanosis.

The rapid HIV test was performed in all our patients. It was positive in 17 (85%) patients (Figure 2).

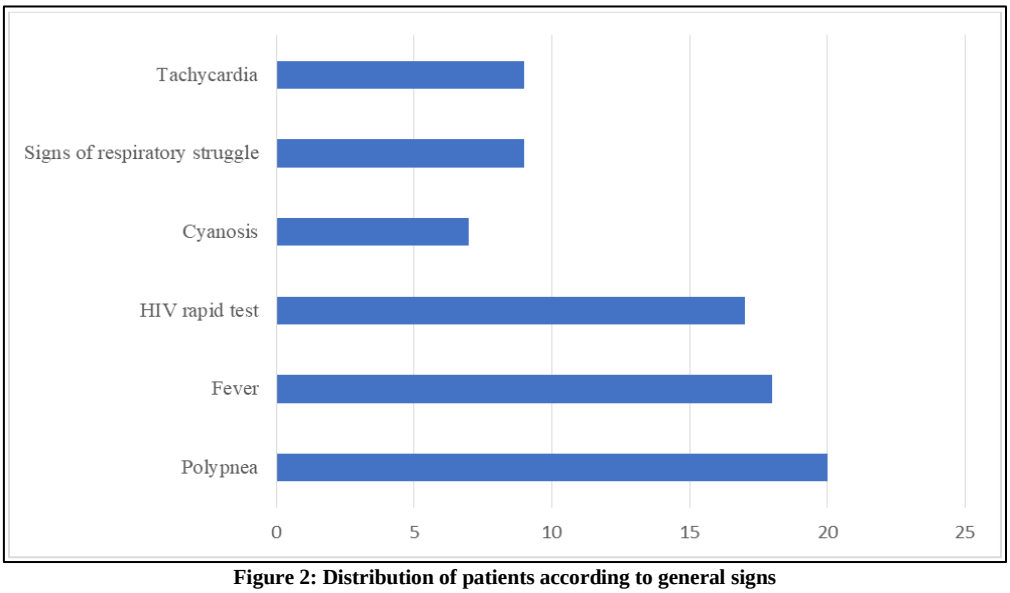

Figure 2: Distribution of patients according to general signs

On chest examination, 11 (55%) patients had bilateral crepitus rales, 4 (20%) had fluid effusion syndrome and 2 (10%) had air effusion syndrome.

Chest X-ray showed diffuse interstitial syndrome in 11 (55%) cases (Figure 3), pleural-type opacity in 4 (20%) cases, miliary in 3 (15%) cases (Figure 4), pneumothorax in 2 (10%) cases (Figure 5), finely ringed clears and large hilum in one (5%) case each.

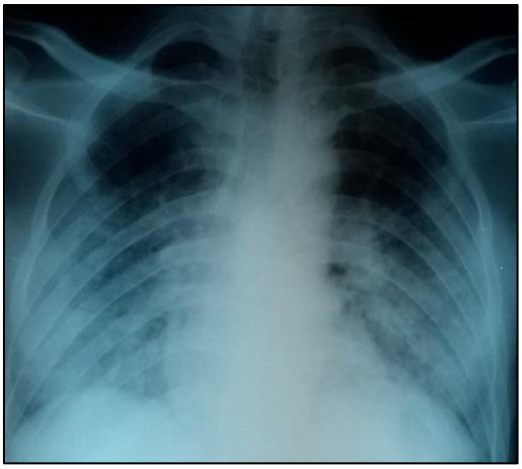

Figure 3: Bilateral interstitial syndrome in a 34 year old HIV positive patient

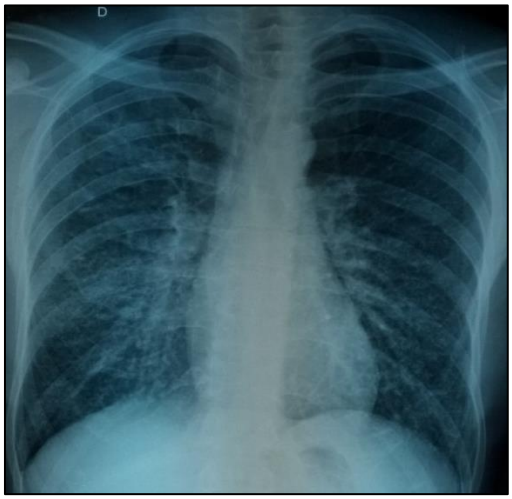

Figure 4: Febrile miliaria in a 32 year old HIV positive patient

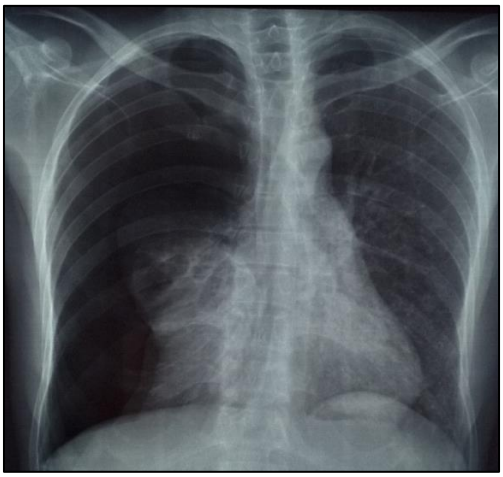

Figure 5: Right total pneumothorax associated with a left interstitial syndrome in a 32-year-old HIV-positive a 32 year old HIV positive patient

Chest CT scan showed a ground-glass appearance in 8 (40%) cases (Figure 6), a focus of alveolar condensation in 6 (30%) cases (Figure 7), diffuse bilateral interstitial syndrome in 5 (25%) cases, pleurisy in 4 (20%) cases, pneumothorax in 2 (10%) cases and mediastinal adenopathy in one (5%) case.

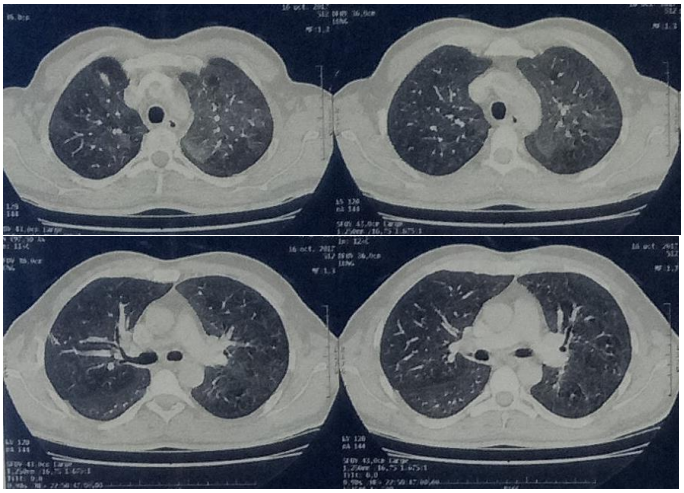

Figure 6: Ground glass appearance in a 32 year old HIV positive patient

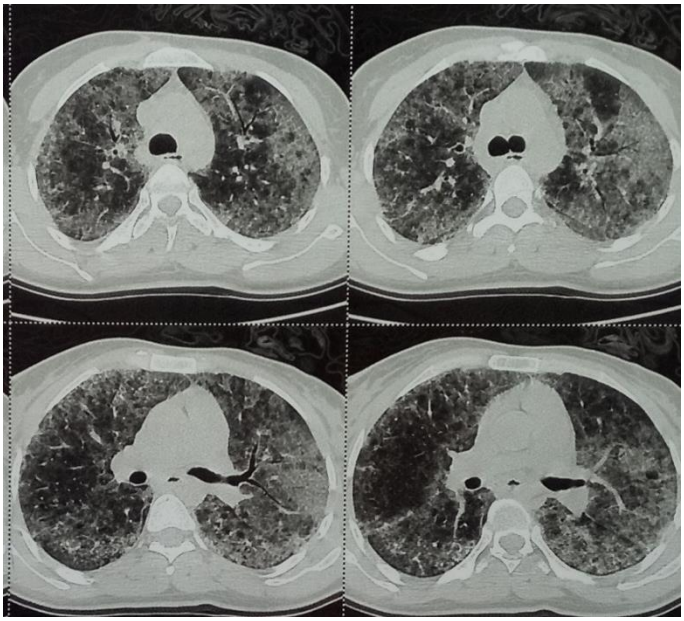

Figure 7: Bilateral diffuse alveolar condensation foci and multiple ground-glass nodules nodules in a 30-year-old HIV-positive female patient

Flexible bronchoscopy was performed in 14 (55%) patients and showed diffuse 1st degree inflammation in 6 (30%) patients and 2nd degree in 8 (40%) patients.

The bronchoalveolar lavage showed a clear fluid and the cellular formula was macrophagic in all cases. Nine (45%) patients had undergone staged bronchial biopsies, the results of which were in favor of a chronic non-specific inflammatory remodeling.

The search for Pneumocystis jirovecii, by direct examination of the bronchial aspiration fluid, was positive in 5 (25%) cases. The search for BKD, common germs, culture on Sabouraud's medium and expert gene were negative in all patients, except for one patient in whom BKD was positive.

HIV serology was positive in 18 (90%) of the 20 patients, the other 2 (10%) had positive hepatitis C serology. The serological status was identified by a screening test (ELISA technique) and then confirmed by a confirmatory test (Western Blot).

All patients had received a TPHA, VDRL. These were negative. Seven (35%) patients had cytomegalovirus viremia.

All patients had had an LDH assay. The LDH was increased in 18 (90%) patients with extremes

ranging from 513 IU/l to 6137 IU/l and a mean value of 1379.3 IU/l. The rest of the cases had a normal level.

In our series, CD4 lymphocyte count was performed in 9 (45%) patients. The mean count was collapsed at 40.6 copies/mm with extremes between 6 and 77 elements/mm.

Trimethoprim-Sulfamethoxazole 160/800 mg was prescribed as first-line treatment in all patients at a rate of 2cp x3/d for 21 days.

This treatment was combined with corticosteroid therapy for 14 (55%) patients, given their respiratory status, at a rate of 240 mg/d for 3 days, then 120 mg/d for another 3 days and finally 60 mg/d until the 10th day. High-flow oxygen therapy was indicated in 10 (50) patients, non-invasive ventilation in 7 (35%) patients and prophylactic heparin therapy in all cases.

The 18 (90%) HIV-infected patients had initiated triple therapy during their hospitalization. Four (20%) patients had received antibacillary treatment (ERIP K4*), one of whom had received bacteriological confirmation and 3 of whom had received treatment for a very suggestive radio-clinical picture. Seven (35%) patients had received Ganciclovir 250 mg twice daily for the treatment of cytomegalovirus infection. Five (25%) patients were put on Fluconazole 150 mg one tablet per day for the treatment of oropharyngeal candidiasis.

The evolution under treatment was favorable in 19 (95%) patients with radio-clinical improvement. Only one death occurred in an HIV-positive patient after a course of chemotherapy for Kaposi's sarcoma diagnosed during hospitalization.

DISCUSSION

The frequency of pneumocystis in Morocco is not well known. Few studies have been conducted to identify the epidemiological aspects of this pneumocystis in our context.

A retrospective study conducted between 2000 and 2009, in the department of parasitology and medical mycology of Ibn Sina Hospital in Rabat, reported 8 cases. [5] Another study reported 6 cases of pneumocystis between 1986 and 1994 in the University Hospital of Casablanca [6]. In our series, 20 patients were identified over a period of 14 years. The number of positive cases in Moroccan series is significantly lower than in American and European series. The rarity with which P. Jirovicii has been incriminated in pneumopathies has been reported by many authors from different African countries (Table 1).

Table 1: Number of cases by study period in various series

Series	Study period	Number of studies
Rabat, Morocco [5]	2000-2009	8
Casablanca, Morocco [6]	1986-1994	6
Rabta, Tunisia [7]	2010-2016	28
Lille, France [8]	1998-2008	73
Londres, UK [9]	1985-2006	498
Lisbinne, Portugal [10]	2003-2007	498
Goteborg, Suéde [11]	1990-2003	108
Texas, USA [12]	1990-2003	79
Our series	2008-2019	12

This difference is certainly due to the underestimation of pneumocystis due to the existence in these countries of other more virulent opportunistic infections, such as tuberculosis. In addition, diagnosis in developing countries is often made late based on clinical and radiological findings without recourse to biology due to the lack of diagnostic resources, the low level of medicalization and the difficult access to care [7].

Pneumocystis can occur in patients of any age. In our series, the most incriminated age group was between 21 and 39 years (63.6%), the average age was 37 years. This is consistent with other Moroccan series which found a predominance in young adults. This may be due to the size of the young population in Morocco.

With a sex ratio (M/F) of 2, our data are comparable to those in the literature. In general, men seem to be more likely to develop pneumocystis than women. This may be related to the high incidence of HIV seropositivity in males. Few authors have noted a female predominance. A study in South Africa of HIV-positive patients found 84 females versus 36 males in a group of 120 patients, which may be explained by the high incidence of HIV infection in women in that country [8].

The insidious onset of symptoms over several weeks associated with a progressive evolution to acute respiratory failure is very typical of pneumocystis according to the literature. [9] We have identified a progressive mode of onset in 81.8% of cases in our study. In contrast, many authors have reported a rather

acute onset in patients with an immunosuppressed background apart from HIV infection [9].

The clinical picture of pulmonary pneumocystis is variable and non-specific. It may include cough, dyspnea, chest pain, hemoptysis, fever, and altered general condition [10].

The standard chest radiograph is the basic supplementary examination in the diagnosis of pneumocystis. It provides information on the appearance, location and extent of the lesions [11]. These are classically characterized by a bilateral, diffuse, fairly symmetrical interstitial lung disease, predominantly peri-hilar or at the bases (Figures 8 and 9). Chest radiology may be normal, especially in the early stages [12]. Patients with acute respiratory failure present with a near opaque "white lung" chest radiograph in advanced stages. Atypical radiographic findings are less common in non- HIV patients than in AIDS patients. These may include pneumothorax, pleural effusion, mediastinal PDAs, pseudocysts, disseminated nodules with varying degrees of excavation, and localized opacities at the apexes [13]. Diffuse interstitial syndrome was the most frequent radiological appearance in our series.

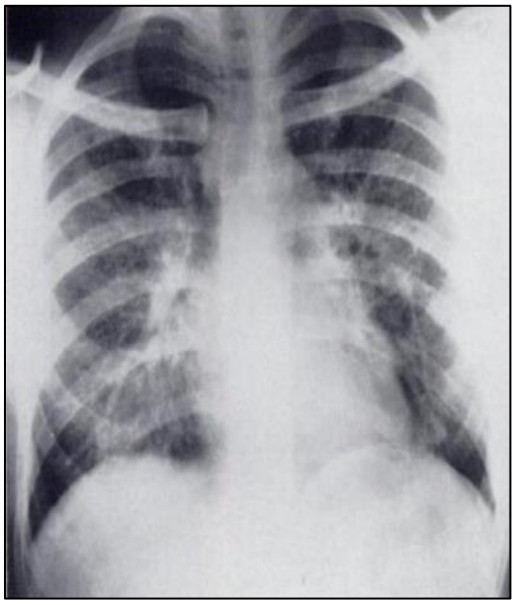

Figure 8: Reticulo-micronodular, peri hilar infiltrates with consolidation in the right lower lung field

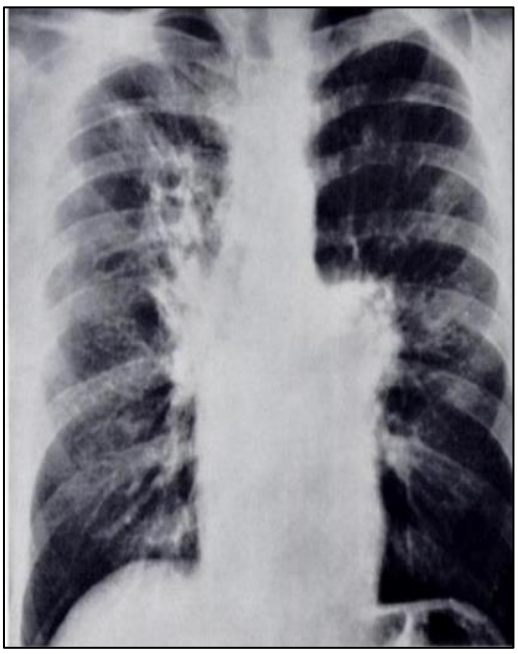

Figure 9: Diffuse interstitial infiltrate and excavated opacities in the right upper lobe

Thoracic scan is the test of choice. It is more sensitive than chest radiography in detecting pulmonary pneumocystis and may therefore be useful in symptomatic patients with normal or suspicious radiographs. It most often shows very suggestive ground glass images and a "crazy paving" appearance resulting from thickening of the interlobular septa (Figure 10-12) [14]. The distribution of the lesions is bilateral and symmetrical with respect to the subpleural regions. These typical images in a patient not receiving prophylaxis are usually sufficient to initiate treatment before confirmation of the diagnosis, especially in an emergency setting. Other lesions that may be seen include cysts, traction bronchiectasis and exceptionally nodular lesions, adenomegaly, calcifications or pleural effusion [15]. In our series, 50% of the patients presented with a ground glass appearance.

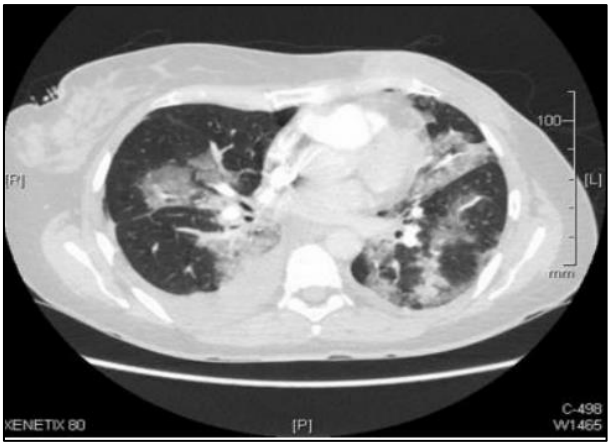

Figure 10: Crazy paving appearance with clear delineation by the inter-lobular septa in a patient followed for a non-Hodgkin's malignant lymphoma

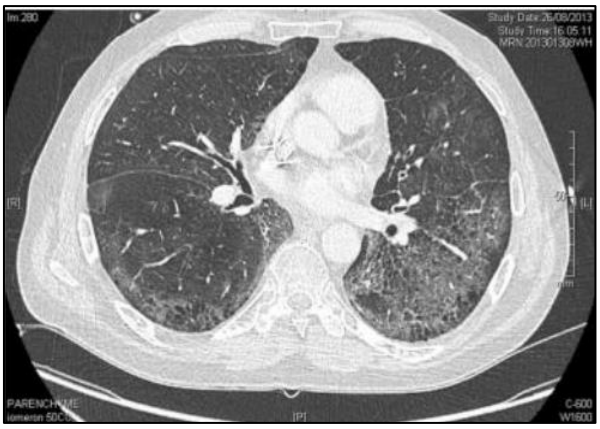

Figure 11: Inhomogeneously distributed ground glass with no connection to the secondary lobules. Respect of the subpleural zone

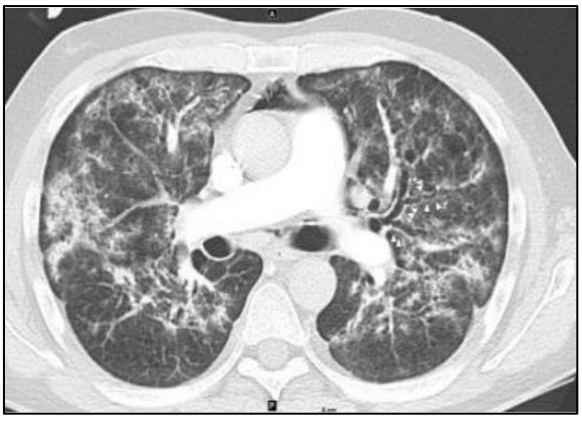

Figure 12: Consolidation of inhomogeneous distribution without connection to secondary lobules, Respect of the subpleural zone

Bronchoalveolar lavage remains the gold standard for the diagnosis of pneumocystis [16].

In case of suspected immunosuppression, the rapid HIV test is used to detect the infection, due to its easy execution, simple and fast reading and low cost. In case of positivity, serological tests are performed to confirm the seropositivity.

Other serologies are performed in patients with immunosuppressive conditions to look for concomitant infections (TPHA, VDRL, hepatitis B and C, Cytomegalovirus...) [17].

The average CD4 lymphocyte count observed in the different series is low compared to the normal value of CD4 lymphocytes which is between 500 and 1600 elements /mm3). The results of our series are in line with those of the literature with an average rate of 40 elements/mm3. Pneumocystis, in HIV-infected patients, generally occurs when the CD4 lymphocyte count is below 200/mm3. The risk is increased when this rate is lower than 100 elements/mm3. This is the case in our series [18].

An elevated LDH level in the blood, greater than 500 mg/dL, has a good predictive value for PCP. However, this level is also elevated in many other pathologies: fungal infections, tuberculosis, toxoplasmosis and lymphomas... During PCP, this level reflects the damage to the lung tissue and the impairment of oxygenation [19].

The goal of treatment is to eradicate the pathogen in order to prevent the development of pulmonary fibrosis and to preserve respiratory function. Associated treatments will depend on the underlying pathology and other infections diagnosed in the immunocompromised patient.

The curative treatment is based on Trimethoprim-Sulfamethoxazole (TMP/SMX) or cotrimoxazole, which is an inhibitor of an enzyme of the folate pathway of P.jirovicii: Dihydro-folate reductase. It is the first-line treatment. It can be administered intravenously in severe forms of pneumocystis and orally in moderate forms or as a relay to intravenous infusions.

For oral administration, the dose is 100 mg/kg SMX + 20 mg/kg TMP per day, in two to four divided doses, for 14 days in HIV-negative patients and for 21 days in HIV-positive patients.

For intravenous infusion in the severely ill subject, the dose is 75 mg/kg SMX + 15 mg/kg TMP per day, in four 60-minute intravenous infusions in 5% aqueous glucose solution.

Toxicity is most common in HIV-infected patients and is most often due to the sulfamethoxazole component. It includes the risk of fever, rash, headache, nausea, vomiting, neutropenia, pancytopenia, aseptic meningitis, nephrotoxicity, anaphylaxis, hepatitis, hyperkalemia and hypoglycemia. Most side effects occur during the first two weeks of use [20].

Pentamidine is an aromatic diamidine active on certain protozoa, its mode of action is unknown. It can be administered intravenously or as an aerosol (used for prevention). The efficacy of pentamidine is equivalent to cotrimoxazole in the curative treatment of pneumocystis. It is in the range of 70 to 86%. The long plasma half-life and the progressive accumulation of the product in the lungs explain the persistence of the therapeutic effect after cessation of treatment [21].

Atovaquone is a structural analogue of the protozoan ubiquinone. It provides activity on P.jirovicii. It is an effective and low toxicity alternative in case of intolerance to TMP-SMX [22].

Dapsone is given with trimethoprim. It is an inhibitor of the 2nd key enzyme of the folate pathway of P.jirovicii: dihydropteroate synthase. The combination of dapsone and trimethoprim, at doses of 100 mg/d and 20 mg/Kg/d orally respectively, has an efficacy comparable to that of cotrimoxazole with much lower toxicity [23].

Clindamycin is an antibiotic that inhibits bacterial growth by stopping RNA-dependent protein synthesis. This therapy is an interesting alternative treatment for PCP [24].

Trimetrexate is a soluble lipid derivative of methotrexate. It inhibits the synthesis of folic acid at the level of dihydrofolate reductase. In combination with folinic acid, it has an antimicrobial effect on Pneumocystis jirovecii without cytotoxic effects on human cells [25].

Symptomatic treatment is based on corticosteroid therapy, which can alleviate the inflammatory reaction in the lungs that often worsens after the start of curative treatment and reduce the deterioration of oxygenation. It is used as an adjunct to initial therapy only in HIV-infected patients with severe pneumocystis (PaO2 less than 70 mmHg on room air) [26]. The US guidelines suggest the following regimen: prednisone 40 mg twice daily for five days, then 40 mg once daily for the next five days, and finally 20 mg daily for the last 11 days.

Mechanical ventilation is indicated in patients with severe pneumocystis who do not improve with treatment. Assisted ventilation with intubation is rarely necessary in HIV-infected patients (less than 10% of

cases), much more frequent in non-HIV patients (40% to 50%) [27].

The evolution is usually towards recovery without sequelae if the treatment is undertaken early and adequately. However, the absence of treatment leads to complications that can be life-threatening in the short term: pneumothorax, pneumomediastinum, acute respiratory failure and aggravation of pulmonary lesions with the appearance of fibrosis [28].

Primary prophylaxis in HIV patients is recommended, to be started as soon as the CD4 cell count is below 200/mm3. The drug of choice is TMP/SMX [29]. After three weeks of well-conducted loading therapy, secondary prophylaxis should be initiated, preferably with TMP/SMX or one of the other drugs mentioned above if TMP/SMX has caused severe side effects [30].

CONCLUSION

Pneumocystis is an opportunistic infection caused by a fungus, Pneumocystis jiroveci, which causes infiltrative pneumonitis in subjects with severe immune deficiency, particularly HIV-infected patients.

The clinical picture is not very specific. However, the triad of hyperthermia, dry cough and dyspnea, in an immunocompromised setting, should lead to the diagnosis. The usual radiological presentation is that of diffuse interstitial lung disease. The ground glass appearance is very suggestive. The diagnosis is confirmed by the detection of the germ in bronchopulmonary samples using numerous staining techniques. The first-line treatment is the combination of trimethoprim and sulfamethoxazole [31].

CONFLICTS OF INTEREST

The authors declare no conflict of interest

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