Histoplasmosis of bilateral adrenal masses and submandibular lymphadenopathy: other diagnosis besides malignancy and tuberculosis

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Abstract. Histoplasma capsulatum is a dimorphic fungus which can cause infection usually in immunocompromised patients. An immunocompetent patient can be affected if he got chronic exposure to soil contaminated with birds or bats guano. We are reporting a case of a 54 years old man, working as trashman at open-air landfill, presented to hospital, with persistent fever and abdominal pain. The patient also complained of enlargement of submandibular lymph nodes. The abdominal ultrasound and CT-scan showed bilateral adrenal masses. Biopsy per laparoscopy of adrenal mass, and aspiration cytology of lymphadenopathy were performed and the results of cyto and histopathology examinations were Histoplasma capsulatum infection. The patient was planned for itraconazole 200 mg bid for 12-24 months. After 6 months of therapy, the patient had no more complains and the lymph nodes have shrinked significantly.

1. Introduction
Histoplasmosis is a fungal infection caused by Histoplasma capsulatum. This dimorphic soil fungus is endemic in Ohio and Mississippi River valley North America, Central, and South America. Pulmonary infection is the typical presentation of histoplasmosis, which may be asymptomatic or can be associated with mild flu-like symptoms. This can become a chronic pulmonary infection or disseminated disease in those with impaired immune systems. This is related with chronic exposure to humid soil contaminated with birds or bats guano [1-5]. Disseminated disease in healthy individuals is very rare. In 99% of cases, the infection is subclinical and self-limited. Male to female ratio is 3-10:1. The incidence in HIV patients is more common than in non-HIV patients (2-5% vs <0,05%). [6] Publications of cases in India from 1995-2011, males were more commonly affected than females (55:6). Although age of presentation varied from 3-83 years, middle-aged and elderly were more commonly affected [7].

Patient with the disseminated disease usually shows similar signs and symptoms to chronic infection like tuberculosis, including persistent long fever/pyrexia, anorexia, nausea, vomiting, weight loss and fatigue [1,5,8,9]. Malignancy is then suspected especially if a patient came with a mass. We report a case of 54 years old non-HIV trashman with persistent fever, abdominal pain, bilateral adrenal masses and enlargement of submandibular lymph nodes which were histo and cytopathologically diagnosed as histoplasmosis.
2. Case presentation
A 54 years old man, came to Mohammad Hoesin hospital, gastroenterology outpatient department, complaining persistent fever and abdominal pain in the last 3 months. He was referred by an internist in the private sector, for having bilateral masses above both kidneys diagnosed from ultrasound, and needed further examination. He also suffered from nausea, vomiting, anorexia and weight loss. He worked as a trashman at an open-air landfill, there was no history of using intravenous drugs, tattoos, or having promiscuity, but admitted that he often got stuck by sharp materials at the landfill. He had no history of diabetes mellitus or malignancy, neither on steroid nor immunosuppressive therapy.

At first presentation, he was conscious, the temperature was 38°C, body mass index was 18,8 kg/m2, other vital signs were normal, and there was submandibular lymph nodes enlargement which were immobile, non-tender, 4 cm and 5 cm in diameter. There was no palpable mass in the abdomen. Laboratory examination results were LDH 425, A1c 5,6 g/dL, albumin 2,8 mg/dL, ureum 42 g/dL, creatinine 0,72 g/dL, urine cortisol 13,1 ug/dL, and HIV non-reactive. Chest x-ray was normal. Whole abdominal MSCT scan showed suggestive bilateral adrenal masses caused by malignancy. Biopsy per laparoscopy was performed and sent for pathology examination. Enlargement of submandibular lymph nodes was suggestive for nodal metastasis of malignancy in the abdomen, fine needle aspiration cytology then was performed.

The smears from adrenal biopsy showed fibrocollagen tissue with the presence of mixed inflammatory cells like lymphocytes, neutrophils, plasma cells, and macrophages. There were numerous microorganisms seen, uniform yeasts with narrow-based budding, mostly intracellular. Smears from the lymph node showed necrotic debris background, mixed inflammatory cells, and microorganisms identic with which was seen from the adrenal biopsy. These microorganisms were consistent with Histoplasma capsulatum. Samples from blood, urine, and aspirate of lymph node were sent for fungal cultures, but the results were negative. Adrenal function was also examined in this patient by measuring morning serum cortisol and the result was within normal limit (13,1 ug/mL).

From all these data, the suspicion of malignancy in the beginning was rejected, and the diagnosis of disseminated histoplasmosis in an HIV-negative patient was confirmed. He was planned for treatment with 200 mg itraconazole bid for 12-24 months. After 6 months of therapy, he showed subsequent improvement, fever subsided and never complained about abdominal pain again, submandibular lymph nodes shranked and could work normally.

Figure 1. Ultrasound in adrenals show masses in suprarenal bilateral.
3. Discussions
Histoplasmosis cases seen outside of endemic areas are usually related with activities associated with high-level exposure with humid, acidic nature of soil enriched with bird or bat droppings, like cleaning of chicken coops, spelunking, excavation, cutting of dead trees, demolition and remodeling of old
buildings [1,2]. The patient, in this case, works as trashman at the open-air landfill, and his working activities are associated with disrupting soil contaminated with various animal feces including birds, chicken, and bats, which was suspected containing Histoplasma spores. This caused aerosolization of microconidia, then inhaled by the patient following infection.

In healthy immunocompetent host, macrophages, lymphocytes and epithelial cells eventually organize and form granulomas that contain the organisms. These granulomas typically fibrose and calcify. This condition leads to some immunity to reinfection. Progressive dissemination of Histoplasma infection can be happened in patients with impaired cellular immunity which involve multiple organs, most commonly the bone marrow, spleen, liver, adrenal glands, and mucocutaneous membrane. The severity of the disease depends on the intensity of exposure, the immune status of the exposed individual and the underlying lung architecture of the host [1,2]. In this case, the patient could get infected because long exposure with soil contaminated with animal feces containing Histoplasma spores, made him vulnerable to infection.

Most Histoplasma infections are usually asymptomatic or mild and self-limited in immunocompetent individuals with low-level exposure. But heavy exposure can lead to a flulike illness with fever, chills, sweats, headache, myalgia, anorexia, cough, dyspnea, and chest pain [1,8,9]. Clinical manifestations of disseminated histoplasmosis were similar to malignancy, as suspected in this patients at the beginning. This was strengthened with the results from slightly elevated LDH, abdominal ultrasound and abdominal MSCT scan showing bilateral adrenal masses, and enlargement of submandibular lymph nodes suggestive of nodal metastases. In immunocompetent patients, histoplasmosis affecting adrenal gland is commonly found. The cause of this tropism for the adrenal gland is unclear. The relative scarcity of reticuloendothelial cells in adrenal glands and adrenal cells contain with rich glucocorticoid can be the explanation for this condition [5].

Distinguishing between various causes of bilateral adrenal masses was not reliable from imaging feature. Therefore biopsy of adrenal masses and fine needle aspiration cytology of lymph nodes were performed, and histopathological and cytopathological examination finally set the suprising diagnosis. The distinctive feature of intracellular uniform yeast confirms Histoplasma infection in both adrenal and submandibular lymph nodes. Histoplasma has a relatively specific morphology, an ovoid yeast measuring 2 um to 5 um on Romanowsky or silver stain, and must be differentiated from other infectious organisms depending on tissue site, such as Pneumocystis jiroveci, Cryptococcus neoformans, Blastomyces dermatitidis, Candida species, Toxoplasma gondii, and Leishmaniasis [4]. Although culture remains the gold standard diagnostic test for histoplasmosis, it has a lot of limitations. Culture results may not be known for more than 1 month and are often false negative [1]. Detection of Histoplasma antigen can also support the diagnosis, but we could not perform it.

Amphotericin is the first line recommended treatment for severe disseminated histoplasmosis, and itraconazole for the mild-moderate condition [1]. Because amphotericin was nephrotoxic, not available in our place, and this patient was not in severe condition, itraconazole 200 mg bid was instituted. Treatment duration of 1-2 years was planned for this patient to reduce the risk of relapse. After 6 months of therapy, the patient showed significant improvement. He never complained of abdominal pain nor fever, could get back to work normally, and the lymphadenopathy had shranked.

4. Conclusions
This case demonstrated that disseminated fungal infection in an HIV-negative patient should also be considered besides malignancy or tuberculosis. Diagnosis could be made by histo or cytopathological examination. Longterm duration of treatment for at least 1 year with itraconazole was chosen and significant improvement was shown.

5. References
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