Recurrent thrombosis and anticardiolipin antibodies associated with adenocarcinoma of the lung

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Summary: A case of adenocarcinoma of the lung, in which high titre anticardiolipin antibodies were associated with recurrent venous thromboses resistant to all forms of therapy, is described. It is suggested that such an autoimmune response may be a contributory factor in the para-neoplastic development of vascular thromboses.

Introduction

Antiphospholipid antibodies, detected either by their ability to react with the prothrombin activator complex in the lupus anticoagulant test¹ or to cross-react with cardiolipin in ELISA² or radioimmunoassays,³ are known to predispose to venous and arterial thrombosis⁴ and recurrent fetal loss⁵ and to be associated with thrombocytopenia⁶ and haemolytic anaemia.⁴ Although originally described in patients with systemic lupus erythematosus, they are known now to occur not only in other connective tissue diseases^{7,8} but also in patients with purely thrombotic manifestations and/or fetal loss, the so-called antiphospholipid syndrome.⁹ They have also been described as a complication of a range of bacterial and viral infections¹⁰ and may occur as a side effect of certain drugs.¹¹

There have also been sporadic reports of their association with malignancy, with the growing number of these reports suggesting that the association may not be fortuitous. The present case report of recurrent severe deep venous thrombosis in a patient with adenocarcinoma of the lung and high titre anticardiolipin antibodies adds further weight to the possibility that these antibodies may be a hitherto unrecognized factor in the development of the thrombotic problems which frequently complicate malignant disease.

Case report

A 51 year old man was admitted with a 3-day history of pain and swelling of the left calf and a one day history of left sided pleuritic chest pain. A venogram confirmed the diagnosis of a deep venous thrombosis affecting the left leg while a

chest X-ray showed changes at the left base consistent with pulmonary infarction. His previous health had been good but he had smoked 25 cigarettes a day for several years. He was treated initially with intravenous heparin and then warfarin, on which he was eventually discharged.

Three weeks later he had to be readmitted with right sided pleuritic chest pain, marked breathlessness and signs now of a massive deep venous thrombosis affecting the right leg. Chest X-ray now showed bilateral basal lung shadowing consistent, once more, with pulmonary infarction. The International Normalised Ratio was therapeutic at 2.54 but tests for anticardiolipin antibodies (see later) were now positive. He was again treated with intravenous heparin for 10 days and commenced on prednisolone and azathioprine, on which he was discharged together with continuing warfarin treatment.

He had to be readmitted on 2 further occasions with recurrent deep venous thromboses of both the left and right legs, in the course of which further chest X-rays now revealed the development of a mass in the right upper lobe. Although bronchoscopy was unhelpful, a computed tomographic scan confirmed the presence of the mass together with enlarged mediastinal lymph nodes and biopsy of one of these nodes at mediastinoscopy revealed the presence of an infiltrating adenocarcinoma. He was treated with palliative deep X-ray therapy and maintained on continuing treatment with aspirin, warfarin, subcutaneous heparin injections, prednisolone and azathioprine. Despite this combined therapeutic approach, he redeveloped further massive venous thrombosis of the left leg (the fifth such event in total and the third involving the left leg) which now was complicated by the development of extensive venous gangrene which progressed, despite continuing full combined anticoagulation with intravenous heparin, aspirin and warfarin and led

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to his death some 7 months after the initial presentation.

Additional investigations

Haemoglobin 10.5 g/dl, white cell count 12.66×10^9 /l, platelets 632×10^9 /l, erythrocyte sedimentation rate 99–128 mm/h, fibrinogen 8.6 g/l (NR 1.8–4.5 g/l), kaolin cephalin clotting time 54 seconds (NR 40–50 seconds), lupus anticoagulant, heat stable inhibitor – patient 59 seconds, control 49 seconds, dilute Russell viper venom time – platelet substitute, patient 59 seconds, control 36 seconds – washed platelets, patient 43 seconds, control 29 seconds, serial tests for anticardiolipin antibodies – IgG 20.6 units, 12.8 units, 9.3 units and 6.3 units (NR <8.0 units) – IgM <1 unit, <1 unit, 1.7 units and 50.4 units (NR <5.0 units), antithrombin 3 – chromogenic 111% (NR 80–120%) – immunodiffusion 0.34 g/l (NR 0.15–0.45 g/l), DNA antibodies, antinuclear antibodies and precipitating antibodies to nuclear and cytoplasmic antigens all negative, immunoglobulins, G 19.7 g/l, A 5.4 g/l, M 0.6 g/l.

Discussion

The association of vascular thrombosis with malignant disease, the so-called Trousseau syndrome,¹² is well recognized but the mechanisms responsible for the recurrent thrombotic tendency, which characteristically may be resistant to full anticoagulation, as in the present case, have not been clearly defined. It has been suggested that some tumours are capable of releasing thromboplastin-like substances which act on pro-coagulant systems in the circulation to produce a hypercoagulable state.¹³ Clinical models in which intravenous injection of various tissue thromboplastins can induce a coagulopathy with both thrombotic and haemorrhagic manifestations with disseminated intravascular coagulation certainly do mimic the features found in some patients with Trousseau's syndrome.¹⁴

The present case, however, showed no evidence of disseminated intravascular coagulation with, in fact, 'acute phase' increases of both fibrinogen and platelets that almost certainly played a predisposing and synergistic role in the development of the recurrent venous thromboses. The finding of high titre anticardiolipin/antiphospholipid antibodies as an additional factor in our patient's recurrent

and severe thrombotic tendency is, therefore, particularly interesting. These antibodies, especially when present in high titre and of IgG isotype, are known to have a predictive value for thrombotic events in patients with autoimmune disorders.⁴ However, this predisposition to thrombosis has also been recognized with antibodies of both IgA and IgM isotypes¹⁵ which is particularly relevant to the present case in which continuing thrombotic events were associated with a change in the isotype of the anticardiolipin antibody from IgG to IgM. Anticardiolipin/antiphospholipid antibodies, which are thought to predispose to thrombosis by interfering with prostacyclin release from vascular endothelium¹⁶ and by interacting with phospholipid antigens in platelets,¹⁷ have only been reported sporadically in patients with malignant disease. Previous reports, which have frequently relied on the lupus anticoagulant test to detect these antibodies indirectly, have described their presence in patients with leukaemia,¹⁸ lymphoma, multiple myeloma,¹⁹ thymoma,²⁰ maxillary carcinoma²¹ and, as in the present report, bronchial carcinoma.²² The growing number of such reports suggests that the association may not be entirely fortuitous.

Autoantibodies arising from what is an immune response directed primarily against tumour antigens have been described as producing autoimmune haemolysis, the Eaton-Lambert (myasthenic) syndrome²³ and paraneoplastic visual dysfunction²⁴ and cerebellar degeneration²⁵ in patients with malignancy. Polymyositis and the peripheral neuropathy that is frequently found in many patients with carcinoma are similarly likely to have an immunological basis. The finding of autoantibodies capable of reacting with phospholipids, which are widely distributed in cell membranes, should therefore not be unexpected. Now that sensitive and reliable assays are available for the detection of anticardiolipin/antiphospholipid antibodies, screening of patients with malignant disease may well reveal a hitherto unsuspected incidence of these potentially pathogenic autoantibodies, especially in those patients with thrombotic manifestations.

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