

Recurrent deep vein thrombosis, ovarian carcinoma and antibodies to mitochondria M5 in a patient with asymptomatic primary "plus" antiphospholipid syndrome: an unusual combination

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ABSTRACT

An asymptomatic thirty-eight-year-old female developed recurrent DVT at the latter end of her first pregnancy and in the puerperium. Blood tests revealed a moderately elevated ANF (1:640) with a speckled pattern, hyperglobulinemia, and antibodies to thyroid tissues. Two months postpartum, following neurological disturbances she was found to have a patent foramen ovale and had developed paradoxical emboli to the brain causing multiple arterial occlusions. However, she also had cerebral venous occlusions as well as deep venous thromboses and pulmonary emboli, indicating a generalised prothrombotic state.

Abdominal ultrasound examination revealed the presence of tumour which, on surgical removal, proved to be an ovarian carcinoma. The only antiphospholipid antibodies detectable were antibodies to mitochondria Type M5 in moderately elevated titres.

Case report

A 38-year-old, in the last trimester of her second pregnancy, developed deep vein thrombosis (DVT) of her left calf. She was investigated for clotting disorders. Her full blood count and C-reactive protein were normal. Prothrombin PCR – G20210A and Factor V Leiden mutations were excluded. The clotting profile showed a low antithrombin III (AT III) level of 66% (normal 87 – 140%) with a low protein C functional level of 69% (normal 75 – 155%). No lupus anticoagulant was present and the anti-phospholipid antibodies; both IgM and IgG were normal. The reduction of the protein C and AT III levels were assumed to be due to active thrombosis from her DVT and it was advised that these levels be rechecked at a later stage. She was put onto low molecular weight heparin for the rest of her pregnancy. Anticoagulation therapy was not continued following the birth of the baby.

Two months after the birth, she presented to the emergency department with a painful right calf. The calf was swollen and tender and a thrombosed varicose vein was noted on the medial aspect. She was referred to a vascular surgeon

who repeated a number of blood tests for clotting abnormalities. Her full blood count was normal with a haemoglobin of 14.1 g/dL, white cell count of 7 890 per mm³ and platelets of 199 000 per mm³. A quantitative D-dimer was slightly elevated at 0.61 ug/mL (normal 0.1 – 0.5). Her prothrombin time international normalised time (INR) was 1.31 with a calculated prothrombin index of 76%. The antinuclear factor (ANF) was positive with a titre of 1:640 and a speckled pattern. The double stranded DNA antibody ELISA test, Crithidia DNA antibodies and extractable nuclear antibody screen were negative. A phospholipid profile was normal. These included the anti-cardiolipin, anti-B2 glycoprotein and anti-prothrombin, immunoglobulins IgG, IgM and IgA. The Factor V Leiden mutation and Prothrombin G20210A mutation were repeated and not detected. Homocysteine levels were normal. A deep vein thrombosis (DVT) of the right leg was suspected. The venous duplex scanning did not confirm any significant clot; however, the peroneal (fibular) vein could not be visualised. She was put onto low molecular weight heparin (LMWH) and discharged.

Two days later, she was readmitted with shortness of breath. She complained of a sudden deterioration of her vision with paraesthesia of her hands and feet and developed visual hallucinations. She was disorientated and confused. There was a left-sided hemianopia with brisk reflexes on the right. No paralysis was noted. Investigations revealed an elevated C-reactive protein of 76.7 mg/L (normal 0.0 – 8.0mg/L) and a normal haemoglobin and platelet count with a mild neutrophilia. Her renal function was normal. Blood cultures were negative. Her chest x ray was normal but her ventilation/perfusion scan showed evidence of bilateral multiple pulmonary emboli. A magnetic resonance imaging (MRI) scan of the brain with angiography confirmed both arterial infarctions and venous thrombosis. There were acute infarcts in the posterior aspect of the right temporal lobe, lateral portion of the right occipital lobe, parasagittal aspect of the left occipital lobe and in both cerebral hemispheres. Venous thrombi were noted in the right

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sigmoid sinus and right jugular vein bulb. She was treated with higher doses of LMWH – enoxaparin 80 mg twice daily, sodium valproate 800 mg three times daily, half-dose aspirin daily and a proton pump inhibitor, esomeprazole and combinations of analgesia with paracetamol and dextropropoxyphene napsylate with dephenhydramine hydrochloride. A trans-oesophageal echocardiogram (TEE) confirmed a patent foramen ovale (PFO). Due to her confused mental state she was unable to perform the appropriate Valsalva manoeuvres for contrast bubble testing; however on colour mapping there was evidence of the defect. On straining, she showed intermittent right to left shunting. However, there was no evidence of clot in any of the cardiac chambers, including the left atrial appendage. The proximal right and left pulmonary arteries were visualised and did not show any evidence of thrombus. The diagnosis was that of deep vein thrombosis, pulmonary embolism with paradoxical embolism from a PFO resulting in a “stroke” syndrome. The patient was continued on full anticoagulation with LMWH and warfarin therapy was instituted. Her mental state improved significantly although she experienced visual hallucinations in the affected visual fields. She continued on oral anticoagulation with warfarin. A computed tomography (CT) brain scan done three weeks following her admission showed infarcts in the right temporal, right occipital and left occipital regions. A filling defect was still noted in relation to the straight sinus compatible with venous thrombosis. Neurologically clinically, there was further improvement.

She continued to complain of pain in her calves. A venous duplex scan did not show any extension of the DVT of her right calf. However, ten days later she was reassessed complaining of severe pain and coldness of her right leg and pain in the left calf. Venous duplex scans now showed thrombosed right popliteal and posterior tibial veins. The superficial and common femoral veins were patent and no clot was documented in the left leg. She was put back onto LMWH as she was due to undergo closure of her PFO five days later.

She was readmitted for closure of the PFO on the 20th June. An Amplatzer device was deployed and the defect was closed. As her INR tended to fluctuate, her cardiologist continued her on LMWH with the warfarin. She was also given celecoxib 200mg daily for the pain in her legs.

She presented to her cardiologist three weeks later with a left facial palsy. A MRI of the brain was repeated which showed recurrent ischemic changes in the right temporal lobe, right occipitoparietal region, right frontal and parietal lobes, with sub cortical involvement in the left occipital and right temporo-occipital lobes. An echocardiogram with Doppler studies suggested a possible vegetation or thrombus on the posterior mitral valve leaflet but was not confirmed. The possible diagnosis of Libman-Sacks endocarditis was considered in view of the previously documented positive antinuclear factor and a decision by the attending doctors was made that the patient required enhanced dosage of anticoagulation with the addition of immunosuppression therapy. Her INR was not in the therapeutic range with a value of 1.51 and a prothrombin index of 66%. Her full blood count showed haemoglobin of 12.2 g/dl (normal 12.4 – 16.7g/dL) with features of mild normochromic anaemia. The white cell count, differential and platelet counts were all normal. The renal function was normal. Acute phase markers showed a slightly elevated C-reactive protein of 10.0 mg/L (normal 0.0 – 8.0 mg/L) Her ferritin value was normal and a quantitative procalcitonin level was 0.02ng/mL (normal < 0.5) suggesting that systemic infection was unlikely. Her ANF titres were again elevated to a titre of 1:640 (speckled). Other antibodies were negative. Anticardiolipin antibodies were again normal and antineutrophil cytoplasmic antibodies (ANCA) levels were negative. Her protein C level was depressed at 58% (normal 75 – 155%) compatible with the use of coumadin therapy. Protein S levels were normal.

She was referred to a specialist physician for treatment of suspected systemic lupus erythematosus. Clinically she had splinter haemorrhages of the

nailbeds of her fingers and mottled change of her toes. Neurologically she had left sided facial weakness, with a visual field compromise and had apraxia with dyslexia. The clinical picture was compatible with the diagnosis of antiphospholipid syndrome. The phospholipids profile was again normal and no lupus inhibitor was demonstrated using the Exner and the Russell’ Viper Venom methods. Her INR at the time of admission was not in therapeutic range and LMWH was again added to her warfarin therapy. It was advised that she maintain her INR at a higher therapeutic range of 2.5 to 3.0. She was put onto aspirin and platelet function studies showed a marked salicylate effect compatible with the use of aspirin. In view of the difficulty of the controlling her INR it was advised that she obtain a home monitoring device, the Roche coagulocheck monitor. She and her husband were instructed on the use of the machine.

She was referred to a rheumatologist (RAA) and further investigations were undertaken. Serum immunoglobulins showed an elevated IgG of 226 IU/mL (reference 74-182 IU/mL), 19.78g/L (reference 6.48 – 15.96g/L). The anti-mitochondrial antibodies were elevated at a titre of 1:320 and thyroid anti-microsomal antibodies were elevated at 73.0 IU/ml (reference 0 – 60). Tests for *Treponema pallidum* were negative and the Plasmoquine was added to her therapy. At a follow-up with the rheumatologist she continued to complain of pain in her left leg and was referred for ultrasonography. This confirmed extensive clot in the proximal superficial femoral vein extending to the popliteal vein and small veins of the calf. An ultrasound of the abdomen showed a large eight by eight centimetre pelvic mass posterior to the uterus in the Pouch of Douglas with associated para-aortic lymph nodes, suggestive of a neoplasm confirmed by CT scan (Fig. 1). At the time of her acute admission with pulmonary emboli and strokes, she had undergone a portable ultrasound of the abdomen and pelvis, which showed a loculated septated fluid collection posterior to the bladder and superiorly to the uterus. The endometrial cavity

showed linear echogenicity consistent with haemorrhage. The radiologist's comment was that it was most likely due to a resolving haematoma, in keeping with the history of treatment with LMWH. However cancer markers – serum CA 153, CA 125 and CA 19-9 were all elevated. She was again referred for gynaecological assessment and a total abdominal hysterectomy was advised. Prior to undergoing this procedure an inferior vena caval filter was inserted. At the insistence of the gynaecologist, her anticoagulation therapy was discontinued and she was put onto heparin therapy preoperatively as the surgeon was concerned about bleeding at the time of surgery. A Factor Xa level was normal indicating that there was no residual effect of the LMWH. In Table I, the laboratory results are listed at presentation in pregnancy, two month following pregnancy and during the acute and second admission. The patient underwent surgery, which confirmed a neoplasm of the left ovary with extension outside the ovary. A papillary serous cystadenocarcinoma was diagnosed (Figs 2A & B). There was no spread to lymph nodes or metastatic tumour in the omentum. She was recommenced on LMWH immediately postoperatively and warfarin and aspirin were restarted when she was able to take orally. Her postoperative course was uncomplicated. She was put onto sertraline to help her cope with hot flushes as she could not have hormone replacement therapy and discharged on anticoagulation therapy. She was referred to an oncologist for chemotherapy and is currently undergoing treatment.

Discussion

The clinical presentation in this patient who presented with recurrent venous and arterial thrombosis was suggestive of the anti-phospholipid syndrome even though her initial antiphospholipid profile was normal. She had two probable contributing causes. The undetected ovarian tumour and the documented positive antinuclear factor (repeated on several occasions) were of significance, the latter suggesting, together with elevated levels of immunoglobulin G as well as antibodies to thyroid, that the

Fig. 1A.

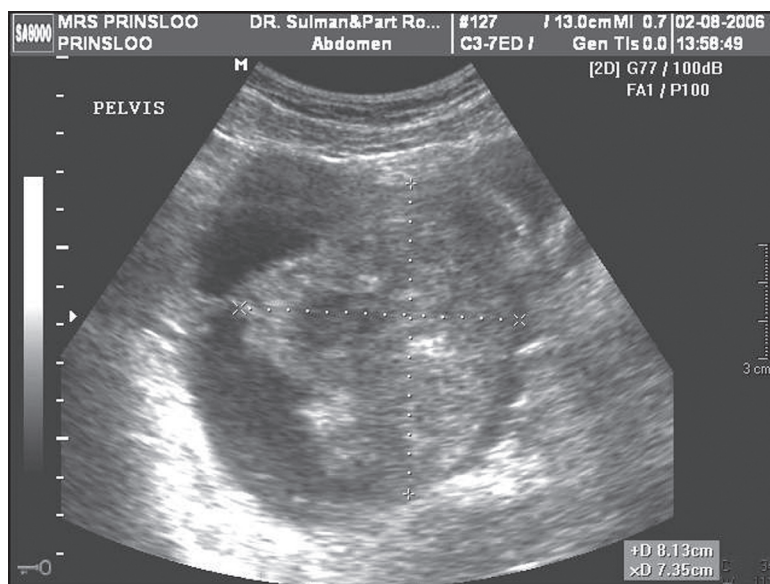


Fig. 1B.

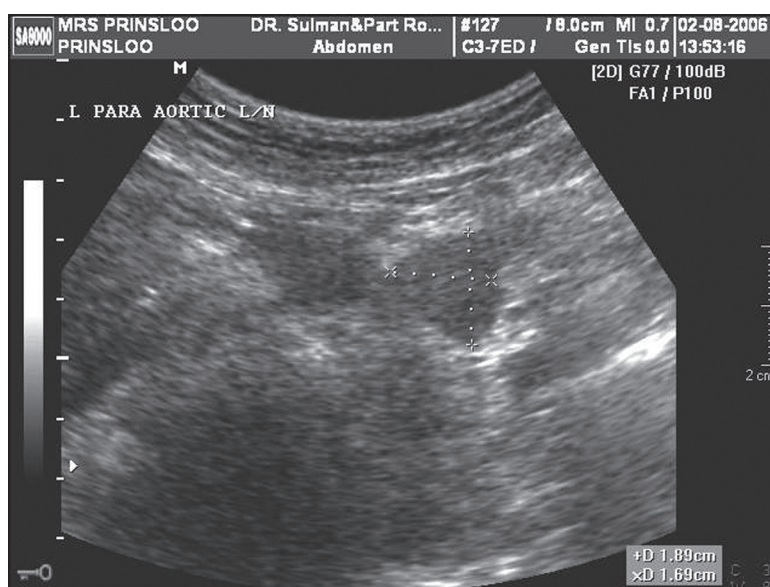


Fig. 1C.

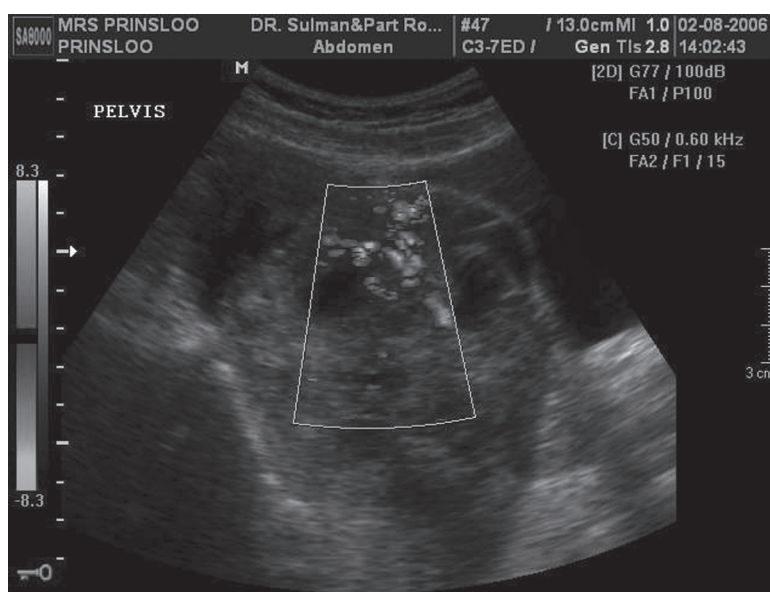


Table I. Laboratory results.

Variable	Presentation in pregnancy	Two months following pregnancy	Acute admission	Second hospital admission	Normal Range
Haemoglobin g/dL	12.5	14.1	12.6	12.2	12.4 – 16.7
White cell count (per mm ³)	8 800	7 890	10 600	5 870	4000 – 12 000
Platelets (per mm ³)	219 000	199 000	156 000	275 000	150 000 – 450 000
C reactive protein (mg/L)	4.7		76.7	10.0	0.0 – 8.0
Prothrombin time (sec)	7.6	12.9	11.3	15.6	7.5 – 10.0
Partial-thromboplastin time (sec)	28.3	30.6		33.4	30.0 – 43.0
Prothrombin time (International normalised time)	0.90	1.31	1.13	1.51	1.00 – 1.25
<i>Factor assays</i>					
Antithrombin III (%)	66	79			87 – 140
Protein C functional (%)	69	67		58	75 – 155
Protein S (%)		87		64	60 – 150
Anti-nuclear factor		1: 640 Speckled		1:640 Speckled	
Anti-phospholipid antibodies	Normal	Normal		Normal	

patient had an underlying connective tissue disorder.

The finding of the patent foramen ovale was co-incidental and was responsible for the embolic cerebral manifestations resulting in stroke. The persistently abnormal low antithrombin levels were attributed to an acquired deficiency resulting from the acute thrombosis and heparin therapy and the low protein C levels to the use of warfarin therapy. In view of her critical condition anticoagulant therapy was not discontinued and levels were not done off anticoagulant treatment. It was never possible to maintain her INR at therapeutic levels despite full warfarin therapy.

The original description and definitions of the “primary” antiphospholipid syndrome (PAPS) was by Asherson (1) in 1988 and the previously reported associations with malignancies with antiphospholipid antibodies were reinforced in 1989 in the first major paper on the “primary: syndrome (2). This association has been more than amply confirmed over the ensuing years. There however appears to be another category of aPL positive patients who do not strictly fall into the PAPS definition in that they either have clinical (*e.g.* frank arthritis, Raynaud’s phenomenon) or demonstrate serological abnormalities (such as an ANA more than 1: 320,

other autoantibodies), which place them in another category (3). This has, for want of a better description, has been termed “Primary Plus” APS into which this patient falls. These patients do not fall into the definition of “lupus – like” disease. As they have features not included in the classification of SLE. It is possible that over time however, if followed chronologically, they may indeed develop defined SLE itself. Our patient in addition to a high level of ANF (1:640), demonstrated elevated immunoglobulins (IgG) and antibodies to thyroid and therefore falls in to this intermediate classification category somewhere between classifiable SLE/ lupus like diseases (LLD) and PAPS, *e.g.*, Primary “Plus”. The relationship of this immunological disturbance and the ovarian carcinoma can only be speculative.

a) Does she indeed suffer from an underlying connective tissue disorder and has coincidentally has developed a malignancy or, b) are these changes consequent on the development of the malignancy?

A pro-coagulant state exists during pregnancy and the postpartum period. In the latter, even normal patients, in the absence of pre-existing coagulopathies, are prone to thrombotic events, *e.g.* deep vein thromboses particularly.

A recent publication by Vázquez-Del Mercado *et al.* has reviewed the many complex molecular mechanisms taking place in both normal pregnancies and in pregnancies complicating the rheumatic diseases (4). These mechanisms occurring normally are primarily directed at protection of the fetus from rejection by the maternal immune system. It is now well established that the antiphospholipid antibodies are associated with fetal losses (early or late) which are not only due to thromboses of the placental vessels themselves because of an hypercoagulable state consequent on the presence of these antibodies but also because of complement activation.

Antibodies to mitochondria (M5) are also directed towards phospholipid, but because their detection, when measured, in early papers, overlapped so greatly with other autoantibodies against phospholipid (*e.g.*, antibodies to cardiolipin, beta2 glycoprotein-1 and prothrombin) they are not usually included in the usual battery of investigational tests performed for antiphospholipid antibodies. The detection of isolated elevations of these antibodies, as in this case, is therefore not only distinctly unusual, but may be of importance in future studies. Indeed, it is more than possible that many cases of so-called seronegative antiphospholipid syndrome (“SNAPS”) patients may be positive for these unusual antibodies.

Tincani *et al.* in 1985 studied 51 sera from SLE patients and found 25 to be aCL positive with a close relationship to anti AMA M5 positivity (5).

Meyer *et al.* in 1987 (6) in a further study on SLE sera suggested that patients with aCL positivity and AMA M5 positivity belonged to two different subsets of SLE or SLE-like syndromes and that the AMA M5 antigen was different from cardiolipin. In a further study from France by Laperche *et al.* (7), the authors suggested that antiAMA M5 represented yet another marker for the antiphospholipid syndrome. It was the only marker present in two of their series of 48 sera. Laperche *et al.* then confirmed this in 1994 (8). In 1998, in a further paper from the Italian group, the detection of AMA M5 was stressed in both primary and secondary

APS and appeared to be statistically associated with thrombocytopenia and recurrent fetal loss (9). Seinturier *et al.* in 2005 reported a patient with Sneddon's syndrome and only AMA positivity (10).

Thrombosis has long been known to be a frequent complication in cancer as was originally pointed out by Trousseau (11) and this complication bears his name, hence "Trousseau's Syndrome". Bick reviewed this association in 2003 (12). In addition to the generation of a procoagulant state by the cancer itself, aggressive anti-tumour therapy and the use of central venous catheters have also been related to an increased risk of thrombosis in patients with malignancies.

The coincidence of malignancies and the presence of antiphospholipid antibodies (aPL) has recently been reviewed in considerable detail by Gomez-Puerta *et al.* (13).

Regarding the frequency of reported solid tumors, these authors found that 6% had renal cell carcinoma, 5% each had tumours of unknown origin, adenocarcinoma of the lung, breast carcinoma and melanoma. 3% had prostatic adenocarcinoma or otorhinological tumours, while only 2% each non-small cell lung cancers, CNS tumours, ovarian, colon and cholangiocarcinoma of the gall bladder. Two authors have only reported ovarian carcinoma in the past (14, 15). The association of aPL and cancers has however also been documented in several important epidemiological studies. The pathological significance of aPL in patients with malignancies is, however, still unclear. It remains an unresolved issue whether the presence of aPL may be considered as an "epiphenomenon" of the malignant disease itself, or whether it contributes directly to the development of thrombosis in this group of patients.

The antiphospholipid syndrome (APS) itself may also be associated with a variety of malignancies, including solid tumours and haematologic neoplasias and has been reviewed by Asherson *et al.* in several publications (16-18). A particularly serious and often fatal development of APS, although fortunately rare, is termed catastrophic APS (Asherson's Syndrome) (19) and this

Fig. 2A.

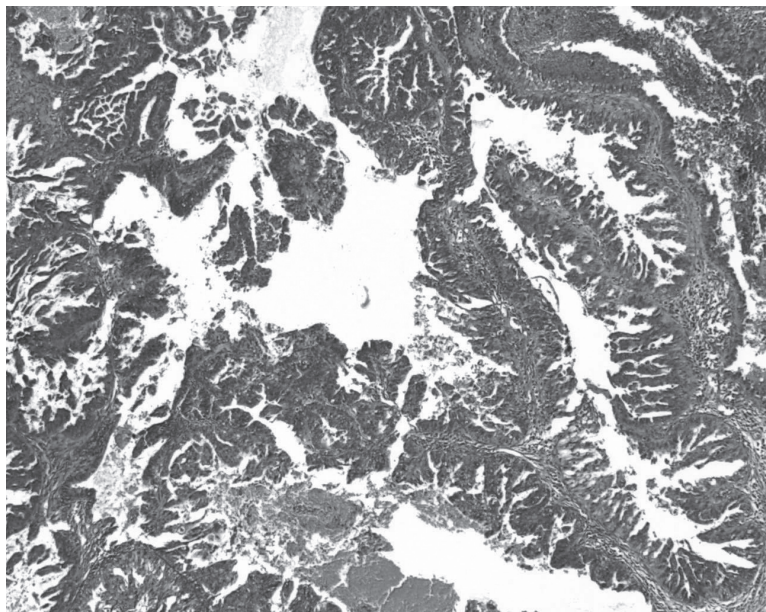
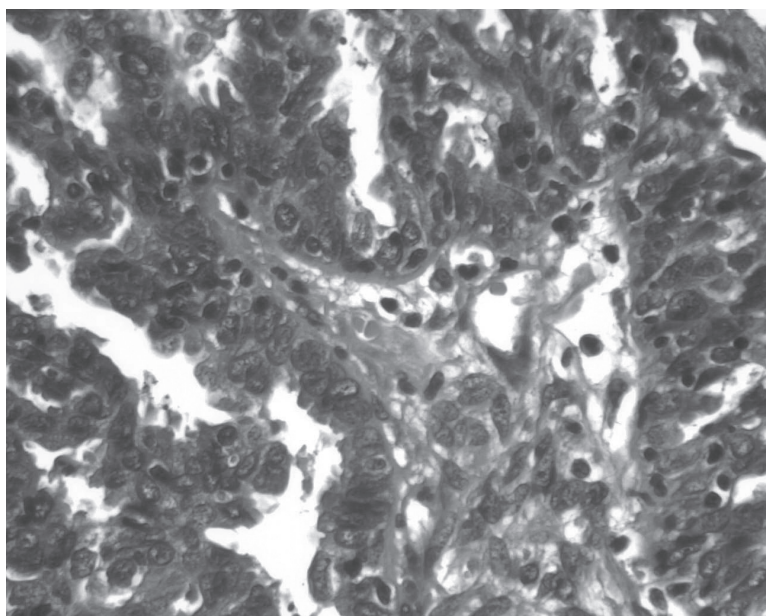


Fig. 2B



has been reported as not infrequently occurring in patients with underlying malignancies (20). The syndrome is characterised by the rapid chronological development of fulminant thrombotic complications that predominantly affect small vessels.

In one large reported group of 216 patients with malignancies, 22% of these patients were found to be anticardiolipin (aCL) positive (21). Compared to the aCL-negative group, the rate of thrombosis among these patients was significantly higher. A high prevalence of aPL (over 60%) was found in a study of Asian patients with cancer-related

thrombosis (22). In this study, anti β 2-glycoprotein-1 IgA antibodies in particular were the most prevalent. Another prospective epidemiological study on the occurrence of malignancies in aPL-positive patients found the presence of carcinoma in 14 of 72 aPL-positive patients. None of these patients had a history of thrombosis and, in one patient with non-Hodgkin's lymphoma, the aPL disappeared when complete remission had been achieved (14).

A further study has in fact confirmed these findings in 100 patients with positive lupus anticoagulants (LAC) (23). Thus, carcinoma is the most frequently

associated disease found in patients with aPL.

In a recent study by Miesbach *et al.* (24), the presence of aPL was found in 39 patients with solid tumours and 19 patients with haematological and lymphoproliferative malignancies. The rate of APS manifestations was higher in patients with solid tumours than in patients with haematological or lymphoproliferative malignancies. The distribution of the aPL antibody subgroups between these two groups, however, did not vary significantly, although the median titre of IgG-aCL was higher in the patients with solid tumours. Haematological and lymphoproliferative malignancies may be associated with the generation of aPL, but their presence does not necessarily enhance the thrombophilic risk in these patients.

It is possible that the presence of these antibodies may be the result of the production of abnormal proteins such as monoclonal immunoglobulins, which accompany monoclonal gammopathy (25). Stimulation of the B cells and consecutive production of a variety of autoantibodies has also been hypothesized. The production of aPL in these patients seems to occur in the absence of thrombotic complications.

This patient presented with recurrent deep vein thromboses complicating pregnancy.

Routine antiphospholipid antibody testing on several occasions was repeatedly negative. But antibodies to mitochondria M5 proved to be positive, establishing the diagnosis of an antiphospholipid syndrome.

However, as has often been stressed in this group of patients, an underlying malignancy might indeed be present or surface within a short time. This patient is an example of a "paraneoplastic syndrome" associated with an unusual antiphospholipid antibody profile, accompanying recurrent deep vein

thrombosis, which proved to be secondary to an ovarian carcinoma, which was initially undiagnosed clinically. The clinical picture was complicated by the presence of a patient foramen ovale resulting in paradoxical emboli to the brain and multiple cerebral infarctions.

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