

Short reports

Increased expression of proliferating cell nuclear antigen in autoimmune hepatitis in a patient with raised serum concentration of CA19-9

T Sohda, Y Iwata, H Shijo, Y Egashira, K Egashira, M Okumura

Abstract

A 52 year old woman had autoimmune hepatitis and an increased concentration of serum carbohydrate antigen 19-9 (CA19-9). The origin of the raised CA19-9 was studied using immunohistochemistry. Liver biopsy section showed chronic active hepatitis with large numbers of proliferated bile ductules. Immunohistochemical analysis revealed that the proliferated bile ductule cells were positive for proliferating cell nuclear antigen (PCNA) and for CA19-9. It is speculated that the raised serum CA19-9 concentration was derived from proliferated bile ductule cells and these cells, which are positive for PCNA, may be able to produce high concentrations of CA19-9.

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Keywords: CA19-9; proliferated bile ductules; autoimmune hepatitis; immunohistochemistry; proliferating cell nuclear antigen

Autoimmune hepatitis is a rather uncommon liver disease occurring predominantly in middle aged people, especially women. Autoimmune hepatitis is known to respond to corticosteroid treatment.¹ Carbohydrate antigen 19-9 (CA19-9) is a tumour marker that is

raised in serum in some malignant tumours such as pancreatobiliary cancers.^{2,3} In this case of autoimmune hepatitis, the serum concentration of CA19-9 was remarkably increased despite the absence of complicating malignancy. We studied the origin of the CA19-9 increase using immunohistochemistry in this case of autoimmune hepatitis.

Case report

A previously well 52 year old Japanese woman had general fatigue, dark urine, and jaundice in November 1994. She had no history of transfusion or alcohol abuse. Physical examination revealed a well nourished, well developed woman. She had no fever, her blood pressure was 114/70 mm Hg, and pulse was 72 beats/min. There was pronounced scleral icterus. The liver was palpable three finger widths below the right costal margin.

Laboratory data showed severe liver dysfunction with jaundice. Total bilirubin and direct bilirubin were 12.8 mg/dl (normal, 0.2-1.2) and 9.6 mg/dl (normal, <0.5), respectively. Serum aspartate aminotransferase activity was 336 U/l (normal, <35), alanine aminotransferase, 283 U/l (normal, <35), γ glutamyltransferase, 99 U/l (normal, 40), and alkaline phosphatase, 262 U/l (normal, 90-230). Immunoglobulin concentrations were as

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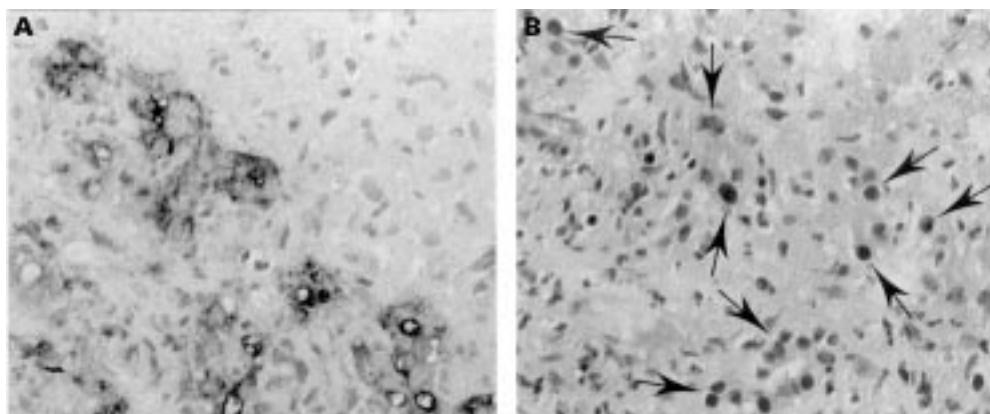


Figure 1 (A) Immunohistochemistry revealed high concentrations of CA19-9 in the cytoplasm and on the apical surface of small bile ductule cells, which were crowded at the periphery of portal areas. (B) A serial section showed that PCNA stained the nuclei of bile ductule cells (arrows), which are positive for CA19-9, and some surrounding hepatocytes. (Avidin-biotin complex method; original magnification $\times 200$.)

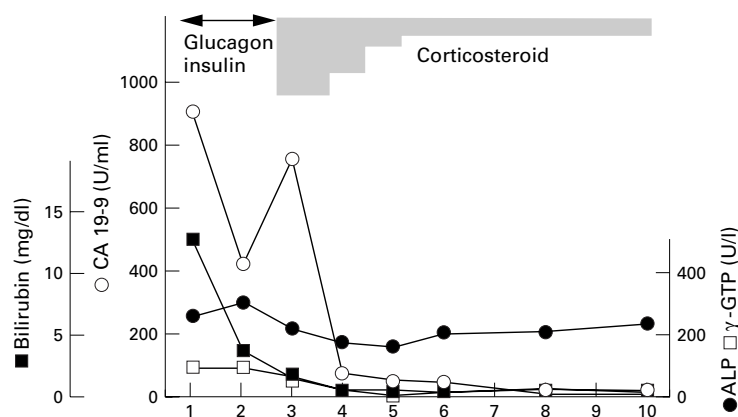


Figure 2 The course of CA19-9, total bilirubin, transaminases (ALP), and γ glutamyltransferase (γ -GTP).

follows: IgG 2980 mg/dl, IgA 544 mg/dl, IgM 284 mg/dl. Hepatitis B virus s antigen and hepatitis C virus antibody were negative. Further investigation revealed a positive anti-nuclear antibody titre of 1:40 and an anti-smooth muscle antibody of 1:40.

CA19-9 concentration was 911 U/ml (normal, <37), carcinoembryonic antigen was 1.3 ng/ml (normal, <2.5), and α fetoprotein (α FP) was 3 ng/ml (normal, <10).

An ultrasound and computed tomography of the upper abdomen showed no evidence of tumorous lesions in the abdominal organs including the liver, biliary system, and pancreas. Endoscopic retrograde cholangiopancreatography revealed no abnormality.

Methods

A diagnostic needle liver biopsy was performed. The liver tissue was fixed in 10% buffered formalin and embedded in paraffin wax for conventional staining and immunohistochemistry.

Immunohistochemical staining was performed using the avidin-biotin complex method. Mouse monoclonal antibodies against Sialyl Lewis (CA19-9 antibody; Novocastra Laboratories Ltd, Newcastle upon Tyne, UK) and proliferating cell nuclear antigen (PCNA antibody; Dako, Glostrup, Denmark) were used at final dilutions of 1/200 and 1/100, respectively. After subtraction, the sections were counterstained with haematoxylin.

Results

Liver section showed severe necrosis of hepatocytes with infiltrating cells, which comprised many lymphocytes and a few eosinocytes, and moderate fibrosis. From the histological findings and serological examination, we diagnosed autoimmune hepatitis. Immunohistochemistry revealed that high concentrations of CA19-9 were localised in the cytoplasm and on the apical surface of small bile ductule cells, which were crowded at the periphery of portal areas (fig 1A). A serial section showed staining for PCNA, a proliferation marker, in the nuclei of bile ductule cells (which were positive for CA19-9) and some surrounding hepatocytes, suggesting that CA19-9 positive cells were proliferated bile ductules (fig 1B).

Discussion

Tumour markers have been recognised to be useful for diagnoses of malignancy. However, benign diseases sometimes cause raised serum tumour makers. α FP derived from proliferating hepatocytes has been known to be raised in the presence of severe liver damage.⁴ Several studies of benign diseases, such as obstructive jaundice without malignancy, have reported increased concentrations of CA19-9.^{5,6} However, in most of those cases, the serum concentrations of CA19-9 have been only mildly raised. At concentrations above 1000 U/ml, the specificity of the CA19-9 assay is reportedly more than 99% for malignant gastrointestinal disease.⁷

The present patient had evidence of neither CA19-9 producing tumours nor obstructive jaundice. Liver biopsy specimen showed severe necrosis in the hepatic lobes and large numbers of proliferated bile ductules. Immunohistochemical analysis revealed that the proliferated bile ductule cells were positive for CA19-9, implying that these cells were responsible for the raised serum concentrations of CA19-9.

It has been reported that obstructive jaundice causes extensive proliferation of bile duct-like structures in the portal area of experimental rat liver.⁸ We speculate that in this case, high concentrations of serum bilirubin suggested intrahepatic cholestasis, and proliferation of small bile ductules by cholestasis may be associated with increased CA19-9. This mechanism may be similar to that in obstructive jaundice with increased CA19-9.

Satomura *et al* reported that CA19-9 was expressed not only in the cytoplasm of malignant ductal cells in pancreatic cancer but also on the apical membranes of ductal cells in normal pancreatic tissue, suggesting the importance of staining pattern of CA19-9, which is cytoplasmic-type or apical-type.⁹ In the present case, there was both cytoplasmic and apical staining for CA19-9 in the proliferating bile ductules while normal bile ductule cells were slightly stained only on the apical surface of the cells. This cytoplasmic staining suggests production of CA19-9 by the cells, which is thought to contribute to the raised serum CA19-9.

PCNA is known to be expressed at increased levels in cells that have high cell proliferation activity such as neoplastic cells.¹⁰ In the present case, the localisation of PCNA positive cells was almost identical to that of CA19-9 positive bile ductule cells, suggesting that unlike conventional bile ductule cells, proliferated bile ductule cells are immature. Thus, we speculated that proliferated bile ductule cells, which are positive for PCNA, have an increased ability to produce CA19-9.

On the 14th day of corticosteroid treatment, transaminase and bilirubin concentrations were normal, and serum CA19-9 was also reduced to normal after six months (fig 2). Although, proliferation of bile ductules is commonly seen in liver diseases with hepatic injury, the clinical course suggests that suppression of hepatitis by corticosteroid treatment results in

a gradual decrease in the number of proliferated bile ductules and serum CA19-9 is normalised.

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A case of systemic pseudo-pseudoxanthoma elasticum with diverse symptomatology caused by long term penicillamine use

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Abstract

A 47 year old man presented with a two year history of increasing cervical dysphagia, dyspnoea, and cutaneous signs. He had been diagnosed 27 years previously with Wilson's disease and was treated with penicillamine (1.5 g daily). Systemic abnormality of elastic fibres was confirmed by light and electron microscopy following biopsy of skin, lung, oesophageal muscle, gum, pharyngeal tissue, and cervical connective tissue. Dysphagia was relieved by cricopharyngeal myotomy. Substitution of trientine dihydrochloride for penicillamine relieved cutaneous and systemic manifestations. This is possibly the first case demonstrating an association between prolonged penicillamine use and biopsy proved systemic pseudo-pseudoxanthoma elasticum. The presenting symptoms may have resulted from the abnormal numbers and properties of elastic fibres, and the changes were caused by penicillamine use, rather than by idiopathic, inherited pseudoxanthoma elasticum.

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Keywords: penicillamine; pseudoxanthoma elasticum; trientine dihydrochloride; Wilson's disease

Penicillamine (D-B-B-dimethylcysteine) is a heavy metal chelator used to treat Wilson's disease (an autosomal recessive abnormality of hepatic copper excretion). Prolonged use at high doses (1-2 g daily) may cause elastic fibre disorders in skin, lung, viscera, blood vessels, and connective tissues.¹⁻⁶ The term pseudo-pseudoxanthoma elasticum (PPXE)³ distinguishes the acquired condition from idiopathic,

genetically controlled pseudoxanthoma elasticum (PXE). We report the manifestations and management of a patient with histologically proved, systemic, penicillamine induced PPXE.

Case report

A 47 year old white man (a non-smoker with no previous lung disease) presented with a two year history of increasing cervical dysphagia necessitating a liquid diet, dysphonia, and progressive effort dyspnoea. He had been diagnosed with Wilson's disease 27 years previously, following an acute psychotic illness, and was treated with penicillamine (1.5 g daily). The Wilson's disease, inherited with an autosomal recessive pattern, affected three of his siblings. There was no history of idiopathic PXE in the family. None of the three affected siblings had PXE-like symptoms (although one has coarse skin), despite treatment with long term penicillamine.

Ten years earlier a benign vocal cord nodule of our patient was excised to relieve dysphonia. Over three years, excision biopsies of skin, a gum dermatofibroma, and thickened pharyngeal tissue indicated changes of PPXE.⁷ Clinical examination consistently revealed a yellow "plucked chicken" appearance of the folded skin of the neck and axillae but no angioid streaks in the retina. Barium studies showed hold-up to flow through the oesophagus at the cricopharyngeus. Manometric investigation demonstrated an abnormal, incomplete or non-relaxing upper sphincter zone with premature closure following deglutition with a pressure of >40 mm Hg (normal, 53 (23) mm Hg). Oesophagoscopy revealed normal squamous mucosa. Dilatation of the narrowed zone by a 60 F gauge Maloney

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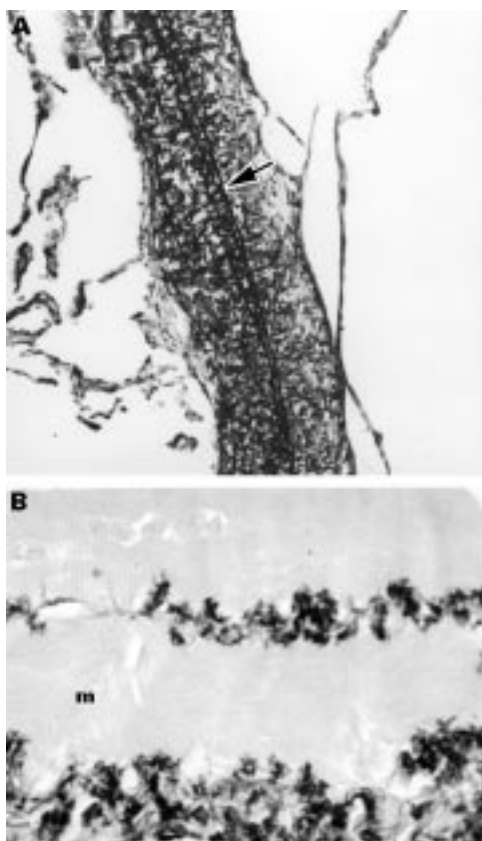


Figure 1 (A) Section of lung stained with elastic Van Gieson. The abnormal elastic fibres are seen as a double contour in the pleura (arrow). (B) Section of upper oesophagus showing the lateral budding of dense groups of elastic fibres running between bundles of striated muscle (m).

dilator was achieved easily. Open lung biopsy was performed at the time of dilatation. As the dysphagia was unrelieved, a longitudinal cricopharyngeal myotomy through the muscle layers of the oesophagus was performed. The toughness of connective tissues within the neck made dissection difficult. Biopsy specimens were taken of skin at the incision site, of muscle fascia, and of oesophageal muscle; these were fixed freshly in formalin and glutaraldehyde. No impairment of wound healing was seen following the procedure.

Light microscopy of all tissues (skin, lung, oesophageal muscle, and connective tissue) showed excess elastic fibres with thickening and lateral budding and the characteristic “lumpy bumpy” appearance of PPXE.^{1 8} In the lung, the pleura (fig 1A) and bronchial walls were involved. Lung parenchyma, otherwise normal, showed some early emphysematous change. Comparison of the oesophageal biopsies with tissue from a normal oesophagus (from an organ donor at transplant harvest) demonstrated the excess and abnormality of elastic fibres within all levels of the wall (fig 1B). Fibres within walls of arteries and veins of all tissues were abnormal. The elastic fibres showed no accumulation of calcium (von Kossa stain was negative).

Transmission electron microscopy confirmed irregularity of the elastic fibres. No normal elastic fibres were seen in any of the biop-

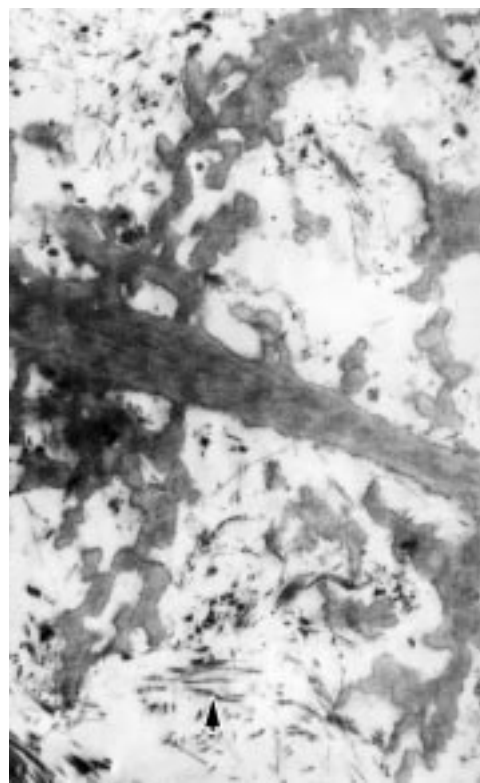


Figure 2 Transmission electron micrograph of an abnormal, arborising, elastic fibre from cervical connective tissue. Normal collagen fibres are arrowed. (Original magnification, $\times 14\,300$).

sies (normal elastic fibres are seen as long wavy strands, forming a delicate anastomosing network between collagen fibres). The abnormal fibres consisted of a central core of uneven thickness with many lateral arborisations. There were branches at right angles to the main fibre with perpendicular lateral arborisations off these producing a “stag-horn” or “fractal” appearance (fig 2). Elastic fibres from skin had shorter and plumper arborisations than those from connective tissue. In the central core, thin microfibrils were embedded in amorphous material. There were no microfibrils in the lateral buds. In oesophageal muscle, some smooth and striated muscle cells were thinned and pulled apart by the abnormal fibres, with fragmented elastic material deposited between them. In contrast to the abnormal elastic fibres, the adjacent collagen fibres were normal in structure (with a normal banding repeat pattern of 64 nm) and arrangement.

Radiographic and symptomatic resolution of cervical dysphagia followed myotomy. Chest radiography and computed tomography showed bilateral pulmonary shadowing with no pleural thickening or lymphadenopathy. Pulmonary function tests⁹ showed a restrictive defect with FEV1 of 3.12 litres (81% of predicted normal), forced vital capacity (FVC) 4.00 litres (84% of predicted), a total lung capacity (TLC) 77% of predicted, and gas transfer 64% of predicted. An immunological screen was negative.

With worsening pulmonary function, empirical treatment with 30 mg prednisolone daily was prescribed. After six weeks there was

a symptomatic improvement in his dyspnoea. This was not sustained, TLC falling to 60% of predicted and gas transfer to 53%. Furthermore, the patient developed a steroid psychosis. The deterioration in physical and mental states, together with histological evidence of multisystem PPXE, triggered the decision to initiate treatment with trientine dihydrochloride (Trientene; K & K-Greeff Ltd, Croydon, UK) at a dose of 300 mg four times a day, and to discontinue penicillamine. Twelve months after the change of medication the cutaneous PXE-like changes were very diminished. Systemically the patient was improved, without dysphagia or dyspnoea. Pulmonary function was stable (FEV1 2.84 litres, FVC 3.79 litres, TLC 77%, and gas transfer 58% of predicted). At 36 months (48 months postoperative), he is neurologically controlled, is swallowing easily, and has stable pulmonary function and chest radiology.

Discussion

We believe this is the first case demonstrating an association between prolonged penicillamine administration and biopsy proved systemic PPXE. We postulate that the presenting symptoms resulted from the abnormal numbers and properties of elastic fibres, and that the changes were caused by penicillamine use, rather than by idiopathic, inherited PXE. It is not known why only one of the four siblings should manifest the changes of PPXE. PPXE, although producing similar cutaneous manifestations to those seen in PXE, has different structural abnormalities and a different aetiology. In PPXE, penicillamine impairment of stable fibre cross links is implicated rather than calcification of fibres (as is the case in PXE).^{3, 8} The lack of family history and ocular signs, together with systemic abnormalities of non-calcified elastic fibres, all serve to define our case as one of PPXE.

In normal extracellular space, elastin polypeptides align into a fibrillar structure that is stabilised by desmosomal interchain cross links, requiring the catalysis of a copper dependent enzyme (mapped to human chromosome 5q23), lysyl oxidase, which is also required for the cross linking of collagen fibres. Penicillamine could possibly chelate extracellular copper, interfering with lysyl oxidase. The correct formation of elastic tissue and collagen needs aldehydes to form stable cross links. Lysyl oxidase mediates the oxidation of lysine residues in collagen and elastin and hydroxylysine residues in collagen. They are oxidised to their respective aldehydes, which react with one another to form stable cross links.^{5, 10} Penicillamine reacts with aldehydes to form thiozolidine compounds, thus impairing the formation of such stable cross links.⁸ Penicillamine does not affect mature collagen but interferes with new production; it may be many years before collagen defects manifest themselves as dermatopathies. PXE-like changes appear par-

ticularly in flexural areas, where the elastic tissue production rate may be high because of stretching stresses.

Myotomy relieved the patient's dysphagia, suggesting that this symptom was predominantly caused by local abnormalities of muscle and connective tissue compliance. Similarly, his restricted pulmonary function may have resulted from abnormal fibres reducing lung elasticity. Penicillamine gave long term control of neurological functions but provoked a diverse symptomatology. The systemic nature of the PPXE made treatment difficult, and there was an insidious progression of symptoms. Penicillamine and trientine dihydrochloride both act as chelating agents, which mobilise abnormally deposited copper and result in a cupriuresis. Trientine dihydrochloride is being developed for use in Wilson's disease for patients who are intolerant to penicillamine. Penicillamine has the property of impairing stable cross links of newly formed elastic fibres with collagen. If penicillamine treatment is abandoned (and trientine has no deleterious effect on the availability of copper for the dependent enzyme lysyl oxidase) switching to the new drug may allow formation of normal elastic linkages, permitting relief from systemic symptoms caused by abnormal numbers and structures of elastic fibres, with a rate of improvement depending on the rate of turnover of fibres in different tissues. Thirty six months after substitution with trientine dihydrochloride in our patient, Wilson's disease was controlled, with objective evidence of improvement in the patients' systemic complications.

The patient is also under the care of Professor H R Matthews (Consultant Thoracic Surgeon) and Dr M Anderson (Consultant Neurologist) of Birmingham Heartlands Hospital. Miss K A Noble (Oesophageal Function Laboratory, Birmingham Heartlands Hospital) performed preoperative manometry. Mr G Mannion gave skilled photographic support. SJD is supported by the Oesophageal Cancer Fund (OCF), Birmingham.

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Intravascular synovial sarcoma

N J Robertson, M H Halawa, M E F Smith

Abstract

A case of intravascular biphasic synovial sarcoma arising from the wall of the left femoral vein in a 34 year old woman is described. This is the third case of an intravascular synovial sarcoma known to be reported in the medical literature. The two previous cases arose from the left femoral vein and inferior vena cava in women of 34 and 31 years old, respectively. A characteristic clinical pattern appears to be emerging—that is, location in large veins of the lower extremity and trunk in young adult females. Synovial sarcoma must be considered in the differential diagnosis of intravascular “tumours”.

(*J Clin Pathol* 1998;51:172–173)

Keywords: femoral vein; synovial sarcoma

Synovial sarcoma is a well defined entity with characteristic clinical and morphological features. It occurs predominantly in adolescents and young adults, and arises most commonly from para-articular soft tissues, particularly around the knee.¹ As far as we are aware, only two cases of intravascular synovial sarcoma have been described in the literature; one arose from the wall of the left femoral vein in a 34 year old woman,² the other from the wall of the inferior vena cava in a 31 year old woman.³ We report a case of biphasic synovial sarcoma arising from the wall of the left superficial femoral vein in a 34 year old woman.

Case report

A 34 year old woman presented in March 1997 with a two week history of a swelling in the left thigh associated with a constant dull aching sensation. Physical examination revealed a firm mass, approximately 7 cm in length and 4 cm in width, within the medial part of the upper third of the left thigh. There were no palpable lymph nodes and no evidence of a tumour in any other part of the limb or elsewhere. The patient was otherwise well. Magnetic resonance imaging (MRI) showed the mass to be predominantly solid with peripheral cystic areas, and to be located within the adductor canal close to the neurovascular bundle. The clinical and MRI features strongly suggested a soft tissue sarcoma. Surgery showed that the tumour arose from the wall of the superficial femoral vein at its confluence with the profunda femoris vein, and completely occluded the lumen of the former vessel. The involved segment of the superficial femoral vein was ligated and excised, and sent for frozen section examination; the diagnosis was intravascular synovial sarcoma.

The patient was treated with chemotherapy and radiotherapy to the tumour bed; there has been no evidence of recurrence.

Pathological findings

The surgical specimen was a segment of superficial femoral vein, 7 cm in length and 3.5 cm in diameter, distended by an ovoid, focally haemorrhagic, yellow and grey tumour that appeared firmly adherent to the vessel wall around its entire circumference (fig 1). Tumour protruded approximately 1 cm beyond one cut end of the vessel. Although predominantly solid, a few cyst-like spaces up to 1 cm in diameter were present in the peripheral part of the tumour. Along its length the vessel was partly surrounded by skeletal muscle and fibroadipose tissue.

Light microscopy examination of frozen and paraffin wax embedded sections revealed the typical morphological features of a biphasic synovial sarcoma—that is, nests of rounded epithelioid cells scattered among sheets of plump spindle cells with many intervening cells of intermediate morphology (fig 2). The epithelioid cells had moderate to large amounts of eosinophilic cytoplasm and ovoid or rounded vesicular nuclei in which occasional indistinct nucleoli were apparent. In some areas these cells lined small gland-like spaces containing homogeneous eosinophilic secretions (fig 2). At the periphery of the tumour, several irregular cyst-like spaces were also lined by cells of this type. The spindle cells had scant amounts of cytoplasm, and elongated hyperchromatic nuclei and were arranged in compact sheets. Mitotic activity was low (approximately three mitoses in 30 high power fields). Scattered throughout most fields were moderate numbers of small spherical calcific concretions.

Immunohistochemistry, using a streptavidin-biotin-peroxidase complex technique, revealed strong cytokeratin expression (MNF 116, Dako 0821, Copenhagen, Denmark) by



Figure 1 Synovial sarcoma distending a segment of the left superficial femoral vein.

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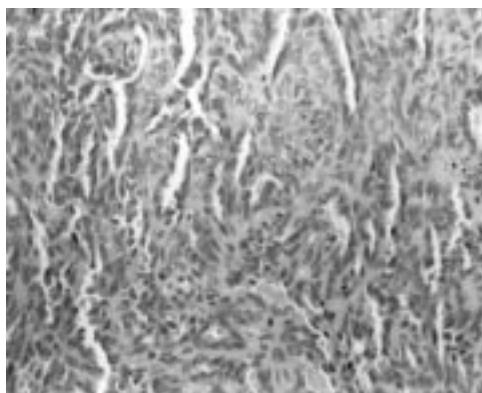


Figure 2 Synovial sarcoma displaying a typical biphasic pattern.

the epithelioid cells and most of the spindle cells. Where the tumour joined the wall of the femoral vein there was patchy fibrosis of the intima and media. Curiously, no residual endothelial cells could be found lining any part of the vessel. In their stead, flattened epithelioid tumour cells, mimicking endothelium but staining for cytokeratin and not for CD34 (Bionostics M87030, Wyboston, UK) or von Willebrand factor (Dako A0082), extended to the cut ends of the vein.

Discussion

Synovial sarcoma most commonly arises from the para-articular soft tissues of the extremities. It is most prevalent in adolescents and young adults (15 to 40 years old), and there is a slight male predominance (1.2:1).¹ It usually arises in close association with tendon sheaths, bursae, and joint capsules, but is uncommonly encountered within joint cavities.⁴ Rarely, it is found at sites having no apparent synovial structures, such as the tongue, parapharyngeal region, and abdominal wall, and consequently its origin

from preformed synovial tissues is doubtful. Our case, and those previously reported,^{2,3} of a biphasic synovial sarcoma arising from, and entirely contained by, a blood vessel appear to exclude a synovial origin for these tumours.

To the best of our knowledge, this is the third case reported of a primary intravascular synovial sarcoma. Interestingly, two cases arose from the wall of the left femoral vein in 34 year old women, and one arose from the wall of the inferior vena cava in a 31 year old woman. Although the number of cases reported is very small, a characteristic clinical pattern seems to be emerging—that is, location in large veins of the lower extremity and trunk in young adult women.

In our case, a layer of flattened, cytokeratin positive tumour cells, mimicking endothelial cells, extended to the resection margins of the vessel. In treating these rare tumours it is, therefore, important to note that tumour cells may extend, in a very subtle manner, beyond the obvious macroscopic limits of the tumour.

Synovial sarcoma must be considered in the differential diagnosis of intravascular “tumours”. Non-neoplastic and neoplastic conditions that may present in this fashion are very diverse, and include intravascular fasciitis, pyogenic granuloma, epithelioid haemangio-endothelioma, and leiomyosarcoma. Biphasic synovial sarcoma can be differentiated from these by virtue of its biphasic growth pattern with gland-like and spindled components, both of which show at least focal cytokeratin positivity.

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A case of systemic pseudo-pseudoxanthoma elasticum with diverse symptomatology caused by long-term penicillamine use.

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