Retroperitoneal fibrosis and scleroderma

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Summary

The association of retroperitoneal fibrosis and systemic sclerosis is reported from a patient positive for the HLA-B27 antigen. This appears to be the first report of such an association. Pathological features common to the 2 syndromes are discussed and the literature is reviewed.

Introduction

Idiopathic retroperitoneal fibrosis was first accurately described by Ormond in 1948 and although some cases may represent adverse effects of vasoactive drugs (Saxton *et al.*, 1969; Stecker *et al.*, 1974; Iversen *et al.*, 1975), particularly methysergide (Graham, 1964; Graham *et al.*, 1966) and others form part of diffuse fibrosing syndromes affecting the mediastinum, lungs, liver, thyroid and orbit (Mitchinson, 1965; Comings *et al.*, 1967; Carton and Wong, 1969; Coopersmith and Appelman, 1971; Palmer, Wolfe and Kostas, 1978), the majority of cases lack a clear aetiology.

This communication reports the development of retroperitoneal fibrosis in a patient who had experienced Raynaud's syndrome for many years, and who was subsequently shown to have scleroderma with evidence of visceral involvement.

Case report

A 50-year-old Caucasian woman was referred to hospital because of painless swelling affecting both legs. Hypertension had been diagnosed a short time before and she was being treated with 2 tablets of 'Navidrex-K' (cyclopentiazide and potassium chloride) daily. The only positive points in her past medical history were toxæmia of pregnancy and surgery for varicose veins 25 and 18 years before her symptoms began. On examination she was moderately hypertensive (BP 170/110 mmHg) with pitting oedema of the right leg and generalized abdominal distension. The latter was not due to ascites, visceromegaly or a palpable tumour and no other abnormal findings were recorded.

The Hb was 11.2 g/dl, WCC $9.6 \times 10^9/l$ with a

normal differential and normal red cell indices and the ESR was 122 mm/hr. The blood urea was 7.5 mmol/l (normal range, 2.5-6.3 mmol/l) and the serum globulin was elevated at 38 g/l (normal range, 20-30 g/l), owing to an increased α_2 fraction. The serum sodium, potassium and calcium concentrations were normal as were random blood glucose and fasting blood lipids, together with liver function tests (bilirubin, alkaline phosphatase and aspartate transaminase), thyroid function tests (thyroxine concentration and T_3 resin), chest X-ray and ECG.

The cause of this patient's oedema was not apparent and she was admitted for further investigation 2 months later. By this time she was complaining of anorexia, vomiting and polyuria, and pelvic examination suggested a left sided mass attached to the side wall of the pelvis. The remainder of the examination was as noted previously although the Hb had fallen to 7.1 g/dl, with an ESR of 140 mm/hr, while the blood urea and serum creatinine had increased to 25 mmol/l and 314 $\mu\text{mol/l}$ respectively (normal range of serum creatinine, 45-125 $\mu\text{mol/l}$). Intravenous urography showed that both ureters were deviated medially and dilated down to the pelvic brim, with bilateral hydronephroses. Barium enema showed enlargement of the pre-sacral space with external compression of the sigmoid colon. A CT scan of the pelvis showed a mass extending between the cervix and rectum at the level of the pelvic brim which was obstructing both ureters. Laparoscopy showed no definite gynaecological abnormality although there was an impression of a mass extrinsic to the sigmoid colon. Serum examination for rheumatoid factor, L.E. cells, immune complexes, paraproteins and ENA was negative. Bone marrow examination, serum complement levels and urinalysis were within normal limits as were X-rays of the skull, chest and spine and pulmonary function tests, including diffusing capacity.

Exploratory laparotomy 2 months later revealed

* Extractable nuclear antigens.

a dense mass of fibrous tissue extending down the posterior abdominal wall from the level of the third lumbar vertebra into the pelvis. This involved the ureters, rectum and sigmoid colon and was obstructing the pelvic veins. A partial left ureterolysis and a right uretero-iliocystoplasty were performed. Histology of tissue removed from multiple biopsy sites showed that the fibrosis was associated with numerous small capillaries producing the appearance of the end-stage of very reactive granulation tissue.

The postoperative course was uneventful and the patient left hospital 3 weeks after the laparotomy with a blood urea of 13 mmol/l. Renal function declined steadily during the next 6 months, and 7 months after surgery the blood urea had reached 21 mmol/l. Repeat i.v. urography showed a filling defect in the left kidney and surgical exploration revealed a pyonephrosis for which a partial nephrectomy was performed. Histology of the kidney showed evidence of severe, chronic pyelonephritis with prominent vascular changes. These included features of benign nephrosclerosis together with the presence of mucoid material in the wall of one arteriole similar to that seen in renal scleroderma. A postoperative urinary fistula closed spontaneously in the subsequent fortnight and she was discharged from hospital, only to be readmitted as an emergency 3 weeks later, acutely uraemic and draining frank pus from the nephrectomy incision. The infection responded to antibiotic therapy and the elevated blood urea (48 mmol/l) fell steadily with i.v. rehydration, correction of acidosis and restriction of dietary protein.

Five weeks later (May 1979) the patient developed a left iliofemoral thrombosis which, together with increasingly unstable renal function led to re-assessment of her clinical state, and she came under the author's care at this time. On direct questioning she described Raynaud's phenomenon affecting the hands for many years, especially after exposure to cold. There was tethering and thickening of the skin on the anterior aspects of both legs with brawny swelling of both hands, microstomia and telangiectasia of the hands and face. Radiological examination of the hands showed calcinosis of the finger pulps and barium studies of the gastrointestinal tract demonstrated absent peristalsis with hypomobility of the oesophagus, stomach and duodenum. The Hb was 13.2 g/dl, WCC $13.6 \times 10^9/l$ with a normal differential and the ESR 78 mm/hr. Blood urea had settled at 19 mmol/l with a serum creatinine of 230 $\mu\text{mol/l}$ and endogenous creatinine clearance of 17 ml/min (uncorrected for body surface area). Autoantibody screen (to thyroid tissue, mitochondria, smooth muscle and nuclei) was negative and DNA binding, α_1 -antitrypsin

levels and repeated pulmonary function tests were all within normal limits. The patient proved to be tissue type HLA A2, A3/B15, B27/CW3/BW4, BW5. She had never taken any of the drugs suspected of being specifically associated with retroperitoneal fibrosis. Treatment with prednisolone (60 mg/day) was started at the end of June 1979 because of the extensive and aggressive nature of the retroperitoneal fibrosis. She also needed alkali supplements (sodium bicarbonate 1200 mg thrice/day) because of persistent acidosis and hypotensive drugs (oxprenolol 40 mg thrice/day and bendrofluazide 5 mg twice/day). During the next 2 months the ESR decreased and the dose of prednisolone was reduced to 15mg/day. Apart from an attack of thoracic herpes zoster which settled rapidly the patient remained symptomatically well although renal function had deteriorated slightly (blood urea, 27 mmol/l; serum creatinine, 320 $\mu\text{mol/l}$). In September 1979, following a slight fall at home, she sustained an undisplaced sub-capital fracture of the right femoral neck which was treated by the insertion of crossed Garden screws. X-ray of the pelvis showed no other abnormality, in particular there was no diffuse decalcification or avascular necrosis attributable to steroids and she made a rapid and complete return to normal mobility.

By January 1980 the ESR had increased again to 96 mm/hr and, although overall renal function was unchanged, a renogram suggested increasing outflow obstruction to the right kidney. The dose of prednisolone was therefore increased to 40 mg/day in an attempt to control the retroperitoneal fibrosis and so prevent progression of the renal impairment. At last review, the ESR had fallen to 43 mm/hr, renal function was stable (blood urea, 32 mol/l, serum creatinine, 325 $\mu\text{mol/l}$) and she continues to require treatment with hypotensive drugs and alkali supplements.

Discussion

Anuria is the most dramatic obstructive manifestation of retroperitoneal fibrosis, although symptoms may also result from involvement of major blood vessels, including the aorta, both venae cavae, renal and portal veins (Partington, 1961; Graham *et al.*, 1966; Carton and Wong, 1969; Saxton *et al.*, 1969; Coopersmith and Appelman, 1971; Ross and Goldsmith, 1971). The dilated pelvic veins observed at laparotomy in this patient suggest that her presenting complaint of swollen legs may have been due to venous obstruction. The hypertension may have been due to encasement of the kidneys in fibrous tissue (Saxton *et al.*, 1969). Scleroderma kidney seems unlikely as a cause of the hypertension because the overall renal function has fluctuated in association with the evolution and

release of obstructive uropathy rather than declining progressively as would be expected with renal scleroderma, and also the excised renal tissue showed changes compatible with scleroderma in only one vessel.

A skin biopsy from the affected areas on the legs was not performed because of fears that it would be slow to heal, but there is little doubt that this patient has the CRST* syndrome variant of scleroderma as well as retroperitoneal fibrosis. It is, perhaps, surprising that the association of the 2 diseases has not been previously reported because vascular abnormalities may be involved in the pathogenesis of both. Kahaleh, Shorer and Lehey (1979) suggested that endothelial injury in patients with scleroderma may be responsible for the abnormal vascular reactivity, which is manifest clinically by Raynaud's phenomenon and by changes in the renal and pulmonary microcirculations (Urai *et al.*, 1958; Cannon *et al.*, 1974; Oliver and Cannon, 1977). Vasoactive drugs other than methysergide, have been associated with retroperitoneal fibrosis (Graham, 1964; Graham *et al.*, 1966; Saxton *et al.*, 1969; Stecker *et al.*, 1974; Iversen *et al.*, 1975), and vasculitis may be a prominent pathological feature (Carton and Wong, 1969; Saxton *et al.*, 1969; Coopersmith and Appelman, 1971; Ross and Goldsmith, 1971). Hollingworth, Denman and Gumpel (1980) describe a patient with retroperitoneal fibrosis and polyarteritis nodosa. They suggest that a primary vasculitis in the retroperitoneal tissues allowed immune complexes to leak from the circulation and that this caused the fibrosis.

The appearance of idiopathic retroperitoneal fibrosis may be mimicked by infection or malignant infiltration so that confirmation of the diagnosis requires laparotomy and histological examination of biopsies from the affected areas. This may constitute a major procedure in patients with severe renal impairment, and it has been suggested that a therapeutic trial of steroids may be the only alternative (Mitchinson, Withycombe and Jones, 1971; Ross and Goldsmith, 1971; Ochsner *et al.*, 1975). The report of diffuse, multisystem fibrosis in 2 offspring of a consanguineous marriage (Comings *et al.*, 1967) suggests that the liability to widespread fibrosis may sometimes be governed by genetic factors. It is interesting that this is the third patient described with retroperitoneal fibrosis and a positive reaction for the HLA antigen B27 (Olsson, 1976; Willscher, Novicki and Cwazka, 1978). There have been no large scale studies of the HLA antigen types of patients with retroperitoneal fibrosis but if this association was confirmed it might provide a useful marker and lessen the need for immediate

diagnostic laparotomy in very ill patients. However HLA antigen typing in scleroderma has given conflicting results, with increased frequencies of B27 (Rabin *et al.*, 1975); B8 (Rabin *et al.*, 1975; Freudenberg *et al.*, 1978; Hughes *et al.*, 1978) and A9 (Rabin *et al.*, 1975; Clements *et al.*, 1978) being reported, although other authors have failed to confirm these results (Birnbbaum *et al.*, 1977; Majsky, Kobikova and Stava, 1979). It is possible that the B27 association is with a particular subgroup of patients with scleroderma who are also likely to develop retroperitoneal fibrosis. However much further work would be needed to establish this point.

The cause of this patient's fractured hip which followed an apparently trivial fall, remains unclear. Avascular necrosis of the femoral head has previously been described in 2 patients with retroperitoneal fibrosis (Kamdar, 1973; Appell and Weiss, 1976), both were female and the avascular necrosis was confined to the side affected by the retroperitoneal fibrosis. The presence of vasculitis in one case (Kamdar, 1973), in the retroperitoneal tissues and in the ligamentum teres suggested a causal relationship between the 2 diseases. However there was no evidence of avascular necrosis or other bone pathology in the present patient. Other factors, possibly the steroid therapy or subclinical renal osteodystrophy may have been contributory.

References

- APPELL, R.A. & WEISS, R.M. (1976) Retroperitoneal fibrosis and avascular necrosis of the femoral head. *Journal of the American Medical Association*, **236**, 2866.
- BIRNBAUM, N.S., RODMAN, G.P., RABIN, B.S. & BASSION, S. (1977) Histocompatibility antigens and progressive systemic sclerosis. *Journal of Rheumatology*, **4**, 425.
- CANNON, P.J., HASSAR, M., CASE, D.B., CASORELLA, W.J., SOMMERS, S.C. & LEROY, E.C. (1974) The relationship of hypertension and renal failure in scleroderma (progressive systemic sclerosis) to structural and functional abnormalities of the renal cortical circulation. *Medicine*, **53**, 1.
- CARTON, R.W. & WONG, R. (1969) Multifocal fibrosclerosis manifested by vena caval obstruction and associated with vasculitis. *Annals of Internal Medicine*, **70**, 81.
- CLEMENTS, P.J., OPELZ, G., TERASAKI, P.I., MICHEY, R. & FURST, D. (1978) Association of HLA antigen A9 with progressive systemic sclerosis (scleroderma). *Tissue Antigens*, **11**, 357.
- COMINGS, D.E., SKUBI, K.B., VAN EYES, J. & MOTULSKY, A.G. (1967) Familial multifocal fibrosclerosis. *Annals of Internal Medicine*, **66**, 884.
- COOPERSMITH, N.H. & APPELMA, H.B. (1971) Multifocal fibrosclerosis with subcutaneous involvement. *American Journal of Clinical Pathology*, **55**, 369.
- FREUDENBERG, J., HOLZMANN, H., SCHNEIDER, S. & KORTING, G.W. (1978) HLA-Antigen Frequenzen bei Patienten mit progressiver Sklerodermie und Morphoea. *Archives of Dermatological Research*, **263**, 197.
- GRAHAM, J.R. (1964) Methysergide for prevention of headache; experience in 500 patients over three years. *New England Journal of Medicine*, **270**, 67.

* Calcinosis, Reynaud's phenomenon, sclerodactylia and telangiectasis.

- GRAHAM, J.R., SUBY, H.I., LeCOMPTE, P.R. & SADOWSKY, N.L. (1966) Fibrotic disorders associated with methysergide therapy for headache. *New England Journal of Medicine*, **274**, 359.
- HOLLINGWORTH, P., DENMAN, A.M. & GUMPEL, J.M. (1980) Retroperitoneal fibrosis and polyarthritis nodosa successfully treated with intensive immunosuppression. *Journal of the Royal Society of Medicine*, **73**, 61.
- HUGHES, P., GELSTHORPE, K., DOUGHTY, R.W., ROWELL, N.R., ROSENTHAL, F.D. & SNEDDON, I.B. (1978) The association of HLA.B8. with visceral disease in systemic sclerosis. *Clinical and Experimental Immunology*, **31**, 351.
- IVERSEN, B.M., NORDAHL, E., THUNNOLD, S., JOHANNESSEN, J.W., OPSTED, J. & WILLASSEN, Y. (1975) Retroperitoneal fibrosis during treatment with methyl dopa. *Lancet*, **ii**, 302.
- KAHALEH, M.B., SHERER, G.K. & LEROY, E.C. (1979) Endothelial injury in scleroderma. *Journal of Experimental Medicine*, **149**, 1326.
- KAMDAR, B.A. (1973) Avascular necrosis of the head of the femur in a case of retroperitoneal fibrosis. *Postgraduate Medical Journal*, **49**, 59.
- MAJSKY, A., KOBIKOVA, M. & STAVA, Z. (1979) HLA and scleroderma. *Tissue Antigens*, **14**, 359.
- MITCHINSON, M.J. (1965) Systemic idiopathic fibrosis and systemic Weber-Christian disease. *Journal of Clinical Pathology*, **18**, 645.
- MITCHINSON, M.J., WITHEYCOMBE, J.F.R. & JONES, R.A. (1971) The response of idiopathic retroperitoneal fibrosis to corticosteroids. *British Journal of Urology*, **43**, 444.
- OCHSNER, M.G., BRANNAN, W., POND, H.S. & GOODLETT, J.S. (1975) Medical therapy in idiopathic retroperitoneal fibrosis. *Journal of Urology*, **114**, 700.
- OLIVER, J.A. & CANNON, P.J. (1977) The kidney in scleroderma. *Nephron*, **18**, 141.
- OLSSON, C.A. (1976) Case records of the Massachusetts General Hospital. *New England Journal of Medicine*, **294**, 712.
- ORMOND, J.K. (1948) Bilateral ureteral obstruction due to envelopment and compression by an inflammatory retroperitoneal process. *Journal of Urology*, **59**, 1072.
- PALMER, P.E., WOLFE, H.J. & KOSTAS, C.I. (1978) Multi-system fibrosis in α_1 -antitrypsin deficiency. *Lancet*, **i**, 221.
- PARTINGTON, P.F. (1961) Diffuse idiopathic fibrosis. *American Journal of Surgery*, **101**, 239.
- RABIN, B.S., RODNAN, G.P., BASSION, S. & GILL, T.J. (1975) HLA antigens in progressive systemic sclerosis (scleroderma). *Arthritis and Rheumatism*, **18**, 381.
- ROSS, J.C. & GOLDSMITH, H.J. (1971) The combined surgical and medical treatment of retroperitoneal fibrosis. *British Journal of Surgery*, **58**, 422.
- SAXTON, H.M., KILPATRICK, F.R., KINDER, C.H., LESSOF, M.H., MCHARDY-YOUNG, S. & WARDLE, D.F.H. (1969) Retroperitoneal fibrosis. *Quarterly Journal of Medicine*, **38**, 159.
- STECKER, J.F., RAWLS, H.P., DEVINE, C.J. & DEVINE, P.C. (1974) Retroperitoneal fibrosis and ergot derivatives. *Journal of Urology*, **112**, 30.
- URAI, L., NAGY, Z., SZINAY, G. & WITTNER, W. (1958) Renal function in scleroderma. *British Medical Journal*, **2**, 1246.
- WILLSCHER, M.K., NOVICKI, D.E. & CWAZKA, W.F. (1978) Association of HLA.B27. antigen with retroperitoneal fibrosis. *Journal of Urology*, **120**, 631.