

## CASE REPORT

# ANTIPHOSPHOLIPID ANTIBODY SYNDROME PRESENTING WITH COMPLEX PARTIAL SEIZURES AND TRANSIENT ISCHAEMIC ATTACKS DUE TO WIDESPREAD SMALL CEREBRAL ARTERIAL THROMBOSIS

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**Antiphospholipid antibody syndrome presenting with complex partial seizures and transient ischaemic attacks due to widespread small cerebral arterial thrombosis**

The neuropathological findings in a young man with the antiphospholipid antibody syndrome presenting with complex partial seizures and transient ischaemic attacks are described. Whilst some of his symptoms could be attributed to large vessel thrombosis, the dominant pathological process was widespread small cerebral arterial thrombosis causing extensive microinfarcts within the cerebral cortex. These findings help to explain the neurological manifestations of the antiphospholipid antibody syndrome.

## Introduction

Antiphospholipid antibodies are present in a significant number of patients with systemic lupus erythematosus and other connective tissue diseases and are associated with arterial and venous thrombosis, thrombocytopenia and recurrent abortion (Mueh, Herbst & Rapaport, 1980; Hughes, 1983). These antibodies may also occur in patients who have no features of connective

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tissue disorders; patients with the antiphospholipid antibody syndrome have the same tendency towards thrombosis. An increasing number of other associations are also reported including livedo reticularis, epilepsy, chorea, migraine, progressive dementia, systemic and pulmonary arterial hypertension and endocardial disease (Hughes, Harris & Gharavi, 1986). *In vitro*, these antibodies prolong all phospholipid dependent coagulation tests, hence the somewhat misleading term 'lupus anticoagulant' (Harris, Gharavi & Hughes, 1985). Antiphospholipid antibodies may also be detected using a solid phase assay with cardiolipin as the antigen (Harris *et al.*, 1987).

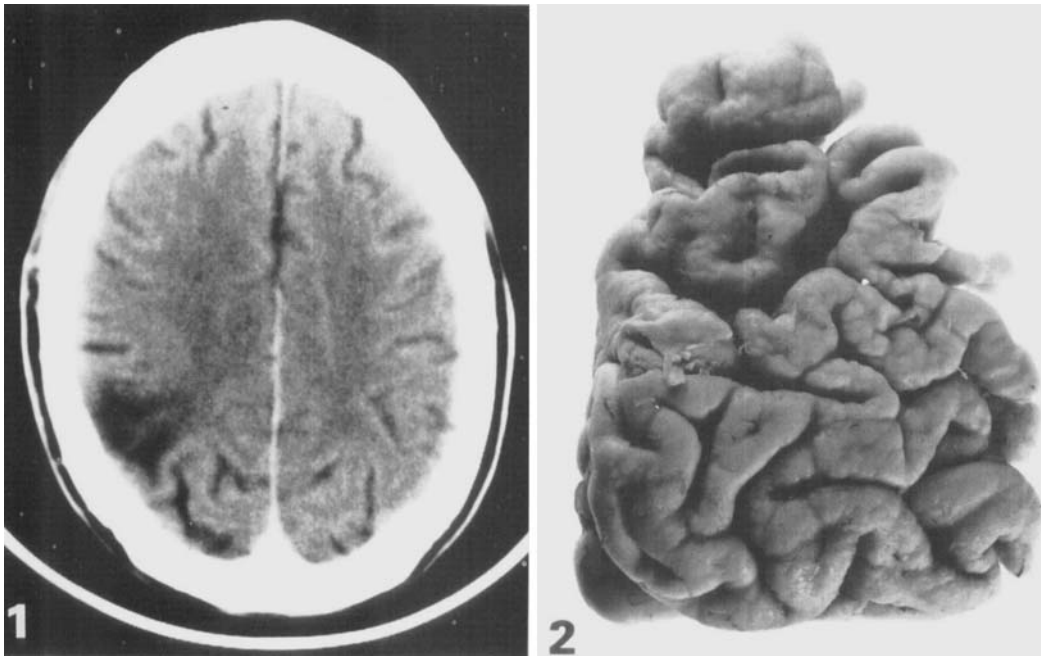
In this report we describe the neuropathological findings in a young man with the antiphospholipid antibody syndrome associated with prominent neurological symptoms which first brought his condition to light.

### Case report

A 40-year-old man presented with an eight month history of complex partial seizures in which he became briefly unresponsive with stereotyped lip-smacking followed by a period of amnesia and confusion. Clinical examination revealed no significant abnormality and he was commenced on carbamazepine. Two weeks later he had two brief episodes of loss of consciousness, left sided facial twitching and cyanosis followed by confusion and headache and one episode of dysphasia and right arm weakness which resolved within 10 minutes. He had suffered a myocardial infarct aged 32 and has a five-year history of mild impairment of renal function and hypertension controlled by metoprolol.

On admission he was unwell with widespread livedo reticularis. Blood pressure was 150/85 mmHg and the murmur of aortic regurgitation was present. Neurological examination showed clumsiness and incoordination of the right arm. Shortly after admission he had a further episode of dysphasia and pyramidal weakness in the right arm which completely resolved over the following month. Investigations revealed a normocytic, normochromic anaemia of  $11.1 \text{ g dl}^{-1}$ , thrombocytopenia ( $98 \times 10^9 \text{ l}^{-1}$ ) and an elevated ESR ( $46 \text{ mm h}^{-1}$ ). Renal function was impaired with urea  $13.6 \text{ mmol l}^{-1}$  (normal 2.0–6.5) and creatinine  $228 \mu\text{mol l}^{-1}$  (normal 60–120). Serum immunoglobulins, C<sub>3</sub> and C<sub>4</sub> were normal but C<sub>3</sub> degradation products (C<sub>3</sub>d) were grossly elevated at 29 units  $\text{ml}^{-1}$  (normal <12). Autoantibodies, including antinuclear and anti-double stranded DNA antibodies, were not detected. The activated partial thromboplastin time was prolonged due to the presence of a lupus anticoagulant; anti-cardiolipin antibodies (ACA) of IgG class were grossly elevated (laboratory assay not standardized at that time); IgM ACA were not detected. EEG was normal but computerized tomography showed marked generalized cerebral cortical atrophy, a small right frontal subcortical infarct and a larger, older infarct in the right parietal region (Figure 1). Skin biopsy from an area of livedo showed thrombotic venous occlusion within the dermis; renal biopsy showed ischaemic glomerular changes but no evidence of thrombosis or vasculitis. Bacterial endocarditis was excluded by echocardiography, repeated negative blood cultures and by normal C-reactive protein levels.

The clinical diagnosis was the antiphospholipid antibody syndrome. Carbamazepine and metoprolol were continued and he was commenced on warfarin and prednisolone. Over the next 2 years he had no further major thrombotic episodes and remained generally well apart from occasional nocturnal complex partial seizures. However, his ACA and C<sub>3</sub>d levels remained grossly elevated with IgG ACA up to 262 units  $\text{ml}^{-1}$  (normal <6) and C<sub>3</sub>d up to 66 units  $\text{ml}^{-1}$  despite continuing drug therapy. He ultimately died suddenly at home, 28 months after his initial presentation.

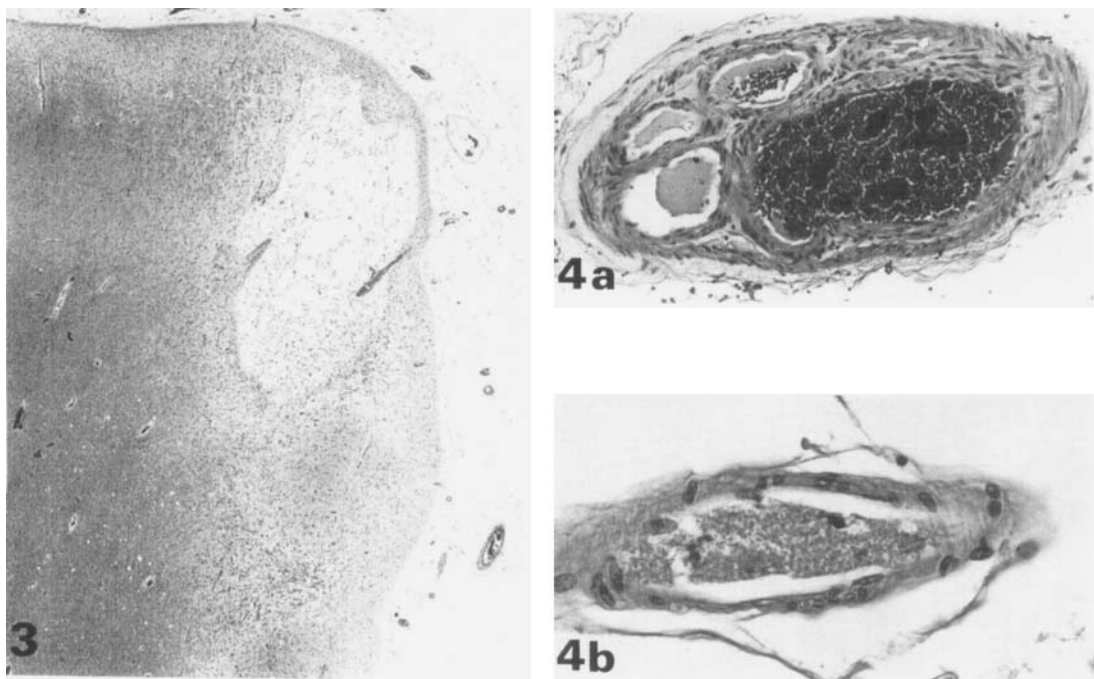


**Figure 1.** Computerized tomographic brain scan showing cortical atrophy and right posterior parietal infarct (bottom left of figure). **Figure 2.** Occipital pole of the right cerebral hemisphere showing granular cortical atrophy.

### **Pathological findings**

At autopsy, external examination of the cerebral hemispheres showed widespread gyral atrophy, most marked in the frontal and parietal lobes and particularly affecting the right posterior parietal area. Stripping the meninges revealed pitting and granularity of the external surface of the cerebral cortex in these areas (Figure 2). A cystic area surrounded by gliosis and consistent with an old infarct 1 cm diameter was present in the right posterior parietal area. Sectioning the brain revealed underlying cortical atrophy; no white matter abnormalities were observed. The cerebellum, medulla, pons and midbrain were normal. The carotid, vertebral and major cerebral arteries were normal with no significant atheroma and no evidence of thrombus or old occlusion. In the remainder of the organs both lungs showed severe pulmonary oedema. The heart showed evidence of a previous anterior infarct associated with extensive recanalization of the left anterior descending coronary artery; the aortic valve cusps were fibrotic and retracted. Both kidneys appeared macroscopically normal.

Histological examination of the cerebral cortex showed widespread small cystic foci associated with gliosis, representing old microinfarcts (Figure 3).



**Figure 3.** Cerebral cortex showing an old cystic microinfarct (top) and a more recent microinfarct (bottom). Haematoxylin and eosin.  $\times 14$ . **Figure 4. a,** Recanalized small superficial meningeal artery representing organization of a previous thrombus. **b,** Small superficial meningeal artery occluded by fresh platelet thrombus. Haematoxylin and eosin. **a,**  $\times 63$ . **b,**  $\times 280$

These were related to numerous areas of old occlusion and recanalization in small superficial meningeal arteries (Figure 4a); arteries occluded by recent platelet thrombus were also present (Figure 4b). Sections from the right posterior parietal area confirmed the presence of a larger old infarct. No abnormalities were present in the white matter, cerebellum, medulla, pons or midbrain. Similar old arterial occlusions were present in the myocardium and both kidneys with secondary small areas of ischaemic damage to myocardium and glomeruli; numerous fresh platelet thrombi were present occluding intramyocardial arteries with scattered recent microinfarcts (Murphy & Leach, 1989). No evidence of hypertensive vascular disease or vasculitis was found in any of the organs examined. Death was ultimately attributed to acute left ventricular failure secondary to diffuse ischaemic myocardial injury.

## Discussion

This patient clearly had many features associated with the antiphospholipid antibody syndrome. Focal cerebral infarction and transient ischaemic attacks

are well documented in the antiphospholipid antibody syndrome (Levine & Welch, 1987) whilst recurrent strokes and multi-infarct dementia are reported in patients with SLE and antiphospholipid antibodies (Asherson *et al.*, 1987). The association of livedo reticularis and ischaemic cerebrovascular disease was first reported in 1965 (Sneddon, 1965). Recent reports have described Sneddon's syndrome in association with antiphospholipid antibodies and suggested that they may have an aetiological role in both the cutaneous and cerebral manifestations of the condition (Levine *et al.*, 1988). Epilepsy, of both generalized and complex partial type, is seen in patients with antiphospholipid antibodies and associations with migraine and chorea are also reported (Inzelberg & Korczyn, 1988; Levine *et al.*, 1987).

The pathological findings in this case underline the basic tendency to thrombosis seen in association with antiphospholipid antibodies. However, the widespread nature of the small vessel thrombosis seen in this case has not previously been documented. This process may explain many of the neurological and other symptoms associated with the antiphospholipid antibody syndrome. Small vessel thrombosis may be difficult to detect clinically until secondary ischaemic damage is advanced, although immunological indices, such as ACA and C<sub>3</sub>d levels, may be useful in monitoring disease activity. Current drug therapy is aimed at immunosuppression and prevention of thrombosis. Although this patient seemed well controlled clinically, he had persistently grossly elevated ACA and C<sub>3</sub>d levels; the pathological findings show that despite treatment small vessel thrombosis was not suppressed.

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