Case Report

Diagnostic and therapeutic approach in a rare case of primary bilateral adrenal tuberculosis

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Here, we report a case of a febrile patient with primary bilateral adrenalitis who was successfully treated with an antituberculous regimen. Primary isolated tubercular adrenalitis is a very rare clinical entity but it should be considered in cases of fever and enlargement of the adrenal glands. Integration of radiological pattern data with epidemiological, clinical and immunological data has high accuracy and specificity, even without histological examination.

Introduction

The evaluation of a patient with fever and adrenal lesions requires differentiation between a variety of pathological conditions, including tuberculosis (TB). Adrenal TB is characterized by a peculiar clinical and radiological pattern, and its diagnosis is difficult to obtain even after biopsy (Lam & Lo, 2001). Here, we report a case of a man with large bilateral adrenal masses and a fever of unknown origin who was successfully treated with an empiric antituberculous regimen.

Case report

A 61-year-old man presented with a 1 week history of high intermittent fever, asthenia and general malaise. The patient had been in good health until 3 months earlier, when he began to have fatigue, low-grade fever and night sweats. A physician prescribed ciprofloxacin for suspected urinary infection, which resulted in the disappearance of the fever. After 3 weeks the patient presented another episode of fever associated with mild upper respiratory symptoms. Ciprofloxacin was given again for other 2 weeks. The fever disappeared, but the patient relapsed a few days after the antibiotic treatment ended and the patient was hospitalized. The patient had always lived in Italy. He worked as a butcher and had never smoked. There was no history of cancer in his family. He had no known risk factors for TB. On admission, his temperature was 38 °C, pulse 90 beats min⁻¹, respiratory rate 22 breaths min⁻¹ and blood pressure 120/70 mmHg. Physical examination revealed only mild cellulitis in his left elbow with moderate

pain. At this site, the patient had a previous trauma caused by a fragment of cow bone. Laboratory tests showed mild leukocytosis and abnormal values for the erythrocyte sedimentation rate and C reactive protein level. Chest X-ray and ultrasound study of his heart and abdomen gave normal results. All blood cultures were negative. Soft tissue infection was considered as the cause of the fever, and empiric therapy with rifampicin (600 mg daily) and ciprofloxacin (500 mg twice daily) was started. The rifampicin treated was stopped after 1 week due to mild hypertransaminasemia. After prompt reduction of the fever and normalization of the inflammatory parameters, the patient was discharged and followed up in a day care centre. Complete resolution of the cutaneous infection was observed and antibiotic therapy was stopped after 3 weeks. One week after the end of the antibiotic therapy, the fever again returned and the patient was readmitted to hospital.

On admission, his temperature was 39 °C, pulse 110 beats min⁻¹, respiratory rate 25 breaths min⁻¹ and blood pressure 130/80 mmHg. Transoesophageal echocardiography was negative. A total body computed tomography (CT) scan was performed and showed enlarged bilateral adrenal masses (6 cm in diameter for both sides). They presented mass-like enlargement and rim enhancement without calcification (Fig. 1a). Magnetic resonance imaging (MRI) of the glands revealed heterogeneous enhancement and colliquative areas without evidence of calcification (Fig. 1b, c). Ultrasound echography examination also confirmed enlarged bilateral glands with disomogeneous patterns and hypoechogenic areas inside. Laboratory studies, bone marrow biopsy, ⁹⁹Tc-scintigraphic whole-body examination, thyroid ultrasound examination and endoscopic studies (oesophagogastrroduodenoscopy and colonoscopy) were negative for infections, malignant metastatic and

Abbreviations: CT, computed tomography; IFN- γ , gamma interferon; MRI, magnetic resonance imaging; TB, tuberculosis.

Fig. 1. (a) Adrenal enlargement with high contrast uptake and rim enhancement demonstrated on CT scan; (b) adrenal enlargement shown on a coronal FS T1 MRI scan; (c) adrenal enlargement shown on an axial FS T1 MRI scan; (d) significant reduction of the volume of the adrenal glands with no pathological contrast uptake on a CT scan after treatment.

primary tumours, and endocrine diseases. Urine cytological examination gave negative results. Blood cultures were negative for both bacterial and fungal pathogens. Serology for cytomegalovirus, Epstein–Barr virus, human immunodeficiency virus, *Bartonella*, *Salmonella*, *Histoplasma*, *Brucella* and *Coxiella* was negative. The tuberculin skin test was negative, but the gamma interferon (IFN- γ) release assay for mycobacterial-specific proteins (Quantiferon-TB Gold; Cellestis) was found to be positive. The clinical condition of the patient quickly worsened and we decided to defer adrenal biopsy considering that radiological findings, positive TB-Gold results and clinical data were strongly suggestive of primary TB localization. Thus, we started empiric antitubercular treatment including rifampicin (600 mg daily), streptomycin (1 g daily), isoniazid (300 mg daily), ethambutol (400 mg three times daily), pyrazinamide (500 mg three times daily). We observed after 2 days an improvement of the patient's general condition with a reduction of inflammatory parameters. After 1 week he showed mild hypertransaminasemia and therapy with rifampicin was stopped not only for this reason but also for the possible catabolic effect of the drug on glucocorticoids. No acute adrenal crisis was observed during therapy and the determined adrenocorticotrophic hormone and cortisol levels were normal during the therapy and follow-up. After 1 month of induction therapy the patient was afebrile without other symptoms. A control CT scan of his adrenal glands and an ultrasound study of his

abdomen documented a relevant reduction of the bilateral adrenal masses (2 cm diameter for both sides) (Fig. 1d). Moxifloxacin (400 mg daily) and isoniazid (300 mg daily) were given as a maintenance anti-TB drug regimen (for 10 months). Another CT and ultrasound of abdomen performed at the end of therapy documented normal sized adrenal glands. Monthly follow-up with ultrasound examination and laboratory parameters was performed until 9 months after the completion of therapy and no relapse of disease was observed.

Discussion

Our patient represents a rare case of bilateral primary adrenal TB without any other organ involvement. Despite a high diagnostic effort, only a presumptive diagnosis was made and it was supported by the prompt and complete response to antitubercular therapy.

Primary tubercular adrenalitis is a rare clinical entity and few cases are reported in the literature. In a systematic review, only 1 case of tubercular adrenalitis out of 370 reports of extrapulmonary TB was observed during a period of 10 years (Edlin, 1978). Adrenal tubercular infection has also been reported as cause of sudden death and as a cause of fever of unknown origin (Ikoma *et al.*, 2004). The diagnosis was often made on autopsy or after adrenalectomy.

Percutaneous biopsy has been proved to be of great value in determining the final diagnosis of adrenal TB, especially when non-diagnostic findings are depicted on CT and MRI scans (Liatsikos *et al.*, 2006). Adrenal biopsy or adrenalectomy was considered in our case, but we decided to defer this procedure because of the rapid aggravation of the clinical picture and of the potential risk of Addisonian crisis. The radiological pattern was crucial to support the diagnosis of adrenal TB infection without a histological examination (Wilms *et al.*, 1983; Guo *et al.*, 2007). In our patient the presence of a pattern characterized by rim enhancement and mass-like enlargement was indicative of an initial involvement of the adrenal glands. During the follow up no sign of calcification was seen in control CT scans and examination of the adrenal function showed it was always within normal range.

Advances in the diagnosis of TB infection have been recently obtained with the development of immunological tests based on the production of IFN- γ by T lymphocytes in response to specific antigens, such as early secreted antigen target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10), which are present in all *Mycobacterium tuberculosis* and pathogenic *Mycobacterium bovis* strains (Menzies *et al.*, 2007; Sauzullo *et al.*, 2008). In the present case, we detected a strong IFN- γ response to mycobacterial peptides as measured by Quantiferon-TB Gold. Although IFN- γ release assays are mainly designed to detect latent TB infection, they could also be useful to support the diagnosis of active TB in selected cases where the diagnosis is difficult to establish with conventional tests.

A prompt clinical and radiological response to antituberculous treatment was seen in our patient. The empiric regimen initially included streptomycin, isoniazid, pyrazinamide, ethambutol and rifampicin. Rifampicin treatment was stopped early due to the development of hypertransaminasemia; in addition this drug could cause the induction of enzymes in hepatic microsomes that increase the catabolism of glucocorticoids (Keven *et al.*, 1998). However, we outline that the patient, in spite of the direct involvement of glands, did not present any sign of a reduction in the plasma cortisol level, such as hypopigmentation, hypotension or dehydration, and values of cortisol and adrenocorticotrophic hormone were normal at the beginning of observation and during follow-up examination.

Taking into consideration the job activity of the patient (he was a butcher), we cannot exclude an infection with *M. bovis*. Reactivation of bovine TB is a risk in people with recent or previous exposure to unpasteurized dairy products. In addition, the IFN- γ assay can potentially detect bovine TB since the antigens used are also present in *M. bovis* (Larsen *et al.*, 2008). This immunological test is actually used for the diagnosis of *M. bovis* infection in

cattle (Buddle *et al.*, 1999). The hypothesis of *M. bovis* infection is also corroborated by the superior virulence *in vitro* of this pathogen, its ability to cause extrapulmonary disease and the difficulty of growing this bacteria in culture (Medina *et al.*, 2006). Pyrazinamide is not active against *M. bovis* and a quinolone antibiotic agent, i.e. moxifloxacin, was used with a completely successful response.

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