CASE REPORT

Tuberculosis as a differential for bilateral adrenal masses in the UK

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SUMMARY

Primary adrenal insufficiency (PAI) is a potentially fatal disease. Adrenal tuberculosis(TB) causing PAI is rare in the developed world. We present a seemingly well, 78-year-old Caucasian woman in the UK who developed adrenal crisis following elective hip surgery. Biochemical tests confirmed PAI and steroid replacement was initiated. Imaging of the abdomen demonstrated bilateral adrenal masses and a fluorodeoxyglucose positron emission tomography (FDG-PET) scan showed increased uptake in both adrenals suggestive of malignancy. Following a retroperitoneoscopic left adrenalectomy, histology showed caseating necrosis with xanthogranulomatous inflammation favouring a diagnosis of TB. She was commenced on anti-TB treatment. Diagnosing adrenal TB in the west can be challenging especially in the absence of extra-adrenal TB. FDG-PET scans can be falsely positive in presence of chronic active inflammatory conditions, such as TB, and a tissue diagnosis is required. It is important that clinicians remain vigilant of this important disease, which can masquerade as malignancy.

BACKGROUND

Primary adrenal insufficiency (PAI) is a potentially fatal disease if not recognised and managed appropriately. Tuberculosis (TB) of the adrenal gland is an important aetiology of PAI and accounts for the majority of patients with PAI in the developing world.[1] In 2016, WHO estimated that the European region accounted for only 3% of the TB burden in the world.[2] Autoimmune adrenal disease is the most common cause of PAI in the west and tuberculous adrenal disease is rarely encountered.[3–5] Adrenal TB especially in the absence extra-adrenal disease can be difficult to diagnose and may be mistaken for adrenal haemorrhage or malignant diseases, such as lymphoma and metastases. Fluorodeoxyglucose positron emission tomography (FDG-PET) scans can become falsely positive due to underlying chronic inflammation and pose as a red herring indicating possible malignancy. Therefore, definitive histological diagnosis is required to prevent misdiagnosis. We wish to highlight the importance of clinicians being vigilant of this important disease, which can masquerade as malignancy causing diagnostic pitfalls.

CASE PRESENTATION

A 78-year-old Caucasian woman was admitted to the intensive care unit (ICU) for presumed sepsis, low blood pressure and hyponatraemia following complications of elective hip surgery for degenerative arthritis. Investigations showed low cortisol levels and she recovered following treatment with glucocorticoid replacement, antibiotics and supportive care.

Prior to the hip surgery, she was apparently well. There had been no recent onset weight loss, loss of appetite or fever. She had not noticed any pigmentation of skin. Her history was significant for community-acquired pneumonia in the previous year. Subsequent chest imaging did not show any residual disease. She has had no history of TB, but did report having a 'bad chest' for some time during her childhood. There was no history of autoimmune disease, brain tumours or cerebral irradiation. She had not been on any oral, inhalational or local steroids. She recalled travelling in Africa for a brief period during the 1960s. On examination (2 months after recovery from hips surgery), she appeared remarkably well. There was no skin pigmentation or lymphadenopathy and her chest and abdominal examination was unremarkable.

INVESTIGATIONS

Investigations during her acute illness revealed a low cortisol level of 29 nmol/L at 15:00. Subsequent short Synacthen test showed a baseline cortisol of 14 nmol/L at 09:50 with a rise to 16 nmol/L after 30 min (normal value of >430 nmol/L). The adrenal corticotropic hormone levels at this time was 61.6 ng/L (normal value of <46 ng/L) favouring a diagnosis of PAI. She had low aldosterone levels of <50 pmol/L (normal value up to 630 pmol/L) and high renin levels of 12.3 nmol/L/hour (0.3–2.2 nmol/L/hour). Adrenal antibodies were negative. An unenhanced CT scan showed bilateral indeterminate appearing adrenal lesions with the left measuring 20 mm with 29 HU and the right measuring 16 mm with 17 HU (figure 1). MRI scan done on the adrenals was normal. A whole body FDG-PET scan done subsequently showed increased uptake in both adrenal glands (standard uptake value (SUV) max 8.5) suggestive of malignancy (figure 2). There were no other hot spots suggestive of a primary lesion in the FDG-PET scan.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for the aetiology of PAI was thought to be metastatic adrenal deposits, lymphoma, granulomatous disease or bilateral adrenal haemorrhage. At this stage, a histological diagnosis was required to plan definitive therapy.

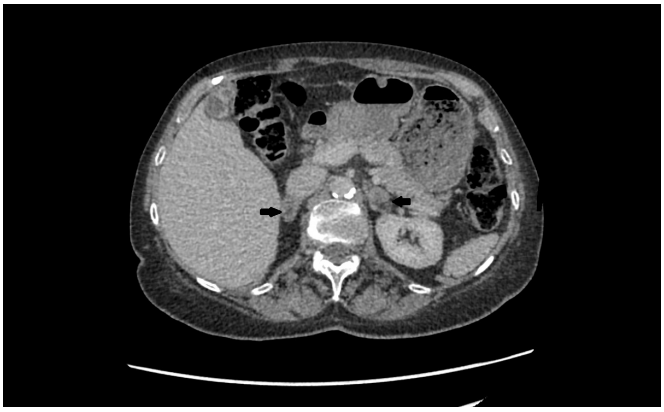

Figure 1 Unenhanced CT image of adrenals showing bilateral indeterminate adrenal lesions. Left adrenal measuring 18 mm and right adrenal measuring 12 mm.

Fine needle aspiration cytology of the adrenal was considered, but difficulty in accessing the adrenal and chance of inadequate sampling prompted a diagnostic adrenalectomy. During surgery, the left adrenal was not clearly identified and appeared to be replaced entirely by a fibrotic, nodular lesion adherent to the overlying peritoneum and the upper renal polar vessels. The left adrenal was excised and histology revealed caseous necrosis with xanthogranulomatous inflammation pointing to a diagnosis of TB (figure 3). However, Ziehl-Neelsen stain for acid-fast bacilli, cultures and PCR for TB as well as QuantiFERON-TB Gold assay were all negative as were her retroviral screening, serology for histoplasmosis and inflammatory markers. A likely diagnosis of adrenal TB causing PAI was made.

TREATMENT

She was commenced on hydrocortisone and fludrocortisone replacement once the diagnosis of adrenal insufficiency was made in the ICU. Following the definitive diagnosis of TB, a 6-month course of anti-TB medication was started. The dose of hydrocortisone was increased as rifampicin causes accelerated cortisol metabolism by induction of Cytochrome P450 3A4 (CYP3A4) in the liver.

OUTCOME AND FOLLOW-UP

She is at present tolerating her medication well and will be monitored for possible drug side effects.

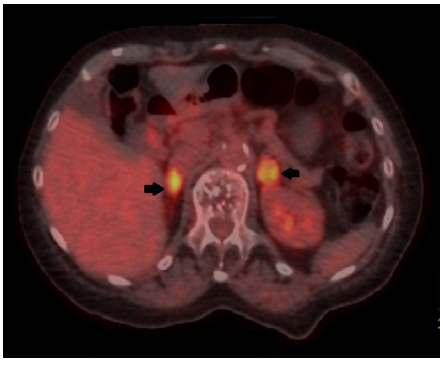

Figure 2 FDG-PET CT scan axial images showing hot spots in bilateral adrenals. FDG-PET, fluorodeoxyglucose positron emission tomography.

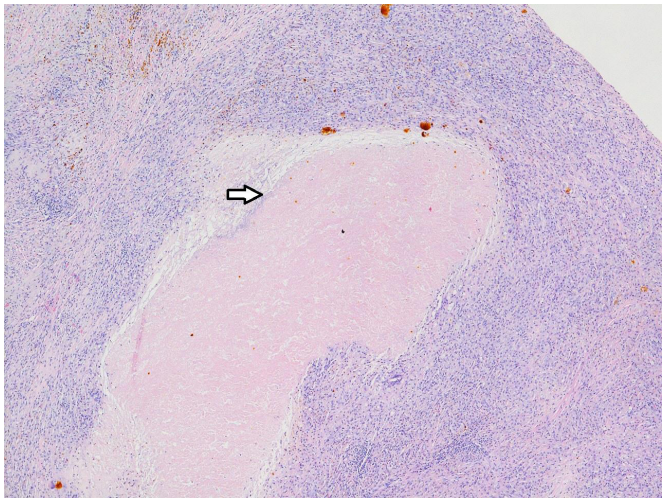

Figure 3 Histology of left adrenal showing caseating granuloma with surrounding chronic inflammatory cells.

DISCUSSION

PAI is a life-threatening disease with inadequacy of glucocorticoid production. This manifestation requires at least 90% of the adrenal gland to be destroyed.[6] Since the first description of Addison's disease in 1855 by Thomas Addison, TB of the adrenal gland has noted to be an important aetiology in PAI.[7] Six of eleven patients described by Addison had TB of the adrenal gland. Although its incidence has a declining trend following the introduction of anti-TB drugs, it is still the most common cause of PAI in the developing world.[1] However, the aetiology of PAI has changed in the west. European studies have shown autoimmunity to be the cause of PAI in 44.5%–94% of these patients while TB and other aetiologies amounting to up to a third of cases.[3–5 8] Apart from TB, histoplasmosis, blastomycosis and various human immunodeficiency-related infections are other rare causes of infectious adrenal enlargement in the west.[9 10]

The symptoms of adrenal insufficiency are often non-specific and include weakness, fatigue, loss of weight, abdominal pain, nausea, vomiting, musculoskeletal pain, hypotension, and so on. This often causes a delay in diagnosis and patients may present with life-threatening adrenal crisis.[11] It is reported that almost 92.9% of patients with adrenal TB have had previous TB in lung or pleura.[12] The onset of PAI in these patients is after a mean±SD duration of 32±15 years when most of the adrenal gland has been destroyed.[12] Therefore, these patients often present later in life.

Diagnosis of TB is difficult especially in the absence of extra-adrenal disease. Bilateral adrenal involvement is more common and seen in almost 80% of cases.[13] This may be because the adrenals can be susceptible to infection by tuberculous bacilli from haematogenous or lymphatic spread from the primary infection. Pathological changes in adrenal TB include tuberculous granuloma, caseous necrosis, fibrosis and calcification. Typical features of adrenal TB on CT scans are enlarged glands, calcifications with peripheral enhancement and low central attenuation. During the early stages of disease, the adrenals may appear enlarged on imaging. However, the adrenal contour may be preserved.[14 15] Later on, the enlarged adrenals lessen or normalise in size due to the increase in fibrosis and calcification. They can then become atrophied with the glandular tissue almost completely replaced with fibrous tissue.[16] As a general rule, enlarged adrenals suggest early TB and active disease, while small, atrophic adrenals indicate chronic long-standing disease.[17]

Patient's perspective

From my point of view, the problem with my adrenal glands has to been seen in the context of the additional medical and social issues, such as general weakness, broken metatarsals in the left foot, urinary and mobility problems, which have confronted me since the beginning of 2018. Because I am not used to it, becoming ill and less active has been a great shock. It has been a very difficult year with many ups and downs.

On 12 January 2018, I had an operation to replace my right hip under the National Health Service at a private hospital in Sheffield. Although I felt well before the operation, afterwards I did not seem to be making a recovery and was transferred to the intensive care unit (ICU) at the Northern General Hospital (NGH) in Sheffield. I have great friends, a supportive church community, but no family in Sheffield. My two children were sent for as I was very ill, developing meningitis and pneumonia among other complaints. The medical staff and the hospital chaplaincy were very supportive to me and my children.

I was later transferred to a ward in the NGH, where because I was so weak, I struggled to get on my feet. The physiotherapists gave me confidence, and later I was able to stand, to walk a short distance with a walking frame and then to use two crutches. The hip replacement was successful but my recovery has been hampered by my stay in ICU and subsequent medical problems and hospital admissions. While I was in NGH, an adrenal deficiency was diagnosed and I was referred to the endocrine department and prescribed hydrocortisone.

Because I live alone in a terrace house up to three very steep hills, with steep stairs and an upstairs toilet, it was difficult for me to return home. Ultimately, I went to a residential care home near where I live for respite arriving on 15 February. It proved difficult and frustrating to contact the community physiotherapist and the OT but ultimately aids were installed in my house, carers appointed and I returned home on 09 April.

Two days later, I had an appointment at the Royal Hallamshire Hospital in Sheffield and blood was taken at the endocrine unit for testing. Later that evening, alone in my house, I was telephoned by someone (I believe from the haematology department) who informed that I should go immediately to the medical assessment unit at NGH as my potassium levels were too high. I was extremely distressed by this as I had only just got home after 2 months. I sat on a chair in the unit until about 02:30 and then was finally admitted to a ward. The potassium levels were reduced but a CT scan showed 'lesions' on my adrenal glands.

I had a further positron emission tomography scan, which showed tumours on both adrenal glands; although an MRI scan of the liver and spleen showed no abnormality.

At that point, there appeared to be differing opinions among the doctors as to the best course of action, which added to the uncertainty.

On 10 May, my daughter came to Sheffield with her family and on 12 May, I was ill at home with urine and chest infections. When the out-of-hours doctor called and prescribed antibiotics, we increased the hydrocortisone.

On 29 May, accompanied by a friend, I was seen at the Royal Hallamshire hospital and was informed that the tumours in the adrenal gland might be cancerous and therefore, I needed removal of the left adrenal for a definite diagnosis. I found this very upsetting and spent some time in the hospital chapel talking to the chaplain. My children were extremely worried

Continued

Patient's perspective Continued

and the wait, until the operation took place on 19 July, was an anxious time.

After discharge from hospital, I spent a short time at the care home, where I had a chest infection necessitating further antibiotics and then returned home on 04 August. My daughter and her family returned to Sheffield on 07 August, and she was able to attend my appointment at the Royal Hallamshire on 16 August, where I was told that analysis of the adrenal gland showed that I had tuberculosis (TB) and I was prescribed medication, which we are introducing in stages.

My children were delighted that the TB is treatable but at the time, I was too overwhelmed by yet another chapter in the long sequence of medical events to think very clearly.

Since then I have reassessed the 6-month overland journey I made accompanied by a friend from Zimbabwe (then Southern Rhodesia) to the UK in my early twenties in 1964, passing through Africa, the Near East, Turkey and finally Europe. Throughout the journey, we hitch-hiked or travelled on cheap local transport. Sometimes, the travelling was very rough especially through Sudan, and I cannot now believe that I was not exposed to TB on this adventure. I was born in the UK but immigrated to Southern Rhodesia in about 1961 when I was 21 or 22. I only started working as a social worker in 1968 after I returned to the UK and completed my training. I cannot remember having the BCG as a child, a teenager or young woman but this may be a lapse of memory.

I am grateful for the care I have received from Sheffield Teaching Hospitals and hope that the medication I have been prescribed will not cause too many side effects.

However, CT or MRI imaging cannot differentiate between other adrenal pathologies, such as malignancy, haemorrhage and fungal infections.

With the increasing use of functional imaging modalities, such as FDG-PET scans, it is important to note the pitfalls that may arise when diagnosing diseases of the adrenal gland. PET/CT is used to diagnose adrenal malignancy as it takes in to account the biochemical differences between benign and malignant cells. FDG is an analogue of glucose taken up by tumour cells. However, FDG is not cancer-specific and false positives can arise in areas with active infection or inflammation.[18–20] In India, where TB accounts for almost one-third of the global burden, a positive PET scan is considered a common cancer mimic.[21] Although an SUV on a PET scan of greater than 2.5 is attributed to malignant process, tuberculous lesions have shown high SUV values almost 10 times as high as this.[22 23]

Around 12% of patients with adrenal TB will have no evidence of active extra-adrenal disease and require biopsy to prove tuberculous involvement of the adrenals.[24] Fine needle aspiration may be performed in adrenal lesions more than 4 cm in size. However, they may be inaccurate in up to 37% of patients.[25] Endoscopic ultrasound (EUS)-guided fine needle aspiration is regarded to have better yield and less side effects compared with percutaneous aspiration.[26] Given the small size of the adrenal lesions and the anticipated difficulty in getting a good sample via a EUS biopsy, it was decided to proceed to surgery in our patient.

Conclusive diagnosis of extrapulmonary TB (EPTB) can be difficult due to its paucibacillary nature. Many cases of EPTB will not have direct lung involvement. Therefore, diagnostic methods aimed at demonstrating the mycobacterium have low sensitivity

and histopathology is considered the method of choice in diagnosing the disease.[27] In endemic countries, caseating granuloma is considered as TB and treated. However, rare fungal diseases, such as histoplasmosis, may result in similar histological features and in such cases, careful clinical judgement is needed in making a diagnosis.[27]

Several cases have been reported in the western world in the recent past.[28–30] Del Borgo *et al* reported a patient with prolonged febrile illness and bilateral adrenal masses diagnosed with acute tuberculous adrenalitis successfully treated with anti-TB medication. The patient did not develop adrenal insufficiency throughout his illness and follow-up.[28] Most other cases presented with constitutional symptoms and were found to have PAI due to adrenal TB. The presentation of our patient is rare as she had been seemingly well until adrenal crisis was provoked by surgical stress. In the absence of a relevant history or other features of TB and the pitfalls of modern imaging, a definitive diagnosis was elusive until after surgery. It is important that although TB is rare in this part of the world, clinicians remain vigilant of the disease.

Learning points

- Adrenal insufficiency due to tuberculosis (TB) is rare in the western world.
- Patients with adrenal TB can present with life-threatening adrenal crisis.
- Diagnosing adrenal TB is difficult and may require adrenal biopsy or excision especially in the absence of extra-adrenal disease.
- Fluorodeoxyglucose positron emission tomography scans can be falsely positive in the presence of TB.

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