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Brief report

Bilateral adrenal enlargement as a first sign of systemic vasculitis

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Abstract

In this case-report we describe the fatal outcome of systemic vasculitis. A 51-year-old man was hospitalised with constant abdominal pain, chest pain, anorexia, fatigue, weight loss, dyspeptic complaints, and a period of high fever at home. Bilateral adrenal enlargement was found without a plausible cause. Endoscopy revealed a reflux oesophagitis grade I, which was treated with famotidine. His complaints disappeared without further treatment. Five days after release from hospital the patient was re-admitted with subfebrile temperature followed by an Addison's crisis due to primary adrenal failure. Laboratory tests for systemic illness were all negative. He was treated with high-dose corticosteroids. Right adrenal biopsy revealed haemorrhage, possibly of older age. After 10 days he returned with severe kidney and heart failure. He was transported to another hospital for haemodialysis. Unfortunately the patient passed away because of cardiac arrhythmias. Postmortem investigation revealed inflammation of middle-sized and small arteries in the adrenal glands, heart, lung and thyroid. In the kidneys, mesangio-proliferative glomerulonephritis was found. A definite classification of the vasculitis could not be made because of the high-dose corticosteroids therapy. Possibly, the haemorrhage of both adrenal glands was caused by venous thrombosis due to the hypercoagulable state, which is often observed in vasculitis. © 1997 Elsevier Science B.V.

Keywords: Adrenal enlargement; Vasculitis

1. Introduction

Vasculitis is a systemic illness of unknown aetiology affecting arteries in various organs. The early manifestations vary considerably and may resemble systemic illness with multiple organ involvement or single organ failure. In this case-report we describe a patient with bilateral adrenal enlargement as the first manifestation of this disease.

2. History

A 51-year-old man was hospitalised with constant abdominal pain, atypical chest pain, anorexia, fatigue, weight loss (4 kg in 1 week), dyspeptic symptoms, and a period of high fever at home. One month previously he had been admitted to the Neurology ward because of a sudden sensory deficit of the right hand and unstable gait. Since these symptoms disappeared spontaneously within 1 day and CT-scanning of the brain was normal, the neurologist concluded that the patient had suffered a TIA.

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Physical examination showed a blood pressure of 165/110 mmHg, temperature 37.4°C and diffuse abdominal pain. Relevant laboratory values on admission were: haemoglobin 11.1 mmol/l, WBC 13.2 $\times 10^9$/l with normal differentiation, platelets 323 $\times 10^9$/l, erythrocyte sedimentation rate 12 mm after 1 h, ASAT 11 U/l, ALAT 15 U/l, LDH 302 U/l, alkaline phosphatase 57 U/l, gamma-GT 24 U/l, creatinine 112 μmol/l, albumen 44 g/l. Urinary sediment showed sporadic leucocytes and erythrocytes. The high blood pressure normalised to average values of 120/85 mmHg without therapy. Echocardiography, performed to analyse his chest pain, was normal as well as perfusion scintigraphy of the lungs. CT-scanning of the abdominal region showed bilateral adrenal enlargement. Reflux oesophagitis grade I was found during upper endoscopy and was treated with famotidine. His abdominal pain disappeared and the patient went home. Further analysis of the adrenal enlargement was planned in an outpatient setting.

However, 5 days after release from hospital he was hospitalised again with complaints of further weight loss (> 8 kg in 3 weeks), progressive inability to perform light work and a slightly elevated body temperature (38°C). Physical examination was normal except for a temperature of 38°C. Laboratory investigation showed: haemoglobin 11.0 mmol/l, WBC 6.0 * 10^9/l (differentiation normal), platelets 149 $\times 10^9$/l, sedimentation rate 24 mm after 1 h. Prothrombin time 13 s (normal 8–11), APTT 24 s (normal 23–32), bleeding time 2 min (normal 1–4), ASAT 21 U/l, ALAT 26 U/l, LDH 410 U/l, gamma-GT 129 U/l, creatinine 161 μmol/l, sodium 130 mmol/l, potassium 5.0 mmol/l, albumen 33 g/l. Urine sediment showed 1–5 leucocytes per field, no erythrocytes. There was no protein present in the urine collected during 24 h. Cultures of urine, blood and sputum, which were taken 4 times each during admission, showed no growth of pathological micro-organisms. Extensive serological investigation, including Epstein-Barr virus, CMV, *Coxiella burnetii*, *Mycoplasma pneumoniae* and toxoplasmosis, gave no clues as to infection. Additional blood analysis (performed before corticosteroid therapy) gave no clues: antineutrophil cytoplasmic antibodies (P-ANCA's, C-ANCA's), antinuclear antibodies (ANA), antibodies against ds-DNA, extractable nuclear and cytoplasmic antigens (ENA), and glomerular basement membrane were all negative, as well as rheumatoid factors. Two days after admission the patient had a typical Addison's crisis and was treated with hydrocortisone 300 mg/24 h for 3 days in the Intensive Care Unit, after blood samples were taken for cortisol and ACTH. Morning cortisol was 0.14 μmol/l (normal 0.16–0.70) and blood ACTH was 670 ng/l (normal 10–100), suggesting primary adrenal insufficiency. Tests for antibodies against adrenal cortex were negative. Right adrenal biopsy showed necrotic tissue and signs of an old haematoma, possibly an infarction. Malignancy could not be excluded. No explanation was found for the decline in blood albumen; urine protein loss was negligible. After 20 days the patient went home with a diagnosis of primary adrenal insufficiency, caused by haemorrhage of both adrenal glands. He was treated with hydrocortisone 20 mg orally twice daily and florinef 0.0625 mg orally per day. However, the cause of the bleeding remained unclear.

Unfortunately, the patient returned after 10 days with signs of multiple organ failure. Physical examination revealed tachycardia with a third heart sound without murmurs, crackles over the lungs, liver 5 cm palpable and a shifting dullness – in general, all the signs of right and left cardiac failure. Laboratory tests had deteriorated: haemoglobin 5.8 mmol/l, WBC 18 $\times 10^9$/l (differentiation: 87% polymorphs, 4% lymphocytes and 8% monocytes), platelets 270 $\times 10^9$/l, sedimentation rate 74 mm after 1 h, CRP 388 mg/l, creatinine 316 mol/l, albumen 19 g/l; complement C3 and C4 were normal. Blood coagulation: bleeding time 5 min (normal, 3–4), APTT 32 s (normal 23–32), prothrombin time 16 s (normal 8–11), fibrinogen degradation products < 10 mg/l, fibrinogen 4.6 g/l (normal 1.6–2.8). Because of the clinical presentation a systemic illness was suspected. P-ANCA, C-ANCA, ANA, antibodies against ds-DNA, ENA, and glomerular basement membrane were all negative again, as well as the rheumatoid factors (tests performed before corticosteroid therapy). Prompt treatment was started in the Intensive Care Unit. Fluid, antibiotics, corticosteroids (hydrocortisone 300 mg/24 h) and dopamine were given. Urine, blood (collected 4 times), sputum and ascites cultures showed no growth. Protein loss in the urine was 0.9 g/l. Creatinine clearance was 6 ml/min. Ultrasound of the kidneys showed an increased den-

sity of the cortex of both kidneys, possibly caused by glomerulonephritis or acute tubular necrosis.

Despite all treatment, kidney and cardiac functions did not improve. At this point the patient was transferred to another hospital for haemodialysis. Ultrasound of the abdomen showed ascites, normal liver parenchyma, a normal spleen and an increased density of the renal cortex. Bone marrow aspirate was normal. Kidney biopsy revealed a necrotizing vasculitis and a mesangio-proliferative glomerulonephritis with crescents.

One day later the patient died due to cardiac arrhythmia and respiratory insufficiency. Postmortem investigation, performed on the same day, showed polymorphonuclear and mononuclear infiltration of the vascular wall of middle-sized and small arteries in the adrenal glands (Fig. 1), heart, lung and thyroid. No micro-aneurysms, eosinophil infiltration or granuloma formation was found. In the kidneys, mesangio-proliferative glomerulonephritis was present. In the adrenal glands thrombotic occlusion had led to haemorraghic necrosis. Furthermore, a fibrinic pleuritis and a pulmonary thrombotic vasculopathy (largely organised thrombotic occlusions of divisions of the pulmonary arteries) were found. The absence of active lesions due to high-dose corticosteroids made it impossible to make a definite classification of the vasculitis. Neuropathological investigation showed no signs of arteriitis or infarction.

3. Discussion

As we look at this case, the most important question that remains is whether there was a relationship between the adrenal enlargement and the fulminant vasculitis. To our knowledge, adrenal haemorrhage as a first sign of vasculitis has not been reported before.

The first time, the patient was admitted the with abdominal pain, dyspeptic symptoms, secondary anorexia and possibly high fever at home. Laboratory tests were normal, except for a high haemoglobin value, which was caused by dehydration due to several days of vomiting. Bilateral adrenal enlargement was unexpectedly found while CT-scanning the abdomen. Retrospectively, these symptoms can be explained by adrenal insufficiency. It is known that

Fig. 1. Adrenal biopsy, taken at autopsy, showing adrenal necrosis (arrow) and signs of peri-adrenal arteritis (arrowhead). H&E stain; 5 × magnification.

laboratory tests and blood pressure can be normal in the pre-crisis period [1–3]. During the second hospitalisation period the patient had a classical Addison's crisis with low sodium, high potassium, hypotension, azotemia, eosinophilia and fever.

Roughly the most common causes of primary adrenal insufficiency are autoimmune adrenalitis, infections (tuberculosis, cytomegalovirus, toxoplasmosis) and metastatic disease. Other less common causes are adrenal haemorrhage (Waterhouse-Friderichsen syndrome, TTP) and medication. In this patient all cultures and virus serology were negative as well as antibodies against adrenal cortex. No signs of a malignant process were found. Parameters for systemic illness, such as ANCA, ANA, and antibodies against ENA and ds-DNA were negative. A needle biopsy specimen gave the reason for the insufficiency, i.e. haemorrhage. The vascular anatomy of the adrenal gland makes it vulnerable to haemorrhage. Precipitating factors include sepsis, ACTH stimulation, catecholamines, haemorrhagic and thrombotic diathesis.

When the patient was admitted for the last time, his condition had deteriorated over a period of 10 days. He suffered cardiac and kidney failure, which needed extensive support. Since there was multiple-organ damage, a systemic illness such as vasculitis (e.g., polyarteritis nodosa, PAN) was suspected. Parameters for systemic illness were still negative. Although blood samples were obtained before the start of high-dose corticosteroid therapy, these parameters could be negative due to the high-dose corticosteroids and the oral treatment for his adrenal insufficiency he received during and after the second admission, respectively. Corticosteroids failed to improve the clinical situation. Kidney biopsy revealed a necrotizing vasculitis. Rapidly progressive glomerulonephritis was present because renal failure developed in a period of weeks. Immunofluorescence investigation of the kidney biopsy in this case might have given additional clues. However, since the patient died the day after the renal biopsy this investigation was cancelled. Angiography, which may have shown typical abnormalities as seen in PAN, was not performed since the clinical condition of the patient was declining rapidly and corticosteroids had already been given. Postmortem investigation showed inflammation of middle-sized and small arteries in multiple organs, including the adrenal glands (Fig. 1). Furthermore, a mesangio-proliferative nephropathy was found, which can be observed in vasculitic syndromes. Churg-Straus vasculitis is a plausible cause due to the pulmonary involvement, but no eosinophil infiltration or granuloma formation was found. Since the patient had no signs of rhinitis, hypereosinophilia or venous involvement, and since PAN can affect bronchial arteries, PAN seems the most plausible diagnosis.

We can only speculate about the cause of the adrenal haemorrhage. The presence of a hypercoagulable state (e.g., the presence of lupus anticoagulans) may have caused venous thrombosis of the adrenal veins [4,5]. Unfortunately, this was not investigated. There were no signs of vasculitis in cerebro, but TIA's can be found in vasculitic syndromes and hypercoagulable states.

4. Conclusion

To our knowledge, this is the first case report of seronegative vasculitis with bilateral adrenal haemorrhage due to a hypercoagulable state, which is often seen in vasculitic syndromes.

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