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Case Report

Pneumocystis pneumonia diagnosed by repeated measurements of β-D-glucan levels

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ABSTRACT

β-D-glucan is extensively employed as a supplementary diagnostic tool for *Pneumocystis* pneumonia (PCP) and typically yields positive results in most cases.

We present a case of a 73-year-old woman with a history of rheumatoid arthritis, who was receiving biological agents and was admitted due to pneumonia.

Initially, the β-D-glucan test was negative. However, as the disease progressed, it eventually turned positive, leading to the diagnosis of PCP. The patient was treated with corticosteroids and trimethoprim-sulfamethoxazole, resulting in pneumonia resolution.

Our findings suggest that repeated assessment of β-D-glucan levels holds diagnostic value in patients without human immunodeficiency virus infection.

1. Introduction

Recently, the utilization of biological agents has become extensive in the treatment of immune-inflammatory disorders, including rheumatoid arthritis (RA). A significant consequence associated with their administration is the occurrence of pulmonary infections [1]. Specifically, *Pneumocystis* pneumonia (PCP) exhibits an accelerated disease progression and presents a higher mortality rate in patients without human immunodeficiency virus (HIV) infection than in those with HIV infection [2], necessitating prompt diagnosis for timely intervention. Serum β-D-glucan demonstrates good sensitivity for detecting PCP and serves as an adjunct diagnostic tool [3]. A patient with a negative serum β-D-glucan level is regarded as improbable for PCP due to the test's high negative predictive value [4]. In this report, we present a case wherein the initial serum β-D-glucan level was low at the onset of the disease but subsequently escalated during the disease course, ultimately leading to the diagnosis of PCP.

2. Case presentation

A 73-year-old woman presented to our hospital with a recent medical history indicating a mild febrile state. She had a 30-year history of RA, initially managed with the administration of disease-modifying anti-rheumatic drugs, supplemented with the introduction of etanercept treatment 16 years ago. However, owing to adverse effects, the treatment regimen was modified, replacing etanercept with oral methotrexate and salazosulfapyridine. Nevertheless, due to inadequate control of her arthritic condition, she was subse-

Abbreviations: PCP, *Pneumocystis* pneumonia; RA, rheumatoid arthritis; HIV, human immunodeficiency virus; CRP, C-reactive protein; LDH, lactate dehydrogenase; WBC, white blood cell; KL-6, Krebs von den lungen-6; CT, computed tomography; PCR, polymerase chain reaction; MSSA, methicillin-susceptible *Staphylococcus aureus*; TMP-SMX, trimethoprim-sulfamethoxazole.

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quently initiated on biological agents 13 years ago, transitioning through infliximab, tocilizumab, abatacept, and most recently, certolizumab pegol (200 mg/2 weeks) as of 2 months ago. Furthermore, since that time, methotrexate was switched to subcutaneous injection (7.5 mg/2 weeks) due to inadequate compliance with oral medication, and it was concurrently administered with oral prednisolone (5 mg/day). Additionally, she had a history of moderately controlled diabetes mellitus with the administration of teneligliptin. The patient had no prior history of pulmonary disease and was admitted with pneumonia, presenting symptoms of low-grade fever and general malaise.

Overall, the physical examination findings were unremarkable. Her lungs were clear upon auscultation. Blood tests revealed elevated levels of C-reactive protein (CRP) at 9.84 mg/dL and lactate dehydrogenase (LDH) at 396 U/L, with a white blood cell (WBC) count of 10,200/μL. The β-D-glucan levels measured using the Fungitec G Test MK II "Nissui" (Nissui Pharmaceutical Co., Ltd., Tokyo) were 12.1 pg/mL (<20.0), and the Krebs von den lungen-6 (KL-6) levels were 384 U/mL (<500), both falling within the normal range. Arterial blood gas analysis showed slight hypoxemia (PaO_2 of 68.7 mmHg while receiving 1.0 L/min oxygen via nasal cannula). Chest radiography showed normal findings, whereas chest computed tomography (CT) (Fig. 1) showed ground-glass opacities and infiltrative shadows in both the upper lobes and the right lower lobe.

Polymerase chain reaction (PCR) test for severe acute respiratory syndrome coronavirus 2 infection was negative. Bacterial culture of the sputum sample revealed the presence of methicillin-susceptible *Staphylococcus aureus* (MSSA). PCR testing for *Pneumocystis jirovecii* DNA in the sputum sample was not conducted. Therefore, the patient was diagnosed with bacterial pneumonia and received antibiotic therapy with tazobactam/piperacillin. Certolizumab pegol and methotrexate were discontinued.

However, the patient continued to have persistent pyrexia following admission, and on the eighth day of hospitalization, her oxygen requirements increased. The chest CT scan (Fig. 2) revealed worsening of the ground-glass opacities and infiltrative shadows, spreading throughout both lungs and surpassing the initial observations upon admission.

The patient presented with antibiotic-refractory pneumonia, prompting contemplation of bronchoscopy for conclusive diagnosis; however, its execution was precluded by the rapid progression of respiratory failure. In response, we modified the antibiotic regimen, transitioning from tazobactam/piperacillin to a combination therapy consisting of meropenem and levofloxacin. Additionally, considering the possibility of methotrexate-associated pneumonia and PCP, the patient received corticosteroid therapy and trimethoprim-sulfamethoxazole (TMP-SMX) at 960 mg/4800 mg per day for 3 weeks (Fig. 3).

Subsequently, the β-D-glucan levels, measured 11 days after admission, elevated to 40.0 pg/mL, providing clinical evidence supporting the diagnosis of PCP.

Following the initiation of PCP therapy, the patient has transitioned to an afebrile state, her oxygen requirements have diminished, and her CT findings have shown improvement. Following the completion of PCP treatment, we gradually reduced the dosage of prednisolone while maintaining it as a therapeutic regimen for RA. As a prophylactic measure, we administered TMP-SMX 80 mg/400 mg per day. Currently, we have not decided whether to reintroduce methotrexate or other biological agents.

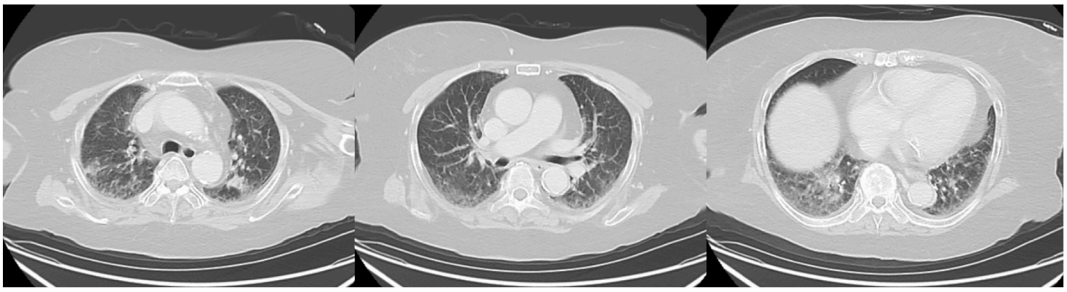

Fig. 1. Findings of chest computed tomography (CT) on admission. Ground-glass opacities and infiltrative shadows in both the upper lobes and the right lower lobe.

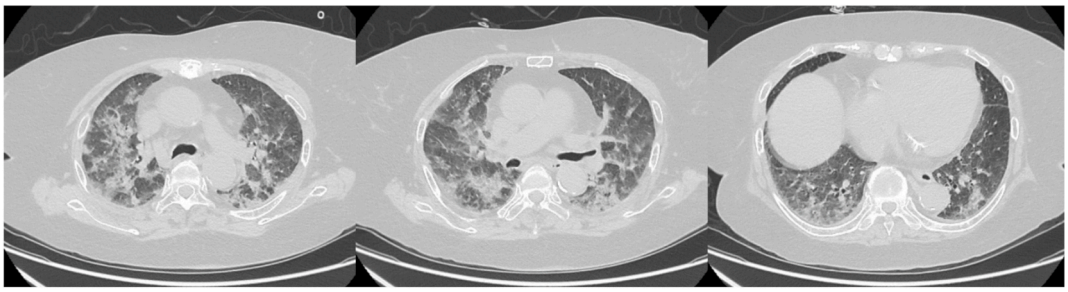

Fig. 2. Findings of chest computed tomography (CT) on the eighth day of hospitalization. Worsening of the ground-glass opacities and infiltrative shadows, spreading throughout both lungs and surpassing the initial observations upon admission.

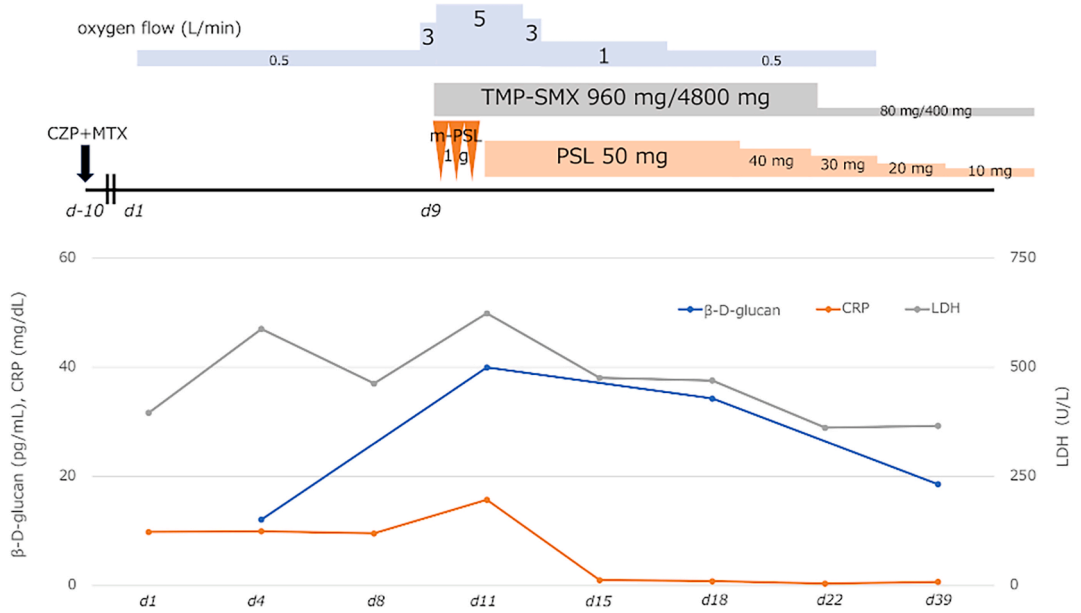

Fig. 3. Therapeutic course of *Pneumocystis* pneumonia. TMP-SMX, trimethoprim-sulfamethoxazole; CZP, certolizumab pegol; MTX, methotrexate; m-PSL, methylprednisolone; PSL, prednisolone; CRP, C-reactive protein; LDH, lactate dehydrogenase.

3. Discussion

We present a case of PCP in a patient with RA who was receiving biological therapy. Initially, the patient exhibited low levels of β-D-glucan; however, subsequent repeated measurements led to the diagnosis of PCP. This case highlights two important findings. First, PCP in non-HIV-infected patients may initially present with negative β-D-glucan levels, which can later increase. Second, repeated measurements of β-D-glucan levels are crucial in diagnosing PCP in non-HIV-infected patients.

PCP is commonly diagnosed using serum β-D-glucan as an adjunct diagnostic tool [3]. A previous study reported a cut-off value of 31.1 pg/mL using the Fujifilm Wako assay, which exhibited a sensitivity of 92.3% and a specificity of 86.1% for PCP diagnosis [5]. This test has a high negative predictive value, indicating that PCP is unlikely in patients with negative serum β-D-glucan [4]. However, precise cut-off values for the test remain undefined, and its sensitivity may be lower in non-HIV-infected patient populations with lower *Pneumocystis* burden [6,7]. A recent study proposed a cut-off value of 8.5 pg/mL using the Fujifilm Wako assay for PCP diagnosis in non-HIV-infected patients [8]. In this case, β-D-glucan levels were measured using the Fungitec G Test MK II, known to yield approximately twice as high levels as the Fujifilm Wako assay [9]. Consequently, the β-D-glucan levels were notably low at the onset of PCP in this patient. Presumably, the diminished β-D-glucan levels observed during the initial phases of the disease were a consequence of a low *Pneumocystis* burden. The subsequent increase in β-D-glucan levels after a few days was likely due to an escalation in the *Pneumocystis* burden resulting from delayed PCP treatment.

Repeated measurements of β-D-glucan levels are crucial in the diagnosis of PCP in non-HIV-infected patients. Pneumonia in patients with RA who receive methotrexate or biological agent therapy can encompass not only bacterial pneumonia but also methotrexate-associated pneumonia or PCP. Distinguishing between these conditions can be challenging. In this case, despite empirical antibiotic therapy with tazobactam/piperacillin, the pneumonia worsened, and the possibility of methotrexate-associated pneumonia and PCP could not be definitively ruled out. Therefore, the patient received corticosteroids and TMP-SMX, while re-evaluating β-D-glucan levels to confirm the diagnosis of PCP. Even if the initial β-D-glucan levels yield negative results, conducting multiple β-D-glucan measurements in patients receiving biological agents with persistent pneumonia is advisable.

In the present case, the confirmation of *Pneumocystis jirovecii* through microscopic identification was not achieved. The microscopic identification of *Pneumocystis jirovecii* poses challenges due to the reduced organism burden and severe conditions, such as hypoxemia, observed in non-HIV-infected patients [10]. Although *Pneumocystis*-specific PCR assays are available for the detection of *Pneumocystis*, these results are not covered by insurance in Japan, and the patients did not provide consent for the test. Given the rapid deterioration of the patient's condition and the alteration of antibiotic therapy and corticosteroid therapies, it is difficult to completely rule out bacterial pneumonia, drug-induced pneumonitis (such as methotrexate-associated pneumonia), or connective tissue disease-associated interstitial disease, as potential causes, all of which may exhibit response to the aforementioned treatments. However, the sputum culture indicated the presence of MSSA and no other identifiable microorganisms. Considering the inefficacy of tazobactam/piperacillin, conventional bacterial pneumonia was unlikely. Other pathologies also present challenges in explaining the elevated levels of β-D-glucan. β-D-glucan exhibits positive results in the context of fungal infections, including candidiasis and aspergillosis, in addition to PCP. Nonetheless, no findings suggestive of these fungal infections were observed apart from PCP. It is worth noting that β-D-glucan can produce false-positive results due to various factors, such as hemodialysis with cellulose membrane filters, use of fungal-derived antimicrobial agents, infusion of blood products containing immunoglobulins or albumins, significant

mushroom consumption, and certain bacterial infections [11–14]. Although the patient received antibiotic therapy with tazobactam/piperacillin, it has been reported that this treatment has no impact on β-D-glucan levels [15]. In the absence of any other identifiable causative factor for the elevated β-D-glucan levels and considering the subsequent improvement of clinical symptoms following PCP treatment, a consistent diagnosis of PCP was established.

4. Conclusions

We describe the case of a patient with RA who developed PCP while receiving biological agents. Despite initially low β-D-glucan levels, subsequent measurements confirmed the diagnosis of PCP. It is important to recognize that negative β-D-glucan results do not exclude the possibility of PCP in non-HIV-infected patients with pneumonia. Microscopic identification of *Pneumocystis jirovecii* in non-HIV-infected PCP cases can be challenging. Therefore, repeated assessment of β-D-glucan levels may serve as a more reliable diagnostic approach for PCP.

Consent for publication

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

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Author contributions

YK, AK, TS, KY, DK, TY, HS, and HM participated in patient management. YK wrote and revised the manuscript. All authors have read and approved the final version of the manuscript.

Declaration of competing interest

The authors have no conflicts of interest associated with this report to declare.

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References

[1] O. Boyman, D. Comte, F. Spertini, Adverse reactions to biologic agents and their medical management, Nat. Rev. Rheumatol. 10 (2014) 612–627, https://doi.org/10.1038/nrrheum.2014.123.
[2] Y.-S. Su, J.-J.J. Lu, C.-L. Perng, F.-Y. Chang, Pneumocystis jirovecii pneumonia in patients with and without human immunodeficiency virus infection, J. Microbiol. Immunol. Infect. 41 (2008) 478–482.
[3] G. Corsi-Vasquez, L. Ostrosky-Zeichner, E.F. Pilkington 3rd, P.E. Sax, Point-counterpoint: should serum β-D-glucan testing Be used for the diagnosis of *Pneumocystis jirovecii* pneumonia? J. Clin. Microbiol. 58 (2019), https://doi.org/10.1128/JCM.01340-19.
[4] A.D. Szvalb, A.E. Malek, Y. Jiang, M.M. Bhatti, S. Wurster, D.P. Kontoyiannis, Serum (1,3)-Beta-d-glucan has suboptimal performance for the diagnosis of *Pneumocystis jirovecii* pneumonia in cancer patients and correlates poorly with respiratory burden as measured by quantitative PCR, J. Infect. 81 (2020) 443–451, https://doi.org/10.1016/j.jinf.2020.07.003.
[5] S. Tasaka, N. Hasegawa, S. Kobayashi, et al., Serum indicators for the diagnosis of *Pneumocystis* pneumonia, Chest 131 (2007) 1173–1180, https://doi.org/10.1378/chest.06-1467.
[6] E.S. Theel, D.J. Jespersen, S. Iqbal, et al., Detection of (1,3)-β-D-glucan in bronchoalveolar lavage and serum samples collected from immunocompromised hosts, Mycopathologia 175 (2013) 33–41, https://doi.org/10.1007/s11046-012-9579-y.
[7] P. Rogina, M. Skvarc, Diagnostic accuracy of (1→3)-β-D-glucan to predict Pneumocystis jirovecii pneumonia in non-HIV-infected patients, Radiol. Oncol. 54 (2020) 221–226, https://doi.org/10.2478/raon-2020-0028.
[8] J. Taniguchi, K. Nakashima, H. Matsui, et al., Low cut-off value of serum (1,3)-beta-D-glucan for the diagnosis of *Pneumocystis* pneumonia in non-HIV patients: a retrospective cohort study, BMC Infect. Dis. 21 (2021) 1200, https://doi.org/10.1186/s12879-021-06895-x.
[9] Y. Bamba, H. Moro, K. Nagano, et al., Comparison between three (1→3)-β-D-glucan measurement kits in Japan for the diagnosis of invasive fungal infection, Kansenshogaku Zasshi 93 (2019) 500–506, https://doi.org/10.11150/kansenshogakuzasshi.93.500.
[10] A.B. Reid, S.C.-A. Chen, L.J. Worth, *Pneumocystis jirovecii* pneumonia in non-HIV-infected patients: new risks and diagnostic tools, Curr. Opin. Infect. Dis. 24 (2011) 534–544, https://doi.org/10.1097/QCO.0b013e32834cac17.
[11] M.A.S.H. Mennink-Kersten, D. Ruegebrink, P.E. Verweij, Pseudomonas aeruginosa as a cause of 1,3-β-D-glucan assay reactivity, Clin. Infect. Dis. 46 (2008) 1930–1931, https://doi.org/10.1086/588563.
[12] Z. Racil, I. Kocmanova, M. Lengerova, et al., Difficulties in using 1,3-β-D-glucan as the screening test for the early diagnosis of invasive fungal infections in patients with haematological malignancies - high frequency of false-positive results and their analysis, J. Med. Microbiol. 59 (2010) 1016–1022, https://doi.org/10.1099/jmm.0.019299-0.
[13] M. Usami M, A. Ohata, T. Horiuchi, K. Nagasawa, T. Wakabayashi, S. Tanaka, Positive (1→3)-beta-D-glucan in blood components and release of (1→3)-beta-D-glucan from depth-type membrane filters for blood processing, Transfusion 42 (2002) 1189–1195, https://doi.org/10.1046/j.1537-2995.2002.00162.x.
[14] M.A.S.H. Mennink-Kersten, A. Warris, P.E. Verweij, 1,3-β-D-glucan in patients receiving intravenous amoxicillin-clavulanic acid, N. Engl. J. Med. 354 (2006) 2834–2835, https://doi.org/10.1056/nejmc053340.
[15] G. Metan, C. Ağkuş, H. Buldu, A.N. Koç, The interaction between piperacillin/tazobactam and assays for Aspergillus galactomannan and 1,3-beta-D-glucan in patients without risk factors for invasive fungal infections, Infection 38 (2010) 217–221, https://doi.org/10.1007/s15010-010-0003-6.