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Pneumocytosis: An Emerging Opportunistic Mycosis of Public Health Importance

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Review Article

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Abstract

Opportunistic mycoses have become a significant causee of morbidity and mortality in both sexes and in all age groups throughout the world. Pneumocytosis caused by Pneumocystis jiroveciiis, a potentially fatal fungal disease, is significant for public health. Pneumocytosis is often the AIDS-defining disease in HIV-infected patients, usually occurring when CD4 count drops below 200 cells/μL. However, the disease is a growing concern to immune compromised patients without HIV infection, such as those who are undergoing organ transplantation, receiving novel immunosuppressive therapeutics or those who have connective tissue diseases. Pneumocytosis is recognized to affect patients all over the world, and is transmitted from person to person through the airborne route. Patients with and without HIV infections have substantially distinct clinical presentations of Pneumocytosis. Disease has a bad prognosis in individuals who are HIV-negative, rapidly progresses, is challenging to correctly diagnose, and produces severe respiratory failure. Interstitial pneumonia in immune compromised patient a patient is the most common clinical symptom. Due to non-specific signs and symptoms, diagnosis of disease poses a problem. Since chest radiographs are not pathognomonic for disease and the organism cannot be cultivated routinely, a definitive diagnosis must be made using histopathology or cytopathology evidence of organisms in tissue, bronchoalveolar lavage (BAL) fluid, or artificial sputum samples. Trimethoprim-sulfamethoxazole (TMP-SMX) is the treatment of choice. Intravenous pentamidine, clindamycin-primaquine, daps one, atovaquone, and echinocandins are among the second-line treatment options in Pneumocytosis.

Keywords: Diagnosis; Immuno compromised; Non-HIV; Opportunistic Mycosis; Pneumocystis Jirovecii; Pneumocystis Jirovecii Pneumonia; Prophylaxis

Introduction

Pneumocystis was first described in 1909 as a stage in the evolution in the life cycle of *Trypanosome cruzi* by Chagas Chagas C [1]. Subsequently, Delanoe and Delanoe in [2] identified it as a distinct organism. Originally categorized as protozoa, P. jirovecii was later placed in the hemiascomycetes class due to similarities in its 16S ribosomal RNA sequence. As opposed to ergo sterol, which is the normal target for antifungal medications, the cytoplasmic membrane of *P. jirovecii* is primarily composed of cholesterol Suk CW, et al. [3], Amber KP [4]. *Pneumocystis jirovecii* pneumonia

(PCP) is a potentially fatal fungal infection that is seen in immunocompromised individuals Kovacs JA and Masur H [5], Catherinot E, et al. [6]. The disease remains an important cause of morbidity and mortality in all immunosuppressed patients generally and HIV-infected patients in particular Calderon EJ, et al. [7], Kaplan JE, et al. [8]. The disease is an emerging threat to immunocompromised patients but do not have HIV infection, such as those receiving novel immunosuppressive therapeutics for malignancy, organ transplantation, or connective tissue diseases Tasaka S [9]. The development of PCP in individuals who were not immunocompromised has been recorded in several studies. However, the clinical course and prognosis of PCP are not well understood Kim TO, et al. [10].

It is believed that pneumocystosis is transmitted from person to person by airborne route. Patients with Pneumocystosis may present with fever, cough, and shortness of breath and, in severe cases, respiratory failure Ricciardi A, et al. [11]. The disease can be difficult to diagnose because of nonspecific symptoms and signs and because the immunocompromised host may have co-infection with other organisms. Pneumocystis cannot be cultured, and thus the diagnosis of PCP requires microscopic examination of the sputum, bronchoalveolar fluid (BAL), or lung tissue Thomas CF and Limper AH [12]. First-line treatment trimethoprim/sulfamethoxazole therapy should be initiated as soon as possible after confirmation of the diagnosis, because the disease is fatal Hughes W, et al. [13]. Poor outcomes are expected when treatment or diagnosis of PCP is delayed Kim TO, et al. 2021 [10]. The primary objective of this paper is to describe Pneumocystis jirovecii as a new pathogen of public health importance. Emphasis is given on the etiology, transmission, epidemiology, clinical spectrum, diagnosis, treatment and prophylaxis.

Etiology

Pneumocystis jirovecii pneumonia (PCP) is an opportunistic infection caused by *Pneumocystis jirovecii* Fillatre P, et al. [14], Salzer HJ, et al. [15]. Chagas first identified Pneumocystis in humans in 1909, but they were mistaken for a new life cycle stage of the protozoan Trypanosoma cruzi Chagas C [1]. Within a very short time it became clear that this organism infects other host species, is not a trypanosome, and was named Pneumocystis carinii after Carini, a colleague of Chagas Delano M and Delano P [2]. The microorganism that causes the human disease is now known as Pneumocystis jirovecii after Czech parasitologist Otto Jirovec, who was one of the first researchers to study Pneumocystis in humans Stringer, et al. JR [16], Stringer JR, et al. [17]. For many years, the organism was still widely regarded as a protozoan. In 1988, DNA sequence analysis revealed that Pneumocystis was a fungus Edman JC, et al. [18]. The genus Pneumocystis includes several species, including P. carinii and P. jirovecii, which infect rats and humans respectively Fillatre P, et al. [19], Amber KP [4].

Hosts

Pneumocystis organisms have been identified in virtually all mammalian species Vargas SL, et al. [20]. *Pneumocystis* organisms encompass a family of organisms that possess a range of genetic characteristics and are host specific Gigliotti F, et al. [21]. *Pneumocystis carinii* is only a Pneumocystis that infects rats, while P. jirovecii is a separate species that infects humans Amber KP [4]. Initial infection with P. jirovecii usually occurs in early childhood; two-thirds of healthy children have antibodies to *P. jirovecii* between the ages of 2 and 4 Pifer, et al. [22]. Hosts with defective cellular and/or humoral immunity are prone to develop PCP. Impaired immunity, such as that caused by human immunodeficiency virus (HIV) infection, hematologic malignancies, solid organ tumors with chemotherapy, rheumatic diseases, and immunosuppressive medications, is associated with the development of PCP Fillatre P, et al. [14], Salzer HJ, et al. [15], Tasaka S [9].

Transmission

Airborne transmission of Pneumocystis has been demonstrated in animal models Dumoulin A, et al. [23]. Transmitted from person to person mainly by inhalation of airborne particles Fink Elman MA [24], Morris, et al. [25]. Human Pneumocystis DNA has been identified in airborne spores in both rural Wakefield A [26] and hospital settings Bartlett MS, et al. [27]. Transmission of Pneumocystis DNA from Immunosuppressed Patients to Immunocompetent health care workers Vargas SL, et al. [28] and transmission of Pneumocystis infection from mother to child is reported by Miller RF, et al. [29].

Epidemiology

Pneumocystis jirovecii occurs worldwide, with humans being the main reservoir Finkelman MA [24], Morris A et al. [25]. Exposure to this pathogen is widespread, especially in developed countries, and more than 80% of children develop antibodies against it by age 4. Innate cellular immunity usually destroys this pathogen. However, immunocompromised patients with low CD4+ lymphocytes are primarly affected Hof H [30], Hughes WT, et al. [31]. In immunocompromised patients without HIV infection, pneumocystis is a major cause of morbidity and mortality Sepkowitz KA, et al. [32].

Until the 1980s, PCP was considered a rare but fatal infection mainly among patients with acute leukemia and other hematologic malignancies. In the 1980s, the global epidemic of human immunodeficiency virus (HIV)

dramatically increased the prevalence of PCP as one of the most common complications Maini R, et al. [33]. However, PCP is an emerging threat to immunocompromised patients without HIV infection, such as those receiving new immunosuppressive therapies for malignancies, organ transplants, or connective tissue diseases Tasaka S [9]. Additionally, patients receiving chronic corticosteroids for conditions including chronic obstructive pulmonary disease and Wegener's granulomatosis may be at risk PCP Hof H [30].

The incidence of PCP has declined substantially with the widespread use of PCP prophylaxis and ART Buchacz K, et al. [34]. Currently, most cases of PCP occur in patients who are unaware of their HIV infection status or not receiving ongoing HIV treatment, and in patients with advanced immunosuppression (CD4 count <100 cells/mm) Wolff AJ and O 'Donnell AE [35]. Although infection rates have declined significantly in the United States and other industrialized countries, this opportunistic infection is a major cause of significant infection in immunocompromised individuals Solano LM, et al. [36]. The HIV-uninfected population at risk for opportunistic infections, including PCP, is growing rapidly due to prolonged survival and escalating use of immunosuppressant's Sepkowitz KA [37], Bateman, et al. [38].

Clinical symptoms

The clinical manifestations of PCP differ significantly in patients with and without HIV infection. In patients without HIV infection, PCP progresses rapidly, is difficult to correctly diagnose, and causes severe respiratory failure with a poor prognosis Tasaka S [9]. In non-HIV patients, it takes about a week from the onset of fever and dry cough to the development of respiratory failure, whereas PCP in HIV-infected patients has a more gradual disease course lasting 2 weeks to 2 months Kovacs JA, et al. [39]. These differences in the clinical features of PCP are thought to be related to differences in the host immune response Tasaka S, et al. [40].

The main clinical manifestation of P. jirovecii is interstitial pneumonia in immunocompromised patients. As a general rule, the onset is usually insidious, with initial nonspecific symptoms, including loss of appetite, diarrhea, possible weight loss, and a dry cough. Tachypnea with a respiratory rate of up to 50 breaths per minute, dyspnea, and fatigue are also common Hof H [30], CDC [41]. Fever may or may not be present. As the infection progresses, respiratory distress and hypoxia worsen, and patients usually report being unable to take deep breaths. Purulent sputum is rare, but when present, it usually indicates an underlying bacterial infection Hof H [30]. If PCP is untreated, the associated mortality is approximately 100%; however, those who receive treatment have a mortality rate of 5% to 40% CDC [41]. Mortality from PCP increases with acute onset of respiratory failure and delay in the diagnosis of PCP Walzer PD and Smulian AG [42], Thomas CF and Limper AH [12].

Diagnosis

The diagnosis of PCP is multifactorial and may include clinical suspicion, patient risk factors, laboratory tests, chest radiograph, chest computed tomography (CT), sputum examination, bronchoalveolar lavage evaluation, or lung biopsy Lange in B and Saleh M [43]. Because Pneumocystis cannot be easily cultured in the laboratory, microscopic demonstration of the organisms in respiratory specimens has been the gold standard for the diagnosis of PCP Catherinot E, et al. [6], Thomas CF and Limper AH [12]. Cysts can be stained with Grocott Gomori methanamine silver, which has good specificity, but its sensitivity is not satisfactory. Because trophic forms predominate over cyst forms, it is assumed that Giemse and Diff-Quick staining of trophic forms has high sensitivity, but it is not stable depending on the skill and experience of the observer. In addition, diagnosis can be difficult in patients using highly active antiretroviral therapy and PJP chemoprophylaxis, which can lead to low P. jirovecii loads, especially in sputum and oropharyngeal wash samples Silva RM, et al. [44], Tasaka S [9].

In recent years, the usefulness of polymerase chain reaction and serum β-D-glucan assay for the rapid and non-invasive diagnosis of PCP has been revealed Tasaka S [9]. PCR method in bronchoalveolar lavage fluid (BAL) shows high sensitivity and good specificity for the diagnosis of PCP Fan LC, et al. [45]. PCR is very sensitive and specific for detecting pneumocystosis; however, however, it cannot reliably distinguish colonization from active disease Larsen HH, et al. [46], Larsen HH, et al. [47]. Semi quantitative real-time PCR improves differentiation between PCP and colonization in HIV-negative immune compromised individuals with acute respiratory syndromes Gronseth S, et al. [48]. On a chest radiograph, PCP usually presents as bilateral or diffuse ground opacities (GGO). A chest X-ray is sometimes normal. High-resolution computed tomography (HRCT) usually shows diffuse GGO with a patchy distribution Kulhman JE, et al. [49], Fujii T, et al. [50]. It is suggested that an early correct diagnosis and prompt therapy especially in the immunocompromised patients is very important to reduce the morbidity and mortality.

Treatment

If clinical symptoms and imaging findings indicate a reasonable likelihood of PCP, then diagnostic evaluation and early treatment should be performed as soon as possible, regardless of immunocompromised status Avino LJ, et al. [51], Kim TO, et al. [10]. Because of its high efficacy,

availability of oral and parenteral formulations, and low cost, trimethoprim (TMP)-sulfamethoxazole (SMX) is a first-line agent for the treatment of mild to severe PCP in both HIV-infected and HIV-uninfected patients Catherinot E, et al. [6], Thomas CF and Limper AH [12], Carmona EM and Limper AH [52]. Unfortunately, the side effects are common and patients with known allergy to sulfonamides cannot tolerate this therapy Cooley L, et al. [53].

Second-line PCP therapeutic options include IV pentamidine, clindamycin-primoquine, dapsone, atovaquone, and echinocandins Klein NC, et al. [54], Dohn MN. et al. [55], Toma E, et al. [56], Tu GW, et al. [57], Kim T, et al. [58]. Atovaquone is less effective but better tolerated than TMP-SMX Limper AH, et al. [59]. Alternatively, pentamidine can be administered intravenously Carmona EM and Limper AH [52]. It is recommended that clinicians wait at least 4 to 8 days before switching drug therapy to a second- or third-line agent because of deterioration or lack of improvement in respiratory function Cooley L, et al. [53]. The recommended duration of treatment is 21 days for HIV-infected patients and 14 days for non-HIV immunocompromised patients Hughes WT, et al. [60]. The guidelines recommend the addition of corticosteroids for HIV-infected patients with PCP Kaplan JE, et al. [8]. Careful observation during PCP therapy is important to assess response to treatment and detect toxicity as early as possible. Post-therapy follow-up includes assessment of early relapse, particularly if therapy has been with an agent other than TMP-SMX or has been shortened due to toxicity Hughes W, et al. [13]. It is advised to undertake additional research on the development of safe, potent and low- cost drugs that can be used for treatment as well as for prophylaxis of this opportunistic fungal disease even by the poor resource nations.

Prophylaxis

There are recommendations for the prevention of PCP for patients with hematologic diseases and solid tumors and recipients of hematopoietic stem cell transplants and solid organ transplants. For immunocompromised patients and other underlying diseases, the indications and dosage for prophylaxis should be carefully considered, taking into account hepatotoxicity, bone marrow suppression Kasiske BL [61], Martin SI and Fishman SA [62]. Although prevention guidelines for HIV-infected individuals are widely accepted and used, there is a lack of widely used in non-HIV patients with compromised immune systems Stern A, et al. [63].

TMP-SMX is the agent of first choice for prophylaxis in HIV-infected and non-HIV-infected hosts. One tablet (80 mg TMP and 400 mg SMX) per day or two tablets 3 times per week is usually recommended. Although the 3-times-weekly regimen was as effective in preventing PCP as the daily regimen, compliance may be improved by the daily regimen Limper AH, et al. [59], Utsunomiya M, et al. [64]. Antiretroviral therapy and PCP chemoprophylaxis with trimethoprim/sulfamethoxazole (TMP/SMX) significantly reduced the incidence of PCP CDC [41]. Patients receiving immunosuppressive drugs after transplantation should receive prophylaxis treatment Tomblyn M, et al. [65].

Other medications that have been studied for the prevention of PCP include pentamidine, atovaquone, dapsone, pyrimethamine, and clindamycin. The most statistically significant results in the prevention of PCP were obtained from patients receiving TMP/SMX doses. Patients who have contraindications to PCP prophylaxis with TMP/SMX as a result of hypersensitivity or scheduled chemotherapy with methotrexate should use second-line agents Stern A, et al. [63]. Resistance to TMP/SMX was observed in both PCP prophylaxis and treatment. Mutations can occur in the Fas gene of the fungal pathogen. These mutations are associated with prior exposure to drugs with a sulfonamide moiety and result in reduced susceptibility to TMP/SMX. However, this reduced susceptibility does not always mean that P jirovecii becomes fully resistant to these drugs Kazanjian P, et al. [66], Navin TR and others [67].

Conclusion

Pneumocystis jirovecii is an opportunistic fungus that can cause life threatening infection in HIV/AIDS patients, STD patients, and chemotherapy patients. Disease carries a poor prognosis. Although P. jirovecii is a common opportunistic pathogen, its development of can be prevented by maintaining a CD4+ lymphocyte count >200 cells/μL. Lung damage and respiratory failure during pneumocystis pneumonia are mediated by marked inflammatory responses of the host to the body. Trimethoprim-sulfamethoxazole with adjunctive corticosteroid therapy to suppress pulmonary inflammation in patients with severe infection remains the preferred treatment. Recognizing patients who are at risk or who are actively developing symptoms similar to P. jirovecii infection is important for recommending prophylaxis or active treatment. It is emphasized that further work on the pathogenesis and environmental reservoir of P. jirovecii may be rewarding.

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