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Case Report

Primary Adrenal Tuberculosis: A Case Report

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Abstract Tuberculosis (TB) is a world-wide epidemic. The World Health Organization estimated a global incidence of around 10 million new cases in 2019, and it is one of the top 10 causes of death in the world with 1.2 million deaths annually. Tuberculosis is mainly a pulmonary disease, and extra-pulmonary tuberculosis accounts for 5% to 15% of all cases. Primary adrenal tuberculosis is rare, constituting 6% of all TB cases. We report a case of primary adrenal tuberculosis, with a discussion of the clinical features, radiologic and pathological findings and treatment outcomes. A review of the current knowledge of this disease is also provided.

Keyword: Primary adrenal tuberculosis

Case Report

A 70-year-old man presented with remittent fever for 2 weeks, there was severe generalized abdominal pain with no radiation, anorexia, or weight loss. No other gastrointestinal symptoms or urinary symptoms were reported. He had been diagnosed with type 2 diabetes mellitus for 30 years, which was poorly controlled, and rheumatoid arthritis for 20 years.

He denied having a previous history of tuberculosis infection but did have a history of contact with pulmonary tuberculosis patients 10 years previously. There was no family history of endocrine neoplasms or early cerebral or cardiovascular disease. He underwent a tuberculin skin test in 2007 which showed induration (unknown diameter) that may be attributed to a prior BCG vaccination.

The general appearance was not pale, there was no facial plethora, and the skin did not easily bruise. Physical examination revealed mild abdominal distension, but no superficial vein dilatation, no purplish striae, no palpable mass, the liver and spleen were not palpable, and there was no lymphadenopathy. Cardiac, respiratory, and neurological examinations showed no abnormalities. There were no signs and symptoms characteristic of adrenal insufficiency. Laboratory analysis was performed, which showed normal findings. There was no evidence of pulmonary tuberculosis via chest radiography. The patient underwent axial helical computerized tomography (CT) of the whole abdomen. This revealed an irregular enhancing hypodensity of the bilaterally enlarged adrenal glands (7.3 cm × 2.9 cm × 6.6 cm on the right, 5.9 cm × 2.6 cm × 6.6 cm on the left) but no intra-abdominal lymphadenopathy (Figure 1). On review of his prior CT scan of the abdomen, the patient had bilaterally enlarged adrenal glands at the time of his initial presentation as well.

A dedicated adrenal washout CT protocol consists of a non-contrast and a contrast-enhanced scan with a delay of 60 to 90 seconds, and a delayed scan at 15 minutes. Absolute enhancement wash out > 60% is proof of an adenoma. The absolute wash out was 63.6% in the present case.

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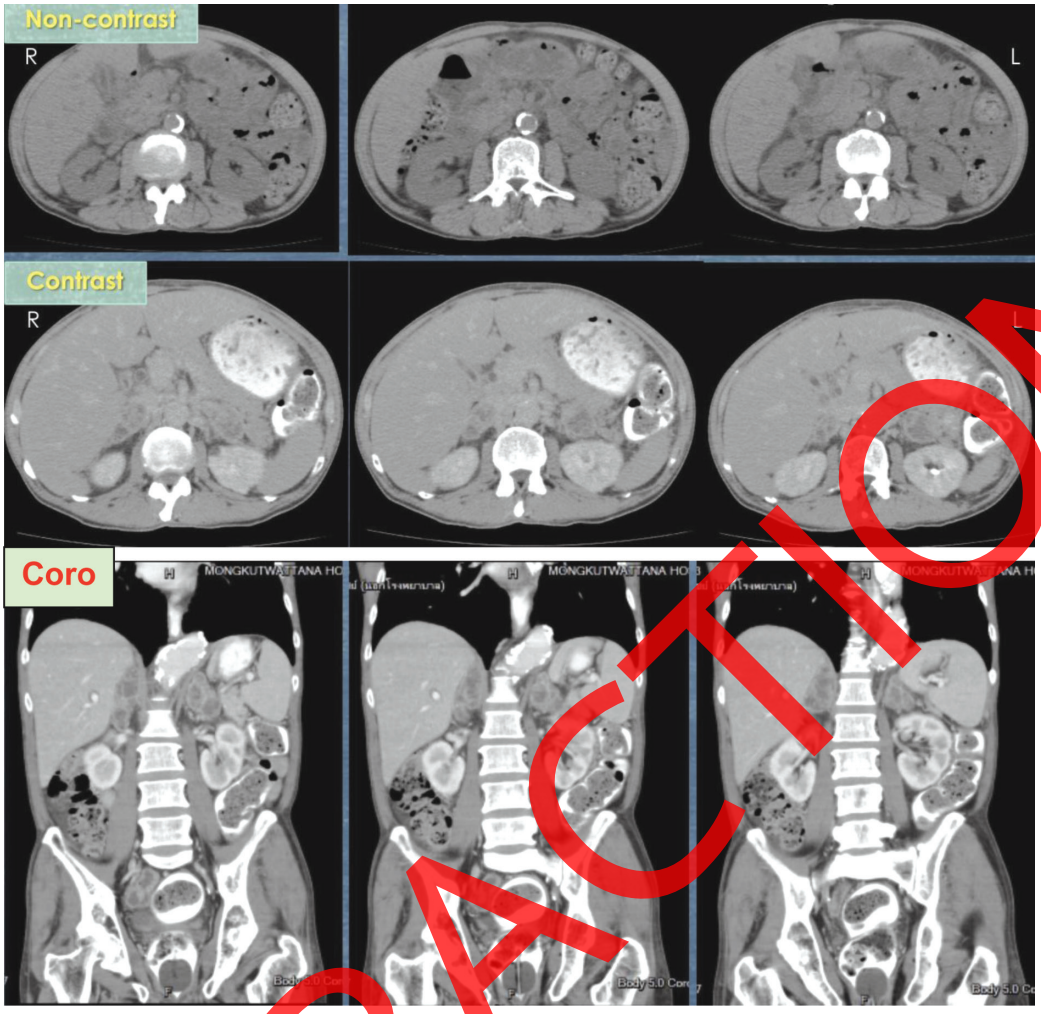

Figure 1 CT scan of the abdomen and pelvis with oral and intravenous contrast. Upper row: the unenhanced image; the middle and lower rows: contrast-enhanced CT scans show enlargement of bilateral adrenal glands with peripheral rim enhancement on the axial (middle) and coronal (lower) views

The biochemical and hormonal data in patients with bilateral adrenal mass are evaluated to compare the differences between adrenal adenomas and other benign lesions and to find the relationship between metabolic parameters and adrenal hormones. We performed an assessment of the production of cortisol in both adrenal glands and autonomous cortisol secretion and found the morning cortisol to be 16.72 ug/dL (normal range, 7 to 28 ug/dL); the one mg overnight dexamethasone suppression test showed cortisol levels of 13.6 ug/dL and 10.70 ug/dL (over 2 times the normal value < 1.8 ug/dL); the midnight serum cortisol level of 1.09 ug/dL; and the 24-hour urine free cortisol for two consecutive days were as shown in Table 1.

Table 1 The results of 24-hour urine free cortisol and urine creatinine tests

	Day 1	Day 2	Normal range
24-hour urine free cortisol (ug/day)	292	230	50-190
24-hour urine creatinine (gm)	0.795	0.593	0.86
24-hour urine vol (mL)	2,700	2,800	

Table 2 The results of 24-hour urine metanephrine, normetanephrine and creatinine tests

	Day 1	Day 2	Normal range
24-hour urine Metanephrine (nmol/day)	571	579	< 1,777
24-hour urine Normetanephrine (nmol/day)	3,962	2,492	< 3,279
24-hour urine creatinine (gm)	0.854	0.802	0.86
24-hour urine vol (mL)	2,500	2,850	

From the above results, it might be concluded that the patient had hypercortisolism and no adrenal insufficiency, but these values still lie within the range of false positives. Because there were no characteristics of Cushing's syndrome, the abnormal examination might be caused by stress from the infection, or there may be other causes instead of Cushing's syndrome, as will be discussed later.

An assessment of the production of catecholamine via the 24-hour urine tests for metanephrine, normetanephrine and urine creatinine is shown in Table 2.

The results in Table 2 show that the 24-hour urine normetanephrine is higher on the first day, but does not exceed two times greater than normal, so it was possible that stress and infection might be the cause of the elevation. Likewise, the signs, symptoms, and radiological examination results did not indicate pheochromocytoma. The patient did not undergo biochemical testing for hyperaldosteronism because of the normal blood pressure.

With these biochemical test results, the prolonged fever and subacute abdominal pain of the patient most likely resulted from infectious diseases. The radiological features with bilateral adrenal enlargement were compatible with tuberculosis and histoplasmosis. However, because the size of the adrenal glands exceeded 6 cm, it was not possible to rule out malignant tumors. The patient therefore underwent laparoscopic left adrenalectomy for diagnostic purposes.

The right lateral decubitus position was used, along with a 10 mm port for the laparoscope, and two 5 mm ports for working instruments. The pathological specimen is shown in Figure 2, showing grossly extensive caseous necrosis, and extensive caseating granulomatous inflammation. On microscopical examination, epithelioid cells were found, including Langerhans giant cells surrounding the necrotic area, with adrenocortical remnants (see Figure 3). A tissue sample was sent for RT-PCR testing for mycobacterium tuberculosis which confirmed the diagnosis.

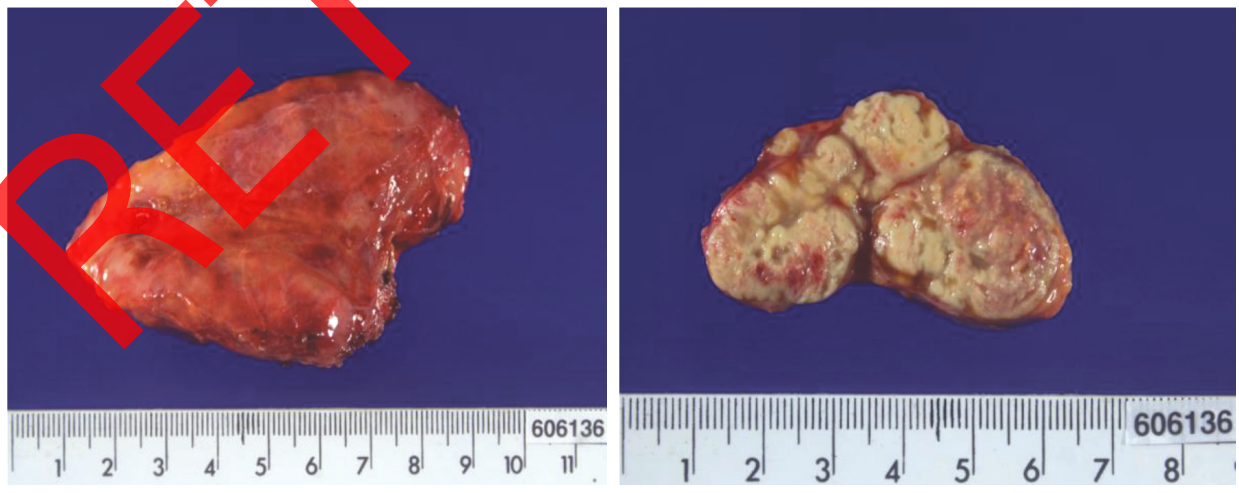

Figure 2 Gross specimen of the left adrenal gland: above, intact surface pathology showing a bulging glandular surface with some adhesion to surrounding soft tissue; below, the cut surface shows extensive caseous necrosis in the central part of the gland

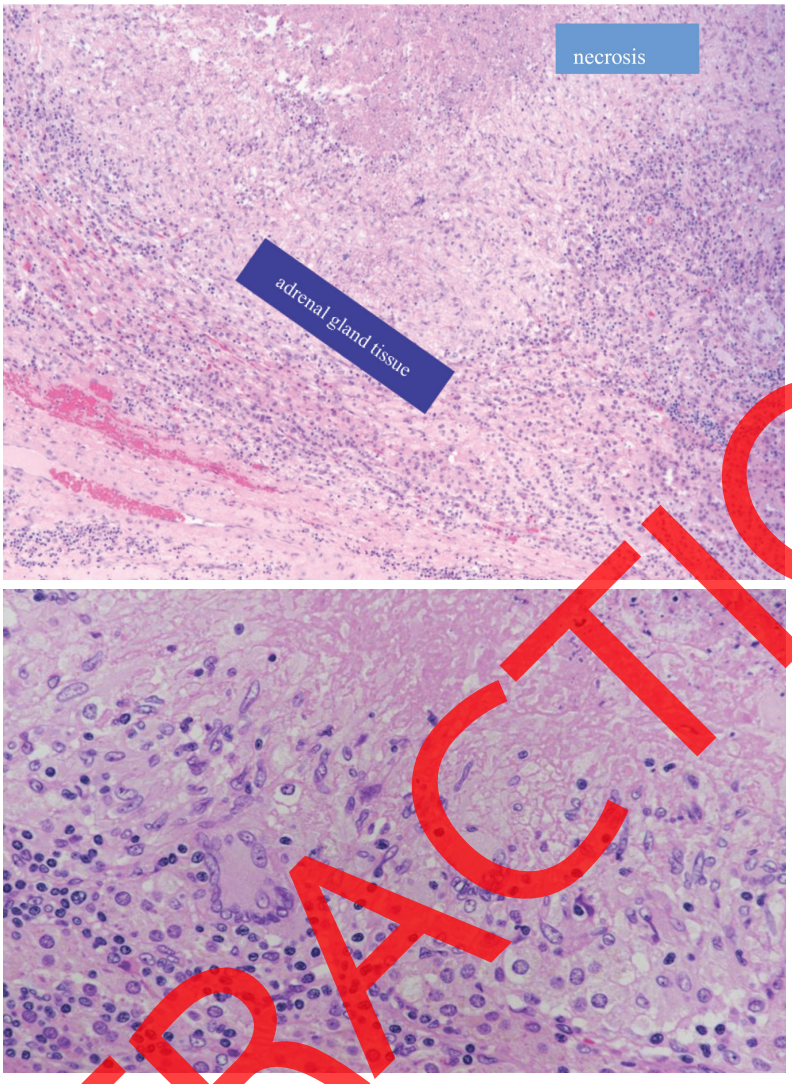

Figure 3 Microscopic examination (Hematoxylin & Eosin): above (10X), extensive necrosis leaving only a thin layer or scattered area of adrenocortical tissue remnants, below (20X), cellular reaction in the lesion including lymphocytes, epithelioid cells and Langhans-type multinucleated giant cells

Based on the pathological and PCR results, it can be concluded that the patient had tuberculosis of the adrenal glands. Treatment consisted of anti-tuberculosis drugs similar to those for pulmonary tuberculosis: Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol for 2 months, followed by Isoniazid and Rifampicin for 4 months, for a total treatment period of 6 months. Follow-up after anti-tuberculosis treatment showed that the patient had improved symptoms without adrenal insufficiency.

Discussion

Primary adrenal tuberculosis accounts for approximately 6 percent of all tuberculosis infections. The mean age of at diagnosis is 61 years1-3 The ratio of male to female patients varies among studies.1,4 Risk factors for tuberculosis include diabetes, steroid medication, cancer, and chemotherapy.[1] Our patient was older than the reported average, but had risk factors including poorly controlled diabetes and the long term use of immunosuppressive drugs. Primary adrenal tuberculosis often presents with symptoms of primary adrenal insufficiency. Symptoms of primary adrenal insufficiency appear when more than 90% of the adrenal glands have been destroyed. Common features of adrenal insufficiency include weight loss, anorexia, nausea, vomiting, lethargy, fatigue, and high grade fever.[2,4,5] One case with abdominal pain was reported from India.[5]

The median duration of symptoms before medical consultation for adrenal tuberculosis is 6 months (range, 0.25 to 92 months).[2-7] However, our patient came for consultation with fever and abdominal pain after only 2 weeks, similar to a case of primary adrenal tuberculosis from Italy.[4] If patients are seen early on in the course of illness, it is possible to provide early diagnosis and care such that adrenal function can be preserved.

Major CT findings in adrenal tuberculosis include bilateral enlargement of the adrenal glands with calcification. When adrenal tuberculosis is active, enhanced CT shows increased enhancement of the periphery of the gland, with the central area showing a lower degree of attenuation. Idiopathic adrenal insufficiency is not characterized by either adrenal enlargement or calcification on CT. According to Guo et al,[5] adrenal gland enlargement on CT is frequently recognized within a year of the disease onset. However, the enlarged adrenals gradually shrink because of fibrosis and calcification.[5] Sun et al[6] identified adrenal gland enlargement on CT images within the first four years after the onset of adrenal gland tuberculosis. In our patient, bilateral adrenal enlargement without calcification was observed. Malignancy cannot be completely excluded by either CT, magnetic resonance imaging (MRI), or positron emission tomography (PET) as bilateral enlargement is also a common finding in malignant lesions.[7,8]

Radiographic features from CT scan depend of the stage of disease. There are two stages. In the acute or recent infection (< 2 years) stage, findings include irregular, central hypodensity, bilateral adrenal enlargement, and peripheral rim enhancement.[3] In the chronic infection stage, findings include adrenal gland atrophy and calcification. The CT findings for our patient showed bilateral adrenal gland enlargement and peripheral rim enhancement, which were compatible with active tuberculosis infection of less than 2 years.

CT findings of bilateral adrenal enlargement could be due to other conditions. In a study of 70 patients with bilateral adrenal gland enlargement, 40% was due to pheochromocytoma, 27% was from adrenal tuberculosis, 10% had primary adrenal lymphoma, 6% was from metastases, 4% had non-functioning adenomas, 4% had primary bilateral macronodular adrenal hyperplasia, and 9% had other conditions such as histoplasmosis.[4] Other radiological characteristics that can help distinguish adrenal tuberculosis from adrenal cancer such as atrophic glands, calcification, and peripheral rim enhancement are often absent.[8]

Every patient with an adrenal incidentaloma should undergo careful assessment for symptoms and signs of adrenal hormone excess.[9] These adrenal tumors may be hormonally active or non-functional, malignant or benign. All patients should undergo biochemical testing for pheochromocytoma, either with plasma or urinary catecholamine measurements. This is particularly important before surgery, which is routinely recommended for tumors larger than 4 cm in diameter, for cases without a clear-cut diagnosis, and for those with increased hormonal secretion or imaging characteristics of malignancy. Hypertensive patients should undergo biochemical testing for hyperaldosteronism. Patients with features consistent with Cushing's syndrome, such as glucose intolerance, weight gain, and unexplained osteopenia should be evaluated for excess cortisol. For the latter, the dexamethasone suppression test and late-night salivary cortisol may be preferred over measurements of urine cortisol.

Adrenal tuberculosis may result in hypercortisolism due functional changes in the hypothalamus-pituitary-adrenal (HPA) axis caused by the cell walls of the mycobacterium, which is a component of lipoarabinomannan (LAM). LAM can stimulate post-inflammatory cytokines such as IL-1β, IL-6 and TNFα, which increase CRH and ACTH secretion from the pituitary gland.[6,10] In addition, stress and poorly controlled diabetes can also contribute to the stimulation of the HPA axis, as was seen in our patient.[6,11-13]

In the present case we chose laparoscopic adrenalectomy for definitive diagnosis. Typically, fine needle biopsy is often performed for the diagnosis of adrenal tumors larger than 4 cm in size, but in our case it was avoided for several reasons. Firstly, the patient's adrenal anatomy was not amenable for accurate image-guided biopsy. Secondly, as the adrenal size was greater than 6 cm, there was a considerable risk of internal organ damage and hemorrhage. Thirdly, CT results showed that the patient's adrenal glands were likely surrounded by necrotic tissue, which could decrease the accuracy of fine needle biopsy. Nirag et al[9] also noted that percutaneous image-based fine needle aspiration of adrenal tumors has incorrect diagnosis rates ranging from 0% to 37%. Mazzaglia et al[10] stated that needle biopsy could be valuable for the diagnosis of metastatic tumors, but is not suitable for differentiating between benign and malignant tumors. A more accurate and safer route for

needle biopsy would be endoscopic ultrasound-guided fine-needle aspiration,[9] but this was not available at our institution. Hence, in our case, laparoscopic adrenalectomy was used to establish a definitive diagnosis.

Treatment for adrenal tuberculosis is based on standard anti-tuberculosis drugs, consisting of isoniazid, rifampicin, pyrazinamide, and ethambutol for 2 months, followed by isoniazid and rifampicin for 4 months, for a total duration of 6 months.[18] If the patient is diagnosed with primary adrenal insufficiency, or is at risk of developing adrenal crisis due to rifampicin increasing cortisol metabolism through cytochrome P450 3A4, it is important to monitor symptoms of adrenal insufficiency, and to adjust steroid dosages accordingly.7,19 The prognosis of adrenal tuberculosis depends on the timing of the diagnosis and treatment. If adrenal insufficiency develops after the treatment, due to atrophy of the glands, it will persist life-long.[19]

Conclusion

Primary adrenal tuberculosis is rare, accounting for approximately 6 percent of all tuberculosis infections. We should be aware of this disease in patients with bilateral adrenal tumors. The disease may cause primary adrenal insufficiency, so early diagnosis and evaluation of hormone function is important. Treatment include anti-tuberculous drugs and surgical intervention when indicated, which can lead to good prognosis and desirable outcomes.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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