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Case Report

Esophageal Histoplasmosis in a Renal Allograft Recipient

L. C. Sharma[1], J. Falodia[1], K. Kalla[4], M. Kalla[2], J. B. Gupta[3], S. S. Gupta[1], P. Beniwal[1], M. N. Singh[1], V. Malhotra[1], D. Agarwal[1]

[1]Department of Nephrology, SMS Hospital and Medical College, [2]Departments of Gastroenterology, [3]Nephrology and [4]Pathology, S. R. Kalla Memorial Gastro and General Hospital, Jaipur, India

ABSTRACT. Histoplasmosis is a progressive granulomatous disease caused by the intracellular dimorphic fungus *Histoplasma capsulatum.* We report a rare case of esophageal histoplasmosis in a renal allograft recipient. A 55-year-old male who received a live, unrelated renal allograft 20 years ago presented with complaints of recurrent fever for ten to 12 months, weight loss over six months, progressive dysphagia more for solids for five to six months and joint pain and swelling involving the bilateral metacarpo-phalangeal and proximal interphalangeal joints. Biopsy from the esophageal ulcers revealed dense inflammation infiltrated with lymphocytes and macrophages with clusters of strongly positive intracellular fungal spores with a clear area or "halo-like" zone suggestive of *Histoplasma capsulatum* invasion. The patient was treated with intravenous liposomal amphotericin B for ten days and later switched over to oral itraconazole. Repeated endoscopy revealed significant improvement of the lesions.

Introduction

Histoplasmosis is a progressive granulomatous disease caused by the intracellular dimorphic fungus *Histoplasma capsulatum.* Although gastrointestinal involvement is common in autopsy series,[1-3] clinical presentation with gut symptomatology is uncommon (3–12%).[4,5]

We report a rare case of esophageal histoplasmosis from a non-endemic area in a renal allograft recipient on long-standing immunosuppression.

Correspondence to:

Dr. Sudeendra S. Gupta,
Department of Nephrology,
SMS Medical College and Hospital,
Jaipur - 302 004, India
E-mail: duccu113@gmail.com

Case Report

A 55-year-old man who received a live, unrelated renal allograft 20 years ago, with stable allograft function, presented with complaints of recurrent fever for ten to 12 months and approximately 8 kg weight loss over six months, progressive dysphagia for solids for five to six months and joint pain and swelling involving the bilateral metacarpo-phalangeal and proximal interphalangeal joints. He was on immunosuppression with two drugs (Prednisolone

10 mg/d and Azathioprine 75 mg/d). On examination, he was moderately built and poorly nourished, weighing 40 kg and had polyarthritis involving the bilateral metacarpophalangeal and proximal interphalangeal joints; otherwise, the cardiovascular, respiratory and abdominal examinations were unremarkable.

The hemogram was unremarkable except for mild anemia (Hb 10.5 gm%) and serum creatinine was 1.2 mg/dL, which was stable during the last six to 12 months. The measured creatinine clearance was 33.5 mL/min. Chest X-ray and computerized tomography (CT) of the thorax did not reveal any opacity, pleural effusion or hilar or mediastinal lymphadenopathy. HIV, HBsAg and anti-HCV were all negative. Blood and urine cultures for both bacteria and fungus were sterile.

Barium swallow revealed a narrowing at the mid- and lower esophagus (Figure 1), and subsequent esophagoscopy showed multiple ulcerated nodular lesions compromising the lumen at the mid- and lower esophagus (Figure 2a). Biopsy from the esophageal ulcers revealed dense inflammation infiltrated with lymphocytes and macrophages, with clusters of strongly Periodic acid-Schiff PAS-positive intra-cellular fungal spores with a clear area or "halo-like" zone suggestive of *Histoplasma capsulatum* invasion (Figure 3).

Considering the patient's long-standing fever, weight loss, polyarthritis and histopathology of esophageal ulcers demonstrating invasion of histoplasmosis, he was diagnosed to have disseminated histoplasmosis.

He was treated with intravenous liposomal amphotericin B for 10 days and later switched over to oral itraconazole. He had a remarkable improvement over the next five days, where his fever disappeared and his polyarthritis started regressing, with progressive gradual improvement in dysphagia. He underwent two sessions of esophageal dilatation. Repeated endoscopy revealed significant improvement in nodularity of the lesions (Figure 2b).

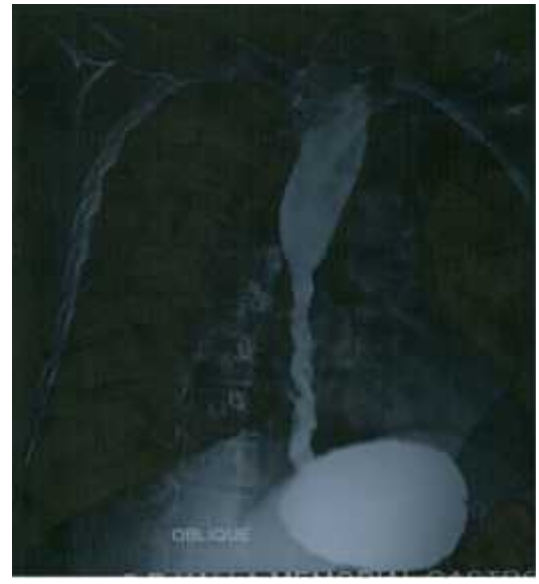

Figure 1. Barium swallow showing narrowing at the mid- and lower esophagus.

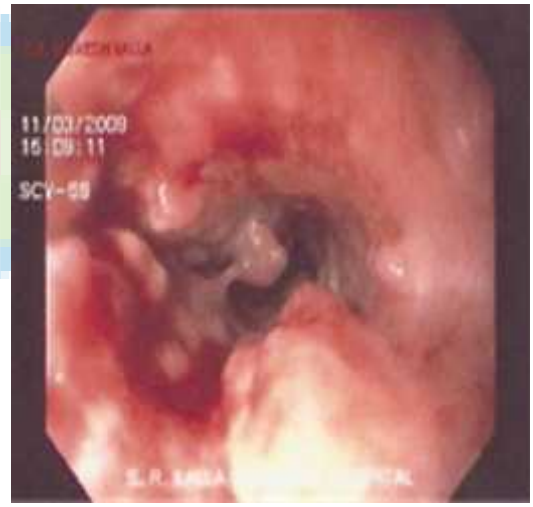

Figure 2a. Esophagoscopy showed multiple ulcerated nodular lesions compromising the lumen at the mid- and lower esophagus.

Discussion

Histoplasmosis presents clinically in different forms – asymptomatic infection; an acute or chronic pulmonary infection; mediastinal fibrosis or granulomas; and progressive disseminated histoplasmosis (PDH, which is typically seen in immunocompromised individuals who account for approximately 70% of the cases).[6]

The spectrum of PDH ranges from an acute rapidly fatal course with diffuse interstitial or reticulonodular lung infiltrates causing respira-

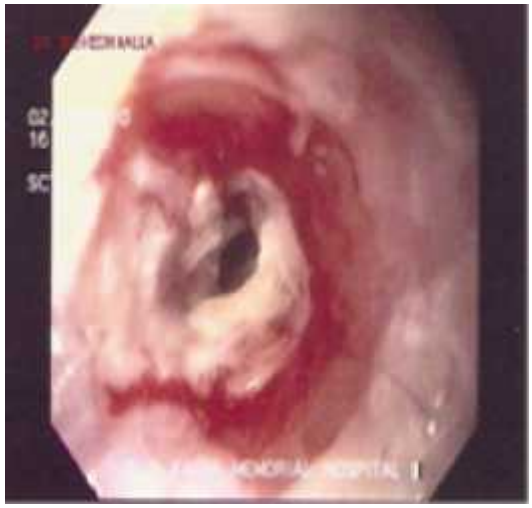

Figure 2b. Significant improvement in nodularity of the lesion.

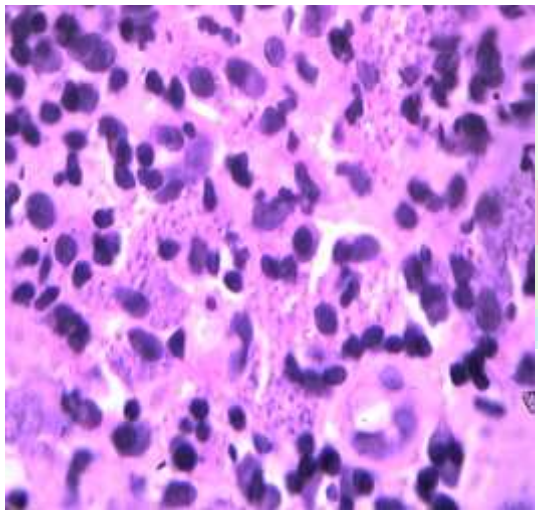

Figure 3. Biopsy from the esophageal ulcers revealed a large number of strongly PAS-positive fungal spores with dense inflammation suggestive of *Histoplasma capsulatum* invasion.

tory failure, shock, coagulopathy and multi-organ failure, to a more subacute and chronic course with a focal organ distribution. The patients may present with fever, weight loss, hepatosplenomegaly, meningitis or focal brain lesions, ulcerations of the oral mucosa, gastrointestinal ulcerations and adrenal insufficiency.[6]

Esophageal histoplasmosis can occur as a result of adjacent mediastinal adenitis during the course of acute infection or as a late consequence of progressive scarring in fibrosing mediastinitis or as a manifestation of progressive disseminated disease. Esophageal involvement in progressive disseminated histoplasmosis has been reported and is clinically distinct from the compressive syndromes resulting from mediastinitis.[7] These patients have underlying immunosuppression and present with dysphagia[8] or bleeding.[9]

Our patient had symptoms of dysphagia, and esophagoscopy revealed compromised lumen with nodular ulcerated lesion and histopathology that demonstrated strongly PAS-positive intracellular yeast cells in clusters with a clear area or "halo-like" zone around the organism, suggestive of histoplasmosis, which, to the best of our knowledge, is the first case to be reported in a renal transplant recipient. The basophilic cytoplasm of *Histoplasma capsulatum* retracts from the relatively thin cell wall, causing the halo-like zone around the organism. There was no evidence of mediastinal lymphadenopathy or fibrosis that could have caused the external compression to the esophagus. As histoplasmosis is uncommon in our country, serological tests for antigen and antibody detection are not widely available and hence, unfortunately, could not be performed.

Mortality without treatment in disseminated histoplasmosis is around 80%.[10] Studies have shown that early therapy with amphotericin B can reduce the mortality to <25%.[10-13] In a recent study of AIDS patients, liposomal amphotericin B was more effective than the standard form of the drug in regard to time to resolution of fever and overall survival.[14] Thus, liposomal amphotericin B may be preferred for patients with severe or moderately severe disseminated histoplasmosis. Itraconazole is used for the treatment of disseminated histoplasmosis in patients with less-severe illness and also for maintenance therapy following an initial response to amphotericin B.[15] The duration of treatment for acute pulmonary histoplasmosis is six to 12 weeks, while that for PDH and chronic pulmonary histoplasmosis is ≥1 year.[6] Antigen levels in urine and serum should be monitored during and for at least one year after therapy for PDH. Stable or rising antigen

levels suggest treatment failure or relapse, which constitute around 10–20% of the cases of PDH and around 80% of those with AIDS.[7]

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