Whipple's disease presenting as adrenal insufficiency[1]

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A 56-year-old white man presented with classic symptoms and signs of Addison's disease and transiently responded to glucocorticoid therapy. Following a relapse, studies led to the diagnosis of Whipple's disease.

Index terms: Case reports • Lipodystrophy, intestinal

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Since its first description in 1907, Whipple's disease continues to be elusive. It can mimic other diseases, and although the treatment is simple and effective, misdiagnosis may be fatal. The following case describes a patient with Whipple's disease who presented with signs and symptoms of adrenal insufficiency that was responsive to steroid therapy.

Case report

A 56-year-old white truck driver was admitted for migratory arthralgias and progressive weakness, anorexia, weight loss, and darkening of the skin. His past medical history was unremarkable except for a remote history of alcoholism and pipe smoking. He was an ill-appearing patient with brown pigmentation of the sun-exposed areas of the face and hands and darkening of the skin about the perineum and nipples (*Fig. 1*). The oral mucosa, however, was pink and moist. His supine blood pressure was 130/80 mm Hg and pulse was 90 beats per minute. When sitting, the blood pressure and pulse were 90/60 mm Hg and 110 beats per minute, respectively. The skin was thin and dry, and there were superficial excoriations noted over both shins. He had mild proximal muscle weakness without atrophy of the arms and legs. There was tenderness over the lower lumbosacral spine.

Because of the suspicion of adrenal insufficiency, a cosyntropin stimulation test was performed prior to institution of intravenous administration of hydrocortisone and saline. The patient responded to this treatment and therapy was continued with orally administered cortisone acetate. However, he began to relapse.

Initially, the serum ACTH measurement was 32 pg/mL (normal, 5–50). The basal serum cortisol value was 12.4 ng/dL, and the one-hour poststimulatory value was 25.9. Endocrine antibody screen including anti-adrenal antibodies was negative. The hematocrit was 30%, and mean corpuscular volume was 77.4. The serum iron value was 35 μg/dL; total iron binding capacity, 278 μg/dL; and saturation, 13%. The Westergren sedimentation rate was 48 mm/hr. The serum sodium value was 132 mEq/L; potassium, 5.2 mEq/L. Liver enzymes, coagulation profile, urinalysis, BUN, and creatinine level were normal. Albumin level measured 3.5 gm/dL; calcium, 8.4 mg/dL. The stool contained moderate fatty acids but no neutral fats and was positive for blood and negative for pathological bacteria, ova, and parasites. The bone marrow examination showed normal cellular elements and increased iron stores. The chest radiograph revealed calcified granuloma in the left lung. The abdominal computed tomogram showed several retroperitoneal lymph nodes (< 1.5 cm). The liver, adrenal glands, spleen, kidney, and pancreas were normal. An upper gastrointestinal series showed several ulcer-like defects in the jejunum. An upper endoscopy revealed a hemorrhagic

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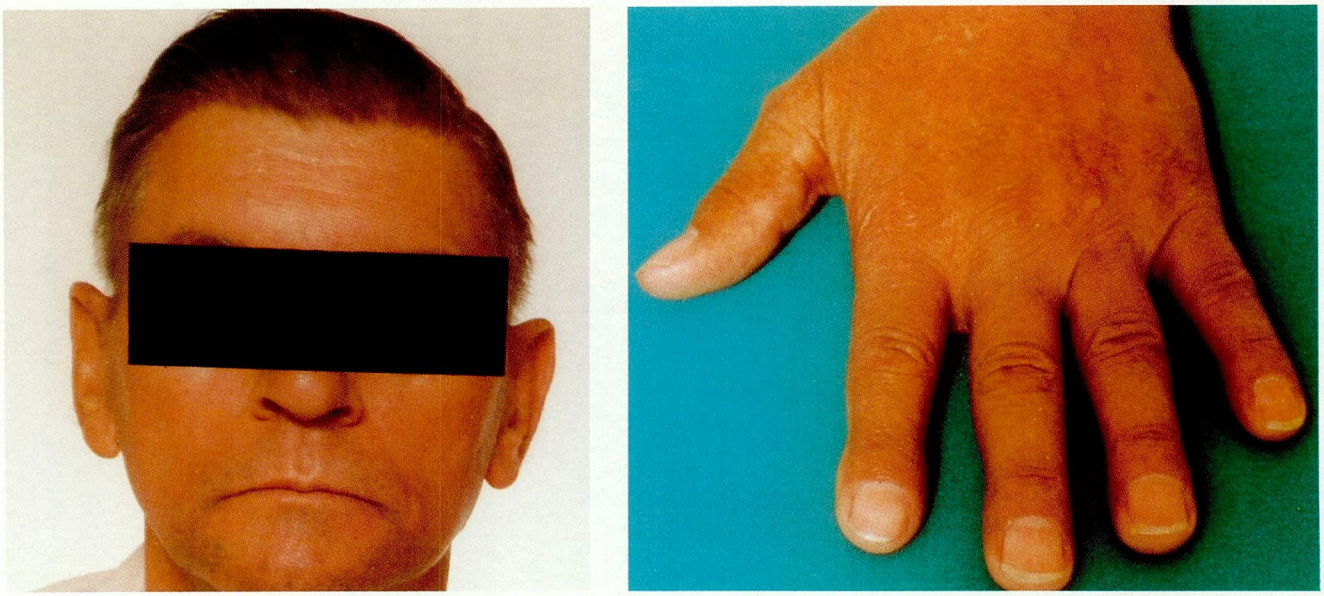

Fig. 1. Face and hand of the patient at initial presentation.

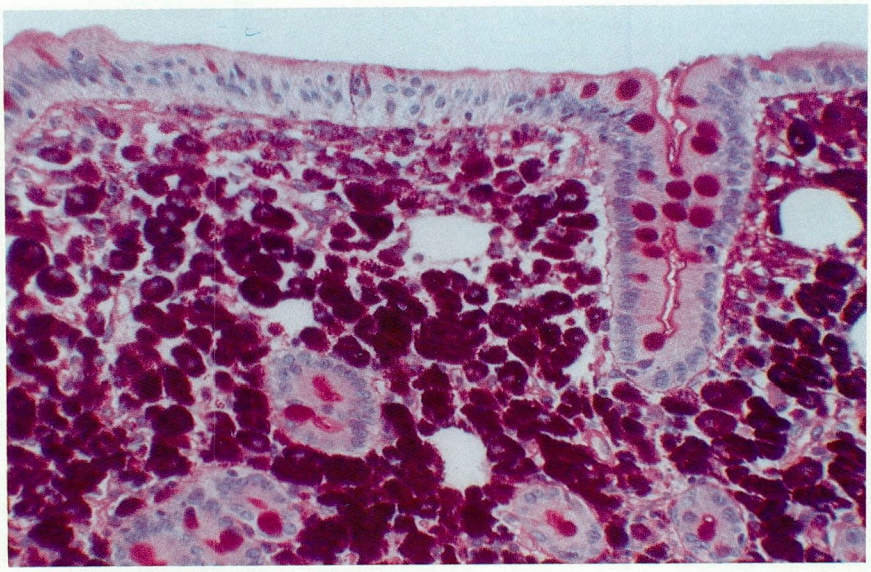

Fig. 2. Biopsy findings showed club-shaped villi with dense infiltrations of foamy macrophages that were PAS-positive (× 400).

granular mucosa extending from the duodenum to the ligament of Treitz. The biopsy result is shown (*Fig. 2*). The patient received 600,000 units of procaine penicillin G intramuscularly every 12 hours. Within 48–72 hours, his fever subsided, his appetite improved, and his sense of well-being returned. After a year of oral antibiotics, he continues to do well.

Discussion

This patient exemplifies a similarity in presentation between adrenal insufficiency and Whipple's disease, a phenomenon that has occurred in the past and continues to be misunderstood. A comparison of these two diseases is shown (*Table*).

George Hoyt Whipple first described this entity in 1907 after observing a 36-year-old missionary who had fulminant signs of this eventually fatal disease.[5] Whipple's description presents a portrait of multiple-organ involvement. He originally classified this as an intestinal lipodystrophy because of an accumulation of fat in the stool and

Table. Features of Whipple's disease and primary adrenal insufficiency

	Whipple's disease	Addison's disease
General		
Etiology	Whipple's bacillus	Idiopathic, 65%; tuberculous, 17%; other, 17%
Age	Peak at 40–49 years	Wide distribution
Sex	Strong male predominance	Idiopathic, F:M = 1.5:1; tuberculous, F:M = 1:1
HLA subtype	B-27 (40%)	B-6
Associated diseases	None	Other autoimmune diseases, diabetes, thyroiditis, hypogonadism, pernicious anemia
Symptoms		
Weakness	90%–100%	100%
Weight loss	95%–100%	100%
Arthralgias	90%	6%
Gastrointestinal symptoms	72%	56%
Signs		
Fever	55%	Common
Hypotension or orthostatis	63%	88%
Hyperpigmentation	33%–47% (scars, sun-exposed areas; spares mucous membranes)	92% (all body and mucous membranes)
Lymphadenopathy	52%	Not common
Laboratory results		
Electrolyte changes	Variable	Hyponatremia, 88%; hyperkalemia, 64%; hypercalcemia, 6%
Hypoglycemia	25%	38%
Steatorrhea	93%	Not common
D-xylose test	78% abnormal	Usually normal
Gastric achlorhydria	40%–50%	2%
Eosinophilia	Common	Common
Lymphopenia	70%	Not common
Cutaneous anergy	Usually abnormal	Variable
ACTH stimulation	Normal	Abnormal
Therapy		
Response to corticosteroids	Transient or none	Complete
Response to antibiotics	Complete	None

Information about Whipple's disease derived from Comer et al[1] and Maizel et al.[2] Information about Addison's disease derived from Nerup[3] and Volpe.[4]

the presence of foamy-type phagocytic mononuclear cells in the mesenteric lymph node and intestinal walls. Unknown to him, however, was that the rod-like bacilli he noted in the lamina propria were actually the digested cell walls of bacteria that were later identified by the use of PAS-positive/diastase-resistant stain.[6] This disease occurs most often in middle-aged American or European white men.[1] Only five blacks and one American Indian have been reported in about 300 cases noted up to 1983. Approximately 12%–18% of patients are women. Multiple cases occur within small communities as well as within kindreds, suggesting an infectious etiology.[2, 7–10] In one series, there was an increased predominance of HLA-type B-27 compared to the usual 10% found in the normal population.[11]

The bacillus can infect any tissue in the body and therefore causes a variety of symptoms. In a series of 18 patients, weight loss, arthralgias, diarrhea, abdominal pain, and fever were the most common symptoms.[6] About one-third of patients had an unexplained cutaneous hyperpigmentation on sun-exposed areas. This is unrelated, however, to adrenal insufficiency.[12,13] Myopathic and neuropathic changes may develop

that range from personality alterations, abnormal reflexes, and seizures to focal demyelization and impaired vision.[14,15] Peripheral and retroperitoneal lymph nodes may contain PAS-positive macrophages or small epithelioid granulomas that mimic sarcoidosis, tuberculosis, berylliosis, or Gaucher's disease.[16] Most recently, the intracellular bacillus has been confused with the *Microbacterium avium-intracellularae* bacillus in patients with acquired immunodeficiency syndrome (AIDS).[17] Abdominal distension, small bowel obstruction, inferior vena cava obstruction, urticaria, and glossitis may also occur.[18,19] About 60% of autopsy cases show various cardiac lesions that include pericarditis, myocarditis, endocarditis, and prosthetic valve vegetations that contain the Whipple's bacillus.[20] Pulmonary nodules and pleural thickening have also been noted.[21] Ninety percent of patients have hypochromic and normocytic anemia,[22] and gastrointestinal dysfunction is also quite common. Steatorrhea occurs in more than 90% of patients, while hypoalbuminemia, hypocalcemia, hypokalemia, and hypocholesterolemia are less frequent. Hypoglycemia may develop in approximately one-fourth of patients, and 40% may show a flat glucose tolerance curve.[16] Patients are usually anergic due to some subtle defect in cellular immune function.[22]

In contrast, primary adrenal insufficiency causes weakness, weight loss, anorexia, and hyperpigmentation in 90%–100% of patients.[1] As noted in the *Table*, a large percentage of patients show electrolyte disturbances, hypotension, arthralgias and myalgias, and gastrointestinal symptoms. A small number show evidence of vitiligo and adrenal calcification. The patient described here showed about 10 of the 13 major signs and symptoms of Addison's disease.

Because of the similarities between these diseases, ACTH and corticosteroids were widely used in the 1950s. Puite et al[9] described a patient who recovered during ACTH therapy but relapsed afterwards. Similar observations of the efficacy of oral steroids were noted by Dellinger et al[12] and Weiner et al.[23] A systematic review of these reported cases and an extensive analysis of 4 patients showed a temporary or a minimal response to ACTH and steroids.[10] The partial responses are not adequately understood. Some might be due to dehydration. Although a number of autopsy studies show small or atrophic adrenals, it is unclear whether the primary disease or the subsequent use of ACTH and steroids caused this.[9,23,24] These studies do not show other endocrine organ (thyroid, parathyroid, testes) involvement with the bacillus despite the fact that most tissues of the body can apparently be infected. Some clinical studies indicate good adrenal reserve in these patients,[9] while others suggest poor basal activity.[4,25,26]

In the early 1950s, Whipple's disease was first treated with antibiotics.[27] However, this treatment was not widely accepted until the late 1960s when electron microscopy showed evidence of a bacterial cause of the disease. Since then, antibiotics have proved the mainstay of treatment, even though approximately one-third of patients may relapse. The present recommended treatment is parenteral penicillin and streptomycin, followed by one year of orally administered trimethoprim-sulfamethoxazole, or one full year of this drug alone.[28]

Although Whipple's disease is a rare entity, its widespread infestation of the body can mimic a variety of illnesses. Its endocrine manifestation is an important point to keep in mind since not only the signs and symptoms but also the response to steroids can sometimes appear to be adrenal insufficiency.

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