Published in final edited form as:

Infect Dis Clin Pract (Baltim Md). 2016 November ; 24(6): e86–e87. doi:10.1097/IPC.
0000000000000453.

Pneumocystis jirovecii Pneumonia in a Treatment-Naive Patient With Chronic Lymphocytic Leukemia

Jeffrey R. Strich, MD^{1,*}, Theresa D. Jerussi, MS², Adrian Wiestner, MD, PhD³, and Steven M. Holland, MD⁴

¹Division of Clinical Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD

²Clinical Center, National Institutes of Health, Bethesda, MD

³Laboratory of Lymphoid Malignancies, National Heart, Lung, and Blood, Institute, National Institutes of Health, Bethesda, MD

⁴Laboratory of Clinical Infectious Disease, National Institute of Allergy and Infectious Disease, National Institutes of Health, Bethesda, MD

Abstract

Pneumocystis jirovecii pneumonia is a known complication in patients with chronic lymphocytic leukemia who are treated with fludarabine-based chemotherapy; however, it is extremely uncommon in treatment naïve patients. Here we report a case of *Pneumocystis jirovecii* pneumonia in a patient with untreated chronic lymphocytic leukemia.

Article Summary

Pneumocystis jirovecii pneumonia (PCP) is a known opportunistic infection in patients with human immunodeficiency virus (HIV) and those receiving immunosuppression or chemotherapy, but is very rarely seen in patients with untreated chronic lymphocytic leukemia (CLL). This case presents a patient with untreated CLL who developed PCP highlighting that PCP should be included on the differential diagnosis of pulmonary infiltrates in patients with CLL who have received treatment and those that are treatment naïve.

Keywords

Pneumocystis jirovecii pneumonia; chronic lymphocytic leukemia; opportunistic infection

*Corresponding Author: Jeffrey R. Strich, MD, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 10 Center Drive, Rm 2C145, Bethesda, MD. 20814, Phone: 301-648-3731, FAX: 301-402-1213, jeffrey.strich@nih.gov.

Disclaimer: The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services

Potential conflict of interest: All of the authors: No potential conflicts of interest

Introduction

Infection is a common complication in patients who have chronic lymphocytic leukemia (CLL). CLL is a heterogeneous disease with a long natural history. About half of the patients never require treatment, while another half of patients will develop active/symptomatic disease that requires treatment [1]. In untreated patients, these infections are typically bacterial infections involving the respiratory tract and associated with hypogammaglobulinemia. However, the spectrum of opportunistic infections expands when patients begin treatment, including alkylating agent-based regimens (e.g., chlorambucil) with or without corticosteroids, purine analogues (e.g., fludarabine) with or without cyclophosphamide, and monoclonal antibodies (e.g., alemtuzumab, rituximab) [2,3]. Because the risk of *Pneumocystis jiroveci* pneumonia (PCP) is increased while receiving therapy for CLL prophylaxis is the standard of care. Infection with *Pneumocystis jiroveci* (*P. jirovecii*) has been identified in patients receiving all of the aforementioned treatment regimens, however, it has only once previously been described in a CLL patient who was treatment naïve [4]. We report a case of PCP in a patient with CLL who had received no prior treatment.

Case Presentation

A 51 year-old male with untreated CLL diagnosed 3.5 years previously, presented with 6 weeks of productive cough, fatigue, and a 10 pound weight loss over 3 months. The cough, productive of green/yellow sputum, was originally consistent with a viral upper respiratory tract infection (URI) as family members, including 3 young children, had symptoms which transiently improved. After 4 weeks the cough persisted and fever prompted empiric levofloxacin for possible bacterial pneumonia. He transiently improved but subsequently worsened with increased sputum and difficulty sleeping due to nocturnal cough.

His past medical history was significant for myasthenia gravis, papillary thyroid carcinoma, and spontaneous splenic rupture. The myasthenia gravis was initially treated with thymectomy and high dose steroids followed by chronic prednisone 10mg every other day for the previous 6 years. Prior immunosuppression around the myasthenia included mycophenolate mofetil, which was stopped when a routine CBC showed lymphocytosis leading to the diagnosis of CLL. His CLL was Rai stage IV (platelets 90–100K), with otherwise good to intermediate disease prognostic markers (Zap 70 negative), mutated immunoglobulin heavy chain variable (IGHV) gene. Cytogenetics showed trisomy 12 and 13q deletion and no indication for CLL treatment. He also had hypogammaglobulinemia (IgG 100–200mg/dL prior to replacement), which was first treated two months prior, prompted by *Cryptosporidium* infection in the setting of 3 weeks of frequent liquid stools.

One week prior to the diagnosis of PCP, his white blood cell count was 37,000 cells/uL with 90% lymphocytes, IgG 887 mg/dL (replacement 2 weeks earlier), and CD4+ T cells 2378 cells/uL. CT chest showed bi-basilar dependent ground glass opacities with scattered bilateral small nodules and bulky mediastinal adenopathy (Figure 1A). Nasal wash was positive for rhinovirus/enterovirus by polymerase chain reaction (PCR). Sputum showed

many neutrophils, few squamous epithelial cells, and oropharyngeal flora on gram stain. He was prescribed azithromycin for possible post-viral bacterial infection.

The following week his cough was worse and diagnostic bronchoalveolar lavage (BAL) was performed. BAL was positive by PCR for both rhinovirus/enterovirus and *P. jirovecii*. The *P. jirovecii* PCR signal was detected at a cycle threshold of 25.63, a level consistent with a diagnosis of PCP. Direct fluorescent antibody testing was negative for *P. jirovecii*, but Gomori's methenamine silver (GMS) stain showed rare structures of *Pneumocystis* (Figure 1B). Cytopathology showed atypical lymphocytes morphologically consistent with CLL in a background of mostly blood and macrophages (Figure 1C). Cultures grew only oropharyngeal flora. He received trimethoprim-sulfamethoxazole for 21 days: 5 days into therapy his cough began to subside and he felt much better. Two weeks later all symptoms had resolved; one month later he had gained back 10 pounds. Repeat chest CT 2 months later showed near resolution of the previous infiltrates (Figure 1D). He remains on prophylactic trimethoprim-sulfamethoxazole and monthly IVIG. He continues to do well and does not require treatment for his CLL.

Discussion

This is the second case of PCP reported in a non-HIV patient with treatment naïve CLL. This patient had pulmonary infiltrates consistent with PCP on CT scan, a positive PCR from a BAL sample, and structures consistent with *Pneumocystis* on GMS staining. Other supporting evidence includes lack of improvement on antibiotics (macrolide and fluoroquinolone) and rapid improvement after switching his antimicrobial therapy to trimethoprim-sulfamethoxazole. Furthermore, he had dramatic improvement on CT scan after completion of trimethoprim-sulfamethoxazole treatment consistent with successful treatment of PCP. While the *P. jirovecii* PCR is very sensitive (87.2%), it can be associated with false positives in patients with pulmonary infiltrates [5]. In this context many of the false positives are biologically true however, they often times represent colonization or subclinical infection and not the active disease. In this patient we believed the positive *P. jirovecii* PCR, consistent clinical presentation, radiographic findings, structures seen on GMS staining, and clinical response correlating with *P. jirovecii* therapy all to be consistent with the diagnosis of active *P. jirovecii* infection.

Most people are asymptotically infected with *P. jirovecii* by age 4, but disease only manifests in the context of significant immunosuppression, such as HIV, organ and bone marrow transplantation, hematologic malignancy, high dose steroids, and immunomodulating monoclonal antibodies [6,7]. The mechanism(s) leading to active *P. jirovecii* infection in CLL following treatment include impaired T-cell function; although B-cell and NK cell abnormalities probably play roles also. While PCP has been associated with CLL in a patient with severe CD4+ T cell lymphopenia (CD4+ count 104/uL) who was previously treated with chlorambucil and prednisone [8], our patient had an elevated CD4+ count. It is noted that this patient had been on chronic low-dose steroids for myasthenia however the dose is below that which is typically thought to predispose to PCP.

The mechanism(s) by which a patient with treatment naïve CLL could develop symptomatic *P. jirovecii* infection is unknown. It has been postulated that parenchymal infiltration with CLL cells interferes mechanically with local immune responses contributing to susceptibility. In the prior case of PCP in CLL, transbronchial needle aspiration demonstrated airway mucosa infiltrated with CLL [4]. Our patient's BAL cytology had atypical lymphocytes consistent with CLL, but he did not have a transbronchial biopsy. It is also possible that our patient has an undefined combined B-Cell and T-cell defect that would have predisposed him to PCP along with the prior *Cryptosporidium* infection.

This case and the prior one suggest that while *P. jirovecii* is a rare cause of pulmonary infection in treatment-naïve CLL, it should be included in the differential diagnosis. Importantly, PCP in untreated CLL can present in an indolent manner, similar to the case in HIV, in contrast to the acute presentation typically associated with non-HIV populations [9].

Acknowledgments

The authors thank the patient reported here for allowing us to present his case, Dr. Henry Masur and Dr. Joseph Kovacs for their critical review, and Kelly Byrne for editing and formatting the manuscript and tables

Financial support: This work was supported by the intramural funds from the National Institute of Allergy and Infectious Diseases and National Cancer Institute

References

1. Hallek M. Chronic lymphocytic leukemia: 2015 Update on diagnosis, risk stratification, and treatment. *Am J Hematol.* 2015; 90:446–460. PMID: 25908509. [PubMed: 25908509]
2. Morrison V. Infectious complications of chronic lymphocytic leukaemia: pathogenesis, spectrum of infection, preventive approaches. *Best Practice and Research Clinical Haematology.* 2010; 23:145–153. PMID: 20620978. [PubMed: 20620978]
3. Gea-Banacloche JC. Rituximab-associated infections. *Semin Hematol.* 2010; 47:187–198. PMID: 20350666. [PubMed: 20350666]
4. Kalkanis A, Judson M, Napier M. *Pneumocystis jirovecii* pneumonia in a patient with untreated chronic lymphocytic leukemia: a novel case and postulations concerning the mechanism. *BMJ Case Rep.* 2013 PMID: 24287485.
5. Azoulay E, Bergeron A, Chevret S, Bele N, Schlemmer B, Menotti J. Polymerase Chain Reaction for Diagnosing Pneumocystis Pneumonia in Non-HIV Immunocompromised Patients with Pulmonary Infiltrates. *Chest.* 2009; 135:655–661. PMID: 19265086. [PubMed: 19265086]
6. Meuwissen JH, Tauber I, Leuvenberg AD, Beckers PJ, Sieben M. Parasitologic and serologic observations of infection with Pneumocystis in humans. *J Infect Dis.* 1977; 136:43–49. PMID: 328785. [PubMed: 328785]
7. Kovacs J, Masur H. Evolving Health Effects of Pneumocystis, One Hundred Years of Progress in Diagnosis and Treatment. *JAMA.* 2009; 301:2578–2585. PMID: 19549975. [PubMed: 19549975]
8. Vavricka SR, Halter J, Hechelhammer L, Himmelmann A. *Pneumocystis carinii* pneumonia in chronic lymphocytic leukaemia. *Postgrad Med J.* 2004; 80:236–238. [PubMed: 15082848]
9. 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; 100:663. PMID: 6231863. [PubMed: 6231873]

Figure 1.

(A) Chest CT showing bibasilar ground glass opacity from admission. (B) Gomori's methenamine silver (GMS) stain showing rare structures consistent with *Pneumocystis*. (C) Cytopathology with atypical lymphocytes morphologically consistent with known history of chronic lymphocytic leukemia. (D) 2 months after completion of therapy with near complete resolution of prior infiltrates.