A 72-year-old woman from southwestern Ontario was admitted to hospital with a 2-month history of progressive generalized weakness, fatigue, nausea, anorexia and 7-kg weight loss. Although previously functionally independent, she now required a walker for ambulation. She had also noted development of presyncope with standing or protracted exertion. She had mild dyspnea but no chest discomfort, cough, night sweats, fevers or other infective symptoms. She was a non-smoker, used alcohol rarely and did not take any prescription medications or illicit drugs. The patient’s past medical history included melanoma and ductal carcinoma in situ, both in remission, as well as idiopathic alopecia. She had a stable history of idiopathic cyclic neutropenia, chronic lymphopenia since 2002 and chronic thrombocytopenia since 2016; she had no history of opportunistic infections.

On examination, her body mass index was 18.86 kg/m². Her supine blood pressure was 94/65 mm Hg and 68/45 mm Hg upon standing, with development of presyncope. She was afebrile without tachycardia or tachypnea, and oxygen saturation was normal on room air. She appeared tanned despite a lack of recent travel, with hyperpigmentation of the face and dorsal surface of the hands. She had no palpable lymphadenopathy, and examination of her cardiovascular and respiratory systems was unremarkable.

Laboratory investigations showed serum sodium of 128 (normal 137–145) mmol/L, potassium 4.1 (normal 3.5–5.0) mmol/L, cortisol 50 (normal 133–537) nmol/L and adrenocorticotropic hormone 187.9 (normal 1.98–12.47) pmol/L, consistent with primary adrenal insufficiency.

The patient’s leukocyte count was 2.8 (normal 4–10) × 10⁹/L with a lymphocyte count of 0.2 (normal 1.0–4.0) × 10⁹/L and neutrophil count of 1.9 (normal 2.0–7.5) × 10⁹/L. Her eosinophil and thrombocyte counts were normal. The low lymphocyte and neutrophil counts were consistent with her history of idiopathic cyclic neutropenia and chronic lymphopenia evident for at least 10–15 years. Her neutrophil counts were 1.7–1.9 × 10⁹/L with most values in the range of 2.10–3.83 × 10⁹/L. The hematology department had assessed the patient in 2007 and 2016 for her longstanding hematologic findings with no underlying cause identified. She had mild elevations in her alanine aminotransferase (ALT) at 36 (normal ≤ 33) U/L and aspartate aminotransferase (AST) at 64 (normal ≤ 32) U/L, but no other clinically significant biochemical abnormalities. In addition to volume replacement, we initiated glucocorticoid and mineralocorticoid replacement promptly.

Autoimmune adrenalitis and malignant disease were considered to be the most probable causes of our patient’s primary adrenal insufficiency. Computed tomography (CT) of the patient’s thorax, abdomen and pelvis showed bilateral adrenal enlargement with heterogeneously enhancing adrenal masses suspicious for metastases, but no other evidence of malignancy, adenopathy or hepatosplenomegaly (Figure 1A, 1B). We also noted scarring in the lung apices, a calcified granuloma anteriorly in the right lower lobe of the lung and a 1.1-cm area of decreased attenuation in the left lobe of the liver of questionable significance on CT imaging.

Given a negative imaging workup for malignant disease, we attempted ultrasound-guided biopsy of the adrenal glands for further characterization of the patient’s bilateral adrenal masses. Unfortunately, adrenal biopsy was not successful; instead, liver histology showed multiple necrotizing granulomas with parasitized macrophages and fungal spores morphologically consistent with *Histoplasma capsulatum* (Figure 2). Despite negative *H. capsulatum* serology, the clinical presentation and histologic findings were highly suggestive of bilateral adrenal histoplasmosis as the
underlying cause of primary adrenal insufficiency. In addition to physiologic doses of glucocorticoids and mineralocorticoids, we began antifungal therapy with twice-daily oral itraconazole for disseminated histoplasmosis.

At 3-month follow-up in the outpatient endocrinology clinic, the patient had substantial improvement in fatigue, weakness and quality of life, with return to independent ambulation and resolution of all her other symptoms. Repeat CT scan of the adrenal glands after 3 months of itraconazole therapy showed substantial improvement with respect to bilateral adrenal enlargement, indicating treatment response and further supporting a diagnosis of bilateral adrenal histoplasmosis (Figure 1C, 1D). The

![Computed tomography (CT) scans of bilateral adrenal enlargement before and after 3 months of treatment with itraconazole in a 72-year-old woman with adrenal histoplasmosis. Abdominal CT scan with intravenous contrast obtained before treatment shows (A) right adrenal gland in unenhanced phase measuring 4.2 × 2.0 cm and (B) left adrenal gland in unenhanced phase measuring 2.1 × 1.8 cm. Noncontrast CT scan of the adrenals obtained after 3 months of treatment with itraconazole shows (C) right adrenal gland measuring 3.0 × 1.6 cm and (D) left adrenal gland measuring 1.6 × 0.9 cm. All measurements represent anteroposterior and transverse dimensions, respectively. Paired pre- and post-treatment axial CT slices correspond to roughly the same anatomic levels and depict the largest cross-sectional area of each adrenal gland.](image)

![Liver histology showing a single non-necrotizing granuloma containing fungal spores consistent with *Histoplasma capsulatum*. (A) Grocott methenamine silver and (B) periodic acid–Schiff–diastase staining of a granuloma at 20× magnification showing numerous fungal organisms (arrows) morphologically consistent with *Histoplasmodium* species.](image)
patient continues to have regular follow-up with her endocrinologist and infectious diseases specialist. She continues with glucocorticoid and mineralocorticoid replacement.

Discussion

Our patient presented with primary adrenal insufficiency most likely secondary to bilateral adrenal histoplasmosis, which is a rare presentation in an immunocompetent host. Histoplasmosis is an infectious disease caused by the dimorphic fungus *H. capsulatum*, found predominantly in soil contaminated with bird or bat guano. A recent epidemiologic study of endemic fungal infections in Ontario, Canada, found 211 confirmed cases of histoplasmosis between 1990 and 2015, with a median of 7.5 cases per year (range 3–13 cases/yr). Incidence rates were highest in geographic regions bordering the Great Lakes and St. Lawrence Seaway. Our patient resided in the South West Local Health Integration Network, classified as the region in Ontario with the second-highest average annual number of histoplasmosis cases.

Infection with *H. capsulatum* occurs through airborne spore inhalation. In a normal adult host, mild exposure typically manifests as an asymptomatic respiratory infection; more substantial exposure may cause acute pulmonary histoplasmosis. In immunocompromised hosts or individuals with pre-existing parenchymal lung injury, chronic pulmonary or disseminated histoplasmosis may occur. Less commonly, as observed in our patient, disseminated histoplasmosis may occur in an immunocompetent host. Such cases are thought to arise from a transient insult to cellular immunity.

Our patient had chronic lymphopenia for at least 10–15 years with lymphocyte counts in the range of 0.20 to 0.34 × 10^9/L. She also had intermittently low neutrophil counts (range 1.7–1.9 × 10^9/L) with most values ranging from 2.10 to 3.83 × 10^9/L. Based on the hematologic findings, it may be suggested that our patient was immunosuppressed. However, importantly, during the 10–15 years of documented hematologic findings, there was no evidence of further decreases in lymphocyte or neutrophil values, no evidence of pancytopenia to suggest bone marrow suppression, and no prior history of opportunistic infections. Her lymphocyte and neutrophil values on presentation to hospital were consistent with her previous values when she had been well. Together, these findings suggest that she was unlikely to be chronically immunosuppressed.

Irrespective of a patient’s immune status, disseminated histoplasmosis develops when primary infection at the site of inhalation undergoes lymphohematogenous spread to solid organs. Macrophages are subsequently recruited to sites of fungal infection, where they undergo parasitization with *H. capsulatum* spores. Disseminated histoplasmosis may manifest as histopathologic findings of diffuse macrophage recruitment and evidence of parasitized macrophages throughout the body; focal aggregation of parasitized macrophages, most often to a single site; and the presence of tuberculous granulomas. Diffuse macrophage recruitment is the most common manifestation of disseminated *H. capsulatum* infection and is the most likely classification in our patient, given the presence of parasitized macrophages and fungal spores on liver biopsy, as well as radiographic evidence of bilateral adrenal masses. When dissemination is diffuse, parasitized macrophages may also be found in the spleen, liver, bone marrow, lymph nodes and adrenal glands.

Disseminated histoplasmosis can be acute, subacute or chronic, and often presents with constitutional symptoms. Our patient presented with weight loss, weakness, fever, malaise and anorexia, symptoms that may be due to fungal infection but could also be attributed to adrenal insufficiency. Disseminated histoplasmosis may also present with hepatosplenomegaly, moderate leukopenia and thrombocytopenia. Our patient had no evidence of hepatosplenomegaly, and given the longstanding nature of her hematologic findings, as outlined above, it is unlikely that they were manifestations of disseminated histoplasmosis.

Adrenal histoplasmosis

As illustrated by this case, disseminated histoplasmosis may infiltrate the adrenal glands and cause primary adrenal insufficiency. Box 1 shows the differential diagnosis for primary adrenal insufficiency.

Infiltration with histoplasmosis does not always cause adrenal hypofunction. A systematic review identified 242 patients globally with adrenal histoplasmosis from 1971–2012, of whom only 41.3% developed clinically confirmed adrenal insufficiency. Although early constitutional symptoms of disseminated histoplasmosis

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**Box 1: Differential diagnosis for primary adrenal insufficiency**

**Causes of primary adrenal insufficiency**

- Autoimmune adrenalitis
- Infectious adrenalitis
- Tuberculosis
- Disseminated fungal infections (histoplasmosis, blastomycosis, cryptococcosis, coccidioidomycosis)
- HIV, cytomegalovirus
- Other (syphilis, trypanosomiasis)
- Hemorrhagic infarction
- Metastatic malignant disease
- Infiltrative disease
- Amyloidosis
- Sarcoidosis
- Hemochromatosis
- Drugs
  - Inhibition of cortisol synthesis (etomidate, ketoconazole, fluconazole, metyrapone, mitotane)
  - Acceleration of cortisol metabolism (phenytoin, barbiturates, rifampin)
  - Immune-related adverse effects (ipilimumab, nivolumab)
- Genetic disorders
  - Adrenoleukodystrophy, adrenomyeloneuropathy
  - Congenital adrenal hyperplasia (certain forms)

Note: Adapted with permission from: Nieman LK. Causes of primary adrenal insufficiency (Addison’s disease). In: UpToDate, Post TW (Ed). UpToDate, Waltham, MA. (accessed Apr. 16, 2019. Copyright © 2019 UpToDate, Inc.). For more information visit www.uptodate.com.
resemble symptoms of adrenal insufficiency, gland destruction sufficient to cause hypofunction is often a late manifestation of chronic disseminated disease and should be suspected in the presence of specific signs including hyperpigmentation, salt craving, orthostasis, relative hyperkalemia, hyponatremia, elevation of adrenocorticotropic hormone and hypocortisolism.

Disseminated histoplasmosis is especially uncommon among patients with intact immunity. When widespread disease occurs in immunocompetent hosts, such as in our patient, the adrenal glands are the most common organ of involvement. In an autopsy series of disseminated histoplasmosis, 82% showed some degree of adrenal involvement, recognized in 3 separate histopathologic patterns: diffuse scattering of parasitized macrophages throughout the sinusoids, focal aggregation of heavily parasitized phagocytes, and extracapsular perivasculitis resulting in thrombosis of the adrenal vessels and subjacent infarction and swelling of the adrenal glands. Based on these pathologic observations, the authors favoured extracapsular perivasculitis with thrombosis and infarction as the most likely mechanism for the development of adrenal insufficiency secondary to histoplasmosis.

A recent review identified 33 cases globally of adrenal histoplasmosis in immunocompetent hosts from 2006 to 2016, of whom 45% had evidence of adrenal insufficiency. In a subsequent case series of 40 patients with adrenal histoplasmosis, 73% had primary adrenal insufficiency and one-third had adrenal crisis at presentation. Thus, adrenal histoplasmosis must be considered as a potential cause of primary adrenal insufficiency, particularly in endemic areas such as southwestern Ontario.

Adrenal histoplasmosis commonly appears on imaging as bilateral adrenal enlargement, which is in contrast to bilateral adrenal atrophy observed with autoimmune adrenalitis, the most common cause of primary adrenal insufficiency in North America. The presence of bilateral adrenal enlargement in primary adrenal insufficiency narrows the differential diagnosis of primary adrenal insufficiency to fungal infection, lymphoma, primary or metastatic cancer, bilateral adrenal hemorrhage, tuberculosis and infiltrative disorders. Definitive diagnosis is best made by image-guided fine-needle aspiration biopsy. In our patient, although we attempted ultrasound-guided biopsy of the adrenal glands, we could obtain only liver tissue.

Unfortunately, percutaneous image-guided adrenal biopsy may yield unsatisfactory results, and technical challenges with needle deviation to nonadrenal locations may uncommonly occur. In a recent systematic review, the pooled nondiagnostic rate among 2013 adrenal biopsies was 8.7%, and based on pooled complication rates from 1339 adrenal biopsies, about 2% veer into a nonadrenal location. Our fine-needle aspiration biopsy obtained hepatic tissue rather than adrenal tissue but still provided a likely diagnosis for this patient’s presentation.

Given the detection of *H. capsulatum* in liver tissue, the imaging characteristics on CT and the decrease in size of bilateral adrenal enlargement after itraconazole therapy, the diagnosis for our patient was most consistent with disseminated histoplasmosis causing primary adrenal insufficiency. Our patient did not have risk factors for bilateral adrenal hemorrhage such as anticoagulant therapy, trauma or meningococcemia, and adrenal hemorrhage was therefore an unlikely cause. Similarly, the reduction in bilateral adrenal size would not have been expected after 3 months of itraconazole therapy if the underlying diagnosis had been neoplasm (primary or metastatic), lymphoma, tuberculosis or infiltrative disease. Although blastomycosis is endemic in southwestern Ontario, the clinical likelihood of histoplasmosis in the liver and simultaneous blastomycosis in the adrenal glands would be low. Moreover, adrenal involvement in blastomycosis compared with histoplasmosis is extremely uncommon, based on evaluation of published literature. Thus, based on the findings described, the most likely diagnosis for our patient was disseminated histoplasmosis causing primary adrenal insufficiency.

Although histopathologic demonstration of fungal spores or isolation from tissue samples are the gold standards for laboratory diagnosis of *H. capsulatum* infection, serology and urinary antigen detection can be helpful in confirming and monitoring infective status over time. However, *H. capsulatum* serology is positive in only 75% of patients with disseminated disease, and detection of antibodies in peripheral blood takes about 4 to 8 weeks, thus rendering serology a nonideal method for diagnosing early acute infections. Detection of antigen in serum and urine has a higher sensitivity at 91.8%, but a major limitation of *Histoplasma* antigen testing is cross-reactivity with several other fungal antigens, such as *Blastomyces dermatitidis* (64%–90% cross-reactivity), which is also endemic in our patient’s region. Thus, although our patient’s fungal serology was negative, histopathologic findings confirmed infection with histoplasmosis and prompted initiation of antifungal therapy.

**Management**

Our patient presented in adrenal crisis, necessitating immediate intravenous stress-dose steroid therapy, followed by weaning to physiologic doses of glucocorticoid and mineralocorticoid replacement. Definitive management with antifungal therapy was initiated with itraconazole, as recommended in clinical practice guidelines published by the Infectious Diseases Society of America. For mild-to-moderate disseminated histoplasmosis, the recommended treatment is itraconazole 200 mg 3 times daily for 3 days, then twice daily for 12 months, but lifelong therapy in immunosuppressed patients may be necessary if the immunosuppression cannot be resolved or in patients who experience a relapse (10%–15%) after discontinuation of therapy. Thus, involvement of an infectious disease specialist is warranted for ongoing monitoring.

With itraconazole therapy, *H. capsulatum* remission rates may be as high as 80%–100%. A retrospective study of clinical outcomes and corticoster reserve in 40 patients with adrenal histoplasmosis found that despite high remission rates, glucocorticoid and mineralocorticoid insufficiency rarely resolves, which may be in keeping with the proposed pathogenesis involving perivasculitis, thrombosis and infarction. Even after 1 year of antifungal therapy, none of the reported patients with primary adrenal insufficiency secondary to adrenal histoplasmosis regained normal adrenal function and, interestingly, 2 of 7 (29%) patients who initially had no evidence of adrenal insufficiency subsequently developed it, signifying the potential for delayed onset of primary adrenal insufficiency. The rationale for delayed-onset adrenal insufficiency despite antifungal therapy remains uncertain.
After 3 months of treatment, our patient reported substantial symptomatic improvement but continues to require glucocorticoid and mineralocorticoid replacement. Remission is at best followed by clinical improvement and decrease in antigen levels.11 In immunocompetent patients, it may not be necessary to continue antifungal therapy despite the persistence of low-level antigenuria if there is no evidence of active infection.11 Because our patient had negative serology and no baseline antigen levels were drawn, remission will be noted through improvement in clinical and imaging characteristics, as shown previously by Mukherjee and colleagues.7 The marked reduction in bilateral adrenal enlargement on CT scan after 3 months of itraconazole therapy indicates treatment response and further supports a diagnosis of adrenal histoplasmosis.

Conclusion
Disseminated histoplasmosis is an important yet infrequently reported cause of primary adrenal insufficiency in an immunocompetent host.1–3 Despite patient factors indicating autoimmunity or malignant disease as high on the differential for our patient’s primary adrenal insufficiency, characteristic imaging features, detection of H. capsulatum in liver tissue, and clinical and imaging evidence of improvement with itraconazole therapy make disseminated histoplasmosis the most likely underlying cause. This report emphasizes the importance of including disseminated histoplasmosis in the differential diagnosis for primary adrenal insufficiency in patients who reside within endemic areas such as southwestern Ontario.

Competing interests: Tisha Joy has received speaker’s honoraria from Amgen, Janssen, Sanofi, Astra Zeneca, Merck, Novo Nordisk, Lilly and Boehringer Ingelheim; has been a principal, co- or subinvestigator on clinical trials sponsored by Novo Nordisk, Amgen, Astra Zeneca; and has done consulting work for Amgen and Novo Nordisk. No other competing interests were declared.

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