CASE REPORT

Disseminated histoplasmosis mimicking relapsed chronic lymphocytic leukaemia

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SUMMARY

Histoplasma microconidia when inhaled are presented in antigenic form to T cells, limiting the extent of infection; however, defects in cellular immunity results in disseminated disease. Chronic lymphocytic leukaemia (CLL) is a lymphoproliferative disorder resulting in functionally impaired lymphocytes, predisposing patients to various opportunistic infections. The author reports a recently treated patient with CLL presenting with constitutional symptoms accompanied by hepatosplenomegaly and diffuse adenopathy. Considering the recent diagnosis and treatment of CLL, initial suspicion was relapsed disease. However, considering the immune deficiency associated with CLL and its treatment, infectious aetiologies were strongly considered. Further investigation revealed a case of disseminated histoplasmosis mimicking CLL in this reported patient. Considering appropriate diagnosis and timely therapy, the reported patient had good prognosis despite being diagnosed with disseminated histoplasmosis. This case highlights consideration of disseminated histoplasmosis in patients presenting with diffuse adenopathy along with hepatomegaly and/or splenomegaly in the right clinical setting.

BACKGROUND

Histoplasma capsulatum is a dimorphic fungus and a common endemic mycosis prevalent in the central and eastern USA, specifically around the Ohio and Mississippi River Valleys.¹ Infection develops when *Histoplasma microconidia* get inhaled and transforms to yeast form in the lungs. These yeasts are rapidly ingested by macrophages and processed by antigen-presenting cell (APC) and presented to T cell as antigens. T lymphocytes work as primary host defence and are crucial in limiting the extent of infection. Susceptibility to dissemination is increased due to impaired cellular immunity resulting in spread of the organism to the adjacent lymph nodes and throughout the reticuloendothelial system.²

Chronic lymphocytic leukaemia (CLL) is a lymphoproliferative disorder resulting in functionally impaired lymphocytes. Defects in immune function related to CLL as well as related to treatment modality, predispose patients with CLL to a host of infections.³ The author reports a case of disseminated histoplasmosis mimicking relapsed disease in a patient treated for CLL.

CASE PRESENTATION

The author reports a 69-year-old man presenting for an outpatient visit with a 2-months history of

intermittent fevers (no particular pattern), daily night sweats and 10 pound weight loss. The patient had a history of CLL treated with combination of fludarabine, cyclophosphamide and rituximab regimen and had completed treatment 9 months prior to this presentation with complete response based on International Workshop Group on CLL response criteria.⁴

The patient was a farmer in rural Missouri and denied smoking, alcohol and illicit drug use. He acknowledged contact with farm animals and poultry in the past 3 months once he resumed his farming occupation.

On his initial evaluation, the patient was febrile (temperature=38.6°C); however, the rest of his vital signs were within normal limits (pulse=88 beats/min, respiratory rate=12 breaths/min, blood pressure=110/72 mm Hg). On examination, the patient had moderate hepatosplenomegaly, and decreased breath sounds in the right lower lobe were noted on pulmonary auscultation.

INVESTIGATIONS

Laboratory tests revealed normal white cell and absolute neutrophil counts and a decreased absolute lymphocyte count ($0.07 \text{ cells} \times 10^9/\text{L}$). Lactate dehydrogenase level was elevated; however, other blood counts, hepatic and renal function tests within normal limits.

To further investigate, the patient underwent CT scan of the chest and abdomen. Multiple enlarged mediastinal nodes measuring between 1 and 2.5 cm, as well as airspace consolidation within the right lower lobe was noted (figure 1). Hepatosplenomegaly with mesenteric and retroperitoneal adenopathy was also noted.

A follow-up F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) scan demonstrated high FDG uptake (maximum standardised uptake value measured up to 15.9) in the mediastinal lymph nodes (figure 2). Retroperitoneal adenopathy along with splenomegaly and hepatomegaly was also noted (figure 3).

DIFFERENTIAL DIAGNOSIS

Considering the patient treated for CLL, presenting with constitutional symptoms, lymphopenia, generalised lymphadenopathy and hepatosplenomegaly, the differential diagnosis included haematological malignancies, infectious aetiologies, granulomatous diseases and other miscellaneous causes. Haematological malignancies especially relapse of CLL or

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Figure 1 CT of the lungs demonstrating multiple enlarged mediastinal nodes and airspace consolidation within the right lower lobe.

lymphomas were strongly considered. Considering immunocompromised state, infectious aetiologies such as Epstein Barr virus (EBV), HIV, *Toxoplasma*, *Mycobacterium tuberculosis* and other atypical mycobacterial infections were considered. Among the endemic mycosis, infections secondary to *Histoplasma*, *Aspergillus* and *Coccidioides* were also considered. Other granulomatous and miscellaneous causes such as sarcoidosis, rheumatoid arthritis and systemic lupus erythematosus were considered.

To investigate infectious aetiologies further, workup including bacterial, mycobacterial and fungal blood cultures, urine Histoplasma antigen and plasma Aspergillus galactomannan antigen tests were ordered. Serological testing for HIV infection (ELISA) and serological testing and plasma PCR for *Toxoplasma gondii*, as well as plasma PCR for EBV, were ordered.

TREATMENT

Urine examination was immediately positive for Histoplasma antigen confirming the diagnosis of disseminated histoplasmosis.

Figure 2 F-18 fluorodeoxyglucose (FDG) positron emission tomography scan demonstrating high FDG uptake in the mediastinal lymph nodes.

Figure 3 F-18 fluorodeoxyglucose (FDG) positron emission tomography scan demonstrating splenomegaly and hepatomegaly and FDG uptake in the retroperitoneal lymph nodes.

Patient was rapidly initiated on intravenous liposomal amphotericin 3 mg/kg daily for 2 weeks. Patient underwent an excisional biopsy of the mediastinal lymph nodes for further diagnostic clarification, considering concerns for relapsed CLL. Histological sections demonstrated normal lymph node architecture, and Gomori methenamine silver stain and periodic acid-Schiff stains highlighted frequent clusters of intracellular microorganism, consistent with histoplasmosis.

Patient completed a 2-week course of intravenous liposomal amphotericin and was then switched to oral itraconazole titrated to a dose of 300 mg twice daily to achieve therapeutic drug levels.

OUTCOME AND FOLLOW-UP

At 3-month follow-up, the patient had good clinical response to this therapy, and urine Histoplasma antigen test was negative. A follow-up CT scan of the chest showed improvement in the adenopathy as well as the right lower lobe infiltrates. Itraconazole therapy was recommended for 1 year to prevent future relapses.

DISCUSSION

The author reports a recently treated patient with CLL presenting with constitutional symptoms accompanied by hepatosplenomegaly and diffuse adenopathy. Considering the recent diagnosis and treatment of CLL, initial suspicion was relapsed

disease. However, considering the immune deficiency associated with CLL and its treatment, infectious aetiologies were strongly considered. Fungal infection, including histoplasmosis has been reported as a late complication in patients with CLL treated with combination of fludarabine, cyclophosphamide and rituximab.⁵ Further investigation revealed a case of disseminated histoplasmosis mimicking CLL in this reported patient. Rapid diagnosis with urinary histoplasma antigen detection, prompted early diagnosis and treatment resulting in good outcome in the reported patient.

As mentioned above, infection with *Histoplasma* occurs by inhaling microconidia which transforms to yeast form in the lungs. These yeast forms are rapidly ingested by macrophages and processed by APC and presented to T cell as antigens. T lymphocytes work as primary host defence and are crucial in limiting the extent of infection.² After inhalation of microconidia, majority of patients develop subclinical, self-limited and unrecognised disease. However, defects in cellular immunity results in progression of the infection, resulting in dissemination.⁶ Disseminated infection in this patient from an endemic area could demonstrate either primary infection or reactivation of latent infection; both resulting from recent immunocompromised state. Viable organisms are known to persist following recovery from the initial episode of latent infection.⁶

Commonly, patients with disseminated histoplasmosis present with fever, loss of weight and other constitutional symptoms. Physical examination often demonstrates lymphadenopathy, with hepatomegaly and splenomegaly. Laboratory tests can reveal leucopenia, anaemia, thrombocytopenia and elevated liver enzymes; however, elevated lactate dehydrogenase and ferritin are suggestive of disseminated histoplasmosis.⁷ The highest yield for antigen detection occurs in patients with disseminated histoplasmosis, being detected in 80%–95% of cases.⁸ Diffuse adenopathy especially in mediastinal and abdominal lymph nodes along with hepatomegaly and/or splenomegaly has been reported on radiological studies and should prompt consideration of disseminated disease in the right clinical setting.⁹

Disseminated histoplasmosis is associated with increased morbidity if untreated and hence treatment is recommended in all cases.¹⁰ Liposomal amphotericin B administered for 1–2 weeks followed by itraconazole for 12 months is recommended in patients with disseminated disease.¹¹ Treatment response is usually monitored by following antigen levels as well as monitoring clinical response during or after treatment.

Considering appropriate diagnosis and timely therapy, the reported patient had good prognosis despite being diagnosed with disseminated histoplasmosis. The patient was recently treated for CLL, and hence the initial suspicion was relapsed disease. However, considering the immune deficiency, infectious aetiologies were strongly considered and workup yielded the diagnosis of histoplasmosis. This case highlights consideration of disseminated histoplasmosis in patients presenting with diffuse

adenopathy along with hepatomegaly and/or splenomegaly in the right clinical setting.

Learning points

- ▶ Chronic lymphocytic leukaemia (CLL) is a lymphoproliferative disorder resulting in functionally impaired lymphocytes, predisposing patients to a host of infections.
- ▶ Histoplasma microconidia when inhaled are presented in antigenic form to T cells, limiting the extent of infection; however, defects in cellular immunity results in progression and dissemination.
- ▶ Liposomal amphotericin B administered for 1–2 weeks followed by itraconazole for 12 months is recommended in patients with disseminated disease.
- ▶ Diffuse adenopathy especially in mediastinal and abdominal lymph nodes along with hepatomegaly and/or splenomegaly should prompt consideration of disseminated histoplasmosis in the right clinical setting.

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