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CASE REPORT

A young woman with a severe bilateral pneumonia as the presenting sign of an adrenal carcinoma

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ABSTRACT

A severe bilateral, culture-negative pneumonia was diagnosed in a 22-year-old woman. Additional diagnostic procedures accidentally revealed a large adrenal carcinoma and hypercortisolism. The adrenal carcinoma was surgically removed, and she received mitotane treatment. This severe and life-threatening infection was the first sign of an immunosuppressive state as part of Cushing's syndrome due to the adrenal carcinoma.

KEYWORDS

Adrenal carcinoma, Cushing's syndrome, pneumonia

CASE REPORT

A 22-year-old woman presented with high fever (>40°C) and progressive dyspnoea, pleurodynia, and abdominal pain for four days. Her medical history was uneventful and she did not complain of cough or sputum production. Physical examination revealed a high respiratory frequency of 40 breaths/min, blood pressure 160/80 mmHg, and a regular heart rate at 104 beats/min. Augmented breathing sounds were heard at the left basal lung fields. Blood tests revealed leucocytosis (16.1 x 10^9/l), and an elevated C-reactive protein (CRP) (516 mg/l). A chest X-ray showed a left-sided infiltrate with pleural effusion.

A community-acquired pneumonia was suspected and treatment was initiated with intravenous amoxicillin (1 gram, four times/day). However, her clinical condition deteriorated and she had to be transferred to the intensive care unit for assessment of potential ventilatory support. Multiple microbiological tests did not demonstrate the causative pathogen: blood cultures (4x) and pleural effusion cultures were negative. There were no signs of tuberculosis. Legionella testing of the urine was negative.

With time, she gradually recovered with an adjusted antibiotic regimen (amoxicillin-clavulanate 1000/200 mg four times/day, erythromycin 500 mg four times/day and rifampicin 600 mg three times/day), and intermittent drainage of the pleural effusion. Computed tomography (CT) showed a bilateral pneumonia with pleural effusion (*figure 1A*). Accidentally, this scan also revealed a large tumour (∅ 12 cm) of the left adrenal gland, highly suspicious for malignancy because of its size and vasoinvasive growth into the renal vein (*figure 1B*).

Hereafter, additional questioning of the patient revealed a progressive increase in weight over the last years, accompanied by irregular menstrual periods, muscle weakness, tiredness, emotional changes (e.g. confusion, agitation), and a loss of libido. A more focused physical examination indeed showed signs of centripetal obesity, with a 'buffalo hump' and 'moon-face'. These findings were accentuated when compared with previous pictures provided by the patient (*figure 2*).

Cushing's syndrome was suspected and additional tests were therefore performed (*table 1*). The test results were indicative of an excess in cortisol production: fasting morning plasma cortisol concentration and free urinary cortisol excretion in 24-hour samples were

Figure 1. *CT scan of A) thorax: bilateral pneumonia with pleural effusion and B) abdomen: a large tumour (12 cm) in the left adrenal gland, with growth into the renal vein*

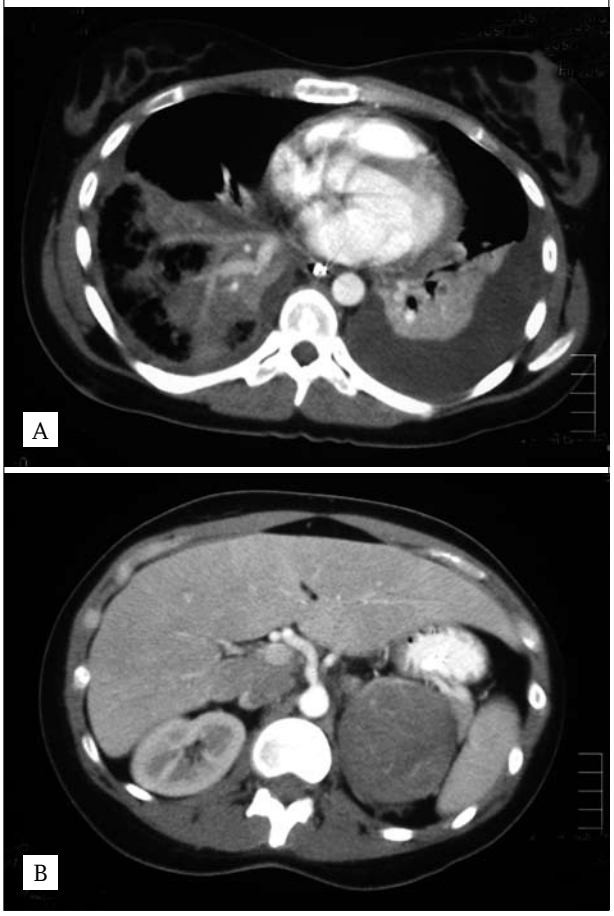
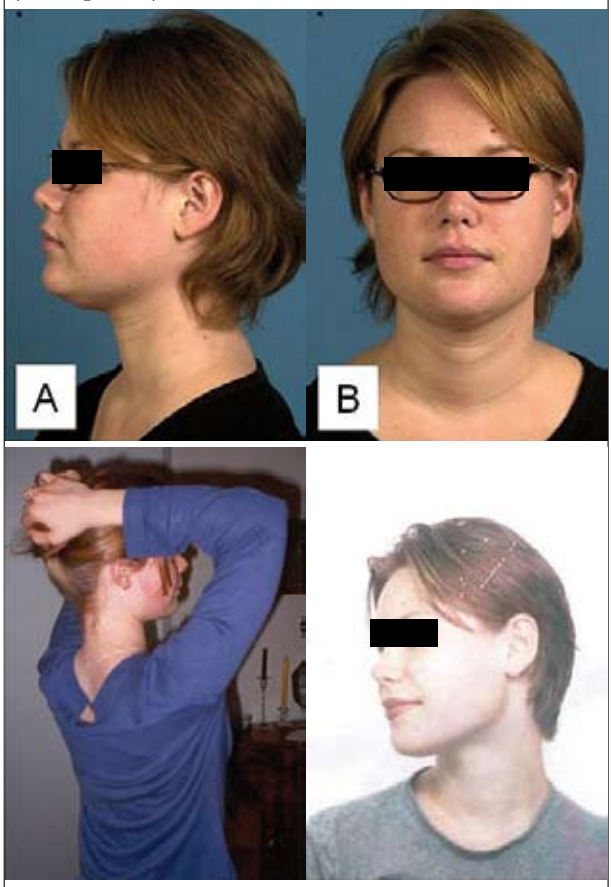


Figure 2. *Pictures of the patient during admission (upper panels), and two years before presentation (lower panels)*



A marked centripetal obesity is noted with a 'buffalo hump' (A) and 'moon-face' (B). Published with permission of the patient.

Table 1. *Biochemical tests demonstrating ACTH-independent hypercortisolism in a young woman with a severe pneumonia and a left adrenal mass*

Test	Result	Reference value
Plasma cortisol*	1.0 µmol/l	(0.22-0.50 µmol/l)
Plasma ACTH*	<4 ng/l	(4-55 ng/l)
24-hour urine cortisol excretion	1072 nmol/24 h	(<220 nmol/24 h)
Plasma cortisol* after *low* dose (1 mg) dexamethasone overnight	0.64 µmol/l	(< 0.1 µmol/l)
Plasma cortisol** after *high* dose (8 mg) dexamethasone i.v.	0.56 µmol/l delta 0.13 µmol/l	(delta >0.19 µmol/l)

***Sober concentration at 09.00 hours. ****Cortisol concentration at 16.00 hours, 7 hours after iv dexamethasone; 'delta' indicates difference between this measurement and the initial measurement of 09.00 hours.**

both elevated. Moreover, adrenocorticotropic hormone (ACTH) concentrations were undetectable. Cortisol concentrations were insufficiently suppressed after administration of dexamethasone (low and high dose), indicative of an ACTH-independent and thus adrenal source of the hypercortisolism. No clinical or biochemical evidence was found for pheochromocytoma or primary hyperaldosteronism.

The patient was referred to a university hospital for adrenalectomy. Histopathologically, an adrenal carcinoma was confirmed. After surgery, she was treated with a daily dose of 2 gram mitotane® (Ortho-para-dichlorodiphenyl dichloroethane (o,p'DDD), divided into four doses a day. She recovered completely. After three years she underwent repeat surgery for a lymph node metastasis; the resection sites were free of tumour. This time, she decided not to

take the mitotane due to severe side effects. Eighteen months later, MRI showed no signs of metastasis and she feels well.

DISCUSSION

This case illustrates a rare cause of a severe and life-threatening bilateral culture-negative pneumonia in a young woman. It demonstrates that a severe clinical course may be indicative of the presence of an immunodeficient state (e.g. haematological disorders, HIV, glucocorticoid excess). In the case presented, an adrenal carcinoma with Cushing's syndrome was the cause of the immunosuppressive state.

Cushing's syndrome

Cushing's syndrome is a synonym for hypercortisolism.[1] This excess production of cortisol can be due to ACTH-dependent (approximately 80% of the cases), or ACTH-independent causes.[2,3] *Table 2* summarises the causes, and their relative prevalence. The incidence of Cushing's syndrome as a result of adrenal carcinoma is very low (0.2 to 2 per million per year), and predominantly in the elderly.[4-6]

The presenting symptoms depend on the severity and duration of exposure to increased glucocorticoid concentrations. The diagnosis is initially often difficult, as the onset is gradual and the disease usually manifests with constitutional symptoms such as tiredness and headache. As the disease progresses, an increase in weight, progressive fatigue, and emotional liability occurs in the majority of the patients; in females, oligomenorrhoea or amenorrhoea, with hirsutism is almost mandatory. A concomitant weight loss is rare and is indicative of a malignant cause of the disease. At physical examination attention should be focused on the presence of hypertension, skin abnormalities (e.g. striae, acne, spontaneous haematoma, yeast infections), signs of centripetal obesity, proximal muscle weakness, and signs of hirsutism and virilisation.

The diagnosis is confirmed by biochemical tests: multiple screening tests in combination with plasma ACTH measurements, followed by a high-dose dexamethasone suppression test (see also *table 1*).[7,8]

These tests are important, as imaging techniques (such as CT and MRI) relatively often show 'incidentaloma' of the pituitary and of the adrenal glands (10 and 5%, respectively), without hypercortisolism.[9,10]

An increase in the rate of infections, even opportunistic ones, is the result of inhibition of the immune system that accompanies glucocorticoid excess.[11] The exact mechanism is unknown, but it seems that inhibition of CD4+ lymphocytes and cytokines plays an important role.[12,13] Several case reports have addressed severe infections as the primary symptom of hypercortisolism.[14,15] Therefore, these cases and the one we presented should be considered as an immunological endocrine emergency.

Untreated Cushing's syndrome is usually fatal as a result of thromboembolic, infectious, or hypertensive complications. At present, specific treatment is available for almost all causes, as depicted in *table 2*. For adrenal carcinoma, adrenalectomy is the therapy of choice followed by adjuvant mitotane (Ortho,para,dichlorodiphenyl dichloroethane (o,p'DDD) treatment.[16] Mitotane will completely block adrenal hormone synthesis, and therefore suppletion of glucocorticoids and mineralocorticoids is necessary. Prognosis depends on age and the presence of metastasis. Five-year survival rates differ per study, but are on average 20%.[17]

Table 2. *Causes of Cushing's syndrome [1] (excluding exogeneous supply of glucocorticoids) and their relative prevalence*

ACTH dependent	**Prevalence**
ACTH hypersecretion by corticotrophic adenoma in pituitary gland (= Cushing's disease)	68%
Ectopic ACTH secretion	12%
ACTH independent	
Adrenal adenoma	10%
Adrenal carcinoma	8%
Bilateral micro- or macro-nodular adrenal hyperplasia	1%
Pseudo Cushing's	
Alcoholism; depressive disturbances	1%*

*In our experience, the incidence of pseudo Cushing's seems higher when looking systematically for it.

CONCLUSION

In the present case, a severe bilateral pneumonia in a young woman was the result of the immunosuppressive state as a part of the Cushing's syndrome related to an adrenal carcinoma. This case illustrates that it is mandatory to find an explanation for a severe infection in young people. It can be the first sign of an underlying immunosuppressive state based on more rare causes, such as an adrenal carcinoma.

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