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Low grade fever, back pain and livedo reticularis in a 60-year-old man

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Case report

A 60-year-old man was admitted to our hospital because of low grade fever, back pain and livedo reticularis on the lower extremities. The patient was a painter by profession and a habitual smoker (one pack of cigarettes daily for 40 years). Apart from a perianal fistula and local abscesses 2 years before, the patient had been well until 18 months before his admission, when he experienced increasing lumbar pain. The pain was radiating in nature, extending to the lower abdomen, groin and posterior surface of the thighs. Fourteen months before his admission he developed low grade fever.

Eight months before his admission a physical examination showed the presence of prostatic hypertrophy. The hematocrit was 38%, white cell count 8,500/mm^3, platelet count 432,000/mm^3, and erythrocyte sedimentation rate (ESR) 50 mm/hr. Blood chemistries, a thyroid function test, prostate specific antigen and urinalysis were all within normal limits. Abdominal ultrasound and computed tomography (CT) scan of the abdomen and lumbar spine, as well as a radionuclide bone scan, were unrevealing. Non-steroid anti-inflammatory drugs were prescribed.

Six months before his admission he continued to have lumbar pain and low grade fever. All examinations were negative, however. The hematocrit was 38.4% and the white cell count was 6,500/mm^3 with 61% neutrophils, 24% lymphocytes and 15% monocytes. The platelet count was 400,000/mm^3 and the ESR was 68 mm/hr. The C-reactive protein was 16 mg/dl. Blood chemistries, prothrombin time and partial thromboplastin time were normal. Liver and muscle enzymes, vitamin B_{12} and folic acid levels, and a serologic test for syphilis, as well as a urinalysis, were all within normal limits. Blood and urine cultures were negative.

Serologic tests for hepatitis B surface antigen, and antibodies to hepatitis C and HIV were negative. Antinuclear antibodies, rheumatoid factor, and antineutrophil cytoplasmic autoantibodies (both perinuclear and cytoplasmic) were all negative. Agglutinating antibodies against the somatic and flagellar antigens of *S. typhi*, CMV-specific IgM antibodies, the Mono test, and the Wright test were negative. A tuberculin test (PPD) was positive.

An echocardiographic examination of the heart was normal. Fiberoptic esophagogastroduodenoscopic examination showed a mild gastritis involving the body and fundus of the stomach. Gastric juice and urine cultures were negative for *Mycobacterium tuberculosis*. Colonoscopy was normal. Thoracic CT scan, and X-ray films of the lumbar spine and pelvis were normal. Biopsy of the temporal artery was unrevealing. Empirical treatment with isoniazid, rifampin, ethambutol and pyrazinamide for four months was not successful.

The patient was finally referred to our hospital. On physical examination his temperature was 37.0°C and his blood pressure 120/80 mm Hg. No peripheral oedema, clubbing, lymphadenopathy or cyanosis were noted. The lungs, heart and abdomen were normal. Livedo reticularis was present on the lower extremities, and on the anterior tibial surface a painless, hard subcutaneous nodule was palpable. A neurologic examination was negative. Rectal examination revealed mild prostatic enlargement. The hematocrit was 40%, and the white cell count was 8,000/mm^3 with 61% neutrophils,

28% lymphocytes, and 11% monocytes. The platelet count was 350,000/mm^3. The ESR was 80 mm/h and C-reactive protein was 4.6 mg/dl. Urinalysis was normal. Urea nitrogen was 34 mg/dl, glucose 116 mg/dl, bilirubin 0.6 mg/dl, calcium 8.8 mg/dl and protein 8.1 g (albumin 4.4 g and globulin 3.7 g/dl). ASAT was 12 U, ALAT 10U, and LDH 261 U. Alkaline phosphatase was 217 U, 5' nucleotidase 19 U and amylase 80 U/l.

An electrocardiogram and chest X-ray were normal. An upper gastrointestinal series with small bowel study were normal. A percutaneous celiac and superior mesenteric artery angiography showed no abnormalities. Biopsy of the sural nerve was unrevealing. Biopsy of the pre-tibial nodule revealed a septal panniculitis with marked small vessel proliferation, and lymphohistiocytic perivascular inflammation with focal granulomatous formation. There was no necrosis of the adipose tissue. A diagnostic procedure was performed.

Differential diagnosis

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The patient was a 60-year-old man with a 14-month history of low grade fever and back pain radiating to the thighs, groin and lower abdomen, who presented with livedo reticularis and a subcutaneous nodule on the lower extremity. In determining the possible causes of his disease, one could easily rule out an infection or malignant process. The patient was too well for the former and the illness was not suffficiently progressive for the latter.

In view of the clinical picture and laboratory findings, one could hypothesize that the patient was suffering from a chronic inflammatory disease producing systemic manifestations.

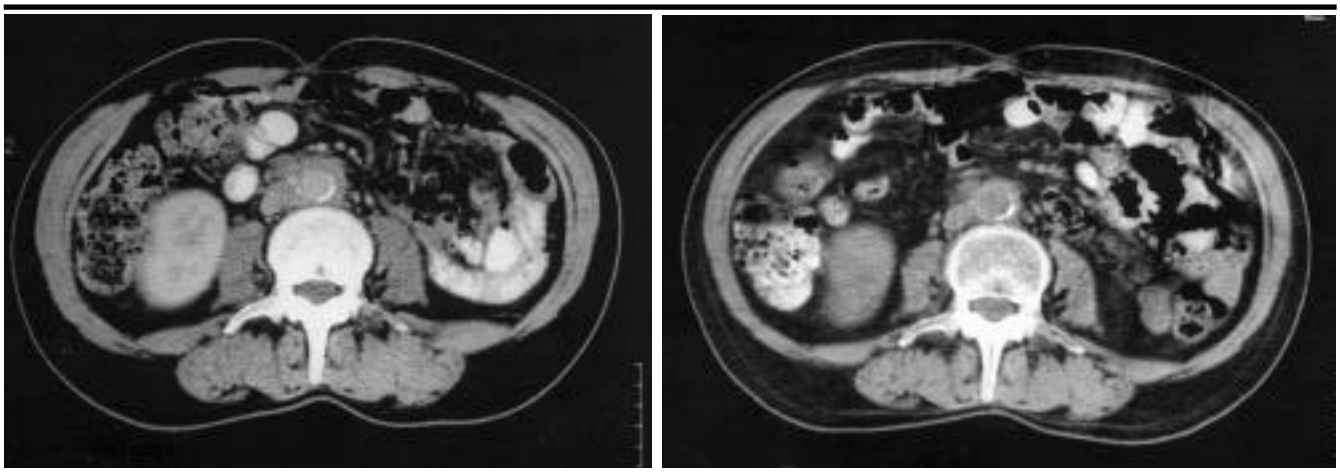
Polyarteritis nodosa (PAN) was a possible diagnosis. PAN often involves the small and medium sized arteries, typically the muscular vessels. Its particular manifestations include ischemia of the tissues perfused by the obstructed vessels and symptoms like fever, weight loss and anorexia due to the accompanying inflammation. The cutaneous lesions of PAN include palpable purpura, infractions, ulcerations, livedo reticularis, subcutaneous nodules and ischemic changes of the distal digits (1). Livedo reticularis and nodular lesions, which are more indicative of medium sized artery involvement, occur in 50% and 15% of PAN patients respectively. Histopathologically the nodular lesions are characterized by necrotizing vasculitis of the arterioles in the subcutaneous tissue with surrounding lobular panniculitis (2, 3).

The patient's clinical picture could be explained by involvement of the visceral and cutaneous vessels. However, arteriographic examination of the hepatic, mesenteric and celiac arteries did not show aneurysms or other vascular irregularities, the sural nerve biopsy was normal, and a biopsy of the nodule showed only septal panniculitis without evidence of vasculitis. These histologic and angiographic findings ruled out the possibility of PAN in this particular patient.

Septal panniculitis is typically seen in erythema nodosum and its variant, subacute migratory panniculitis. In contrast, pancreatic panniculitis, Weber-Christian disease, erythema induratum and systemic vasculitis are primarily lobular panniculitides.

Erythema nodosum (EN) refers to a syndrome of crops of painful nodules often occurring on the anterior surfaces of both lower extremities. Subacute nodular migratory panniculitis is thought to be a variant of erythema nodosum but deserves attention because of some of its particular clinical and histologic features. This process consists of a few discrete, minimally painful nodules occurring in a unilateral fashion on the arterior aspects of the legs (3). We believe that our patient displayed the typical clinical and histological findings of nodular migratory panniculitis. It is considered to be a hypersensitivity reaction to a variety of antigenic stimuli and thus may appear as a side effect of treatment, as well as during the course of several diseases.

Among the various diseases associated with erythema nodosum, it may be pertinent to discuss in this context tuberculosis and regional enteritis. Tuberculosis occasionally presents with a puzzling picture. If a patient with tubercu-



(a) **(b)**

Fig. 1. (**a**) Post-contrast CT of the abdomen at the level of the lower pole of the right kidney demonstrates a mildly enhancing mantle of soft tissue density encasing the abdominal aorta. There is atheromatous calcification of the aortic wall. (**b**) Non-contrast CT at the same level, two months later. The mantle of soft tissue density has decreased in size. The definition of the aortic wall margin is poor.

losis also has a musculoskeletal disease, it almost always takes the form of a joint or spinal infection. Tuberculomas of the bone, once relatively common, have now become a very infrequent event. In our patient a CT scan of the lumbar spine was normal and there was no pulmonary disease. He had a positive tuberculin skin test, but urine and gastric fluid specimens cultured for tubercule bacilli were negative. Thus we retain that tuberculosis was not a likely diagnosis.

Crohn's disease is a chronic inflammatory bowel disease that most commonly involves the distal ileum and colon, but which can affect any portion of the alimentary tract from the mouth to the anus. Numerous types of cutaneous manifestations have been described, including ulcerations, fistulas, abscesses, pyoderma gangrenosum and erythema nodosum. It is interesting to note that the bowel disease activity appears to correlate with the erythema nodosum activity. Perianal lesions are also common in Crohn's disease and may be present in 43% - 94% of patients with intestinal involvement. These lesions can antedate the appearance of abdominal symptoms by 5 years and may be the primary manifestations of Crohn's disease in 8% of patients (4). In our patient there was a history of perianal disease two years before his admission, but his distal ileum was normal on a small-bowel study. Thus, we consider that Crohn's disease was not a probable diagnosis.

Among the other possible diagnoses in our patient one must consider retroperitoneal fibrosis (RPF). This disorder can affect all age groups, but is most common in persons between 50 and 70 years of age. It occurs about two to three times more frequently in males than in females (5, 6). Patients with RPF usually demonstrate obstruction of the ureters resulting in hydronephrosis (6), but frequently also have general symptoms of chronic inflammation such as fever, fatigue and weight loss. Pain in the lower back, the lower abdomen or the lumbo-sacral region is the most common presenting symptom and was in fact present in our patient. RPF may result in discrete retroperitoneal masses which are often bilateral in distribution. It may involve the ureters, kidneys, aorta, vena cava, duodenum and biliary tree, resulting in obstruction. With the widespread use of CT scanning, increasing numbers of patients are being found with periaortic masses without urinary obstruction. In rare cases the inflammatory mass may involve the sympathetic nerves. Thus RPF can reduce cutaneous blood flow and consequently produce livedo reticularis.

RPF can be either idiopathic or secondary. Secondary RPF may have numerous causes such as infection, trauma, malignancy, atherosclerosis, drugs and autoimmune diseases. Various disorders also are associated with RPF, including idiopathic mediastinal fibrosis, Riedel's thyroiditis, pseudotumor of the orbit, sclerosing cholangiitis and pulmonary hyalinizing granuloma. Different combination of these disorders can affect the same patient, suggesting that RPF may be the expression of a systemic disease (7, 8).

Microscopic examination of the involved tissue in RPF patients shows fibroblastic proliferation with abundant collagen deposition and a mixed inflammatory infiltrate composed of lymphocytes, plasma cells, macrophages and rare eosinophils. This inflammatory infiltrate is to be found predominantly within and around the vessel walls (9). The mechanisms that could account for the fibrosis in the retroperitoneal space remain unclear. RPF is probably immunologically mediated in view of its response to corticosteroid and immunusuppressive therapy and its occasional association with other immune-mediated diseases (10). Biopsy-proven vasculitis at an incidence of approximately 7% has been demonstrated in patients with RPF (11). In addition, RPF with vasculitis can involve almost any organ system and can coexist with any kind of vasculitis, such as necrotizing vasculitis (10), granulomatous vasculitis (12) and aortitis (13). Pathologic studies of the retroperitoneal mass in a patient with RPF in an early phase revealed arteritis and periaortitis with giant cell infiltration (14). Postmortem findings have included massive periaortic and periarterial fibrosis and debris in the inflamed adventitia of the aorta (15). All of these findings suggest that the fibrosis responsible for the clinical manifestations of RPF may be linked to vasculitis and the inflammatory process.

In our patient a biopsy of the pre-tibial nodule revealed septal panniculitis. The inflammatory infiltrate that had spread around the small interlobular vessels was associated with an accumulation of histiocytes and giant cells. There was marked vascular proliferation. It is interesting that subacute nodular panniculitis has been reported with idiopathic RPF (16) and it is believed that this cutaneous pathology is closely related to RPF.

In conclusion our diagnosis in this patient was idiopathic RPF with subacute nodular migratory panniculitis.

Diagnostic procedure

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The reported negative abdominal CT scans performed previously in another hospital were not available for review.

A CT scan of the abdomen and pelvis (Philips Tomoscan LX/C) was performed before and after the i.v. administration of contrast material. Ten mm consecutive axial images were obtained from the diaphragm to the pubis. This study showed calcification of the aortic wall and a mantle of soft tissue density (max. thickness 5 mm) encasing the lower abdominal aorta (Fig. 1a). Mild dilatation of the right pelvocalyceal system and right ureter to the L3 level were also noted. Following contrast administration, mild enhancement of the soft tissue density was noted. The findings were consistent with retroperitoneal fibrosis. The remainder of the abdomen and pelvis were unremarkable.

Patient follow-up

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After the diagnosis of RPF was established, methylprednisolone 48 mg daily with gradual tapering and azathioprine 150 mg were started. Two months later, the patient was asymptomatic and the inflammatory parameters including ESR and CRP had returned to normal.

A new CT scan (Fig. 1b) demonstrated minimal residual findings, with poor definition of the aortic wall border, and resolution of the mantle of dense soft tissue surrounding the aorta. The right pelvocalyceal system and ureter had a normal appearance.

References

1. BOKI KA, DAFNI U, KARPOUZAS GA, PAPASTERIADES C, DROSOS AA, MOUTSOPOULOS HM: Necrotizing vasculitis in Greece: Clinical, immunological and immunogenetic aspects. A study of 66 patients. *Br J Rheumatol* 1997; 36: 1059-66.
2. AMBRUS J:. Small and medium vessel primary vasculitides. *In* RICH (Ed.): *Clinical Immunology*, Vol. 2, Mosby-Year Book, Inc. 1996; 1198-223.
3. REED RJ, CLARK WH, MIHM MC: Disorders of the panniculus adiposus. *Hum Pathol* 1973; 4: 219-307.
4. LOCKHART-MUMMERY HE: Crohn's disease: Perianal lesions. *Dis Colon-Rectum* 1975; 18: 200-4.
5. ORMOND JK: Bilateral obstruction due to envelopment and compression by an inflammatory retroperitoneal process. *J Urol* 1948; 59: 1072-9.
6. BAKER LRI, MALLINSON WJM, GREGORY MC: Idiopathic retroperitoneal fibrosis: A retrospective analysis of 60 cases. *Br J Urol* 1987; 60: 497-503.
7. STEWART TWJ, FRIBERG TR: Idiopathic retroperitoneal fibrosis with diffuse involvement: Further evidence of systemic idiopathic fibrosis. *South Med J* 1984; 77: 1185-7.
8. MITCHINSON MJ: Aortic disease in idiopathic retroperitoneal and mediastinal fibrosis. *J Clin Pathol* 1972; 25: 287-93.
9. MITCHINSON MJ: The pathology of idiopathic retroperitoneal fibrosis. *J Clin Pathol* 1970; 23: 681-9.
10. ZABETAKIS PM, NOVICH RK, MATERESE RA, MICHELIS MF: Idiopathic retroperitoneal fibrosis: A systemic connective tissue disease ? *J Urol* 1979; 122: 100-2.
11. LITTLEJOHN GO, KEYSTONE EC: The association of retroperitoneal fibrosis with systemic vasculitis and HLA-B27. *J Rheumatol* 1981; 8: 665-9.
12. HOFFMAN WW, TRIPPEL OH: Retroperitoneal fibrosis: Etiologic considerations. *J Urol* 1961; 86: 222-31.
13. JONES EA, ALEXANDER MK: Idiopathic retroperitoneal fibrosis associated with an arteritis. *Ann Rheum Dis* 1966; 25: 356-60.
14. MITCHINSON MJ: Retroperitoneal fibrosis revisited. *Arch Pathol Lab Med* 1986; 110: 784-6.
15. REED WG, STINELY RW: Massive periaortic and periarterial fibrosis. *N Engl J Med* 1959; 261: 320-3.
16. BONNET C, ARNAUD M, BERTIN P, TRERES R, GOTTERON RD: Idiopathic retroperitoneal fibrosis with systemic manifestations. *J Rheumatol* 1994; 21: 360-2.