

## CASE REPORT

### Disseminated histoplasmosis mimicking an acute appendicitis

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#### Abstract

**Introduction:** Histoplasmosis can present in a myriad of clinical manifestations, which often makes its diagnosis difficult and occasionally, deceptive. **Case Report:** We describe a case of a 33 years old gentleman who was clinically diagnosed as acute appendicitis at initial presentation in view of a one-week history of fever, right lower quadrant abdominal pain- and guarding at right iliac fossa. He had thrombocytopenia and lymphopenia on presentation. Mesenteric lymphadenitis and small bowel lesion were found intraoperatively, which was respectively biopsied and resected. Histopathological result confirms disseminated histoplasmosis. Retroviral screen was positive. He was treated with amphotericin B for one week, subsequently switched to oral itraconazole, followed by initiation of highly active antiretroviral therapy (HAART). **Discussion:** This case illustrates the various nature of histoplasmosis presentation. A high index of suspicion is needed to clinch the diagnosis and subsequently institute prompt treatment as disseminated disease can be fatal if left untreated in an immunosuppressed host.

**Keywords:** Disseminated Histoplasmosis; Gastrointestinal Histoplasmosis; Histoplasma capsulatum

#### INTRODUCTION

Histoplasmosis is a fungal disease caused by *Histoplasma capsulatum*, which is granulomatous in nature.<sup>1</sup> It is a dimorphic fungus with two distinct varieties, which are *Histoplasma capsulatum var. capsulatum* and *Histoplasma capsulatum var. duboisii* which can affect human.<sup>2</sup> *Histoplasma* is a soil dweller that thrives in areas contaminated with bat and bird excreta.<sup>3</sup> The disease was also known as Darling's disease, first described by Samuel Taylor Darling in 1906, who observed three cases of canal labourers who presented with symptoms of fever, cachexia, and splenomegaly; with pustular eruptions and ulcers around the face and anus, ulcerations in the gastrointestinal tract; with lymph node, spleen, liver, and lung involvement. In autopsy, followed by histopathological studies, granulomas were seen, with presence of microorganisms that were surrounded by a clear, refractive, non-staining rim; which he named as *Histoplasma capsulatum*.<sup>4</sup> Infections by *Histoplasma capsulatum* are usually self-limiting, although 0.05% of acute infections result in severe and progressive dissemination.<sup>5</sup>

The disease has variable clinical features, with dissemination usually occurring in the setting of immunocompromised host<sup>1</sup>. Here, we described a case of disseminated histoplasmosis in a newly diagnosed HIV positive patient who presented with symptoms and signs of acute appendicitis.

#### CASE REPORT

A 33 years old gentleman, working as a legal advisor, presented with a one-week history of fever, associated with abdominal pain which subsequently became more localized to the right iliac fossa. He has a history of loss of appetite and loss of weight, but was unable to quantify the amount. There was no significant past medical or past surgical history.

Upon physical examination, he was tachycardic and febrile, with documented temperature of 38.6°C. Blood pressure was stable, with a reading of 117/69mmHg. Subcentimeter cervical lymph nodes were palpable. The abdomen was soft on palpation, with tenderness at right iliac fossa with localised guarding. Per rectal examination was normal. Respiratory and cardiovascular system

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examination was unremarkable. He was admitted to the surgical ward with the impression of acute appendicitis and was planned for laparoscopic appendicectomy the next day.

Full blood count showed thrombocytopenia, lymphopenia, and microcytic hypochromic anemia. Haemoglobin was 13.2 g/dl, MCV: 79, MCH: 25; total white cell count was 6.4, ANC: 4.3, absolute lymphocyte count: 1.3 (subsequently reducing trend till 0.3), and platelet count was  $59 \times 10^9/L$ . Dengue IgM and IgG were negative. Full blood picture showed iron deficiency anaemia with mild hypochromic microcytic cells and some pencil cells. White cell count was normal, while thrombocytopenia was likely due to peripheral consumption or destruction. Large platelets were seen. Iron studies confirmed iron deficiency anaemia with transferrin saturation of 10.2%. Renal function and electrolytes were normal. There was hypoalbuminaemia with albumin level 31 g/L, but otherwise liver function test was normal. Serum amylase was normal, and urinalysis was unremarkable. Chest x-ray (Fig. 1) showed few calcified nodules at perihilar region, but there was no air under diaphragm.

Ultrasound abdomen was performed, which showed a well defined irregular hypoechoic collection at the right iliac fossa adjacent to the caecum, measuring 2.3 x 2.0 x 1.5 cm (AP x W x CC). Immediately adjacent to the lesion, there was an enlarged peritoneal lymph node with loss of fatty hilum measuring 1.5 cm. At the region of iliac fossa, multiple other enlarged peritoneal lymph nodes are noted. With these ultrasound abdomen findings, he was planned for diagnostic laparoscopy, with platelet optimisation via transfusion before, and during the procedure.

Intraoperative findings revealed normal appendix. However, there were multiple enlarged mesenteric nodes, some appeared inflamed with overlying sloughs and minimal surrounding fluids. Small bowel lesion was noted 40cm from terminal ileum, but no diverticulum seen. The liver, gallbladder, stomach, and large bowel were normal. The laparoscopic examination was converted to open lower midline laparotomy, for small bowel lesion resection. The mesenteric lymph node was biopsied simultaneously.

Tuberculosis workup was done in view of intraoperative findings, keeping in mind of gastrointestinal tuberculosis as a differential

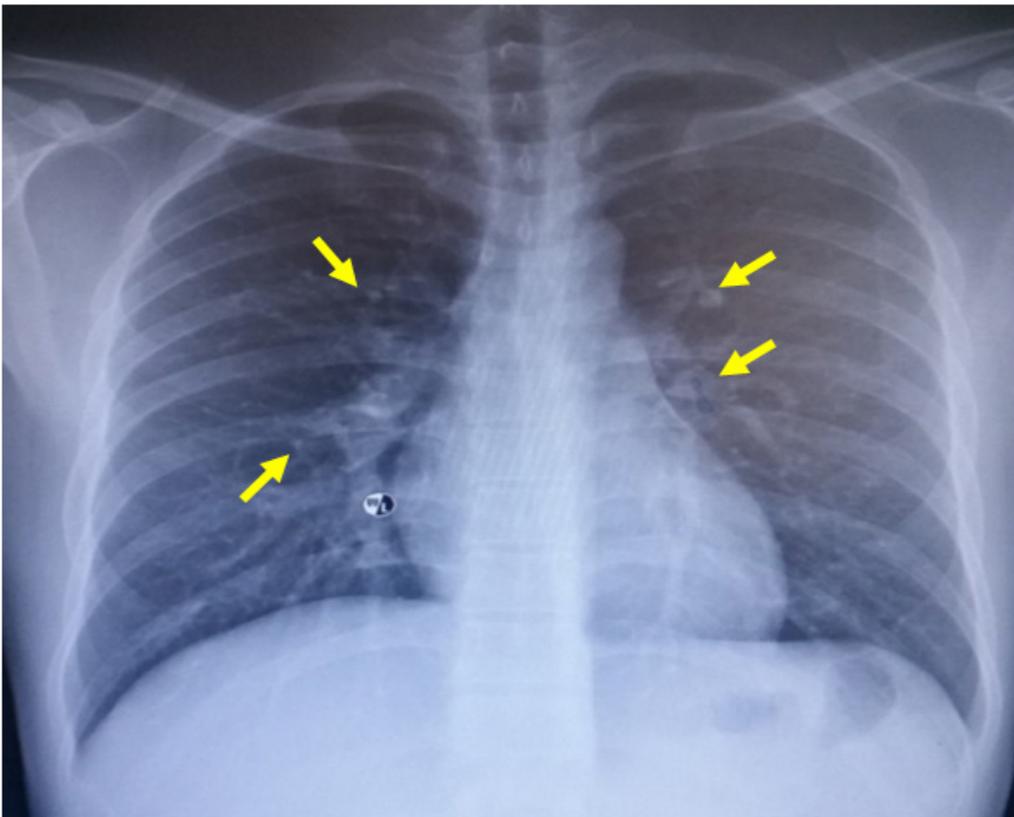


FIG. 1: Chest x-ray showing calcified nodules at perihilar region (shown with yellow arrows)

diagnosis. Mantoux test was negative (0mm), and ESR was slightly raised at 42 mm/hr. Retroviral screen was positive. Screening for hepatitis B and hepatitis C were negative. He admitted to casual unprotected sex two years ago but denied previous blood transfusion or intravenous drug use. His CD4 was only 14 cells/mm<sup>3</sup>, with HIV viral load of 141,657 copies/ml. Serum LDH was raised at 356, and VDRL/ RPR was negative.

CT neck, thorax, and abdomen showed

thickened distal ileum with enlarged low attenuation peripancreatic, mesenteric, and cervical lymph nodes. The histopathological examination result of the mesenteric nodes and small bowel resection (Fig. 2) were consistent with histoplasmosis. Fungal blood cultures were, however, negative for histoplasmosis.

He was treated for disseminated histoplasmosis involving gastrointestinal, bone marrow, and lymph nodes. He was started on IV amphotericin

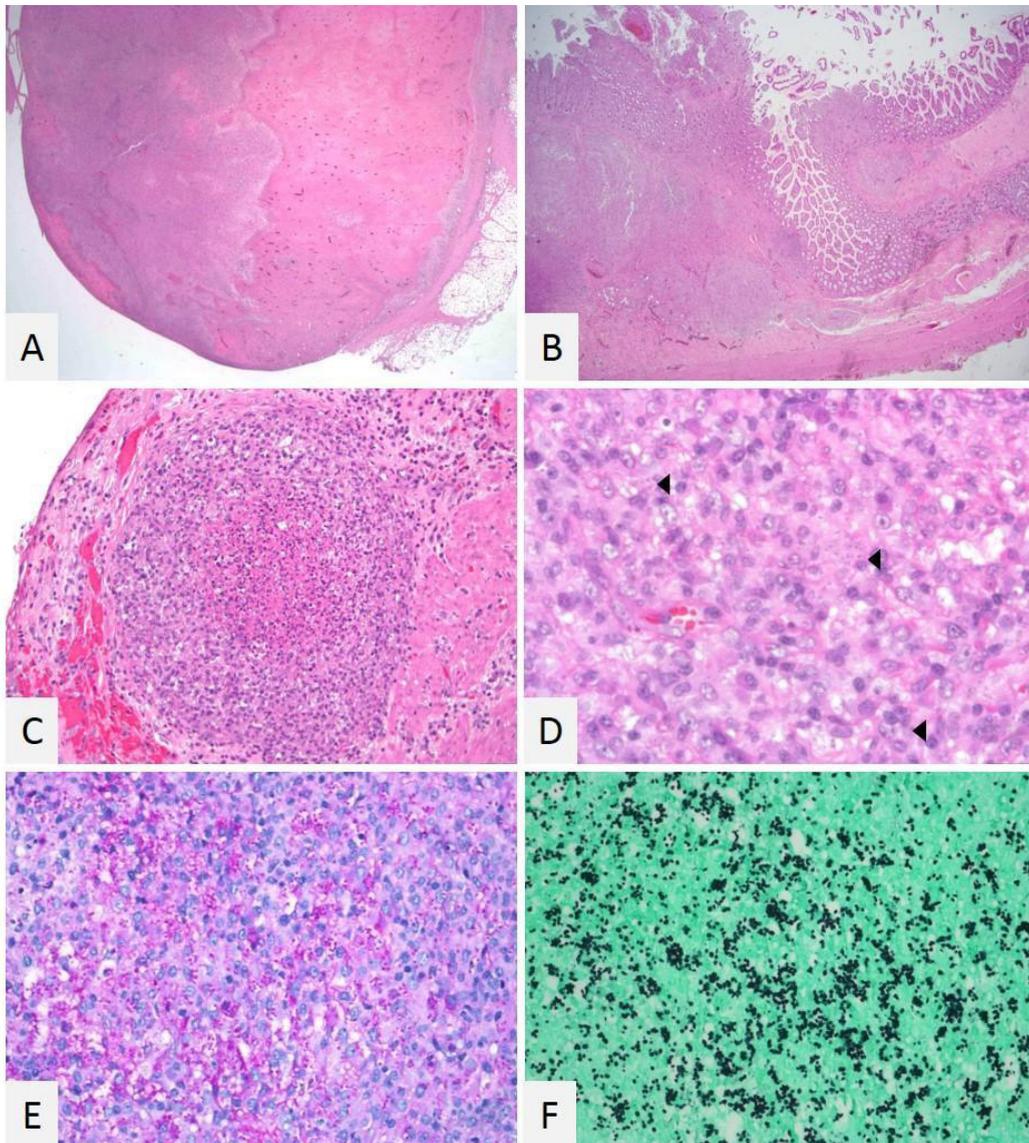


FIG 2: (A) Mesenteric lymph node with total effacement of normal lymphoid architecture and central necrosis by histiocytes, and (B) small bowel resection specimens showing transmural histiocytic infiltration (H&E, x 40). (C) Granulomatous inflammation with central necrosis are seen within the bowel wall (H&E, x 200). (D) Sheets of histiocytes filled with numerous small yeasts (arrowhead) (H&E, x 400). The yeasts are better highlighted with (E) periodic acid Schiff (PAS) stain (x 400) and (F) Grocott methanamine silver (GMS) stain (x 400).

B for one week, and subsequently switched to Itraconazole 200mg tds for three days, then 200mg bd. He was started on HAART (tenofovir-entricitabine and efavirenz) two weeks after treatment of histoplasmosis. Upon discharge, he was well and afebrile. His haemoglobin was 9.1 g/dl, white cell count: 2.0, absolute lymphocyte count 0.3, ANC 1.2; and platelet  $101 \times 10^9/L$ .

He was well one month after discharge. There was no fever, appetite has improved and there was no abdominal pain. Full blood count shows improvement with haemoglobin 11.7g/dl, white cell counts 4.9, with lymphocyte count 1.4, and platelet count  $116 \times 10^9/L$ .

## DISCUSSION

Histoplasmosis is the commonest endemic fungal disease in both immunocompetent and immunocompromised hosts. Healthy hosts however, remain asymptomatic or have only mild pulmonary symptoms.<sup>6</sup> In some individuals, the disease become disseminated, with a 25% association of disseminated disease with immunodeficiency disorders.<sup>7</sup> Risks for dissemination include AIDS, immunosuppressive medications, extremes of age, idiopathic CD4 lymphocytopenia, and common variable immunodeficiency, or biologic agents that interfere with the action of tumour necrosis factor  $\alpha$ , such as infliximab and etanercept. In some individuals who recovered following an initial exposure, a reactivation with progressive dissemination can occur once they become immunosuppressed.<sup>8</sup> It is also interesting to note that disseminated histoplasmosis in AIDS patients are increasing in number even in areas where histoplasmosis is not endemic.<sup>7</sup>

In the case that we describe above, the patient has disseminated disease that involved the bone marrow as evidenced by cytopenia; lymph nodes- which include the cervical, mesenteric, and peripancreatic lymph nodes; as well as gastrointestinal involvement; as evidenced by the presence of *Histoplasma capsulatum* from the biopsy of small bowel lesion. The calcified nodules seen on chest x-ray could possibly represent healing from prior exposure to the disease. Disseminated histoplasmosis is more likely when the CD4 count is less than 200cells/mm.<sup>9</sup> The most common symptoms of disseminated histoplasmosis are fever (89.1%), respiratory symptoms (38.1%), and weight loss (37.4%), while common physical findings include splenomegaly (72.0%), hepatomegaly

(68.1%), and lymphadenopathy (41.2%).<sup>5</sup>

All gastrointestinal manifestation of histoplasmosis is likely due to haematogenous dissemination of the disease, as the acquisition of the microconidia via gastrointestinal route through water or food ingestion has never been proven.<sup>6</sup> In gastrointestinal histoplasmosis, such as in our case report, 30-50% of patients present with abdominal pain, fever, weight loss, or diarrhea.<sup>8</sup> Other reported complications of gastrointestinal involvement are bleeding, bowel obstruction and perforation, protein-losing enteropathy, and hypogammaglobulinemia.<sup>9</sup> In patients with disseminated histoplasmosis who underwent autopsy, 70-90% were found to have gastrointestinal involvement, and 59.6% were found to have colon involvement. However, in life, the diagnosis was made in only 3-12% of patients.<sup>9</sup> This is because clinically, only 20% of patients with dissemination are symptomatic, and pulmonary lesions usually precede gastrointestinal symptoms, as seen in our patient, who had calcified nodules on chest x-ray. The entire gastrointestinal tract or segmental involvement can be present.<sup>7</sup> The pathologic findings of GI tract histoplasmosis include mucosal ulceration, diffuse lymphohistiocytic infiltration of the bowel wall, submucosal nodules, polypoid lesions, and obstructing masses. The terminal ileum and the colon are the most frequently involved organs.<sup>6</sup> The terminal ileum is likely to be involved due to the abundance of lymphoid tissue present in the form of Peyer's patches.<sup>8</sup> This explains the reason why it may mimic an acute appendicitis at presentation, such as in our patient.

A study done in 1950 by Raftery et al from Michigan over a period of ten years, analysed 2135 surgical specimens of cases of appendicitis and mesenteric adenitis. The study concludes that 5% incidence of histoplasmosis were found in acute and chronic appendicitis, while 43% of patients presenting with mesenteric adenitis were found to harbour histoplasmosis. This study shows the significance of histoplasmosis causing appendicitis, as well as histoplasmosis as the cause for mesenteric adenitis.<sup>10</sup>

As illustrated in our case, histoplasmosis can be difficult to diagnose. Failure to establish a diagnosis in the immunosuppressed patients can be fatal.<sup>3</sup> The diagnosis of histoplasmosis involves a variety of procedures such as direct microscopic examination, cultures, antigen detection, and serologic tests for antigen detection.<sup>8</sup> Antigen can be detected in the

urine of 90% of the patients, although false negative is common especially in localised site of dissemination. This method offers a rapid method of diagnosis, and useful for monitoring of response to therapy, where the level will fall and subsequently become undetected in successful therapy. Meanwhile, serologic tests are less sensitive in disseminated disease, especially in immunosuppressed patients. A positive serologic test also indicates prior infection, which may cause confusion in diagnosis. Cross reactions with other fungal infection can also occur.<sup>8</sup>

In disseminated histoplasmosis, cultures are positive in 85% of cases, although multiple specimens must be cultured to achieve the highest yield. *Histoplasma capsulatum* takes 4 to 6 weeks to grow, and in suspected disseminated cases, three sets of fungal blood cultures should be obtained. Other than that, direct microscopic examination of fresh clinical specimens such as lymph nodes or other tissues stained with Diff-Quik, GMS, Giemsa, or Wright Giemsa stain aid in rapid diagnosis, although it is less sensitive than cultures.<sup>8</sup> 52.9% patients yielded positive culture result for blood, broncho-alveolar lavage, lymph node, liver and spleen specimens, but GI specimens yield higher positive results up to 90.9%.<sup>9</sup>

The appearance of gastrointestinal disease in histoplasmosis may mimic a lot of other diseases such as Crohn's disease, tuberculosis, lymphoma, and carcinoma. At times, since histoplasmosis are not considered to be part of the differential diagnosis, it may lead to unnecessary surgical interventions or inappropriate therapies.<sup>9</sup> In addition to histoplasmosis, other fungal infections such as penicilliosis and cryptococcosis should be considered too, especially in the immunosuppressed.<sup>1</sup> Untreated disseminated histoplasmosis has a mortality rate of 83%.<sup>7</sup> Studies, however, showed that amphotericin B could reduce the mortality to less than 25%.<sup>8</sup> The Infectious Disease Society of America suggest liposomal amphotericin B 3 mg/kg daily, or amphotericin B lipid complex 5mg/kg daily, or deoxycholate amphotericin B 0.7 to 1mg/kg daily for one to two weeks, followed by itraconazole 200mg twice a day for at least twelve months in moderately severe to severe progressive disseminated histoplasmosis. In mild to moderate cases, the treatment is itraconazole 200mg twice a day for 12 months.<sup>11</sup>

In conclusion, histoplasmosis has become more widespread than expected.<sup>2</sup> The fact that the infection has increasingly been reported in

AIDS patients in areas where histoplasmosis is not endemic makes it important that this diagnosis be considered when dealing with an acute abdomen in AIDS patients.<sup>7</sup>

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