Lesson of the Week

Bilateral adrenal masses

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Bilateral adrenal enlargement is often the result of disseminated malignant disease, and this diagnosis is particularly likely to be considered in a patient with severe weight loss. We describe such a patient in whom bilateral adrenal masses, visualised by computed tomography (CT), were the result of disseminated histoplasmosis occurring at least 20 years after the original infection.

Case history

A 74 year old woman had been unwell for three months with anorexia, nausea, upper abdominal pain, headache, low back pain, and 20 kg weight loss. She was born in Calcutta and at the age of 37 settled in London, remaining in Britain with the exception of a six month visit at the age of 54. She was lethargic, blood pressure was 100/60 mm Hg, and she had epigastric tenderness. Haematological concentrations were: blood urea 8.6 mmol/l (52 mg/100 ml), plasma creatinine 120 µmol/l (1.4 mg/100 ml), sodium 129 mmol(mEq)/l, potassium 4.5 mmol(mEq)/l, albumin 27 g/l, and globulin 43 g/l. Alkaline phosphatase activity was 320 IU/l, aspartate transaminase activity 57 IU/l, haemoglobin concentration 17.2 g/dl, white cell count $3.9 \times 10^9/l$ (19% lymphocytes), and erythrocyte sedimentation rate <1 mm in first hour. The chest radiograph was normal and abdominal ultrasound showed an enlarged liver with increased echo pattern, compatible with metastases or cirrhosis. Ultrasound also detected a 5 cm retroperitoneal mass in the region of the splenic hilum, probably of pancreatic or lymph node origin. Endoscopy showed a hiatus hernia with oesophagitis; barium enema appearances were normal.

Liver biopsy showed non-specific changes. One month after presentation she was confused and oedematous and her supine blood pressure was 80/60 mm Hg. Abdominal CT scan confirmed the hiatus hernia and showed fatty infiltration of the liver and large adrenal masses consistent with secondary deposits in both adrenal glands (fig 1). Blood urea concentration was 2.6 mmol/l (16 mg/100 ml), plasma sodium 132 mmol/l, potassium 2.7 mmol/l, albumin 19 g/l, globulin 46 g/l, and bilirubin 33 µmol/l (1.9 mg/100 ml); serum enzyme activities were: alkaline phosphatase 741 IU/l, aspartate transaminase 76 IU/l, and γ-glutamyltransferase 224 IU/l. Although random plasma cortisol concentrations were raised (770-810 nmol/l; 28-29 µg/100 ml), progressive hypotension suggested adrenal failure and she was treated with parenteral dexamethasone, fludrocortisone, and saline. CT guided biopsy of an adrenal gland could not be performed because the blood pressure failed to improve and the prothrombin time was prolonged (ratio 1.5). Despite continued management of adrenal failure hypotension persisted and she died.

Patients with adrenal masses and adrenal failure caused by chronic disseminated histoplasmosis may have symptoms and CT findings indistinguishable from those of malignancy

At necropsy both adrenal glands were replaced by 4-5 cm diameter friable, yellow brown, partly necrotic masses resembling metastatic deposits. In addition, lung hilar nodes were enlarged and there were several rounded white areas 0.1-0.5 cm diameter in the renal parenchyma. Histologically there was little residual glandular tissue in the adrenals, which consisted of collections of macrophages and lymphocytes around areas of caseous necrosis. Within macrophages and the necrotic areas were numerous yeast like fungal organisms (fig 2). The hilar nodes from the lung showed an identical picture, and the pale areas in the kidney consisted of caseous granulomas and fungal organisms. The organisms were rounded and had a uniform size (approximately 4 µm diameter). There were no larger forms and they stained with methenamine silver (Grocott's modification) but were mucicarmine negative. The lack of larger forms made a diagnosis of blastomyces or cryptococcus infection unlikely, the latter also being excluded by the negative mucicarmine test. The positive methenamine silver stain ruled out leishmania infection. The organisms were considered to be *Histoplasma capsulatum*. This was further supported by a strong reaction obtained by indirect immunofluorescence labelling with histoplasma antisera and absence of staining with antisera to other yeasts (cryptococcus, candida, blastomyces). Review of the liver biopsy sample taken during life showed a single yeast like organism in a Kupffer cell but no evidence of liver disease was found at necropsy.

FIG 1—CT scan showing fatty infiltration of liver and massive bilateral adrenal masses.

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Discussion

Histoplasmosis is due to a dimorphic saprophytic fungus that grows well in soil fertilised by bird excreta. In endemic areas of the United States, Africa, and Asia up to 90% of people have positive reactions to skin testing with histoplasmin. Most infections are acquired by the inhalation of spores of *H capsulatum* and are asymptomatic, but large aerosol inhalations produce an acute self limiting illness with patchy pneumonitis and hilar lymphadenopathy. Chronic progressive pulmonary disease and acute or chronic forms of disseminated histoplasmosis are unusual and often associated with abnormal host defence mechanisms.¹ Dissemination occurs in 70% of asymptomatic cases—to lymph nodes, liver,

FIG 2—Macrophages from destroyed adrenal gland containing intracytoplasmic *Histoplasma capsulatum* (arrowed). Haematoxylin and eosin $\times 1000$ (original magnification).

spleen, kidney, and lung and less often to brain, eye, adrenal glands, and skin. Immunity develops over three months, the foci of infection heal, and granulomas or calcified areas are formed. In a minority the disease remains active, affecting one in 2000 infected cases in epidemics² to one in 500 000 in areas where the disease is endemic.¹ It affects the reticuloendothelial system and produces a wide range of disease, which is usually fatal if untreated. Acute disease often affects the young, with fever, cough, weight loss, diarrhoea, vomiting, enlarged liver and spleen, haematological abnormalities, and abnormal chest x ray appearances. Chronic disease affects adults; here infection tends to be focal with granulomatous oropharyngeal ulceration, gastrointestinal lesions, osteomyelitis, meningitis, or adrenal failure, and calcified scars may be visible radiologically in lung, liver, or spleen.¹

The disease has rarely been acquired in Britain^{3,4} but there are 13 reported cases of chronic disseminated disease that have been imported.^{5,7} Ten of these patients died, and in eight of 10 necropsies disease had spread to the adrenals. Our patient shows the diagnostic difficulties that this unusual condition presents, particularly in non-endemic areas. The infection lay dormant for at least 20 years before the insidious onset of ill health. Symptoms of lassitude, severe loss of appetite and weight, and the absence of fever or a raised sedimentation rate suggested a diagnosis of malignancy. This view was strengthened by the CT picture of bilateral adrenal masses. Persistent hyponatraemia and the onset of hypotension suggested adrenal insufficiency but despite treatment the blood pressure failed to improve.

Adrenal disease in histoplasmosis ranges from isolated cortical foci of parasitised macrophages to a more generalised infection with extensive infarction, caseation, and massive swelling of underlying adrenal tissue.^{1,5,8} The latter change is associated with adrenal insufficiency, but the antemortem diagnosis of adrenal failure is difficult.⁵ This case shows that the CT and macroscopic appearances are indistinguishable from carcinoma. Such findings may become more frequent with improved imaging techniques,⁹ and they

emphasise that histological evidence is always required before attributing such appearances to malignant disease. Adrenal biopsy will differentiate malignant, mycotic, or tuberculous causes of adrenal enlargement.

In endemic areas it has been considered that reinfections are the cause of the late appearance of disseminated disease. These British cases, however, support the view that waning immunity, with time, may precipitate the reactivation of quiescent foci of yeasts lying in macrophages. In this case we suspect that the initial infection occurred in India before age 37 or at age 54 (1964), as that country is known to be a reservoir for the infection and acquisition of the disease in Britain has been reported in only two cases.^{3,4} Histoplasmosis must be remembered as a cause of bilateral adrenal masses and adrenal failure, often occurring many years after infection. Similar, sporadic cases will continue to appear throughout the world. Chronic disseminated histoplasmosis with adrenal masses is therefore a prime example of an uncommon, unpredictable, but curable disease, the symptoms and CT appearances of which are indistinguishable from malignant disease. However closely the macroscopic appearance of tissue resembles tumour, histological diagnosis should be considered, although positive fungal serology (including histoplasma) may avoid this.

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A healthy 5 year old boy had a urinary infection that responded to antibiotic treatment. Subsequently he had a renal sonar test that showed a scar at the lower pole of the right kidney. A renal scan has been recommended. Is this really necessary and what does the test involve?

A renal sonar test is a good, non-invasive test in experienced hands and can show not only kidney scars but also dilatation of the ureters, bladder capacity, and post-micturition residue. The reliability of the test is directly related to the skill and experience of the operator. The kidneys and ureters should be assessed with the bladder full and a plain x ray picture of the abdomen should be taken at the same time to show renal calculi and spinal lesions.¹ Isotope scanning necessitates an intravenous injection either of technetium labelled diethylene triamine pentacetic acid (^{99m}Tc DTPA) or di mercapto succinic acid (^{99m}Tc DMSA). ^{99m}Tc DMSA provides information about the shape and size of the renal cortex, and provides objective evidence of renal scarring. A dynamic 30 minute study after the injection of ^{99m}Tc DTPA will show the size, shape, and relative function of each kidney and provide information about the pelvicaliceal system, ureters, and bladder. Observations during micturition can show vesicoureteric reflux, and blood samples at two and four hours will enable glomerular filtration rate to be measured.² Although this test is not essential to management it provides much valuable baseline information.—K VERRIER JONES, consultant paediatric nephrologist, Cardiff.

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