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Double Infection in a Patient with Chronic GVHD Post Allogeneic Transplant: "Hickam's Dictum" Trumps "Occam's Razor"!—A Case Report with Review of Literature

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Abstract

Double pneumonia with *Pneumocystis jirovecii* (PCP) and *Mycobacterium tuberculosis* (MTB) has been reported in patients with acquired immune deficiency syndrome. A similar immune-suppressed state exists in allogeneic transplant survivors treated for graft-versus-host disease (GVHD). The clinical features and imaging findings could be quite similar in both the etiologies. Reaching a timely diagnosis and initiation of appropriate therapy is essential to prevent complications. We report a patient who had concurrent PCP and MTB pneumonia while on treatment for chronic GVHD. We describe the diagnostic challenge, the treatment, and outcome of this patient. We intend to sensitize physicians to consider more than one etiology in this subset of patients.

Keywords

- *Pneumocystis jirovecii*
- mycobacterium tuberculosis
- allogeneic transplant
- stem cell transplantation
- double infection
- graft-versus-host disease
- ruxolitinib

Introduction

Pneumocystis jirovecii is a common cause of pneumonia (PCP) in patients with acquired immune deficiency syndrome (AIDS) and can also occur concurrently with pulmonary tuberculosis (TB).[1] Patients undergoing allogeneic transplantation are severely immunosuppressed and have low CD4 counts, similar to those with severe human immunodeficiency virus (HIV) infection. The immune deficiency is further worsened in patients treated for graft-versus-host disease (GVHD). We recently encountered double pneumonia (PCP and *Mycobacterium tuberculosis*) in a patient who had GVHD. Traditionally, medical students have been taught to synthesize all possible symptoms into a single diagnosis. "Occam's razor" ("entities should not be multiplied without necessity") is often quoted to reinforce this point.[2] Notable exceptions to this rule are geriatric and immunosuppressed patients. An alternate rule is the "Hickam's dictum" ("A man can have as many diseases as he well pleases").[3] This case is presented as an essential learning point for practicing physicians.

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Case Report

A 33-year-old lady was diagnosed with *BCR-ABL*-positive B cell-acute lymphoblastic leukemia (ALL) in July 2019. Induction chemotherapy was started, and she achieved remission with undetectable measurable residual disease. Six months later (February 2020), she underwent allogeneic stem cell transplantation (10/10 HLA-matched sibling donor). She received Fludarabine–Busulfan conditioning and GVHD prophylaxis with cyclosporine and methotrexate. She developed grade 2 gut acute GVHD, which initially responded to steroids. Unfortunately, there was a GVHD recurrence (gut, liver) after 4 months (June 2020), which was steroid-resistant but responded to ruxolitinib (August 2020). She continued imatinib in the posttransplant period.

In February 2021 (day + 340; medications: ruxolitinib 5 mg twice daily, imatinib 300 mg once daily, cotrimoxazole prophylaxis), she presented with fever and fatigue. There were no localizing symptoms and no active GVHD. Blood cultures were sterile. Blood counts were normal, and cytomegalovirus DNA was undetectable. She was treated with azithromycin for presumed respiratory infection and responded. However, 2 weeks later (D + 354), she presented with progressive shortness of breath, anorexia, and worsening fever. There was no cough or expectoration. Chest imaging showed right-sided pleural effusion (mild) and bilateral consolidation (►**Fig. 1A**). Though the possibility of pulmonary TB was suggested, pleural fluid tests (adenosine deaminase, smear for acid-fast bacilli, cartridge-based nucleic acid amplification test [CBNAAT], cultures, and cytology) were negative for TB. We deferred empirical antituberculosis treatment (ATT) and gave another course of oral antibiotics for presumed bacterial infection. Imatinib, ruxolitinib, and cotrimoxazole prophylaxis were continued. However, dyspnea worsened, fever persisted, and she developed tachycardia, tachypnea with diffuse crepitations. Arterial blood gas analysis showed hypoxia (partial pressure of oxygen: 80 mm Hg) and respiratory alkalosis. A high-resolution computed tomography (HRCT) scan of the thorax showed bilateral nodular and patchy consolidation with a "tree-in-bud" appearance (►**Fig. 1B**). The differential diagnoses considered were pulmonary TB, atypical pneumonia, fungal pneumonia, reactivation of GVHD, and post-transplant lymphoproliferative disorder. Diagnostic bronchoscopy with bronchoalveolar lavage (BAL) was planned. BAL cytology and galactomannan were negative. The CBNAAT of the BAL fluid was positive for rifampicin-sensitive *Mycobacterium tuberculosis* (later, the BAL culture also grew ycobacterium tuberculosis [MTB]), and we started 4-drug ATT.

However, even after a week, there was no improvement in the hypoxia, and she continued to have a high-grade fever. We started prednisolone (1 mg/kg), considering the possibility of lung GVHD. Though the fever persisted, this led to rapid improvement in hypoxia. The persistence of fever despite the ATT and the improvement with steroids suggested the possibility of dual infection like PCP. This was confirmed by the BAL fluid PCR which was positive for *P. jirovecii*. Immediately, we started therapeutic dose cotrimoxazole and continued steroids and ATT. Within 24 hours, the fever resolved, and the patient showed improvement in appetite and general condition. After 28 days, cotrimoxazole was stopped. Steroids were tapered and stopped after further 3 weeks. Repeat imaging after 4 weeks showed significant radiological clearance (►**Fig. 1C**).

Discussion

Despite advances in supportive care, infections are the primary cause of death in 8% of autologous and 17 to 20% of patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT).[4] Pneumonia is the most common infection after stem cell transplantation and is associated with high mortality.[5] Suppression of cell-mediated immunity occurs in allogeneic HSCT recipients due to the conditioning regimens, immunosuppressive drugs, and GVHD. The reduction in CD4 T cells makes them prone to develop TB and PCP infections.[6] In allotransplant survivors, the median time of onset of PCP was 169 days, and TB was 452 days.[7] Though concurrent PCP and MTB pneumonia have been reported in patients with AIDS, we believe that this is the first report of this in a post-transplant patient.

PCP is caused by the fungus *P. jirovecii* and is predominantly seen in patients with HIV-AIDS and low CD4 counts.[8] Immunocompetent individuals may have asymptomatic lung colonization and may spread the pathogen to immunosuppressed patients.[9] Among HIV-negative patients, use of glucocorticoids, defects in cell-mediated immunity, hematologic malignancies, and organ transplantation are risk factors for PCP.[10]

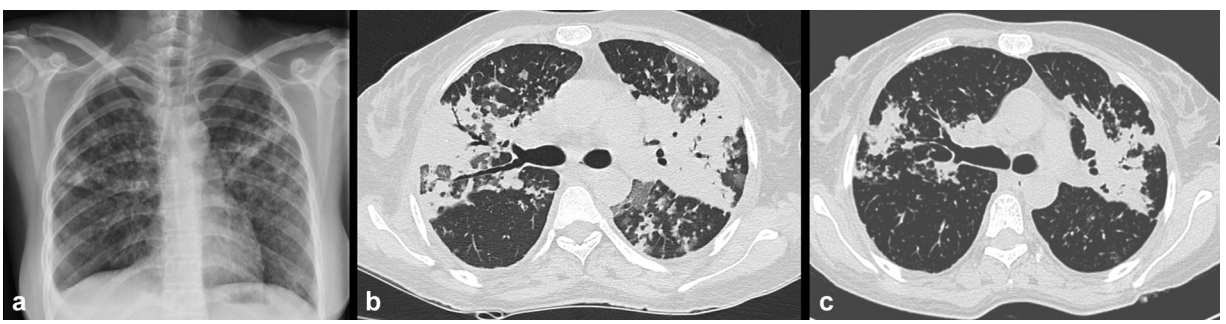

Fig. 1 Radiological findings in the patient. At the time of diagnosis, the chest radiograph showed mild right pleural effusion (1a), while the computerised tomography images (1b) revealed bilateral parenchymal involvement with patchy consolidation. Imaging done 4 weeks after (1c) treatment with ATT and cotrimoxazole showed radiological clearance.

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After the start of widespread use of cotrimoxazole prophylaxis, the incidence of PCP in allogeneic HSCT patients has decreased dramatically (from 16% in the 1980s to 1–2.5% in recent times).[11] However, PCP in non-HIV patients is generally more severe. Allogeneic transplant patients with PCP have higher mortality than the other subsets of patients.[12] Interestingly, PCP has also been reported in the setting of immune restitution disease, possibly a pre-existing infection being unmasked by reducing immunosuppression.[13] The incidence of TB in HSCT patients has been reported to vary from 0.001% in developed countries to >10% in developing countries.[14] TB has been reported to be more frequent in allogeneic than autologous recipients.[15] Lung is the most commonly affected organ in 50 to 100% of patients.[16] Extrapulmonary and disseminated presentation are exceedingly common, especially in patients who develop chronic GVHD due to the suppressed T cell function.[17] The reported mortality of TB pneumonia in allogeneic recipients can be as high as 50% making it essential to suspect TB early and initiate therapy.[18]

The characteristic chest radiograph findings in PCP are diffuse, bilateral, interstitial infiltrates predominantly in the perihilar region. Less common patterns are lobar infiltrates, nodules, cavitations, and pneumatocoeles.[19] In the initial stages, when the chest radiographs are normal, HRCT scans of the thorax may show ground-glass opacities or small cystic lesions.[20] The radiology findings in TB in transplant patients are variable. Focal infiltrates, miliary pattern, nodules, or pleural effusion are common, while the classic cavitary changes are unusual.[21] CT scans may show consolidation, nodules, tree-in-bud appearance, and ground-glass opacities.[22] Thus, in these severely immunosuppressed patients, the radiological features of PCP and MTB pneumonia can overlap, making coinfection diagnosis impossible without microbiological support. Bilateral, perihilar predominant, patchy ground-glass opacities may indicate PCP, while hilar and mediastinal lymphadenopathy and pleural effusions may point toward TB.[23] The best investigative modality for the diagnosis is BAL that is safe, minimally invasive, reproducible, and with a diagnostic yield comparable to lung biopsy.[24] PCR is the most sensitive test to diagnose pneumocystis, especially in non-HIV patients where the cyst burden is low.[25] Compared with culture, CBNAAT for TB has sensitivity of 84% and specificity of 99% for respiratory samples in smear negative cases.[26] False positive CBNAAT reports can occur with history of recent TB, less mycobacterial DNA per PCR cycle threshold, and a chest radiograph not suggestive of active TB. Hence, culture remains the gold standard for detection of TB.[27]

The additive immunosuppression due to chronic GVHD, ruxolitinib, and imatinib might have contributed to the double infection in our patient. Ruxolitinib suppresses T cell function by reducing their ability to produce proinflammatory cytokines.[28] Imatinib has also been found to be immunosuppressive, especially T cell function.[29] Among allogeneic transplant patients developing PCP beyond 9 months, 79% had ongoing chronic GVHD. Infections may occur despite being on cotrimoxazole prophylaxis; this may reflect reduced adherence, improper dosing, or even resistance.[30] The strength of this study is to sensitize the physician to consider multiple differentials for lung infiltrates in an immunocompromised setting. The weakness is that we could not assess for alternate causes of immunosuppression like low CD4 or immunoglobulin levels.

Conclusions

We present this case to highlight the possibility of multiple infections in immunosuppressed patients. The diagnosis in these cases requires a consistent effort involving various departments.

Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient has given her consent for images and other clinical information to be reported in the journal.

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Conflict of Interest

None declared.

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References

1 Orlovic D, Kularatne R, Ferraz V, Smego RA Jr. Dual pulmonary infection with Mycobacterium tuberculosis and Pneumocystis carinii in patients infected with human immunodeficiency virus. Clin Infect Dis 2001;32(02):289–294
2 Wikipedia contributors, (Hickam's dictum,) *Wikipedia, The Free Encyclopedia*.
3 Hickam's dictum. [Internet].
4 Tomblyn M, Chiller T, Einsele H, et al; Center for International Blood and Marrow Research National Marrow Donor program European Blood and MarrowTransplant Group American Society of Blood and Marrow Transplantation Canadian Blood and Marrow Transplant Group Infectious Diseases Society of America Society for Healthcare Epidemiology of America Association of Medical Microbiology and Infectious Disease Canada Centers for Disease Control and Prevention. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant 2009;15(10):1143–1238
5 Cordonnier C. Pneumonia After Hematopoietic Stem Cell Transplantation. Transplant Infections. 2016:251–269
6 Ip MS, Yuen KY, Woo PC, et al. Risk factors for pulmonary tuberculosis in bone marrow transplant recipients. Am J Respir Crit Care Med 1998;158(04):1173–1177
7 Yoo JH, Lee DG, Choi SM, et al. Infectious complications and outcomes after allogeneic hematopoietic stem cell transplantation in Korea. Bone Marrow Transplant 2004;34(06):497–504
8 Thomas CF Jr, Limper AH. Pneumocystis pneumonia. N Engl J Med 2004;350(24):2487–2498
9 Ponce CA, Gallo M, Bustamante R, Vargas SL. Pneumocystis colonization is highly prevalent in the autopsied lungs of the general population. Clin Infect Dis 2010;50(03):347–353
10 Yale SH, Limper AH. Pneumonia in patients without acquired immunodeficiency syndrome: associated illnesses and prior corticosteroid therapy. Mayo Clin Proc 1996;71(01):5–13

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11 Chen CS, Boeckh M, Seidel K, et al. Incidence, risk factors, and mortality from pneumonia developing late after hematopoietic stem cell transplantation. Bone Marrow Transplant 2003;32(05): 515–522
12 Kovacs JA, Hiemenz JW, Macher AM, et al. Pneumocystis carinii pneumonia: a comparison between patients with the acquired immunodeficiency syndrome and patients with other immunodeficiencies. Ann Intern Med 1984;100(05):663–671
13 Wu AKL, Cheng VCC, Tang BSF, et al. The unmasking of Pneumocystis jiroveci pneumonia during reversal of immunosuppression: case reports and literature review. BMC Infect Dis 2004;4(01):57
14 Ramos JF, Batista MV, Costa SF. Tuberculosis in hematopoietic stem cell transplant recipients. Mediterr J Hematol Infect Dis 2013;5(01):e2013061
15 de la Cámara R, Martino R, Granados E, et al; Spanish Group on Infectious Complications in Hematopoietic Transplantation. Tuberculosis after hematopoietic stem cell transplantation: incidence, clinical characteristics and outcome. Bone Marrow Transplant 2000;26(03):291–298
16 Russo RL, Dulley FL, Suganuma L, França IL, Yasuda MA, Costa SF. Tuberculosis in hematopoietic stem cell transplant patients: case report and review of the literature. Int J Infect Dis 2010;14 (Suppl 3):e187–e191
17 George B, Mathews V, Srivastava V, Srivastava A, Chandy M. Tuberculosis among allogeneic bone marrow transplant recipients in India. Bone Marrow Transplant 2001;27(09):973–975
18 Ramos JF, Batista MV, Costa SF. Tuberculosis in hematopoietic stem cell transplant recipients. Mediterr J Hematol Infect Dis 2013;5(01):e2013061-e
19 Crans CA Jr, Boiselle PM. Imaging features of Pneumocystis carinii pneumonia. Crit Rev Diagn Imaging 1999;40(04):251–284
20 Hidalgo A, Falcó V, Mauleón S, et al. Accuracy of high-resolution CT in distinguishing between Pneumocystis carinii pneumonia and non- Pneumocystis carinii pneumonia in AIDS patients. Eur Radiol 2003;13(05):1179–1184
21 Singh N, Paterson DL. Mycobacterium tuberculosis infection in solid-organ transplant recipients: impact and implications for management. Clin Infect Dis 1998;27(05):1266–1277
22 Jung JI, Lee DG, Kim YJ, Yoon HK, Kim CC, Park SH. Pulmonary tuberculosis after hematopoietic stem cell transplantation: radiologic findings. J Thorac Imaging 2009;24(01):10–16
23 Barnes PF, Steele MA, Young SM, Vachon LA. Tuberculosis in patients with human immunodeficiency virus infection. How often does it mimic Pneumocystis carinii pneumonia? Chest 1992;102(02):428–432
24 Chellapandian D, Lehrnbecher T, Phillips B, et al. Bronchoalveolar lavage and lung biopsy in patients with cancer and hematopoietic stem-cell transplantation recipients: a systematic review and meta-analysis. J Clin Oncol 2015;33(05):501–509
25 Armbruster C, Pokieser L, Hassl A. Diagnosis of Pneumocystis carinii pneumonia by bronchoalveolar lavage in AIDS patients. Comparison of Diff-Quik, fungifluor stain, direct immunofluorescence test and polymerase chain reaction. Acta Cytol 1995;39 (06):1089–1093
26 Lombardi G, Di Gregori V, Girometti N, Tadolini M, Bisognin F, Dal Monte P. Diagnosis of smear-negative tuberculosis is greatly improved by Xpert MTB/RIF. PLoS One 2017;12(04):e0176186
27 Theron G, Venter R, Calligaro G, et al. Xpert MTB/RIF results in patients with previous tuberculosis: can we distinguish true from false positive results? Clin Infect Dis 2016;62(08):995–1001
28 Elli EM, Baratè C, Mendicino F, Palandri F, Palumbo GA. Mechanisms underlying the anti-inflammatory and immunosuppressive activity of ruxolitinib. Front Oncol 2019;9:1186
29 Appel S, Balabanov S, Brümmendorf TH, Brossart P. Effects of imatinib on normal hematopoiesis and immune activation. Stem Cells 2005;23(08):1082–1088
30 Williams KM, Ahn KW, Chen M, et al. The incidence, mortality and timing of Pneumocystis jiroveci pneumonia after hematopoietic cell transplantation: a CIBMTR analysis. Bone Marrow Transplant 2016;51(04):573–580

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