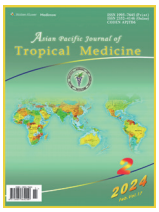

Case Report

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Bilateral adrenal histoplasmosis in a Malaysian tertiary hospital: Report of four cases

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ABSTRACT

Rationale: Adrenal histoplasmosis can present as bilateral adrenal enlargement with constitutional symptoms and/or adrenal insufficiency. Often these patients are initially investigated as secondary adrenal metastases before eventually their diagnosis established by histopathological examination of the adrenal tissues.

Patients concerns: We report 4 cases of patients aged 55-78 who presented with hypocortisolism and bilateral adrenal masses.

Diagnoses: Bilateral adrenal histoplasmosis.

Interventions: Three patients received antifungal treatment for at least one year while 1 patient passed away before the initiation of antifungal treatment.

Outcomes: Two patients' adrenal function recovered not requiring any steroid replacement, while 1 patient still requires long-term steroid replacement.

Lessons: Adrenal histoplasmosis should be excluded in patients from endemic areas presenting with bilateral adrenal masses and adrenal insufficiency. Usually patients have an exposure to bird droppings, bat guano or soil contaminated with histoplasmosis fungi. Histopathological examination of biopsied adrenal tissues is still the gold standard investigation as serology and molecular diagnostic methods are still not widely available in most centers in Malaysia.

KEYWORDS: Adrenal histoplasmosis; Histoplasmosis; Bilateral adrenal masses

1. Introduction

Histoplasmosis is an opportunistic, inhalation-acquired systemic mycosis, caused by the endemic dimorphic fungi *Histoplasma* (*H.*) *capsulatum*. Histoplasmosis is endemic in Southeast Asia, especially in Malaysia, since Ponnampalam reported in 1964 that 10.5% of Malaysians were positive in histoplasmin skin tests[1,2]. Baker *et al*. reviewed 407 cases of histoplasmosis in Southeast Asia reported between 1932 to 2018, and noted that up to 18.7% of these cases were in Malaysia, with as much as 27.6% of these Malaysian patients diagnosed with disseminated histoplasmosis[1].

Adrenal histoplasmosis can occur as a consequence of disseminated histoplasmosis especially in immunosuppressed individuals during the active disease or during reactivation of the disease, presenting as unilateral or bilateral adrenal enlargement with constitutional symptoms and/or adrenal insufficiency[3]. Often, these patients are initially investigated as malignancies with secondary adrenal metastases before eventually having their diagnosis established by histopathological examination of the adrenal tissues.

2. Cases report

Informed consents were obtained from the patients for the publication of this cases report and any accompanying images.

We report 4 cases presented as bilateral adrenal masses and later diagnosed with adrenal histoplasmosis by histopathological examination in Pusat Perubatan Universiti Kebangsaan Malaysia from 2008-2018. The patients' clinical information are shown in Table 1.

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All of these patients were of Malay ethnicity, with the mean age of (68.8±10.3) years. Two of them were retired army officer, while 1 was a retired agricultural officer. One patient had exposure to bat guano in his residence. One of them had diabetes, while another had chronic kidney disease due to long-standing hypertension. None of them were HIV positive. The commonest presentation was constitutional symptoms including weight loss, low-grade fever and anorexia while two presented as Addisonian crisis.

All of the cases had bilateral enlarged adrenals on abdominal computed tomography (CT) with the largest dimension ranging from 3.0-7.3 cm. Three scans revealed homogenously enhanced hypodense enlarged adrenals while one scan showed heterogeneously enhanced enlarged adrenals. All of them were diagnosed histopathological with the presence of small ovoid yeast-like organisms identified in Periodic-Acid-Schiff and Gomori Methenamine-Silver stains in the adrenal necrotic tissue with granulomatous inflammation; however, surprisingly none of them had positive blood fungal culture, which we could not find the reason for this phenomenon (Figure 1). Serology test were not performed as it was not available in our hospital setting. Three of them completed antifungal treatment for at least one year but two had residual primary adrenal insufficiency requiring steroid replacement. One patient passed away due to old age at the age of 78 years old, while another patient passed away due to presumed hospital acquired infection (Table 1).

3. Discussion

Histoplasmosis is an opportunistic, inhalation-acquired systemic mycosis caused by the dimorphic fungi *H. capsulatum*. This organism is often found in soils contaminated with bat guano or bird droppings as it thrives well in nitrogen-rich soil. Endemic in Malaysia and the Asia Pacific region, histoplasmosis may present with a spectrum of disease varying from asymptomatic inoculation, acute or chronic pulmonary histoplasmosis, or even disseminated histoplasmosis[1]. Bahr *et al*. reported *H. capsulatum* being successfully isolated from soil samples from bat-infested caves near Kuala Lumpur, as well as documented cases of both immunocompentent and immunocompromised patients infected with histoplasmosis after traveling to Malaysia[2].

Histoplasmosis is an occupational hazard, with the risk increasing with the duration of exposure and the concentration of spores in the working environment[4]. Occupations or hobbies with a high risk of exposure to *H. capsulatum* includes bridge inspector or painter, chimney cleaner, construction worker, demolition worker, gardener, heating and air-conditioning system installer, microbiology laboratory worker, pest control worker, restorer of historic or abandoned buildings, roofer and cave explorer/spelunker. In our case series, patients from Cases 2 and 3 were exposed to bat guano, or soil probably exposed with bat guano. The remaining patients from Cases 1 and 4 were military officers who had a history of military training in jungles and caves.

Patients are often evaluated for tuberculosis or malignancies and proceeded with abdominal imaging. Ultrasonography may reveal suprarenal masses, described as having a hypoechoic to heterogenous echopattern with preserved adrenal gland outlines. Computed tomography may show adrenal enlargement with necrosis or dense calcification. The differential diagnosis of bilateral adrenal masses with constitutional symptoms include metastases, lymphoma, adrenal infiltration or infection. Gajendra *et al*. reported in 2015 that 83% of her 12 adrenal histoplasosis patients had bilateral adrenal masses[5]. In contrast, all our patients had bilateral adrenal involvement with adrenal masses >4 cm in size, and none of them had calcifications seen in the CT scan.

It may be difficult to rule out adrenal tuberculosis both clinically and radiographically. Clinically, adrenal tuberculosis can also present with an Addisonian crisis, in addition to constitutional symptoms such as fever, anorexia and weight loss. Radiographically, similiarly to adrenal histoplasmosis, adrenal tuberculosis may also present with adrenal enlargement with hypodensity and peripheral rim enhancement[6].

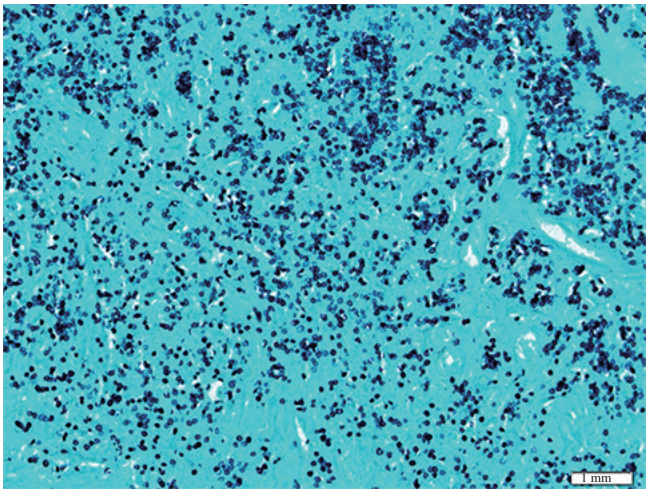

Figure 1. Gomori Methenamine-Silver stain of biopsied adrenal tissues (×40) in a 67-year old agricultural officer with bilateral adrenal masses showing numerous fungal yeasts in the necrotic area.

Table 1. Clinical summary of the 4 cases of bilateral adrenal histoplasmosis.

Items	Case 1	Case 2	Case 3	Case 4
Age, year	78	55	67	75
Sex	Male	Male	Male	Male
Comorbids	Nil	Nil	Chronic Kidney Disease	Diabetes Mellitus
Exposure risk	Military officer	Exposure to bat guano in residence	Agricultural officer	Military officer
Clinical presentation/ Anorexia hypotension/ Hyperpigmentation/ Hepatosplenomegaly	Yes/No/No/No	Yes/Yes/Yes/No	Yes/Yes/Yes/No	Yes/Yes/No/No
Initial diagnosis	Malignancy	Histoplasmosis	Histoplasmosis	Histoplasmosis
Anti-fungal treatment	No	Completed 1 year of oral itraconazole	Completed 1 year of oral itraconazole	Completed 2 weeks of IV amphotericin followed by 1 year of oral itraconazole
Post-treatment Hypocortisolism	Deceased due to presumed hospital acquired infection before anti-fungal treatment initiated	Persistent, still requiring steroid supplement	Persistent, still requiring steroid replacement	Not requiring steroid replacement but passed away 3 years later due to old age
Left adrenal size	3.6 cm×2 cm	6.7 cm×5.4 cm×2.7 cm	5.3 cm×4.7 cm×7.3 cm	3.9 cm×3.1 cm
Right adrenal size	4 cm×2 cm	7.3 cm×4.0 cm×3.4 cm	4.0 cm×6.2 cm×6.0 cm	3.4 cm×2.9 cm
CT scan features	Heterogenous hypodense	Homogenoushypodense	Homogenoushypodense	Heterogenous hypodense
Histopathology	Intracellular small ovoid yeast-like organism (PAS and GMS stain positive) with occasional narrow based budding and clear halo seen	Necrotic tissue with focal vague granulomas seen at edge of tissue fragment. PAS and GMS stains show presence of yeast bodies	Necrotic tissue with lymphoplasmacytic cells with granulomas; numerous fungal yeasts (GMS and PAS stains)	Necrotic tissue with thin walled rounded yeast like bodies with budding (PAS and GMS stains)
Fungal (blood) culture	Negative	Negative	Negative	Negative
Baseline am cortisol (>250 nmol/L)	420 nmol/L	150 nmol/L	<28 nmol/L	<28 nmol/L
ACTH (1.3-16.7 pg/mL)	13 pg/mL	727.50 pg/mL	449.90 pg/mL	532.10 pg/mL
Synacthen test on diagnosis	Not performed	Not performed	Not performed	Not performed
Anti-fungal treatment	No	Completed 1 year of oral itraconazole	Completed 1 year of oral itraconazole	Completed 2 weeks of IV amphotericin followed by 1 year of oral itraconazole
Post-treatment hypocortisolism	Deceased due to presumed hospital acquired infection before anti-fungal treatment initiated	Persistent, still requiring steroid supplement	Persistent, still requiring steroid replacement	Not requiring steroid replacement but passed away 3 years later due to old age

CT: Computed tomography; PAS: Periodic acid-Schiff; GMS: Gomori Methenamine-Silver.

In Case 1, the 18-FDG PET/CT showed hypermetabolic adrenals, as increased FDG uptake in infectious diseases due to increased glucose metabolism in these cells. Similar to previous reports, hypermetabolic adrenals in an 18-FDG PET/CT can be a result of invasive adrenal infections[7]. A histopathological examination confirmation is vital to confirm the diagnosis of 18-FDG PET/CT avid adrenal masses, especially when fungal and mycobacterial infections are prevalent. Tsai *et al*. also pointed out the possible advantage of using 18-FDG PET/CT to evaluate the therapeutic response in treatment of adrenal histoplasmosis, aside from its diagnostic value[8].

The gold standard diagnostic method is tissue culture, which requires highly specific cultures, making the process tedious and complicated. Histopathological examination of tissue samples will show small ovoid yeast cells 2-4 micrometer in size, either extracellular or within macrophages, using Gomori methenamine silver or periodic acid-Schiff stains. Antigen testing from body fluids often shows high rates of cross-reactivity with other fungi and is still not commercially available in most countries. Serological testing of *H. capsulatum* antibodies are still not widely available in most centers, whereas molecular diagnostic methods to detect *H. capsulatum* antibodies are still not validated or available commercially[9].

To date, there is very limited evidence on the radiological surveillance of the adrenal masses to assess if the adrenal masses reduce in size following 1 year of treatment. Few case reports have documented persistent adrenal masses and the presence of histoplasma organisms in the adrenal tissues of immunocompetent patients despite completing 1 year of treatment[10]. Further studies are required to determine if patients with adrenal histoplasmosis

may require prolonged therapy despite their immunocompetency status.

Persistent hypocortisolism is a known complication of adrenal histoplasmosis. Singh *et al*. in India reviewed 40 bilateral adrenal histoplasmosis patients diagnosed in the past 12 years and reported that none of their patients regained adrenal function despite completing a year of anti-fungal treatment. A further follow-up of 2-8 years also failed to show normalization of the hypocortisolism. Interestingly, 2 out of their 7 eucortisolemic patient developed new onset hypocortisolism albeit completion of a year of anti-fungal treatment[11].

There are several limitations in this study, including its retrospective design and the heterogenous workups of the patients. Patients included in this study were from the adrenal biopsy cohort hence patient with adrenal histoplasmosis who did not undergo adrenal biopsy would have been missed.

4. Conclusions

Adrenal histoplasmosis should be excluded in patients from endemic areas presenting with bilateral adrenal masses, especially with the presence of adrenal insufficiency. A detailed history of exposure to bird droppings, bats guano or soil contaminated by bird droppings and/or bats guano is crucial. Histopathological examination of biopsied adrenal tissues is still the gold standard as serological and molecular diagnostic methods are still not widely available.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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Authors' contributions

Both KWH and NAW were involved in the care of the patients and conception of the work. KWH acquired the data and drafted the manuscript. NAW made critical revision on the manuscript. Both KWH and NAW approved the manuscript for publication.

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