A CASE FOR DIAGNOSIS

A 62 year old diabetic with weight loss and lung lesions


Case history

A 62 year old retired paratrooper was referred by his general practitioner with new onset diabetes and a 13 year history of hypertension, which had recently been difficult to treat. He complained of frequent headaches, ankle swelling, thirst and urinary frequency. Previously, he had received various antihypertensive treatments, including diuretics, β-blockers, calcium channel antagonists, and angiotensin-converting enzyme (ACE) inhibitors. He was currently taking prazosin 1.5 mg and bendrofluazide 5 mg daily. He smoked 20 cigarettes·day⁻¹, and had been diagnosed as suffering from chronic obstructive pulmonary disease, for which he took inhaled salbutamol as required. His alcohol intake was 80 g·week⁻¹.

On examination, the only abnormal findings were a blood pressure of 190/110 mmHg, and mild pitting oedema of both ankles. Fundoscopy showed grade I hypertensive changes, and his urine tested positive for glucose only. Initial investigations showed a normal full blood count, sodium 140 mmol·L⁻¹, potassium 2.6 mmol·L⁻¹, urea 6.2 mmol·L⁻¹, creatinine 71 µmol·L⁻¹. Random serum glucose was 12 mmol·L⁻¹, and the major fraction of glycosylated haemoglobin (HbAIC) 10.2% (normal range up to 5.9%). Chest radiography showed a small left-sided pleural effusion. A resting electrocardiogram (ECG) indicated left ventricular hypertrophy, and an echocardiograph revealed moderately good left ventricular function, with normal valves.

A diagnosis of diabetes mellitus was made, and dietary treatment initiated. When this failed, gliclazide 80 mg b.d. was added. The patient’s hypertension was treated with bendrofluazide 2.5 mg and enalapril 10 mg daily, and the hypokalaemia was corrected with Sando-K.

On review 1 month later, blood sugars were still high, HbAEc was still 10.2%, and blood pressure 170/100 mmHg. Because of tiredness, general malaise and weakness, the patient was then prescribed twice daily insulin.

After another month, the patient returned complaining of weight loss and depression. Oral candidiasis, balanitis, and generalized pigmentation were now apparent. The ankle oedema was much worse, and a proximal myopathy was noted. Hypokalaemia was still present. Tests were performed and gave the following results: Random cortisol, 2,000 mmol·L⁻¹ (normal <800 mmol·L⁻¹); high dose dexamethasone suppression test, no suppression; adrenocorticotropic hormone (ACTH), 161 ng·L⁻¹ (normal <100 ng·L⁻¹); computed tomography (CT) of the pituitary gland, partially empty sella, no mass lesion; CT of the abdomen, a 1 cm mass in the right adrenal gland, otherwise normal.

Figure 1 shows the chest radiograph taken 2 months after initial presentation. A percutaneous lung biopsy was performed (fig. 2). Treatment was commenced, and a further chest radiograph taken 6 weeks later (fig. 3).
CASE FOR DIAGNOSIS: DIABETES, WEIGHT LOSS AND LUNG LESIONS

BEFORE TURNING THE PAGE: INTERPRET THE FIGURES. WHAT TREATMENT SHOULD BE GIVEN? SUGGEST A UNIFYING DIAGNOSIS. WHAT WOULD YOU DO NEXT?
Interpretation of the radiograph, CT and histology

The posteroanterior (PA) chest film (fig. 1) shows multiple cavitating lesions in both lung fields. The lung biopsy (fig. 2) shows well-stained fungal hyphae invading the lung parenchyma. A number of fungal infections would produce this picture, including mucormycosis and aspergillosis. Subsequent culture yielded Aspergillus fumigatus. The fungal pneumonia responded to i.v. amphotericin, and oral fluconazole.

The second chest film (fig. 3) shows resolution of the lesions, but a left-sided pleural effusion and consolidation of the lingula, with loss of volume.

Interpretation of laboratory tests

The very high random cortisol and high ACTH level suggests Cushing's syndrome. This is confirmed with the high-dose dexamethasone suppression test. The pituitary CT scan, as suspected, shows no evidence of a pituitary cause for Cushing's syndrome.

DIAGNOSIS: "Cushing's syndrome with secondary hypertension and diabetes mellitus. Invasive aspergillosis".

Treatment and clinical course

Treatment with metyrapone was initiated and resulted in normalization of serum cortisol levels. Repeat CT scan confirmed the impression from the chest radiograph (fig. 3) that the lesions had resolved, but showed collapse of the lingula, with left hilar lymphadenopathy. Bronchial carcinoma was strongly suspected.

Because of the patient's poor clinical condition and the CT findings of an adrenal lesion, bilateral adrenalectomy was undertaken, in order to cure his Cushing's syndrome and obtain a firm histological diagnosis of malignancy. Histology revealed bilateral deposits of metastatic bronchial carcinoid tumour. The patient was discharged home in June 1995 on steroid replacement, but died 3 months later. No postmortem was performed.

FINAL DIAGNOSIS: "Cushing's syndrome secondary to bronchial carcinoid, with metastatic spread".

Discussion

Despite intensive investigation, including blood cultures, auto-antibodies, and antineutrophil cytoplasmic antibodies (ANCA), it was only when a percutaneous lung biopsy was performed that the diagnosis of invasive aspergillosis became clear. A. fumigatus is a ubiquitous fungal pathogen, spread by airborne spores; these are present all year round but especially in the autumn. Several distinct diseases exist. Colonization may be found in patients with chronic lung disease. Allergic bronchopulmonary aspergillosis usually occurs in atopic individuals, and results from endobronchial growth of the fungus and the ensuing type I and III hypersensitivity reactions. Reversible airways obstruction, fleeting pulmonary shadowing, bronchiectasis, and fibrosis may all be found. There is an associated peripheral eosinophilia, positive skin-prick test, and precipitin formation. Alternatively, an aspergilloma may form within an existing cavity. This produces few symptoms, but may lead to massive pulmonary haemorrhage. Invasive aspergillosis is usually found in immunocompromised hosts, such as those with leukaemia, collagen vascular disease, or immunosuppressive regimens. The fungal spores germinate within the lung and sprout hyphae, which invade the parenchyma, and may disseminate to distant sites, such as the central nervous system. Typical symptoms of infection may be absent due to immunosuppression. The radiographic features are of consolidation and cavitation. Precipitins can be positive or negative. Skin testing is negative, and biopsy is the only way to secure a diagnosis. Even with intravenous amphotericin and oral imidazoles, mortality remains high, unless the underlying disease is tackled concomitantly.

Excess glucocorticoid production, "Cushing's syndrome", is rare. Seventy percent of cases are due to a pituitary adenoma (Cushing's disease). Of the rest, one third are due to ectopic ACTH production, and two thirds to an adrenal adenoma/carcinoma/hyperplasia. Tumours secreting ACTH include: small cell carcinoma of the lung; Islet cell pancreatic tumours; thymomas; and bronchial carcinoid tumours. The latter account for only 1% of all cases of Cushing's syndrome [1]. This case illustrates most of the important features of ectopic ACTH production. Typically, patients lack the more long-standing features of Cushing's disease, such as moon face, striae, and truncal obesity; the picture being dominated by hypokalaemia, weight loss, pigmentation, hypertension, and frank diabetes. Investigations typically show hypokalaemia, diabetes, and a grossly raised serum cortisol, which cannot be suppressed by high-dose dexamethasone. Classically, ACTH is said to be grossly elevated in ACTH-dependent disease, and low in ACTH-independent cases. However, Howlett et al. [2] reported a spread of ACTH levels, which overlap between cases of ACTH dependent and independent disease, only differing widely in the cases of manifest disease. Moreover, in a review of 15 cases of bronchial carcinoid tumour as a cause of Cushing's syndrome [3], only half had ACTH values above twice normal, as here, none of the subjects had symptoms of chest disease at presentation, and only five had an abnormal chest radiograph. A further five had CT evidence of a neoplasm, and the remainder were in the pre-CT era, but went on to develop abnormal chest radiographs up to 10 yrs later.
**Keywords:** Aspergillus fumigatus, bronchial carcinoid, Cushing's syndrome.

**References**

