CASE REPORT

A rare case of pulmonary toxoplasmosis in a patient with undifferentiated inflammatory arthritis on chronic methotrexate and corticosteroid therapy

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SUMMARY

Pulmonary toxoplasmosis is a serious pulmonary condition caused by the protozoan *Toxoplasma gondii*. It typically affects immunocompromised patients presenting acutely with cough, fever, myalgias, arthralgias and lymphadenopathy, and chronically with persistent cough and dyspnoea. Because of its protean features, it can mimic many more common lung conditions in the immunocompromised patient, including atypical pneumonia, *Pneumocystis* pneumonia and interstitial lung disease. In this article, we present the case of a 55-year-old woman who presented to our hospital with persistent dyspnoea and cough, initially suspected to have an arthritis-related interstitial lung disease. She received a final diagnosis of pulmonary toxoplasmosis after lung biopsy demonstrated *Toxoplasma* cysts, later confirmed by serology. Treatment with trimethoprim-sulfamethoxazole resulted in significant improvement of her respiratory symptoms after 3 months.

with pharmacological immunosuppression are rare.^{5–7}

CASE PRESENTATION

A 55-year-old woman with a history of undifferentiated inflammatory arthritis managed with chronic prednisone and methotrexate presented to an outpatient pulmonologist with a 2-month history of a disabling non-productive cough and progressive shortness of breath. She denied any fever, chills, night sweats, haemoptysis, sore throat, fatigue, malaise, nausea, vomiting, weight loss, sick contacts, lymphadenopathy, neurological deficits, ocular complaints or recent travel history. Approximately 9 months before presentation, she reported diffuse myalgias, symmetric arthralgias in the hands and knees, morning stiffness lasting greater than 30 min, intermittent low-grade fever and right knee inflammatory arthritis. She was diagnosed with undifferentiated inflammatory arthritis because of her atypical presentation and serological studies (detailed in the 'Investigations' section). She was empirically started on prednisone 7.5 mg daily with improvement in her musculoskeletal symptoms. She remained on the same dose of prednisone over 9 months because she would experience recurrence of myalgias and arthralgias during tapering attempts. She was also started on methotrexate 17.5 mg weekly about 4 months prior to this presentation, but stopped taking this medication 3 weeks prior to presentation due to dyspnoea. Despite stopping methotrexate, patient experienced worsening dyspnoea.

She reported a history of acute Lyme disease 4 years prior, manifesting with complete heart block that was transient and resolved with 2 weeks of intravenous ceftriaxone. She noted a remote history of tobacco use of two packs daily for 30 years (60 pack year smoking history), but quit 9 years ago. There was no documented history of asbestos exposure, lung malignancy or allergies to pollen, dust or mites. She reported a family history of unspecified leukaemia in her father. Of note, she noted having two pet cats and a rabbit for years, but no other animal or hobby exposures. She also reported ingestion of partially cooked hamburgers.

Vital signs on presentation were within normal limits, including normal oxygen saturation of 97% on room air and normal oral temperature. Physical examination revealed no weight changes and

BACKGROUND

Pulmonary toxoplasmosis is a potentially fatal pulmonary disease caused by *Toxoplasma gondii* that is usually asymptomatic in immunocompetent hosts, but can present with serious and life-threatening manifestations in those with significant immune compromise. Exposure to toxoplasmosis as estimated by serology is 11% in the USA, but as high as 80% in Europe and Africa.¹ Source of infection is attributed to direct ingestion of food or water contaminated with cat faeces containing *Toxoplasma* oocysts, ingestion of oocysts in uncooked meat, transplacental transmission to the intrauterine fetus and rarely due to blood transfusions and organ transplantation.² The clinical manifestations of toxoplasmosis are variable and dependent on affected organs. Acute pulmonary infection presents with non-specific symptoms of productive or dry cough, fever, myalgias, arthralgias and lymphadenopathy, whereas chronic pulmonary infection manifests with persistent cough and dyspnoea.³ Mortality in patients with pulmonary toxoplasmosis in the face of immune compromise is noted to be as high as 55%.⁴ High suspicion of pulmonary toxoplasmosis should exist in late-stage patients infected with HIV (CD4 counts <100 cells/mm³), especially if there is poor adherence to highly active antiretroviral therapy and toxoplasmosis/*Pneumocystis* prophylaxis.³ Cases in patients

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Figure 1 Chest radiograph showed right airspace disease that could represent pneumonia or haemorrhage.

an unremarkable musculoskeletal examination with preserved range of motion in the upper and lower extremities with no joint erythema or swelling. Lungs were clear to auscultation with no wheezing, crackles or areas of consolidation, and all other systems examined were normal.

INVESTIGATIONS

Nine months prior to presentation, she had an extensive workup for arthritis. At that time, antinuclear antibody titre was positive at 1:320 ($\leq 1:40$), erythrocyte sedimentation rate was elevated at 48 mm/hour (0–20 mm/hour), and C reactive protein was elevated at 5.0 mg/dL (< 1.0 mg/dL). Rheumatoid factor, anti-cyclic citrullinated peptide antibody, anti-double-stranded DNA antibody, anti-Smith antibody, anti-SSA/Ro antibody, anti-SSB/La antibody, anticardiolipin antibody and serum protein electrophoresis were negative. Joint fluid aspirate from her right knee revealed cloudy fluid with white blood count (WBC) of 3416 (0–20/ μ L), red blood count of 8000 (0–1000/ μ L), 49% segmented cells and was negative for crystals and culture growth. Urinalysis was normal with normal renal function.

During her current presentation, a complete blood count and electrolyte panel were within normal limits. WBC was 10.1×10^9 /L (4.8 – 10.8×10^9 /L). She tested negative for HIV, and her IgE serology was within normal limits at 82 IU/mL (1–165 IU/mL). Erythrocyte sedimentation rate was mildly elevated at 35 mm/hour (0–20 mm/hour), and C reactive protein was mildly elevated at 1.71 mg/dL (< 1.0 mg/dL).

Chest X-ray revealed (figure 1) right base patchy airspace disease that was consistent with pneumonia. A CT of the chest showed extensive bilateral ground-glass opacities and subcentimetre bilateral hilar lymphadenopathy more prominent on right than left side (figure 2A). Pulmonary function tests (PFTs) were consistent with a moderate restrictive pattern with a forced vital capacity (FVC) of 2.23 L (67% predicted), a forced expiratory volume in 1 s (FEV₁) of 1.63 L (61% predicted) and a FEV₁:FVC ratio of 73%.

Transthoracic echocardiogram (TTE), cardiac exercise stress test and Holter monitoring were also ordered to evaluate for a cardiac aetiology for patient's shortness of breath given her

Figure 2 CT scans of the chest are displayed. (A) On initial presentation, CT chest showed extensive bilateral ground-glass opacities. There was also small bilateral lymphadenopathy. (B) CT chest 3 months later showed resolution of ground-glass opacities and lymphadenopathy.

prior history of acute Lyme disease with complete heart block. TTE showed 66% left ventricular ejection fraction and grade I diastolic dysfunction, unchanged from a prior study; exercise stress test was negative, and Holter monitor did not reveal any arrhythmias.

In light of an undiagnosed pulmonary disease in a patient with a rheumatological condition, a bronchoscopy and transbronchial biopsy was performed. Pathology reports from bronchoscopy with lung biopsy demonstrated nodular lymphohistiocytic interstitial infiltrates with non-specific inflammation. Gomori methenamine silver (GMS) stain revealed small cystic bodies with periodic acid–Schiff positive and granular material suggestive of toxoplasmosis (figure 3A,B). A significant histiocytic population was demonstrated by CD68 immunohistochemistry, although immunostaining was negative for CD1A and S100. Culture from bronchial washings grew *Staphylococcus aureus* and *Candida*. *Toxoplasma* serology was positive for IgG antibody titres at 139 IU/mL (normal < 7.1 IU/mL) and negative for IgM antibody titres. CT brain revealed non-specific hypodensity in the right basal ganglia, but subsequent MRI showed no acute intracranial abnormality.

DIFFERENTIAL DIAGNOSIS

Given the patient's history of symptomatic undifferentiated inflammatory arthritis, a diagnosis of rheumatoid arthritis-related interstitial lung disease was initially assigned. The possibility of histiocytosis X was entertained given the prominence of histiocytes on immunohistochemistry from bronchoalveolar lavage (BAL) samples and her prior smoking history, although

Figure 3 (A) Histology revealed cysts containing bradyzoites characteristic of *Toxoplasma* (indicated by arrow). Tachyzoites were not identified. (B) Small cystic bodies incorporating granular material were seen by Gomori methenamine silver stain characteristic of *Toxoplasma* (indicated by arrow).

subsequent negative immunostaining of CD1A and S100 made this diagnosis unlikely. Given the ground-glass opacities on CT and restrictive findings on PFTs in the face of methotrexate use, methotrexate lung disease was considered.⁸ However the presence of infection on biopsy that responded to appropriate therapy ruled out this diagnosis. Suspicion for a cardiac aetiology was low given a negative workup from echocardiogram, exercise stress test and Holter monitoring. Other aetiologies of interstitial lung disease were not pursued after biopsy confirmed infection.

Occult infection in this immunocompromised host was highly suspected. We ultimately assigned a diagnosis of pulmonary toxoplasmosis based on historical findings of immunosuppressive medications, exposure to cats and consumption of partially cooked hamburgers, as well as a positive serology for *Toxoplasma* and characteristic histological staining of *Toxoplasma* cysts from lung biopsy. PCR analysis of BAL fluid was not performed as the presence of *Toxoplasma* cysts on GMS staining was not suspected and only found incidentally. An additional invasive BAL procedure to obtain more sample for PCR analysis was deferred. Our patient did test positive for IgG antibodies, suggesting a more subacute to chronic infection from *Toxoplasma*.

TREATMENT

Due to cost-prohibitive reasons and inadequate insurance coverage, patient was unable to afford pyrimethamine, atovaquone or sulfadiazine. She was subsequently started on sulfamethoxazole–trimethoprim 1600–320mg two times per day, and completed a total course for 3 months. After completing the regimen, she was transitioned to a low dose of sulfamethoxazole–trimethoprim 800–160mg tablet one time per day for prophylaxis given her continued need for immunosuppressive medication for her undifferentiated inflammatory arthritis.

OUTCOME AND FOLLOW-UP

Our patient experienced significant resolution of her cough and dyspnoea within the next 2 months. Repeat CT chest at 6 weeks showed complete resolution of the previous extensive bilateral ground glass opacities (figure 2B). Concern for spread of toxoplasmosis to other sites, particularly the brain, was addressed. CT brain and MRI brain did not reveal any intracranial abnormalities.

DISCUSSION

Pulmonary toxoplasmosis can be difficult to diagnose due to a non-specific and variable presentation and low awareness among healthcare providers due to its rarity. Symptoms are non-specific and include productive or dry cough, fever, myalgias, arthralgias and lymphadenopathy. Acute presentations of pulmonary toxoplasmosis may mimic a viral upper respiratory tract infection.⁹ CT findings of ground-glass opacities and peribronchovascular thickening may mimic other pulmonary conditions of atypical pneumonia, pneumocytosis and methotrexate lung disease.¹⁰ Thus, patients with pulmonary toxoplasmosis may escape detection or are misdiagnosed, delaying proper antiparasitic treatment and leading to significant morbidity and mortality.

Source of infection is from ingestion of food or water contaminated with cat faeces containing *Toxoplasma* oocysts, ingestion of oocysts in uncooked meat, transplacental transmission to the intrauterine fetus and rarely due to blood transfusions and organ transplantation.² Our case report patient satisfied two of these exposure risk factors as she took care of a pet cat for years and ingested partially cooked hamburgers.

Immunosuppression is an important risk factor. Late-stage HIV (CD4 <100 cells/mm³), especially poor compliance with prophylaxis, is the most commonly reported risk factor.^{3 11} There are a few reports of pulmonary toxoplasmosis from medication-induced immunosuppression.^{5–7} There are also reports of other subtypes of toxoplasmosis from medication-induced immunosuppression,^{12–14} including one describing cerebral toxoplasmosis in a patient receiving methotrexate and infliximab.¹⁵ Interestingly, our patient received prednisone and methotrexate, which are medications with an immunosuppressive side effect profile. Thus, a high suspicion for pulmonary toxoplasmosis should exist in patients with febrile lung disease who have HIV and in individuals immunocompromised due to other aetiologies including immunosuppressive therapy.

Diagnosis of pulmonary toxoplasmosis is made from identification of tachyzoites or *T. gondii* DNA from BAL. Samples from BAL should be cultured, undergo GMS staining and undergo PCR amplification for *Toxoplasma*.¹⁶ Chest radiographs are variable and may demonstrate reticulonodular infiltrates, nodular opacities and/or coalescence opacities.¹⁰ CT findings may include diffuse interstitial infiltrates and ground-glass opacities with thickening of the interlobular septa that may be comparable to *Pneumocystis jirovecii* pneumonia.¹⁰

First-line treatment is with sulfadiazine and pyrimethamine, administered concurrently with leucovorin to prevent folate deficiency.¹⁷ Alternate treatment regimens include clindamycin and pyrimethamine^{18 19} or trimethoprim–sulfamethoxazole.²⁰ Regimens containing atovaquone plus pyrimethamine, or atovaquone plus sulfadiazine, or atovaquone monotherapy have also been suggested in the literature.^{21 22} Treatment is recommended for a total of 4–6 weeks.²³ If persistent immunosuppression exists after initial therapy, secondary prophylaxis with trimethoprim–sulfamethoxazole or pyrimethamine plus sulfadiazine is continued indefinitely.²³ Our patient received trimethoprim–sulfamethoxazole for 6 weeks as she was unable to obtain first-line treatment due to cost-prohibitive reasons and lack of insurance coverage. Due to continued need for immunosuppressive medication (prednisone) to control her undifferentiated inflammatory arthritis, she was continued on a lower dose of prophylactic trimethoprim–sulfamethoxazole indefinitely. Given concern for *Toxoplasma* infection of other organ systems, particularly the brain, interval CT brain and/or MRI brain was performed in our case report. There are no guidelines in the

Learning points

- ▶ Toxoplasmosis should be strongly considered in a patient who is on long-term immunosuppressive therapy, including corticosteroids and methotrexate, especially with a history of handling cat litter and history of ingestion of poorly cooked meat.
- ▶ Diagnosis of pulmonary toxoplasmosis is challenging due to lack of specific clinical features, absence of universal diagnostic criteria, low awareness among clinicians and variable clinical presentation.
- ▶ Other diagnoses such as viral upper respiratory infection, atypical pneumonia and *Pneumocystis* pneumonia may act as mimics of pulmonary toxoplasmosis in immunosuppressed patients and may delay prompt and proper management of this life-threatening disease.
- ▶ Promptly treated patients of pulmonary toxoplasmosis make a complete recovery with preservation of lung function.

literature on when interval brain imaging is recommended in known cases of toxoplasmosis.

Mortality in pulmonary toxoplasmosis is noted to be as high as 55%.⁴ One of the largest case series with 64 cases of pulmonary toxoplasmosis documented a mortality rate of 37% with a median survival time of 150 days.¹¹ Even in patients achieving a clinical response due to prompt medical treatment in this case series, relapse was experienced in 23%.¹¹

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Competing interests None declared.

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