Non-HIV *pneumocystis pneumonia*

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Summary

Human immunodeficiency virus (HIV)-uninfected *Pneumocystis jirovecii pneumonia* (non-HIV PCP) can develop in patients with autoimmune diseases, malignancies, and other diseases, and it can lead to potentially lethal respiratory dysfunction showing a high mortality (1-3). Over the past decade, a paradigm shift in the treatment of autoimmune disease such as rheumatoid arthritis (RA) (4, 5) and inflammatory bowel diseases (IBD) has been brought about by the introduction of biologics (6-8). While the emergence of innovative biologic agents targeted at specific molecules and pathways in the immune system have altered the clinical course of autoimmune disease patients and improved their quality of lives and social outcomes, increasing incidence of non-HIV PCP have been noticed (4-8). In the field of solid organ transplant recipients and malignancies, the emergence of new generation of immunosuppressive agents, such as rituximab and cytotoxic agents could result in frequent occurrence of non-HIV PCP (9-13). Today, although every clinician could encounter PCP patients, there is no established standard treatment for non-HIV PCP. We review recent topics and some aspects to improve the treatment of non-HIV PCP.

KEY WORDS: pneumocystis jirovecii pneumonia, *human immunodeficiency virus*, *non-HIV PCP, rheumatoid arthritis, β-D-glucan.*

Introduction

Pneumocystis jirovecii pneumonia (PCP) remains one of the most prevalent opportunistic infections in immunosuppressed patients. Effective prophylaxis of PCP and the availability of highly antiretroviral therapy have reduced the morbidity and mortality of PCP in HIV-infected patients. On the other hand, the risk and the incidence of PCP without HIV infection (non-HIV PCP) has increased as the number of patients receiving chemotherapy or immunosuppressive agents has been rapidly growing (1-3).

The incidence of PCP without HIV infection (non-HIV PCP) has increased as the number of patients receiving chemotherapy or immunosuppressive agents did.

The mortality of patients with non-HIV PCP is diverse and ranges from 0 to 70% (1, 3-9), compared with the mortality of HIV-infected PCP patients, which ranges from 10 to 20% (1, 3, 10). The higher mortality among non-HIV patients has been attributed to severe lung inflammation (1, 3, 5), although the exact etiology for these large differences in mortality has not yet been determined. Also, the evidenced-based standard treatments, or the therapeutic strategies, are not established yet. These could lead to doctor's and patients' delays, resulting in a high mortality of non-HIV PCP. We review issues reported in the recent publications and recommend the therapeutic strategy for HIV-uninfected PCP.

Clinical manifestations

Clinical symptoms in non-HIV PCP differ from those in HIV-PCP. While almost all the HIV-infected PCP patients show cough, sputum and dyspnea, these respiratory symptoms are less likely seen in non-HIV PCP patients at initial visit. In the article published in 2014 by Roux et al., cough, sputum and hypoxia were less frequently seen in the non-HIV PCP patients than in those with HIV-PCP except for those with fever at initial visit. On the other hand, CRP was much higher in

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the non-HIV-PCP patients than those with HIV-PCP (14). These suggest that early diagnosis as non-HIV PCP is very difficult for clinicians due to poor respiratory symptoms compared with HIV-PCP. This results in a high mortality of non-HIV PCP patients who were commonly misdiagnosed as bacterial *pneumonia* in a general medicine ward. It is outstanding that the severity of non-HIV PCP might be underestimated by conventional prognostic guidelines for community acquired *pneumonia* (15, 16). If PCP is suspected, chest CT scan should be performed (Figures 1, 2).

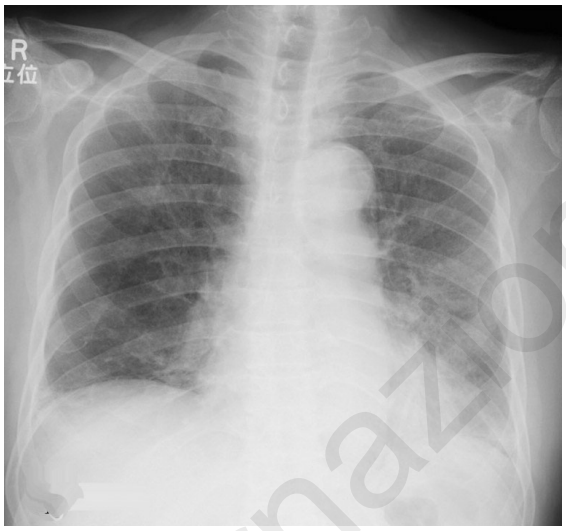

Figure 1 - Chest X-ray shows bilateral reticular shadows in the both lungs.

Diagnosis

Poor diagnosis as non-HIV PCP could contribute to a high mortality. There is no cultural method for *P. jrovecii* (4), thus microscopic findings such as Grocott or Diff-Quik staining are commonly used. Although Diff-Quik is specific and useful, it requires high expertise and has a low sensitivity in the diagnosis of non-HIV PCP (17). *P. jirovecii*-PCR in induced sputum and BALF are very sensitive in the diagnosis of PCP, however colonialization is commonly seen in 20% of healthy person and 30% of patients who have chronic pulmonary diseases (18). β-D-glucan and KL-6 are one of the most useful tools in the diagnosis of PCP and are widespread (19-22). Tasaka reported that serum-β-D-glucan is useful in the diagnosis of non-HIV PCP. Its cutoff value of 31.1 pg/ml had a sensitivity of 92% and a specificity of 86% for the diagnosis of non-HIV PCP (23). In another study including 111 AIDS patients described by Watanabe, its cutoff value was 23.2 pg/ml for the diagnosis of PCP (24). Esteves et al. documented that combination of KL-6 and β-D-glucan has a high sensitivity and specificity in the diagnosis of non-HIV PCP (25). While some studies for the diagnostic markers of non-HIV PCP have been reported, we sometimes experience a case of HIV-uninfected PCP with a positive microscopic findings, showing lower than normal level markers. In our study, 10 of 33 non-HIV PCP patients had a definite diagnosis with a positive microscopic findings that showed a β-D-glucan level of lower of than 31.1 pg/ml. If non-HIV PCP is suspected, empiric therapy should be recommended for a few days, resulting in a good prognosis as mentioned later (16). In general practice, diagnosis as non-HIV PCP should be standardized in a positive conventional PCR and high serum level of β-D-glucan with the compatible clinical symptoms and the radiological findings (Figures 1, 2). Microscopic findings of *P. jirovecii* is reliable, however they are not necessary in diagnosing PCP due to its low sensitivity and the requirement of expertise as above mentioned.

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Recently, loop-mediated isothermal amplification (LAMP) method for PCP has widely been spread as diagnostic tools for PCP (26-28). While the LAMP method for PCP is a potential diagnostic replacement for PCR, the essence of this method remains the same: it shows nothing except for the existence of either infection or colonization.

The results that LAMP of *P. jirovecii* is positive could just mean a colonization as well as PCR could. The negative results for PCR or LAMP method of *P. jirovecii* are valuable because it means that PCP is not present.

Treatment

Efficacy of combination therapy of corticosteroid and Sulfamethoxazole/Trimetoprim (TMP-SMX) has been confirmed for HIV-infected PCP. However, there is no evidenced based treatment for non-HIV PCP. The etiology and pathophysiology of non-HIV PCP is quite different from HIV-infected PCP. It is evident that most of the clinical manifestation of PCP is derived from immune response to *Pneumocystis jirovecii*. Pneumocystis elicits many kinds of immune responses, including those by lymphocytes, macrophages, neutrophils, dendritic cells, and epithelial cells (1, 29). Anti-non-HIV PCP therapy must be different from one of HIV-infected PCP. In addition, the association of *P. jirovecii* cyst have been reported to be one-tenth in HIV-uninfected PCP, compared with HIV-infected PCP (3). Therefore, the sensitivity of conventional staining methods for diagnosis of HIV-uninfected PCP is lower than the one for PCP with HIV. Thus, low dose of TMP-SMX should be administered in the treatment of non-HIV PCP once it is suspected, since it works and toxicity of

Low dose of TMP-SMX should be administered early once non-HIV PCP is suspected.

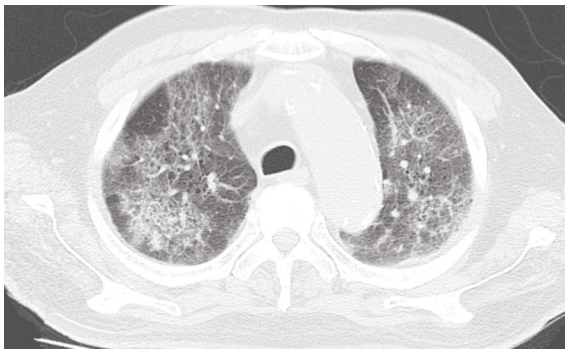

Figure 2 - Chest CT shows panlobular ground-glass opacities in the both lung fields.

TMP-SMX is dose-dependent. Mori documented that combination therapy of corticosteroid and low-dose TMP-SMX is effective and high-dose TMP-SMX is not necessary (18). High-dose TMP-SMX could result in renal failure or volume overload if parenterally administered. In our study, non-HIV PCP patients who had received high-dose of TMP-SMX showed a high mortality compared with those who had received low-dose of TMP-SMX without a statistical difference (50 *vs* 23.8%, p=0.165). We recommend that combination of low-dose TMP-SMX (4-6 tablets) with corticosteroid therapy for HIV-uninfected PCP.

Prophylaxis

Guidelines have been published for the use of PCP prophylaxis in patients with cancer, including hematopoietic stem cell transplant (HCT) recipients (30, 31), as well as in solid organ transplant recipients (32). In contrast, there are no published guidelines for PCP prophylaxis among patients with rheumatologic diseases receiving immunosuppressive drugs. Chemoprophylaxis has been recommended in patients with rheumatologic diseases such as *Systemic lupus erythematosus*, Dermatomyositis/ Polymyositis and Wegener's granulomatosis who are treated with significant doses of glucocorticoids (≥20 mg of prednisone daily for one month or longer) in combination with a second immunosuppressive drug, particularly a cytotoxic agent due to a high incidence of PCP (33-35).

TMP-SMX is the first choice prophylaxis for non-HIV PCP as well as HIV PCP, and it is the only agent showing more effectiveness than placebo in prospective randomized trials (grade A recommendation).

TMP-SMX is the first choice prophylaxis for non-HIV PCP as well as HIV PCP, and is the only agent demonstrated to be more effective than placebo in prospective randomized trials (grade A recommendation) (36, 37). The dosage usually recommended is one tablet daily or two tablets three times per week. There was no statistical differences among the regimens for PCP occurrence by a meta-analysis. Atovaquone is advocated to be the alternative for PCP prophylaxis in patients who are not tolerable for TMP-SMX.

Prognosis

The mortality rate of non-HIV PCP is higher than that of HIV-PCP as mentioned above (1, 3-10). While many studies have reported potential prognostic factors of HIV-PCP, few studies evaluated risk factors for non-HIV PCP. Some documented that high A-aDO2, combined bacteremia, elevated BUN and preexisting lung disease were independently poor prognostic factors (38, 39). Also, it has been reported that early diagnosis and treatment initiation could lead to improved survival in non-HIV PCP (15, 16, 38). In other studies, it was reported that low serum albumin levels and mechanical ventilation were independent predictors of mortality by multivariate analyses (40, 41). In our study, performance status of 2-4, treatment delay and high (severe) disease activity were unfavorable prognostic factors by an univariate analysis (42). More studies and analyses are needed.

Early diagnosis and treatment initiation could lead to improved survival in non-HIV PCP.

Conclusion

While an emergence of non-HIV PCP has been increased with development of new immunosuppressive agents and biologics (4-8), there are many clinical issues to discuss regarding non-HIV PCP. Especially, approach to definite diagnosis and the quest for accurate treatment and chemoprophylaxis for non-HIV PCP should be discussed. Further studies are warranted and are believed to improve outcome of non-HIV PCP.

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