

LESSON OF THE MONTH

Unable to see the wood for the trees

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Case history

A 48 year old man with 17 year history of primary Sjögren syndrome (pSS) presented with a sudden swelling of the left lower limb without pain, fever or any other symptom. The diagnosis of pSS was based on xerophthalmia, xerostomia, and swelling of the parotid glands in the presence of positive antinuclear antibodies (ANA), rheumatoid factor (RF), anti-Ro (85 IU ELISA, normal range <25 IU), anti-La (37 IU ELISA, normal range < 25 IU), and typical pathological findings in a minor salivary gland biopsy specimen. During 17 years, the clinical course was characterised by recurrent swelling of the parotid glands without evidence of extraglandular disease or significant changes in his laboratory profile.

On admission, diffuse non-tender swelling of the whole limb was observed without lymphadenopathy. The rest of the physical examination was normal. He was admitted to hospital with suspected deep vein thrombosis (DVT) and treatment with intravenous heparin was started. An ultrasound Doppler examination up to the left inguinal area could not confirm DVT, but in view of the suggestive clinical picture, intravenous heparin was continued. Table 1 summarises laboratory tests on admission. A chest radiograph was normal.

Two days after admission, the patient became anuric with progressive dyspnoea. Physical examination was suggestive of pleural effusion, confirmed on chest radiograph and thoracentesis, which revealed a transudate without malignant cells. Electrocardiogram was normal. Central vein pressure was found to be high (24 mm Hg). Blood tests showed renal deterioration with blood urea nitrogen 83 mg/dl and serum creatinine of 4.3 mg/dl. The

patient was treated with diuretics, dopamine, and haemodialysis—with a significant improvement in his dyspnoea but none in his renal function. He developed fever with a temperature of 39°C. Ultrasound of the abdomen was normal and there was no evidence of hydronephrosis or a space occupying lesion. Doppler ultrasonography of the renal arteries and veins was normal.

Five days after admission, in view of the urinary sediment, increased erythrocyte sedimentation rate (ESR), cryoglobulinaemia and low C4 concentrations (table 1), it was assumed that the acute renal failure was caused by cryoglobulinaemic vasculitis. Pulses of intravenous methylprednisolone (1 g/day ×3) followed by oral prednisone (80 mg/day) and a single pulse of 750 mg cyclophosphamide were given but, although becoming afebrile, no improvement in his renal function was observed.

Nine days after admission, the patient experienced sudden faintness and pain in the left lower abdominal quadrant. He looked pale and sweaty. Blood pressure was 90/60, pulse 112/min, the abdomen was tender, mainly in the lower abdominal quadrant, rectal examination was normal. The haemoglobin decreased to 7.2 g/d. Although partial thromboplastin time was not excessively prolonged and platelet count was above 100 000/mm³, an acute internal haemorrhage was suspected. Heparin was stopped and packed blood cells with fresh frozen plasma transfusions were given. Computed tomography of the abdomen demonstrated thickening of the iliopsoas and moderate amount of peritoneal fluid, suggestive of a retroperitoneal haematoma (fig 1). The patient was stabilised haemodynamically and the haemoglobin concentration increased to 9.5 g/dl.

In view of the persisting renal failure and cryoglobulinaemia, plasmapheresis was added. Eleven days after admission, an improvement in urinary output was observed at first and the renal function slowly returned to normal. Repeated abdominal computed tomography showed disappearance of the peritoneal effusion, but findings consistent with retroperitoneal haematoma were still present.

Twenty one days after admission, the patient was feeling well and released from hospital without any pathological findings on physical examination except for the dry mucosal membranes. The oedema of the left limb was completely resolved. Renal function tests,

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Table 1 Laboratory results

Test	at admission	2 days after	Test (normal)	2 days after
ESR	87 mm 1st h	90 mm 1st h	RF (ELISA0-60)	759 IU/ml
Hb	9.3 g/dl	9.3 g/dl	ANA	positive
WBC	5100/mm ³	9000/mm ³	anti-dsDNA	normal
PLT	245000/mm ³	210000/mm ³	anticardiolipin	normal
BUN	20 mg/dl	83 mg/dl	C3 (101-186)	104
Creatinine	1 mg/dl	4.3 mg/dl	C4 (16-47)	3
Urine analysis			Cryoglobulins	40%*
protein		300 mg/dl		
casts		hyaline and granular		
RBC		+++		

ESR: erythrocyte sedimentation rate, RF: rheumatoid factor, ANA: antinuclear antibodies, *IgM-k monoclonal RF.

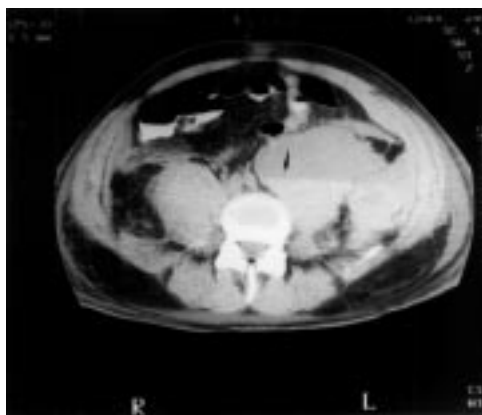


Figure 1 Computed tomography of the upper pelvic region demonstrating a mass anterior to the left iliopsoas muscle (arrow) with free fluid level, suggestive of retroperitoneal haematoma.

complete blood cell count, ESR, cryoglobulins, and C4 levels returned to normal. High doses of oral prednisone were continued and azathioprine was added.

Three months later, still taking 10 mg prednisone and 100 mg of azathioprine daily, the patient presented again with painless swelling of the left lower limb. The arterial pulses were normal. A non-tender hard consistency mass of 6 cm diameter was palpated in the left lower abdominal quadrant. Ultrasound Doppler did not show evidence of thrombosis but the limb venous flow was slow while no flow was shown in the left iliac vein, interpreted as a result of possible thrombosis of the left iliac vein. Anticoagulant treatment was restarted. Ultrasound localised the left lower abdominal quadrant mass in the retroperitoneum, with thickening of the iliopsoas consistent with an organised retroperitoneal haematoma. After two weeks of oral anticoagulant treatment, repeated Doppler ultrasonography demonstrated venous thrombosis in the saphenous, common and superficial femoral and left iliac veins. Computed tomography showed: "Thickening of the iliopsoas and retroperitoneal fascia and a soft density process, irregularly enhanced by the contrast medium, in proximity to the origin of the iliac vessels. Hypodensity was noted within the lumen of the ilio-femoral vein. Interpretation: compatible with thrombosis and/or organised haematoma, though another process such as lymphadenopathy cannot be ruled out".

Despite satisfactory anticoagulation, there was no improvement in the limb swelling and further increase in the dimensions of the palpable mass was noticed. A fine needle aspiration was considered, but the risk of a closed biopsy under anticoagulant therapy withheld the decision. Magnetic resonance imaging of the lower abdomen disclosed a 8×5×7 cm solid mass that seemed to be a primary tumour although its origin could not be defined.

The patient underwent laparotomy and an open biopsy of the mass. Pathological studies confirmed diffuse large cell lymphoma, (kera-

tan negative, S-100 negative, Pan B positive, Pan T negative, CD30 negative), clinical stage III.

Discussion

Primary SS is usually characterised by a stable course of exocrine and extraglandular manifestations. The increased risk of malignant lymphoma is well documented.¹ Mixed cryoglobulinaemia is a known manifestation of both lymphoproliferative disorders and connective tissue diseases, especially pSS, where it may be found in up to 37% of patients² consisting of IgMk mononuclear RF in most cases.² Cryoglobulinaemia, as well as serum and urinary monoclonal gammopathy³ in a patient with pSS may however herald lymphoma.⁴ Although cryoglobulinaemic vasculitis generally responds to high dose corticosteroids, and in this case also to intravenous cyclophosphamide and plasmapheresis, this does not exclude an underlying lymphoma. Lymphoma induced the venous obstruction and the following cascade of events, and probably responded partially to these treatments. The supposed retroperitoneal haematoma, which was in part responsible for the delay in the correct diagnosis, probably reflected a heparin induced bleeding within the lymphoma. True retroperitoneal haematoma is a rare complication of anticoagulant treatment.⁵ Though computed tomography is considered an accurate non-invasive method for detecting retroperitoneal haematoma, it is by no means pathognomic and may be easily confused with a retroperitoneal tumour.⁶

Patients with an abdominal mass other than a palpable liver or spleen should undergo early diagnostic laparotomy⁷ as multiple imaging procedures seldom bypass eventual biopsy, and frequently delay definite histological diagnosis.⁸ This is especially true in a patient who is prone to lymphoma. Most patients with retroperitoneal non-Hodgkin's lymphoma need laparotomy to confirm the diagnosis.⁸

The lesson

- The unexplained presenting symptom—in this case, the mysterious limb oedema—should never be neglected. Diluted but not solved by other medical emergencies, each treated successfully, it remained the clue to the correct, alas delayed, diagnosis.
- The potential development of lymphoma in patients with pSS must always be remembered, especially in the context of unusual or unexplained clinical manifestations, or both, for example, cryoglobulinaemic vasculitis. The latter may prove to be clues to the evolution from pSS, an exocrine disease with polyclonal B cell activation to more systemic disease with polyclonal, oligoclonal, and monoclonal B cell activation, thus potentially heralding lymphoproliferative disease with monoclonal activation.
- Aggressive immunosuppression may mask not only inflammatory signs but also partially suppressed lymphoproliferative disorders.

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Historical images

Series editors: W Grassi, C Cervini



Figure 10 Dolichostenomelia.
 Apert. Dolichostenomelia, arachnodactylie. In: Marfan A-B, Apert, Aviragnet, Bernard L, Garnier M, Hallé J, Milian. *Maladies des os*. Paris: Librairie J-B Baillière et fils, 1912.