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CASE REPORT

Adrenal carcinoma causing secondary amyloidosis: report of the first case in the literature

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ABSTRACT

In a 53-year-old male patient with metastatic adrenal carcinoma, treatment with mitotane was instituted but he was lost to follow-up. Two years later, he presented with oedema and nephrotic-range proteinuria. The rectal and renal biopsies revealed an accumulation of secondary amyloid material. The patient died of respiratory failure caused by the progressive pulmonary metastases. This is the first report of a patient with adrenal carcinoma who developed secondary amyloidosis.

INTRODUCTION

Adrenal carcinomas may either be functional, when their hormonal secretions result in clinical consequences such as Cushing's syndrome, or nonfunctional.[1,2] The most common symptom is abdominal pain together with palpable mass.[2] The most frequent sites of metastases are the liver (85%), lungs (60%), bone (10%) and lymph nodes (10%).[2] Secondary amyloidosis might be seen during the course of malignancies, the most common of which are Hodgkin's disease and renal cell carcinoma.[3] Until now, secondary amyloidosis causing nephrotic syndrome in a patient with adrenal carcinoma has not been reported. We describe a patient with metastatic adrenal carcinoma who developed secondary amyloidosis leading to nephrotic syndrome, and died due to respiratory failure caused by the progressively enlarging pulmonary metastases.

CASE REPORT

A 53-year-old male was admitted to our hospital in December 1998 with mild abdominal pain, weakness and fatigue. On admission, his vital signs were normal. He had conjunctival pallor; breath sounds on the lower part of the left lung were diminished. The left upper quadrant of the abdomen was mildly tender to palpation. He had no lymphadenopathy and no organomegaly.

Laboratory data revealed a low haematocrit level (23.4%) and a high erythrocyte sedimentation rate (55 mm/h). Urea, creatinine, glucose, albumin levels, urinalysis, and the tumour markers CEA, CA 19.9, AFP, β-hCG, NSE were normal. Also, the steroid hormone levels, namely, testosterone, dehydroepiandrosterone, dehydroepiandrosterone sulphate, androstenodione, aldosterone, oestradiol, 11-deoxycortisol, cortisol, 17-OH-progesterone, were within the normal ranges. Thorax CT showed masses containing necrotic hypodense areas in both lung fields, the biggest of which was 9 cm in diameter. Abdominal MRI showed a regularly contoured mass measuring 7 x 9 cm in diameter originating from the left adrenal gland and containing calcified areas. The mass was displacing the tail of the pancreas anteriorly and the spleen laterally.

A thoracic fine needle aspiration (FNA) biopsy to the biggest pulmonary mass in the left lung was conducted. The histopathological examination of the biopsy specimen showed adrenal carcinoma cells with moderate degrees of anaplasia. The FNA biopsy of the left adrenal mass also revealed the same pathology. The immunohistochemical staining of both biopsy specimens was positive for vimentin,

but negative for cytokeratin and D11. According to the adrenal carcinoma staging system proposed by MacFarlane[4] and modified by Sullivan *et al.*,[5] we diagnosed the patient as stage IV adrenal carcinoma. The patient was started on treatment with mitotane 1000 mg orally, four times a day. He was discharged to come to regular follow-up visits but he was lost to follow-up.

In August 2000, 20 months after the initial admission, the patient was readmitted with complaints of dyspnoea, increasing fatigue and swelling of the legs. He stated that he had not been taking the mitotane regularly as it caused gastrointestinal upset. His blood pressure was 100/65 mmHg, pulse rate 88 beats/min and temperature 36.7°C. His conjunctivae were pale. Breath sounds were diminished on the lower parts of both lungs. He had no lymphadenopathy, no hepatomegaly and no ascites, but the spleen was enlarged 2 cm below the costal margin. He also had pretibial oedema.

Laboratory data revealed: haematocrit 0.26%, leucocytes 7,900/mm^3 (with a normal differential), platelets 391,000/mm^3, ESR 130 mm/h, urea 73 mg/dl, creatinine 4.1 mg/dl, total protein 4.8 g/dl and albumin 1.0 g/dl. Serum glucose, electrolytes, ALAT, ASAT, bilirubins and lipids were normal. Urinalysis revealed 4+ proteinuria and oval fat bodies in the sediment. Creatinine clearance was 15 ml/min and the protein excretion was 10 g/day. Serum protein electrophoresis revealed elevated alpha and beta globulin regions with normal gamma globulins. C3 and C4 complement levels, and serum and urine immmunoelectrophoresis were all normal. Antinuclear antibody, anti-dsDNA, p-ANCA, c-ANCA, cryoglobulins, HBsAg, anti-HCV and anti-HIV were negative. PPD skin test (Mantoux) was also negative.

Thorax CT revealed bilateral pleural effusion with persistence of the pulmonary metastases (*figure 1*). Abdominal MRI also demonstrated that the size of the left adrenal mass was the same (*figure 2*). Examination of the pleural fluid revealed a transudate with no growth in cultures (including Lowenstein media) and no pathological evidence of malignant cells. The rectal biopsy revealed AA-type amyloid accumulation in the submucosa. Later, a kidney biopsy was undertaken which showed amyloid accumulation with Congo red staining and it was sensitive to treatment with potassium permanganate. Immunohistochemistry confirmed that the deposited protein was AA-type amyloid. The patient was put on colchicine 1.5 mg/day but he died three months after the diagnosis of secondary amyloidosis due to progression of pulmonary metastases causing respiratory failure.

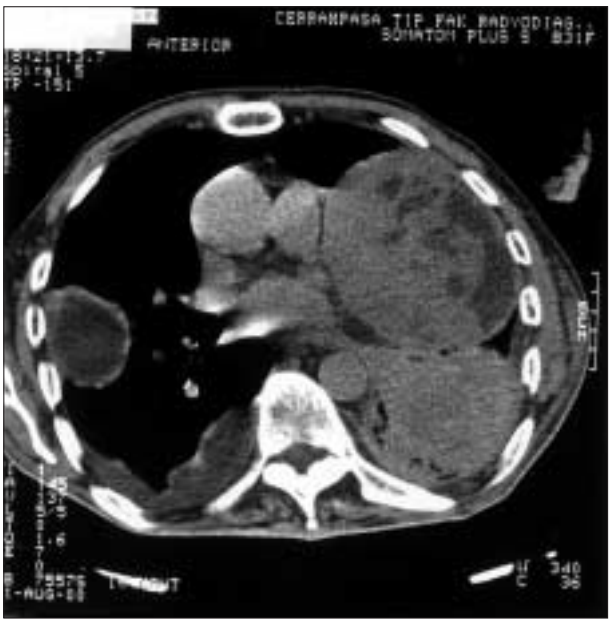

Figure 1
Thorax CT showing pleural effusion more prominent on the right and bilateral pulmonary metastases containing necrotic hypodense areas, the biggest of which measured 9 cm in diameter and was on the left

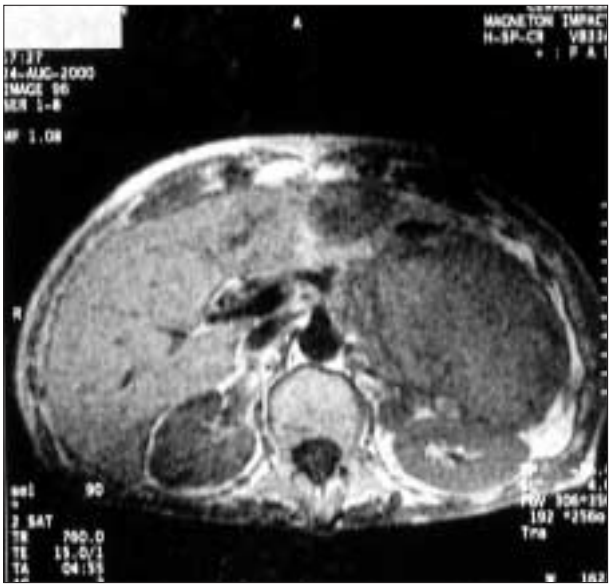

Figure 2
Abdominal MRI showing a partially regularly contoured mass with heterogenous intensity measuring 7 x 9 cm in diameter
The mass originates from the left adrenal gland and displaces the pancreas and the spleen.

DISCUSSION

In this case, the diagnosis of adrenal carcinoma was reached by FNA biopsy, which has a high degree of accuracy and is an important tool in diagnosing adrenal masses.[1] If the FNA biopsy of adrenal tissue is positive for malignancy, this has a positive predictive value of 100%.[1] It has also been reported that most adrenal malignancies measure >6 cm in diameter. The survival rate of patients with stage I or II disease is better, while those with stage IV disease have the shortest survival.[2] One study reported that 10 of 11 adrenal carcinoma patients died after 24 months.[6] Until now, mitotane has been shown to be the only drug to have some effect in the treatment of patients with metastatic adrenal carcinoma.[7-9]

Systemic amyloidosis might be associated with malignancies, the majority of which are accounted for by the immunocyte dyscrasias.[10,11] Hodgkin's disease and renal cell carcinoma are other cancers which might be associated with secondary amyloidosis.[12] In a large autopsy series, amyloidosis was found to have an incidence of 0.4% in cancer patients, the most common underlying malignancies being multiple myeloma, Hodgkin's disease and renal cell carcinoma.[3,13] However, it is uncommon to encounter amyloidosis in other types of cancers. In a literature search, no cases of surrenal carcinoma ending in secondary amyloidosis could be cited.

Serum amyloid A (SAA) is an acute phase protein produced by the liver[14] after stimulation from activated macrophages[15] and SAA serves as the precursor of AA-type amyloid.[16] Tumour cells activate macrophages, thereby triggering the formation of amyloid.[17] Also, the patient may lack the proteolytic enzyme which breaks down SAA protein[18] and this causes formation of AA-like fragments available for amyloid formation.[19] In addition, it has been reported that SAA and AA proteins are polymorphic; so, some molecules might be more 'amyloidogenic' than others.[20]

Secondary amyloidosis is more frequent in renal cell carcinoma than other cancers because it grows relatively slowly leading to a long-term stimulation of SAA protein production.[21] In other cancers, patients probably die before they have had time to develop secondary amyloidosis. In our case, the patient was diagnosed when he had stage IV adrenal carcinoma. We do not exactly know how much time elapsed before the first occurrence of the disease and the diagnosis of stage IV carcinoma. After diagnosis, he was prescribed mitotane, which he did not take regularly. In spite of this, he had stable disease for nearly 20 months with no regression or progression. This might have led to a longer period of inflammatory stimulus leading to secondary amyloidosis. Also, no clinical and laboratory evidence of any superimposed chronic infections or inflammatory diseases was found. In our country, one of the frequent causes of secondary amyloidosis is familial Mediterranean fever (FMF). However, our patient's family history and clinical presentation was not compatible with FMF or familial amyloidosis.

Clinical and histological resolution of systemic amyloidosis after removal of the tumour has been reported.[22] Our patient did not undergo surgery as it was shown to be of no use in metastatic adrenal disease.[2] He was prescribed mitotane which he did not take regularly and there was no regression of disease activity within this period.

Here, we present the first report of a case of adrenal carcinoma, which caused secondary amyloidosis ending in nephrotic syndrome. This complication should be born in mind in long-standing cases with proteinuria that are unresponsive to therapy.

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