

# Addison's disease due to disseminated histoplasmosis: A case report

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*Addison's disease, also known as primary adrenal insufficiency, can manifest as generalized mucocutaneous hyperpigmentation. The common causes of Addison's disease in developing countries are mycobacterium and fungal infections. Histoplasma capsulatum is a dimorphic fungi, which may disseminate to the adrenal glands and skin, causing Addison's disease and skin lesions such as macules, acneiform pustular eruptions, erythematous papules, nodules, keratotic plaques with or without crust and mucosal ulceration.*

*We present a case of a 45-year-old male with Addisonian pigmentation for one year together with multiple skin-colored flat top papules on both inguinal areas 3 months earlier. Cutaneous lesions were carefully physical examined might easily lead to the cause of Addison's disease by using biopsy from skin lesions which found histoplasma capsulatum same as found in fine needle aspiration (FNA) from right adrenal mass.*

**Keywords:** Addison's disease, disseminated histoplasmosis.

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โรคแอดดีสัน หรือภาวะต่อมหมวกไตทำงานไม่เพียงพอแบบปฐมภูมิ การพบสีผิวและเยื่อ  
ทั่วร่างกายมีสีคล้ำขึ้นอาจเป็นอาการแสดงของโรคแอดดีสัน สาเหตุที่พบบ่อยในประเทศกำลังพัฒนา  
ได้แก่ การติดเชื้อวัณโรค และเชื้อรา ฮีสโตพลาสโมซิส เป็นราสองรูป ซึ่งสามารถกระจายไปยัง  
ต่อมหมวกไตและผิวหนังทำให้เกิดโรคแอดดีสันและผื่นผิวหนัง เช่น ผื่นราบ, ตุ่มหนองคล้ายสิว,  
ผื่นนูนแดง, ตุ่มนูน หรือปื้นหนาอาจมีหรือไม่มีสะเก็ดปกคลุม หรือแผลที่บริเวณเยื่อได้

รายงานฉบับนี้เป็นการนำเสนอผู้ป่วยอายุ 45 ปี ที่มาด้วยเรื่องผื่นคล้ำขึ้นมานาน 1 ปี  
และพบตุ่มนูนที่ขาหนีบทั้งสองข้างมานาน 3 เดือน การตรวจร่างกายอย่างละเอียดจะสามารถค้นหา  
สาเหตุของโรคแอดดีสันได้ง่ายโดยอาศัยการตัดชิ้นเนื้อจากผิวหนัง ซึ่งพบเชื้อ ฮีสโตพลาสโมซิส  
เช่นเดียวกับที่พบจากการใช้เข็มเจาะดูดเซลล์จากก้อนในต่อมหมวกไตด้านขวา

**คำสำคัญ:** โรคแอดดีสัน, ฮีสโตพลาสโมซิส.

Addison's disease also known as a primary adrenal insufficiency was first described by Thomas Addison in 1855.<sup>(1)</sup> Early symptoms are nonspecific, such as chronic worsening fatigue, loss of appetite, generalized weakness, hypotension and weight loss. The symptoms usually develop when 90% of adrenal glands have been destroyed.<sup>(1)</sup> Increasing adrenocorticotrophic hormone induces melanogenesis producing cutaneous manifestation as generalized mucocutaneous hyperpigmentation which is prominent on sun-exposed skin and over pressure points. In developing countries, disseminated tuberculosis and fungal infections are common causes of Addison's disease.<sup>(1)</sup>

### Case Report

A 45-year-old male presented with progressive darkening of the skin and lip together with fatigue and postural hypotension for one year (Figure A-E). Three months earlier, he noticed multiple asymptomatic skin colored papules on bilateral inguinal areas (Figure F). His remarkable loss of weight by 20 kg in 3 months that led him to hospital. Physical examination showed generalized hyperpigmentation which was more prominent on the axillary folds, inguinal areas, old scars on the lower back, palmar and plantar creases. He also had multiple brownish macules on the lips and buccal mucosa. Interestingly, he had multiple firm, flat-topped, skin-colored to erythematous papules and nodules on bilateral inguinal areas.

Due to his classic presentations, adrenal insufficiency was suspected and his blood examination showed typical picture (serum sodium: 128 (136 - 145 mEq/l), serum potassium: 5.5 (3.5 -

5.1 mEq/l), serum morning cortisol: <1.25 ug/dl (7 - 25), serum adrenocorticotrophic hormone (ACTH): 1,189 pg/ml (0 - 71), dehydroepiandrosterone sulfate (DHEA-S): 19.3 ug/dl (80 - 560) together with bilateral adrenal glands enlargement revealed by computed tomography imaging (CT). Routine laboratory tests, including complete blood cell count, liver and renal function tests were normal. Chest X-ray imaging showed no infiltration. Skin biopsy of the papule from the right inguinal area (Figure F) showed diffuse interstitial inflammatory cells infiltration, predominantly lymphohistiocytes, in the entire dermis (Figure G). Periodic acid-Schiff (PAS) and Gomori's methenamine silver (GMS) (Figure H) stains revealed infiltrations of numerous non-septate yeast-like organisms. Fine needle aspiration was used on the right adrenal mass. The tissue stained by Gomori's methenamine silver (GMS) showed budding yeasts, compatible with histoplasmosis infection. Finally, the cultured tissue from the right adrenal mass identified *Histoplasma Capsulatum*. His final diagnosis was Addison's disease due to disseminated histoplasmosis.

### Discussion

Addison's disease, also known as a primary adrenal insufficiency, is a rare chronic disorder of the adrenal glands due to inadequate production of glucocorticoid, mineralocorticoid and androgen. In developing countries, infections such as tuberculosis, histoplasmosis, cryptococcosis and coccidioidomycosis are its common causes.<sup>(1,2)</sup> Initially, patients with Addison's disease usually have nonspecific symptoms like chronic fatigue, malaise, anorexia, unintentional weight loss, nausea and vomiting. Hypoglycemia and symptoms of postural



**Figure 1.** Figure A-E Generalized mucocutaneous hyperpigmentation with prominent on palmar crease (Figure C) and old surgical scar (Figure E). Figure F: Multiple skin colored papules on right inguinal area. Figure G: Biopsy specimen from the right inguinal papule. Hematoxylin and eosin stain, magnification X100 showed diffuse interstitial inflammatory cell infiltration, predominantly lymphohistiocytes, in entire dermis. Figure H: Gomori's methenamine silver (GMS), magnification X 400 stains showed numerous non-septate yeast-like organisms in entire dermis.

hypotension appear later.<sup>(2)</sup> Addisonian pigmentation is the hallmark of Addison's disease, characterized by generalized mucocutaneous hyperpigmentation which is prominent on sun-exposed areas, skin creases, mucosal membranes, scars and areola of breast.<sup>(3)</sup> Hyperpigmentation, caused by compensatory ACTH secretion from the pituitary gland, which stimulates melanocortin-1 receptors on the surface of dermal melanocytes, leads to melanogenesis.<sup>(4)</sup> Hyponatremia and hyperkalemia are also laboratory clues to diagnosis.<sup>(2)</sup> Low morning serum cortisol level and high ACTH level are the first step in laboratory evaluation of Addison's disease, and ACTH stimulation test is used to confirm the

diagnosis.<sup>(3)</sup> Importantly, the investigation for the underlying cause of the Addison's disease should be performed in parallel. Careful physical examination particularly cutaneous lesions and imaging evaluation such as computed tomography (CT) examination and magnetic resonance imaging (MRI) whole abdomen are recommended to identify the underlying causes such as metastasis, infiltration, hemorrhage, infarction, and infection.<sup>(2)</sup>

Our patient presented with fatigue, postural hypotension and Addisonian hyperpigmentation for 1 year; therefore, Addison's disease was suspected. The diagnosis of primary Addison's disease was confirmed by abnormal laboratory results

including abnormal electrolytes (hyponatremia and hyperkalemia), low serum morning cortisol and high serum ACTH level.

As mention above, infection is the most common cause of the Addison's disease in developing countries and skin manifestations are frequent. The prevalence of skin lesions in disseminated tuberculosis and disseminated histoplasmosis are 0.1% - 2.5% and 2%, respectively.<sup>(5,6)</sup> Therefore, skin biopsy from suspected lesions is very helpful to diagnose due to fast and minimal invasive procedure.

In our patient a careful skin examination showed multiple firm, flat-topped, skin-colored to erythematous papules and nodules on bilateral inguinal areas which tuberculous or fungal infection or metastasis are suspected. Skin biopsy of the right inguinal papule revealed non-septated yeast like organism identified as *Histoplasma Capsulatum*. In addition, CT scan of lower abdomen showed bilateral adrenal glands enlargement. The right and left adrenal glands are measured 5.4 × 2.7 cm and 5.2 × 3.2 cm, respectively. The differential diagnosis are infections or metastasis cancer. FNA from right adrenal gland with GMS and PAS stain found the organism and the final culture identified as *Histoplasma capsulatum*. Pulmonary examination and chest X-ray was normal.

Histoplasma infection is caused by dimorphic fungi *Histoplasma capsulatum*, found in contaminated soil with bat or bird droppings. Inhalation of the organism into the lower respiratory track is the primary route of infection. Most infected patients are asymptomatic or have mild symptoms which often

make the diagnosis difficult.<sup>(7)</sup> The Histoplasma infection can be divided into two forms which are pulmonary infection (75%) and disseminated histoplasmosis (25%).<sup>(8)</sup> Most patients with disseminated histoplasmosis develop the disease through asymptomatic hematogenous spreading. Occasionally, cell-mediated immunity against histoplasmosis is developed; however, there are usually remaining viable organisms in various organs, which can be reactivated later.<sup>(9)</sup> A self-limiting disease sometimes occurs in immunocompetent host, but the dissemination occurs more in immunocompromised host.<sup>(10)</sup> Addison's disease, due to disseminated histoplasmosis, is rare with estimated incidence of 0.3%.<sup>(6)</sup> Approximately, 6% of the patients have, disseminated histoplasmosis on the skin manifesting as macules, acneiform pustular eruptions, erythematous papules, nodules or keratotic plaques with or without crust and mucosal ulceration.<sup>(11)</sup> The diagnosis of histoplasmosis infection can be performed by detecting organisms from the sputum, blood or infected organs, detection of antigens in blood or urine by enzyme-linked immunosorbent assay (ELISA) or polymerase chain reaction (PCR), or detection of antibodies against *Histoplasma spp.* in the blood. Histoplasmin skin test is not definitive. Gold standard for diagnosis is the culture method.<sup>(6)</sup>

We report atypical case of Addison's disease caused by disseminated histoplasmosis. Here we would like to address the imperative detection of skin lesion as the clinical clue and skin biopsy as effective minimal invasive method in identifying the cause of the systemic infection.

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