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Anti-neutrophil cytoplasmic antibody-associated paraneoplastic vasculitis

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Summary: A 68 year old man presented with a systemic necrotizing vasculitis and elevated levels of anti-neutrophil cytoplasmic antibody (ANCA) which responded to treatment with steroids and cyclophosphamide, with a decrease in the titre of ANCA until its disappearance. Four months later he presented with weakness, loss of weight, aphonia and dysphagia. A computerized tomography scan showed a solid mass in the anterior mediastinum, and histological studies revealed an undifferentiated adenocarcinoma. Vasculitis improved although the malignancy progressed and ANCA was persistently negative. Our case demonstrates an association between ANCA and paraneoplastic vasculitis.

Introduction

Vasculitis is a syndrome that may complicate infections, hypersensitivity, rheumatic and neoplastic disorders.[1] When associated with malignancy, it has been reported to occur both before and after the diagnosis of neoplasia,[2] or it can give a clue to a recurrence.[3] However, little is known about its evolution in these cases, and no data are available about the relationship between anti-neutrophil cytoplasm activity (ANCA) and paraneoplastic vasculitis.

We report a patient who had a systemic necrotizing vasculitis which antedated the discovery of the neoplasm and which improved, although the malignancy progressed. We also present the evolution of ANCA and its correlation with vasculitis, independently of the course of malignancy.

Case report

A 68 year old man was admitted to hospital in October 1992 because of malaise, anorexia, weakness and weight loss of 6 kg in the 3 months prior to admission. Physical examination was unremarkable. Laboratory findings disclosed: haemoglobin, 7.1 g/dl; white blood cell count, 5.21 × 10^9/l with 71% neutrophils; urea, 20.3 mmol/mm; creatinine, 592.2 μmol/l; and electrolytes within normal limits. Immunoglobulins, C3, C4, CH50, anti-nuclear antibodies, rheumatoid factor and hepatitis B surface antigen were normal or negative. C-ANCA was negative and P-ANCA was positive (ELISA). Renal function continued to degrade rapidly, and the serum creatinine rose over 4 days to 724.8 μmol/l. A percutaneous renal biopsy was performed and revealed two glomeruli totally sclerosed, two were normal, and the remaining one showed segmental necrotizing glomerulonephritis. Blood vessels showed no changes of note. Immunofluorescence studies were negative. A regimen of oral prednisone, 0.75 mg/kg/day, and cyclophosphamide, 0.8 mg/kg/day, was started. His general condition and renal function improved and a decrease in the titre of P-ANCA was observed until its disappearance (Figure 1).

In February 1993, the patient was readmitted to the hospital with intense weakness, loss of weight, and progressive aphonia and dysphagia. Renal function was stable and P-ANCA was negative. A computerized tomography scan showed a solid mass located in the anterior mediastinum, with atelectasis of the left upper lobe and a left pleural effusion (Figure 2). Fine-needle aspiration cytology

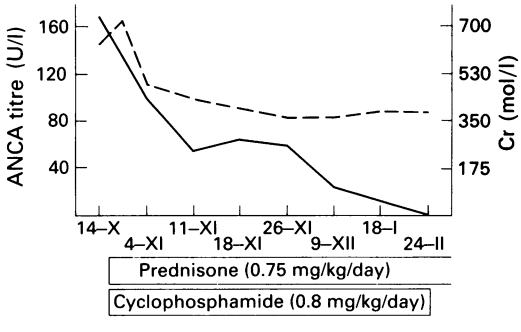

Figure 1 Relation of ANCA titre and renal function. —— = ANCA titre; - - - = serum creatinine (CR).

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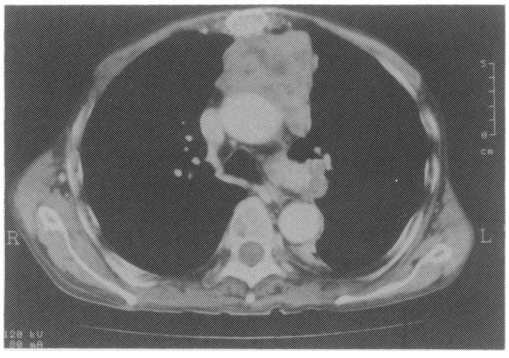

Figure 2 A computerized tomography scan showing a solid mass with necrotic areas located in the anterior mediastinum.

and a closed pleural biopsy demonstrated malignant cells compatible with undifferentiated adenocarcinoma. Surgical treatment was contraindicated because of poor pulmonary function tests. Radiotherapy was started with a total dose of 4,000 rad, but the malignancy progressed and the patient died 2 months later.

Discussion

Patients with malignant neoplasia may have manifestations other than those which can be ascribed to the tumour itself. It is known that these disorders are associated with a large number of vasculopathic syndromes.[2-4] A statistically significant association between vasculitis and lympho- or myeloproliferative malignancies was noted when compared with all other tumours.[2] The most common clinical vasculitis manifestation associated with malignancy is a cutaneous vasculitis, although vasculitis may also affect internal organs.[1,2,4] Paraneoplastic vasculitis may either appear after the malignancy has already been recognized or preceding the discovery of the neoplasia.[2] In our patient, 4 months after the diagnosis of vasculitis, a computerized tomography scan revealed a mass in the anterior mediastinum, shown to be adenocarcinoma. Unfortunately, an exact diagnosis of the type of adenocarcinoma was not possible, but the clinical aspects were most compatible with a bronchogenic adenocarcinoma. Furthermore, of all solid neoplasms, bronchogenic carcinoma is the most frequently associated with vasculitis.[2,3]

This case presents two aspects of special interest: the independent course of vasculitis and malignancy, and the evolution of ANCA. Recently, Rivera *et al.*[5] reported a patient with vasculitis which antedated the discovery of a non-Hodgkin's lymphoma. In that case, both disorders showed a parallel course, suggesting a pathogenic association. In our patient, the neoplasia persisted longer than the clinically evident vasculitis and he died as a direct result of the malignancy. Paraneoplastic vasculitis does not necessarily have a bad prognosis.[3,6] Sánchez-Guerrero *et al.*[3] reported nine out of 11 cases in which vasculitis resolved spontaneously, and in the remaining two cases, treatment with prednisone was successful. In our patient, treatment with prednisone and cyclophosphamide resulted in an excellent response and an improvement of renal function.

Whether immunosuppressive regimens should be employed in the treatment of the vasculitis is a matter for discussion, since these drugs have the theoretical attendant risk of provoking malignancy or its dissemination. In this case, the possibility that the immunosuppressive therapy accelerated the development of malignancy cannot be excluded. However, it seems unlikely since a low-dose immunosuppressive regimen was employed and there was a short temporal relationship between the two disorders.

Antibodies against some antigen(s) of the neutrophil cytoplasm components, i.e. ANCA are present in the blood in primary systemic vasculitis. In secondary vasculitis, as may be associated with systemic lupus erythematosus, Henoch-Schönlein purpura, and essential mixed cryoglobulinemia, these antibodies are usually absent. The presence of ANCA in paraneoplastic vasculitis has not been reported previously with the exception of a single report from Rivera *et al.*,[5] who reported the presence of ANCA in a patient with lymphoma-associated vasculitis. In both cases, ANCA was closely related to vasculitic activity as assessed by the level of renal function. Thus, in our patient, the maximal ANCA titre was observed in the active phase of the disease, while with treatment the renal function improved, and ANCA became undetectable over a 4-month period (Figure 2). However, while in Rivera's case, vasculitis paralleled tumour activity, in our case both disorders followed an independent course.

Although the random presentation of two unrelated disorders in our patient cannot be excluded, the close temporal relationship of these two diseases makes this explanation less likely. Because of this association, it seems that the pathophysiology of the two disease processes, malignancy and vasculitis, may be interrelated. Several mechanisms by which tumour-associated vasculitis might occur can be postulated:[2-4] (a) The formation of immune complexes of tumour-associated antigens/antibodies which deposit in vessel walls and produce inflammation; (b) the deposition of tumour antigens in the vessel wall which allows *in situ* immune complex formation; (c) direct effects of tumour cells on the endothelium.

The pathogenesis of necrotizing systemic vasculitis is not completely understood. It is possible that ANCA is directly involved in its development[7] and similar mechanisms may be applicable to the pathogenesis of paraneoplastic vasculitis.[4] Our case supports a potential pathogenic link between ANCA and tumour-associated vasculitis.

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