A 78-year-old man presented to his primary care physician with a 4-month history of worsening fatigue, generalized weakness, and anorexia, and reported an unintentional weight loss of about 25 lb (11.4 kg). He reported subjective fevers, chills, drenching night sweats, dry mouth, a nonproductive cough, dyspnea with minimal exertion, and nausea with occasional emesis. He became light-headed on standing and had become largely bedridden in the preceding month. He reported no headache, changes in vision, dysphagia, chest pain, palpitations, flushing, abdominal discomfort, changes in bowel habits, melena, or rash.

Striking features of this patient’s history include his weight loss and symptoms of postural hypotension. Constitutional symptoms such as fever, drenching night sweats, or clinically significant weight loss can be caused by chronic infections, rheumatologic illness, or cancer. His postural light-headedness suggests orthostasis, which may arise from hypovolemia, adrenal insufficiency, autonomic or peripheral neuropathy, or cardiac dysfunction. These conditions may contribute to generalized weakness, as would anemia or a myopathic disorder. He also has focal respiratory and gastrointestinal symptoms that may point to a localized process.

The patient’s medical history was notable for myasthenia gravis, which had been diagnosed 5 years earlier and was now well controlled with mycophenolate. He had undergone corneal transplantation in both eyes for Fuchs’s endothelial dystrophy 15 years earlier and had been treated for vitiligo with methoxsalen and ultraviolet radiation 40 years earlier. His current medications included mycophenolate, pyridostigmine, and timolol–dorzolamide and fluorometholone ophthalmic drops. He was a retired neuroscientist who was born and raised in India and immigrated to the United States 45 years ago. He lived with his wife and two adult children, all of whom were healthy. The patient had a remote history of cigarette use and reported no use of alcohol or recreational drugs. His last travel outside the United States was to India 8 years earlier.

Some notable potential contributors to the patient’s current condition have emerged. He has a history of autoimmune diseases requiring treatment with immunosuppressive agents and is from India, where tuberculosis is endemic. Given his long-term use of mycophenolate, it is possible that the cause of his symptoms is an opportunistic infection, such as tuberculosis, cytomegalovirus (CMV), or invasive fungal disease, or a noninfectious condition, such as cancer. Subacute bacterial endocarditis is possible, as is autoimmune polyendocrine syndrome type 2, which is characterized...
by vitiligo, adrenal insufficiency, type 1 diabetes mellitus, and thyroiditis. Pure red-cell aplasia and thymoma are associated with myasthenia but would be unlikely to explain several of this patient’s presenting symptoms.

The patient reported the development of escalating pain, erythema, and blurred vision in his right eye, without antecedent trauma, 18 months earlier; 1 month before the onset of these symptoms, he had traveled to the Great Smoky Mountains, after which he sustained a brief febrile illness. Ophthalmologic evaluation showed vitritis in one eye. The results of blood and urine cultures were negative. Induration at the site of a tuberculin skin test measured 12 mm in diameter; he had never been vaccinated with bacille Calmette–Guérin.

Serum antibody testing for Lyme disease, toxoplasma, and *Bartonella henselae* was negative, as were tests for CMV antigen, rapid plasma reagin, and urinary histoplasma antigen. Antinuclear antibodies, antineutrophil cytoplasmic antibodies, cyclic citrullinated peptide antibodies, and rheumatoid factor were not detected. Genotyping for HLA-B27 was negative, and an enzyme-linked immunosorbent assay was negative for the human immunodeficiency virus (HIV). Vitreous fluid showed a polymorphous cellular infiltrate, and a smear and culture for acid-fast bacilli were negative. Polymerase-chain-reaction studies of the vitreous for lymphoma, CMV, varicella–zoster virus, herpes simplex virus, *Mycobacterium tuberculosis*, and toxoplasma were also negative. Chest radiography, performed because of concern about tuberculosis, showed patchy basilar lung opacities. Computed tomography (CT) of the chest revealed mild basilar lung atelectasis and nodules measuring 1.6 cm in diameter on both adrenal glands, with a density of 35 to 45 Hounsfield units (a density of 10 units or less is considered to be consistent with benign adrenal nodules) (Fig. 1).

The patient was treated with isoniazid, which was discontinued after 1 month, owing to unacceptable side effects. Despite empirical treatment with acyclovir, ophthalmic prednisolone, and oral prednisone, a progressive erythema developed, and the patient lost vision in the right eye. Corneal dehiscence with globe rupture occurred 10 months before the current presentation, and the patient underwent emergency enucleation of the right eye. Pathological examination of the eye showed nonspecific granulomatous inflammation in the anterior ciliary body, posterior chamber, and subretinal space.

Uveitis, or inflammation of the middle anatomical structures of the eye, can be caused by infection (e.g., herpesvirus infection, syphilis, toxoplasmosis, tuberculosis, and *B. henselae* infection), by inflammatory conditions (e.g., seronegative spondyloarthropathies, sarcoidosis, Behçet’s syndrome, systemic lupus erythematosus, and granulomatous polyangiitis [formerly known as Wegener’s granulomatosis]), and by cancers such as lymphoma. In this patient, the negative serologic, microbiologic, and vitreous testing renders most of these causes unlikely, with the exception of tuberculous ophthalmitis, since extrapulmonary tuberculosis can be difficult to detect. The Vogt–Koyanagi–Harada syndrome, which is characterized by uveitis, vitiligo, and neurologic abnormalities, can affect persons of South Asian descent, although most such patients are women, and the diagnostic criteria require the involvement of both eyes and no history of ocular surgery. The incidentally discovered adrenal masses in this patient prompt consideration of invasive processes with ocular and adrenal involvement.

On physical examination, the patient’s temperature was 38.0°C, pulse 101 beats per minute, blood pressure 95/62 mm Hg with minimal orthostatic change, respiratory rate 12 breaths per minute,
and oxygen saturation 98% while he was breathing ambient air. He appeared chronically ill. His left pupil was round and reactive to light, with no papilledema or Roth’s spots on funduscopic examination. A prosthetic right eye was present. Mucous membranes were dry. His neck was supple, without palpable thyroid abnormalities. The jugular venous pressure was less than 5 cm of water. Examination of the lymph nodes, heart, lungs, abdomen, and extremities was unremarkable. Motor strength was rated 4 out of 5 in the proximal arms and legs, with normal strength in the distal arms and legs. Cranial-nerve function, sensation of light touch, and proprioception were preserved. There were multiple confluent patches of depigmentation on the patient's face, trunk, and extremities, without notable hyperpigmentation of the oral mucosa or the palmar creases.

The examination suggests hypovolemia. There are diffuse pigmentation defects, presumably the result of vitiligo. Interpretation of pigment heterogeneity can be challenging in a patient with vitiligo in whom primary adrenal insufficiency is suspected, although hyperpigmentation in patients with adrenal insufficiency often involves areas not exposed to sun, including the oral mucosa, palmar creases, and axillae. There is evidence of proximal myopathy, which may be seen in patients with glucocorticoid excess, hypothyroidism, electrolyte derangements, myositis, or rhabdomyolysis.

The patient's sodium level was 132 mmol per liter, potassium 4.3 mmol per liter, chloride 102 mmol per liter, bicarbonate 21 mmol per liter, blood urea nitrogen 16 mg per deciliter (5.7 mmol per liter), creatinine 1.5 mg per deciliter (132.7 μmol per liter), and glucose 86 mg per deciliter (4.8 mmol per liter). The results of liver-function tests were normal; the albumin level was 3.1 g per deciliter. The white-cell count was 3280 per cubic millimeter, with 50% neutrophils, 25% lymphocytes, 1% atypical lymphocytes, 18% monocytes, and 6% eosinophils. The hematocrit was 31.6%, with a normal mean corpuscular volume. The platelet count was 93,000 per cubic millimeter. Peripheral-blood red cells were characterized by anisocytosis, with scattered teardrop forms and no schistocytes. Levels of thyrotropin and creatine kinase were normal. The results of routine and fungal blood cultures subjected to lysis centrifugation were negative.

The patient's pancytopenia may indicate a viral or disseminated mycobacterial or fungal infection. Autoimmune or myelophthisic disorders are also possible; the teardrop red cells on blood smear are consistent with the latter. Coagulation studies may be helpful to evaluate the patient for disseminated intravascular coagulation. Thrombotic thrombocytopenic purpura should be considered in light of his mild renal insufficiency, although the absence of schistocytes argues against this diagnosis. The white-cell differential count shows an increased proportion of monocytes, which may indicate recovery of the bone marrow after an active systemic process. The patient's hyponatremia, fatigue, and hypotension should prompt further investigation of the adrenal glands, including measurement of serum levels of cortisol. Given the finding of adrenal nodules on the CT scan obtained earlier, adrenal imaging is also warranted.

Serum levels of cortisol and corticotropin, measured at 8 a.m., were 17.1 μg per deciliter (472 nmol per liter) (normal range, 6 to 24 μg per deciliter [166 to 662 nmol per liter]) and 228 pg per milliliter (50 pmol per liter) (normal range, 7 to 69 pg per milliliter [2 to 15 pmol per liter]), respectively. Repeat testing on a separate day at 7 p.m. revealed a cortisol level of 21.2 μg per deciliter (585 nmol per liter) and a corticotropin level of 563 pg per milliliter (124 pmol per liter). A dedicated adrenal CT scan revealed diffuse enlargement of both adrenal glands (maximum dimension, >3 cm) without discrete nodules; the adrenal parenchyma appeared diffusely heterogeneous and showed minimal contrast enlargement at 60 seconds and limited washout (less enhancement) at 15 minutes (Fig. 2).

In normal circumstances, the hypothalamic–pituitary–adrenal axis exhibits diurnal variation, with maximal production of corticotropin and cortisol in the morning and a nadir in the evening. The high levels of corticotropin paired with normal concentrations of cortisol in this patient, with no diurnal variation, suggest either corticotropin hypersecretion with excessive cortisol production and hyperplasia of both adrenal glands or primary adrenal insufficiency. However, the patient's presentation is inconsistent with Cushing's syndrome, and the finding of heterogeneously enlarged adrenal glands with high retention of contrast material on dedicated adrenal CT argues
against adrenal hyperplasia as a cause of adrenal enlargement. The clinical features are more suggestive of primary adrenal insufficiency arising from an infiltrative adrenal process, with a cortisol level that is inadequate in the context of the patient’s systemic illness and in comparison with the magnitude of the elevation in his corticotropin levels. Typically, more than 90% of adrenal tissue must be destroyed to cause a clinically significant impairment in adrenal function, whether by mass effect, hemorrhage, or autoimmune destruction; the last condition, which is associated with circulating adrenal autoantibodies, should be considered in light of the patient’s history of autoimmune disease, but it is usually marked by progressive adrenal atrophy rather than enlargement.

The constellation of adrenal infiltration, pan-

tocytopenia, and a history of uveitis points to the presence of a disseminated infectious, inflammatory, or malignant process. The antecedent travel to the Great Smoky Mountains is of particular interest, since histoplasma and cryptococcus species are widespread in this region and can cause ophthalmitis and adrenal disease. These clinical features may also be present in disseminated tuberculosis, although a search for disseminated disease has not been fruitful so far. Urinary testing for histoplasma antigen and serum testing for cryptococcal antigen and 1,3-β-D-glucan should be performed. Given the suspicious appearance of the adrenal glands, an adrenal biopsy may also be indicated.

Tests for urinary histoplasma and serum cryptococcal antigen were negative. The level of serum 1,3-β-D-glucan was 85 pg per milliliter (normal value, <79). CT-guided needle biopsy of the adrenal gland was performed. Pathological analysis of the specimen showed areas of loosely organized, granulomatous inflammation within larger areas of diffuse necrosis. Abundant small, budding yeast forms were detected on staining with Gomori methenamine silver (Fig. 3). A fungal culture grew Histoplasma capsulatum. Immunohistochemical analysis of adrenal tissue (performed by the Infectious Diseases Pathology Branch of the Centers for Disease Control and Prevention) was also consistent with H. capsulatum infection. Reexamination of a specimen from the previously enucleated right eye revealed necrotizing granulomas with rare yeast forms; immunohistochemical analysis confirmed the presence of ocular organisms that were consistent with H. capsulatum. The patient recalled that fresh bird droppings had fallen onto his forehead and possibly into his right eye during his visit to the Great Smoky Mountains.

H. capsulatum is a dimorphic fungus that thrives in the soil and caves of regions with a moderate climate, particularly in the presence of bird feces or bat guano. Although bats are natural hosts for histoplasma, birds are not; thus, the history of direct contact with bird feces would not be expected to explain this patient’s presentation, although his travel to an endemic area is a critical piece of his history. Immunohistochemical assays for H. capsulatum can occasionally cross-react with blastomycoses or cryptococcus. Although the mildly elevated level of 1,3-β-D-glucan in this patient is not
specific for *H. capsulatum* infection, the finding of a cell-wall antigen that is present in many fungi but notably absent in *cryptococcus* may render disseminated *cryptococcus* less likely. The results of the patient's adrenal culture provide proof of infection with *H. capsulatum*.

Whole-body positron-emission tomography (PET) performed after the administration of $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) showed $^{18}$F-FDG avidity exclusively in the adrenal glands. Although itraconazole is generally considered the preferred initial therapy for *H. capsulatum* infection, the patient was treated with fluconazole, owing to concerns about itraconazole-mediated adrenal suppression. He received 5 mg of prednisone twice daily, and his energy level promptly improved. Hyperkalemia developed 1 week after the initiation of treatment, and fludrocortisone and oral salt supplementation were added to his regimen. After 1 month of therapy, the patient's weight, energy level, blood pressure, and blood counts normalized. Prednisone was withdrawn, and a repeat measurement of cortisol at 8 a.m. revealed a level of 2.1 μg per deciliter (58 nmol per liter), necessitating the resumption of glucocorticoid supplementation. A follow-up CT scan obtained after 9 months of treatment with fluconazole showed a reduction in the size of the adrenal lesions.

Liposomal amphotericin B or amphotericin B deoxycholate is recommended as initial therapy for severe, disseminated histoplasmosis; itraconazole is recommended for milder disease. Fluconazole is less effective than itraconazole for the treatment of disseminated histoplasmosis and is generally reserved for patients with intolerance to itraconazole. In this patient, the concern regarding azole-mediated suppression of adrenal hormone synthesis (typically associated with ketoconazole) prompted the use of fluconazole, which is considered to have minimal suppressive effects on adrenal activity. The results of $^{18}$F-FDG PET imaging, the normal results of liver-function tests, and the negative fungal blood cultures suggest that the patient's infection was limited to the adrenal glands (and previously, the eye); a bone marrow biopsy might have been helpful to more fully define the extent of disease, given the initial cytopenias. The presumably low burden of disease may have contributed to the patient's favorable response to fluconazole.

**Figure 3. Histochemical Analysis of an Adrenal-Biopsy Specimen.**

Staining with Gomori methenamine silver reveals abundant small, budding yeast forms (black). Image courtesy of Dr. Danny A. Milner, Brigham and Women’s Hospital, Boston.

**Commentary**

This case illustrates the broad range of findings associated with disseminated histoplasmosis complicated by adrenal insufficiency. The patient's age and history of treatment with immunosuppressive drugs predisposed him to disseminated infection, which probably followed inhalational exposure to *H. capsulatum*. He had a febrile illness shortly after returning from a region in which histoplasmosis is endemic and then had uveitis, which worsened with empirical glucocorticoid treatment. After a period of 18 months, he presented with symptoms of primary adrenal insufficiency associated with proliferation of histoplasma in his adrenal glands. The diagnosis was established by linking the circumstances of his initial episode of uveitis with clinical, laboratory, and radiographic evidence of a disseminated disease process and, ultimately, by obtaining a culture of an adrenal biopsy specimen that showed *H. capsulatum*.

In a minority of patients exposed to *H. capsulatum*, clinically significant disease develops — most commonly pulmonary histoplasmosis. Disseminated histoplasmosis occurs predominantly in elderly persons, infants, and persons with defective cell-mediated immunity. Occasional cases have been reported in patients taking mycophenolate, most of whom were concurrently receiving other immunosuppressant agents. Clinical manifestations of disseminated histoplasmosis include fever, fatigue, nausea, vomiting, weight loss, and
anorexia. Physical examination may reveal hepatosplenomegaly, lymphadenopathy, or both, and laboratory studies may reveal pancytopenia, abnormal liver function, and in severe cases, renal failure or coagulopathy.\textsuperscript{1,5,6}

One of the most debilitating and well-described complications of disseminated histoplasmosis is Addison’s disease, which can result from adrenal infiltration. In an early case series, adrenal insufficiency was observed in up to half of patients with disseminated histoplasmosis, which was the most common cause of death.\textsuperscript{7} Ocular histoplasmosis is rare; intraocular infection leading to uveitis, with or without granuloma formation, has been reported in some immunosuppressed patients with disseminated histoplasmosis.\textsuperscript{8-12} A distinct presumed ocular histoplasmosis syndrome, with peripheral chorioretinal scarring, neovascularization, and macular hemorrhage, has also been described.\textsuperscript{13} Patients with this syndrome may have reactivity on histoplasmin skin testing or they may have intrathoracic calcifications, but fungi are rarely recovered from the eye. The syndrome is postulated to result from a vigorous cellular immune response to fungal antigens.

The urinary histoplasma-antigen test has emerged as a noninvasive assay that can be used to detect disseminated disease. The test has a sensitivity of more than 90% in patients with HIV infection or other conditions that compromise the immune system,\textsuperscript{1} although false positive results of tests for other endemic mycoses are possible, owing to antigenic cross-reactivity.\textsuperscript{14} This patient’s urinary antigen test was negative on two occasions despite clinical symptoms, a finding that may reflect a low sensitivity of this test for infection, which is restricted to the adrenal glands and eye. This case illustrates the need for maintaining a broad view of potential causes of systemic disease, especially in immunocompromised patients.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Drs. Francisco Marty, Danny A. Milner, and Ronald P. McCaffrey for their contributions to the evaluation of this patient and their guidance on an earlier version of the manuscript.

REFERENCES


Copyright © 2011 Massachusetts Medical Society.