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CASE REPORT

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A case of naganishial pleuritis in a kidney transplant recipient

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Abstract

The *Naganishia* species is a mycosis, previously classified as a non-*neoformans Cryptococcus* species. The increased number of naganishial infections occurs predominantly in immunocompromised conditions, especially in people living with HIV with low CD4 cell count, primary immunodeficiencies, and iatrogenic immunosuppression. The lungs can serve as the primary site of infection, leading to various pulmonary manifestations. However, naganishial pleural effusions are unrecognized and challenged in diagnosis because of their presentation, which can mimic tuberculous pleural effusion. Herein, we report the case of a 53-year-old man who had undergone kidney transplantation for more than 2 years and presented with chest tightness and dyspnea. Computed chest tomography demonstrated left pleural nodules and pleural effusion, later confirmed as exudative pleural effusion with a lymphocyte predominance. Pleuroscopy revealed multiple small pleural nodules, and biopsies of these nodules were performed. *Naganishia* spp. was identified by the 18S rRNA sequencing technique.

KEYWORDS
cryptococcosis, kidney transplantation, *Naganishia*, pleural effusion, pleural infection

INTRODUCTION

Cryptococcus spp. are encapsulated yeasts belonging to the basidiomycete group. While numerous Cryptococcus species exist in the environment, only *C. neoformans* and *C. gattii* are the primary causes of infections in humans.[1] In 2015, there was a milestone in the taxonomy of Cryptococcus by phylogenetic analysis, characterizing genus *Naganishia*.[2] *Naganishia* spp. is increasingly reported as a human pathogen and is predominantly found in immunocompromised individuals.[3] Herein, we describe the unusual case of a kidney transplant patient who presented with left pleural effusion. The diagnosis of Naganishia-related pleural effusion was ultimately confirmed through pleuroscopy with pleural nodule biopsy.

CASE REPORT

A 53-year-old male presented with a history of chest tightness and dyspnea for 2 weeks. Seven years prior, he had undergone a kidney transplantation as a therapeutic measure for uremia. Subsequently, he had been under treatment with tacrolimus and mycophenolate mofetil for maintenance of immunosuppression therapy. He had a history of *C. neoformans* meningitis 5 years ago, and his condition improved following a two-week course of liposomal amphotericin B, followed by 1 year of fluconazole.

Physical examination revealed a body temperature of 38°C. There were no palpable lymph nodes, abnormal neurological signs, or skin lesions observed. Chest auscultation indicated marked diminished breath sounds over the left lung. Chest radiography showed the presence of a left pleural effusion (Figure 1A). Computed tomography of the chest demonstrated a loculated left pleural effusion with circumferential nodular pleural thickening (Figure 1B). Serum cryptococcal antigen and anti-HIV were negative. A thoracentesis was performed, yielding cloudy yellow pleural effusion that exhibited exudative characteristics, with elevated nucleated cell count of 591 cell/cumm, predominantly mononuclear cells (80%), and an adenosine deaminase (ADA) level of 26.9 U/L. Quantitative real-time PCR testing for tuberculosis produced undetectable results. Fluid cytology

analysis revealed mixed leukocytes without evidence of tumours or pathogens.

Pleuroscopy with pleural biopsy was performed and the thoracoscopic examination showed diffuse small, whitish nodules at the posterior parietal pleura and the left lower lobe of lung, along with multiple fibrous pleural adhesions (Figure 2A). Pleural fluid staining and culture failed to identify microorganisms. A histopathology revealed poorly-formed granulomas. Gomori methenamine silver (GMS) stain demonstrated the existence of round to oval-shaped organisms, approximately 6–7 μm in size, with binary fission and a central clear septum (Figure 2B). These findings significantly raised suspicions of *Talaromyces marneffei* infection. Intravenous liposomal amphotericin B was prescribed an induction therapy. He developed acute kidney injury 5 days later. Consequently, the antifungal agent was adjusted to voriconazole. Two weeks later, 18S rRNA gene sequencing results indicated a 98% identity with *Naganishia* spp. As a result, the ultimate diagnosis was revised to naganishial pleural infection. The patient was discharged and continued with a maintenance regimen of itraconazole 200 mg twice daily. Subsequent clinical assessments at the six-months revealed an absence of adverse events or any recurrence of the pleural infection.

DISCUSSION

Non-*neoformans* cryptococcal infections are increasingly observed in immunocompromised patients with impaired cell-mediated immunity other than HIV/AIDS, especially organ transplant recipients.[4] Although pleural involvement in cryptococcal infections is a rare occurrence, with approximately only 50 cases documented in a literature,[5] it's

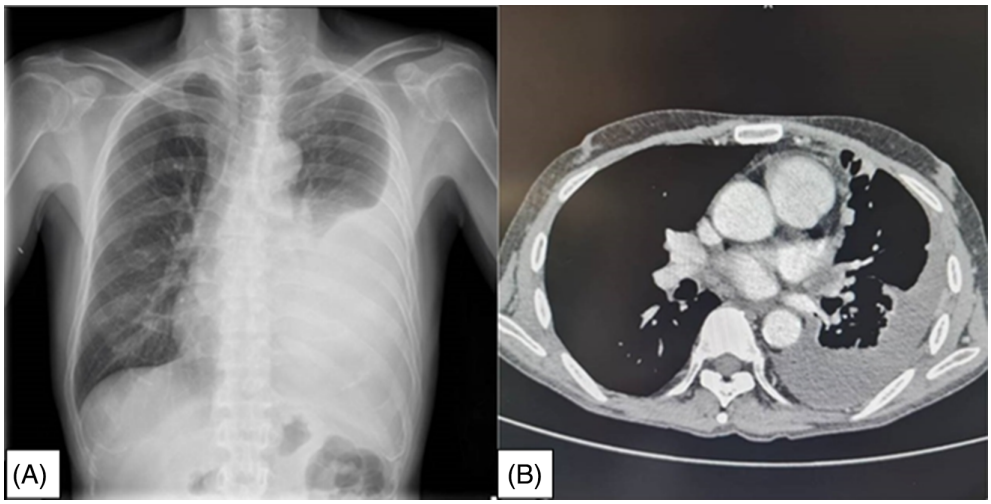

FIGURE 1 Chest radiography showed the presence of a left pleural effusion (A), Chest CT showed a loculated left pleural effusion with circumferential nodular pleural thickening (B).

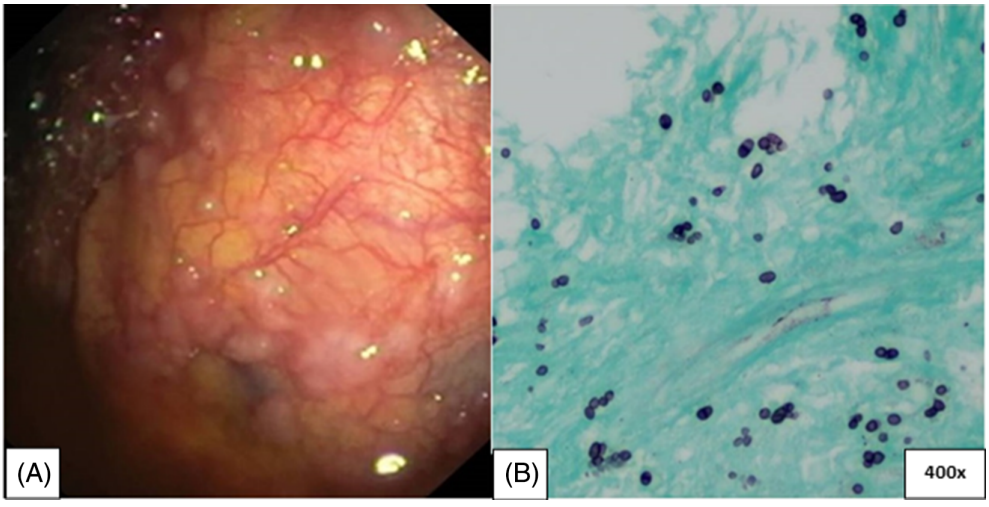

FIGURE 2 Pleuroscopy showed diffuse clear small nodules at the left posterior parietal pleura (A), GMS stain 400× showed round to oval shaped organisms size about 6–7 μm with feature of binary fission and central clear septum (B).

noteworthy that most of them are attributed to *C. neoformans*, with only two reported instances of naganishial pleural effusions.[6,7]

Previous case reports indicated that cryptococcal pleural fluid analysis typically exhibits an exudative nature with lymphocyte predominance.[8,9] However, exudative pleural effusion with a lymphocytic predominance can be observed in various diseases. This shared characteristic poses a significant challenge in diagnosing cryptococcal pleural effusion. Furthermore, the low positivity rate of *Cryptococcus* spp. in pleural effusion culture can complicate the diagnostic process. Another test, such as the cryptococcal antigen (CrAg) test, is effective and generally accepted in serum and cerebrospinal fluid. However, it remains unfamiliar in the context of pleural effusion specimens. There is evidence that the CrAg test cannot detect serotypes B or C of non-*neoformans* cryptococcal species, including *Naganishia* spp.[10] In our patient, the serum CrAg also yielded a negative result. There have been case report indicating that elevated levels of ADA (ADA >40 U/L) can be observed in cryptococcal pleural effuson,[8] making it challenging to differentiate from tuberculous pleural effusion (TPE). Nevertheless, in our patient's case, the ADA level was <40 U/L. Therefore, pleuroscopy and pleural biopsy were performed, demonstrating the nodules in the parietal pleura with a distinct appearance from tuberculosis. In a previous retrospective study, an examination of the gross thoracoscopic appearance of a sago-like nodule (less than 5 mm, solid, and caseous nodule) showed a significant correlation with TPE.[11] However, in our patient, there was uncertainty regarding the cleanliness of the pleural nodule, as it did not resemble typical tuberculosis characteristics. GMS staining showed round to oval yeast-like forms with binary fission, a characteristic that could lead to misdiagnosis as *T. marneffei*. Nowadays, molecular identification and strain typing methods are emerging and have been used to differentiate between fungal serotypes and molecular types. *Naganishia* spp. was successfully identified by 18S rRNA sequencing technique.

Treatment recommendations for non-*neoformans* cryptococcal infections are limited. A previous systemic review showed that amphotericin B alone was used in most previous cases of naganishial infections with itraconazole as an alternative treatment.[4] In our case, voriconazole was prescribed for 2 weeks with subsequently itraconazole with clinical and radiological response. Several interactions between itraconazole and tacrolimus have been reported. Tacrolimus dosage should be reduced to between 20% and 50% of the original dose to achieve target trough blood concentrations to prevent its toxicity.[12,13] Newer azoles, such as voriconazole and posaconazole, may serve as alternative treatments for naganishial infections. However, further study is needed to confirm their efficacy and safety.

In conclusion, it is crucial to recognize naganishial infections, particularly in immunocompromised patients. Naganishial pleural effusion are increasingly reported and can present with lymphocyte-predominated pleural effusion.

AUTHOR CONTRIBUTIONS

Tanapat Tassaneeyasin and Dararat Eksombatchai drafted the manuscript. Prawat Chantharit, Arunee Singhsnaeh, and Viboon Boonsarngsuk revised the manuscript. All authors have read and approved the final version of the manuscript.

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DATA AVAILABILITY STATEMENT

Data available on request from the authors.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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