

Addison's Disease as Presenting Symptom of Infection with *M. tuberculosis*

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Abstract

Addison's disease due to primary isolated bilateral tuberculous adrenalitis is a very rare clinical entity. Here we describe a patient whose only manifestation of TB-infection was adrenal insufficiency.

Keywords: Addison's disease; Tuberculosis; Adrenal insufficiency

Introduction

In his original paper in 1855 Thomas Addison described the clinical and autopsy findings of 11 patients with adrenal insufficiency [1]. Six of these patients suffered from disseminated tuberculosis (TB). Bilateral destruction of the adrenal glands by Mycobacterium tuberculosis is a well-known cause of Addison's disease, especially in resource limited settings and among HIV-patients. However, Addison's disease as the first and only presentation of active TB infection is rare. Up till now only a few patients presenting with adrenal insufficiency as the only manifestation of TB have been reported in the literature [2].

Case Report

A 66-year old man was referred to our hospital, after having been diagnosed with Addison's disease during his stay in Ireland. He attended the Irish hospital because of weight loss, general fatigue and dizziness. He did not report night sweats, pulmonary complaints or fever. His family history was positive for diabetes mellitus, but not for other auto-immune diseases. Upon presentation, his blood results

were as follows: sodium 130 mmol/l (136-146 mmol/l), potassium 4.7 mmol/l (3.5-5.1 mmol/l), creatinine 112 µmol/l (59-104 µmol/l). Morning cortisol was low and did not rise after ACTH-stimulation, indicating inadequate adrenal function. ACTH levels were not measured. After starting hydrocortisone substitution, he regained his appetite, increased in weight and all his other complaints disappeared.

When he attended our hospital, serum sodium was 131 mmol/l (135-145 mmol/l), so 9-alpha-fludrocortisone was added to his medication. On re-evaluation of his medical history he reported tuberculosis exposition at primary school-age with a positive tuberculin skin test (TST). Follow-up by chest X-ray revealed no abnormalities. He had never been treated for tuberculosis. On physical examination, the patient's skin appeared darkened, which was most prominent on his palmar creases. As autoimmune adrenalitis is thought to be the most common cause of Addison's disease in the western world, auto-immune serology was performed. Anti-TPO and anti-parietal cell antibodies were positive, but autoantibodies against adrenal 21-hydroxylase were negative. As these results did not confirm the diagnosis autoimmune adrenalitis, a CT-scan of the abdomen was performed in search for an alternative diagnosis. The CT-scan revealed bilateral enlarged adrenal glands with calcifications and no other pathology (Figure 1).

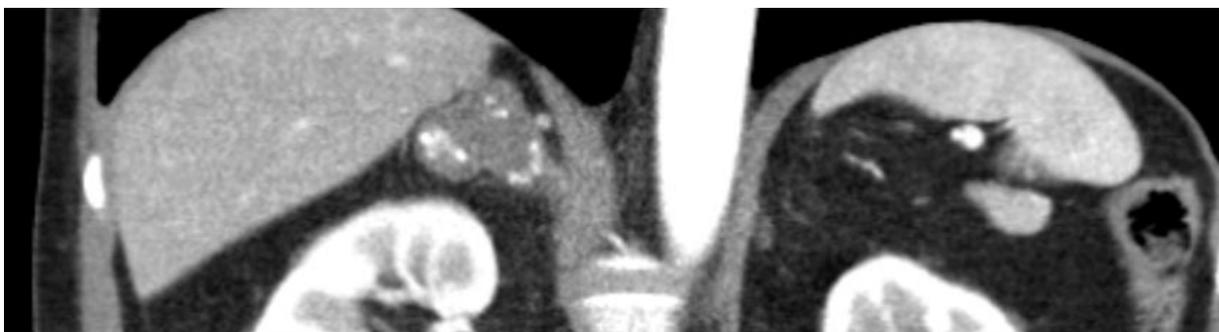


Figure 1: Coronal view of the CT-scan showing an enlarged right adrenal with calcifications

An infectious cause was suspected and the patient was tested for TB, syphilis and HIV. Both the TST and the interferon-gamma release assay (Quantiferon) were positive. The patient tested negative for syphilis and HIV. As these results, taken together with the outcome of the CT-scan, were strongly suggestive for mycobacterial infection of the adrenals, a CT-guided fine needle aspiration of the right adrenal was performed for confirmation. An aspirate of the right adrenal was positive for *M. tuberculosis* DNA, the culture for *M. tuberculosis* turned out negative, which was possibly due to the small sample retrieved from the aspiration. A chest X-ray did not show signs of (active) TB. Taken together, we concluded that the adrenal insufficiency was caused by destruction of both adrenal glands by *M. tuberculosis* infection. Interestingly, no signs of other organ involvement were found.

Discussion

Primary adrenal insufficiency is a rare disorder, with a prevalence of 93-140 cases per million population in the developed countries [3]. At the time of discovery of the disease, infection with *M. tuberculosis* was the most common cause of bilateral adrenal destruction. Nowadays, in the developed world, auto-immune adrenalitis represents the primary cause of Addison's disease, being responsible for 80-90% of the cases [3]. No recent data are available on the incidence of Addison's disease caused by TB. However, as the incidence of TB has declined, the incidence of Addison's disease secondary to it is diminishing. In the developing world however, tuberculous adrenalitis is still the major cause of Addison's disease.

While primary tuberculous adrenalitis is a very rare clinical entity, in a large retrospective study, postmortem examination of 871 patients with active TB, adrenal involvement was seen in 52 patients (6%) [4]. Interestingly in 14 out of these 52 patients, the adrenal glands were the only involved organs. Unfortunately, clinical data on these patients were not reported. It is known that the adrenals are a preferred site for dissemination of *M. tuberculosis* but the pathophysiology of adrenal tropism is not understood. Upto 90% of the adrenals needs to be destructed before patients will demonstrate symptoms of Addison's disease and most cases of adrenal infection by *M. tuberculosis* are diagnosed 10 to 15 years after initial infection [5]. During this period the adrenals are ultimately, mostly irreversibly, destroyed. Upon treatment of TB, recovery of normal adrenal function may occur [6] but usually does not [7,8]. The young age at which our patient was exposed to *M. tuberculosis*, together with the calcification in the adrenals, suggests a total destruction of both adrenals. It is therefore not likely that his adrenal function will recover after treatment with anti-tuberculous chemotherapy.

In our patient, the enlarged adrenals with calcifications, as seen on the CT-scan, was a clue to the final diagnosis. Enlargement of the adrenal glands is often seen in active infection, while small or calcified adrenals are more often found in dormant or remote infection [9-12]. Calcifications of the adrenal glands are suggestive for adrenal TB9; in auto-immune adrenalitis, calcifications are not likely to be found [9,12]. Calcifications of the adrenals also can be found in other diseases, such as histoplasmosis, coccidiomycosis, carcinoma, metastases or hemorrhage and the absence of calcifications does not rule out tuberculous adrenalitis [9]. A positive TST-test and a positive interferon-gamma release assay do not confirm the diagnosis of tuberculous adrenalitis because auto-immune adrenalitis and

tuberculosis can coincide and both tests do not prove an active infection. In a series of patients described by Vita et al., 6 out of 13 patients with proven auto-immune adrenalitis also had evidence of extra pulmonary TB9, emphasizing that the presence of (pulmonary) tuberculosis does not establish the diagnosis of tuberculous adrenalitis. The diagnosis in our patient was confirmed by a positive *M. tuberculosis* PCR of the aspirate obtained via CT-guided fine needle aspiration.

Our patient had enlarged adrenals, suggesting active infection, however the calcifications and the young age he was exposed to TB suggest a remote infection. The negative culture for *M. tuberculosis* of the aspirate suggests remote infection, however, while only a small amount aspirate was obtained, active infection cannot be ruled out. In combination with the knowledge he was never treated for tuberculosis, we therefore decided to treat our patient with anti-tuberculous chemotherapy. Shrinkage of the adrenal glands after over 1 year of anti-TB treatment has been reported [13].

In conclusion, this case shows that tuberculosis continues to be a cause of Addison's disease in the Western World. This case stresses the importance of making a diagnosis in patients presenting with Addison's disease and not relying on absence of symptoms and the suggestion of the most probable (auto-immune) cause.

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