Letters to the Editor

Remitting symmetric seronegative synovitis with pitting edema associated with B-cell non-Hodgkin’s lymphoma

Sirs, Cantini et al. have recently reviewed the literature concerning paraneoplastic remitting seronegative symmetrical synovitis with pitting edema (RS3PE) (1). We report here a further case of RS3PE associated with B-cell non-Hodgkin’s lymphoma (NHL).

A 64-year-old woman presented in June 1999 with a 4-week history of marked swelling of both hands and feet. She also complained of fever (<38.5°C), mild weight loss, pain and stiffness of the shoulder and pelvic girdles, and Raynaud’s phenomenon. At the physical examination pitting edema of the hands and feet and tenosynovitis of the finger flexors were observed. No signs of skin, eye or urogenital tract disease were detected. Laboratory investigations showed a erythrocyte sedimentation rate (ESR) of 86 mm/hr, C-reactive protein (CRP) 20.2 mg/dL (n.v. < 0.5), normocytic anemia (10.8 g/dL), and sero- positivity for HCV-Abs. Rheumatoid factor and antinuclear antibodies were negative. Other assays, including serum lactate dehydrogenase (LDH) and β2-microglobulin, also yielded normal results. The HLA phenotype was A2, A74, B44, B57. X-rays of the hands, feet and sacro-iliac joints were normal.

The patient was thoroughly evaluated for a possible paraneoplastic syndrome; the only abnormality found was a hepatic hilar adenopathia 15 mm in diameter, disclosed by abdominal ultrasonography and diagnosed as a lymph node caused by HCV infection. The patient failed to respond to indomethacin, but dramatic improvement was obtained within 8 days with methylprednisolone 8 mg /5 days a week. Fever disappeared and a complete remission of the girdle pain and stiffness were seen. However, due to the persistence of a raised CRP and mild left knee synovitis the therapy was not tapered.

Two months later intermittent fever and polyarthralgia involving the proximal interphalangeal and metacarpophalangeal joints, wrists, knees, and left elbow reappeared. CRP was 26.8 mg/dL and haemoglobin 9.6 g/dL. Liver enzymes and LDH were normal. No signs of infections were observed. Abdominal ultrasonography was unchanged. Steroids were increased to 20 mg 5 days a week, and sulfasalazine and hydroxychloroquine were added. The fever disappeared, morning stiffness and polyarthritis greatly improved, haemoglobin rose (11.7 g/dL) and CRP decreased (4.3 mg/dL).

In November 1999 the fever reappeared. Haemoglobin was 9.5 g/dL, CRP 14.7 mg/dL, LDH 435 IU/L (n.v. < 230) and β2-microglobulin 4.0 mg/L (n.v. < 2.5). Abdominal ultrasonography demonstrated a coeliac hypo-anhydrogenic adenopathy 50 × 31 mm diameter and 3 hilar adenopathies of 20, 27 and 27 mm. Ultrasound-guided fine-needle biopsy demonstrated a large cell NHL of B-cell origin (CD20+). Clinical staging did not show supra-diaphragmatic involvement. Only very rare CD20+ lymphomatous large cells were observed in the bone marrow biopsy. After a first cycle of polychemotherapy with CHOP, the fever disappeared. When last evaluated, in July 2000, the NHL was in complete remission and the patient was no longer receiving steroids. No signs of arthritis or myalgia were present and there was no residual flexor contraction of the fingers. CRP was within normal limits.

The possibility of a clinical picture indistinguishable from RS3PE and induced by an occult neoplasm has been clearly identified for solid cancers (1), but is less evident for B-cell malignancies. Only 3 other cases of RS3PE associated with B-cell lymphoproliferative disorders have been reported. However, just one was similar to the case described here, in that RS3PE preceded the diagnosis of NHL, although it differed in that there was a complete lack of response to low-dose steroids (2). In our patient, the prompt and persistent disappearance of distal swelling suggested at first that it was a truly “remitting” syndrome. The persistence of a raised CRP and the reappearance of fever after a period, however, were clues for an association with an occult malignancy. This hypothesis had already been considered at presentation due to the presence of systemic signs.

The other 2 cases reported in the literature were quite different: RS3PE arose in patients with long-standing, untreated, low-grade B-cell lymphoproliferations. In one (3) the rapid achievement of a persistent remission of the rheumatologic syndrome with a short course of low dose steroids suggested a chance association between the two disorders. In the other (4), the picture was caused by diffuse lymphomatous marrow involvement and peristosis of the bone adjacent to synovitis, suggesting a direct role of NHL in its pathogenesis. This is at variance from what is commonly observed in RS3PE, which is usually due to diffuse tenosynovitis. In our patient induction of the synovitis by inflammatory cytokines (in this case, perhaps secreted by lymphomatous cells) might be hypothesised.

References

Fabry’s disease mimicking familial Mediterranean fever

Sirs, We describe a patient with Fabry’s disease whose diagnosis was made on the basis of kidney biopsy findings. Given the clinical features and ethnic background of the patient, familial Mediterranean fever (FMF) was the most probable diagnosis prior to the biopsy. Although several reports have noted the similarities between the clinical findings of Fabry’s disease and various rheumatic disorders (1), we are unaware of any report suggesting mimicry between Fabry’s disease and FMF.

A 20-year-old male patient from central Turkey was referred to our hospital with proteinuria. His past medical history included recurrent painful attacks in the abdomen and distal extremities, accompanied by fever of 6 years duration. He had been treated with non-steroid anti-inflammatory drugs during the painful episodes. On admission, his blood pressure was 110/70 mmHg and he had markedly dried skin; the rest of the examination was normal. Urinalysis showed proteinuria with acellular urine and daily urinary protein excretion was 1.6 g. All other biochemical, haematological and immunological parameters were normal except for the erythrocyte sedimentation rate (ESR), which was 50 mm/hr.

M. BARONIO, MD
B. CERUDELLI, MD
C. CAPPELLI, MD
A. PASCARELLA, MD
P. AIRO, MD
Servizio di Immunologia Clinica 11 Divisione di Medicina e 2 Sezione di Ematologia, Spedali Civili, Brescia, Italy.

Letters to the Editor

Page 787
Letters to the Editor

The intermittent nature of his complaints, the presence of fever during the attacks, and the ethnic background of the patient led us to consider FMF in the presumptive diagnosis. The presence of proteinuria, which may be attributable to the development of amyloidosis, was also taken as evidence of FMF. A renal biopsy, however, revealed diffuse marked vacuolation of the glomerular cells compatible with Fabry’s disease. On specific questioning he reported diminished sweating during the last 6 months. Retrospective ophthalmological examination disclosed corneal and lenticular opacities. α-galactosidase A activity in the leucocytes was 1.1 nmol/mg protein/hr (normal 50-150). Consequently, the diagnosis of Fabry’s disease was made.

Fabry’s disease is a rare, X-linked disorder of glycosphingolipid catabolism resulting from deficient activity of the lysosomal hydrolase α-galactosidase A and characterised by the progressive systemic deposition of glycosphingolipids in most of the body fluids and tissues. Clinical manifestations include angiokeratoma, palmar erythema, conjunctival telangiectasis, painful neuropathy, intermittent fever, arthralgia, hypohydrosis, and lenticular opacity, abdominal pain and proteinuria, as well as renal dysfunction. The most debilitating symptom of Fabry’s disease is pain, which is generally episodic, lasting from minutes to several days. Although pain is felt initially in the extremities, it may radiate to the other areas of the body including the abdomen and back. Attacks of abdominal pain or flank pain simulating appendicitis or renal colic have also been reported (2). Furthermore, the association of painful attacks with low-grade fever and an elevated erythrocyte sedimentation rate is a well-known feature of Fabry’s disease (3).

FMF, on the other hand, is marked by recurrent episodes of fever with painful manifestations in the abdomen, chest, joints or skin (4). The clinical findings of Fabry’s disease - including painful abdominal attacks, fever and an elevated ESR associated with these attacks can be easily confused with those of FMF in the absence of other findings indicative of Fabry’s disease (Table I). In addition, renal involvement characterised by proteinuria as seen in our case may lead to the suspicion of renal amyloidosis secondary to FMF.

In conclusion, the differentiation of these two disorders is important not only for etiological purposes but also for therapy, follow-up and genetic counselling. Although specific therapies for Fabry’s disease remain ineffective, at least the patient will not be subjected to unnecessary colchicine therapy for presumed FMF. Patients who have been diagnosed with FMF should be carefully questioned and examined for the presence of other features suggestive of Fabry’s disease such as skin lesions, hypohydrosis, or ocular lesions. Deficient enzymatic activity may guide the diagnosis in doubtful cases.

A. DINC, MD, Asst. Prof
I. SIMSEK, MD, Resident
S. PAY, MD, Asst. Prof
K. CAGLAR, MD, Asst. Prof
C. CAN, MD, Asst. Prof

1 Division of Rheumatology, 2Dept. of Internal Medicine, 3Division of Nephrology, 4Dept. of Pathology, Gülhane School of Medicine, Ankara, Turkey.

Please address correspondence to: Dr. Ayhan Dinc, GATA Romatoloji Bili̇m Dalı, Etilik, 06010 Ankara, Turkey.

E-mail: adinc@gata.edu.tr

References


Table I. Comparison of the clinical features of FMF and Fabry’s disease.

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>FMF</th>
<th>Fabry’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset</td>
<td>10-30 years</td>
<td>10-30 years</td>
</tr>
<tr>
<td>Sex</td>
<td>Affects both sexes</td>
<td>Exclusively affects males, females usually asymptomatic</td>
</tr>
<tr>
<td>Ethnic background</td>
<td>Jewish, Arabian, Turkish, Armenian</td>
<td>Affects all ethnic groups</td>
</tr>
<tr>
<td>Prevalence</td>
<td>1/200 - 1/10,000 in certain ethnic groups</td>
<td>1/40,000</td>
</tr>
<tr>
<td>Duration of attack</td>
<td>1 to 3 days</td>
<td>2 hr. to 3 days</td>
</tr>
<tr>
<td>Fever</td>
<td>Usually associated with painful attacks</td>
<td>Usually associated with painful attacks</td>
</tr>
<tr>
<td>Abdominal symptoms</td>
<td>Common (peritonitis, constipation)</td>
<td>Rare (pain due to abnormal intestinal motility, diarrhea)</td>
</tr>
<tr>
<td>Cutaneous manifest</td>
<td>Occasional (erysipeloid erythema, HSP**)</td>
<td>Common (angiokeratoma, hypothyrosis pupura)</td>
</tr>
<tr>
<td>Nervous system</td>
<td>Very rare; aseptic meningitis</td>
<td>Common; acroparesthesia, seizures, S.V.A†</td>
</tr>
<tr>
<td>Cardiovascular system</td>
<td>Rare; pericarditis</td>
<td>Common; LVH‡; valvulopathy, conduction abnormality</td>
</tr>
<tr>
<td>Renal involvement</td>
<td>30-60% of patients before the advent of colchicine; amyloidosis leading to proteinuria, ESRD*</td>
<td>Common; Isolated proteinuria, ESRD*</td>
</tr>
<tr>
<td>ESR, WBC</td>
<td>Increased during attack</td>
<td>Increased during attack</td>
</tr>
<tr>
<td>Genetics</td>
<td>Autosomal recessive (Chromosome 16 p 13.3)</td>
<td>X-linked recessive (Chromosome X q 22)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Clinical</td>
<td>Enzyme analysis, genetic test</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Depends on susceptibility to amyloidosis; with colchicine prophylaxis prognosis is good</td>
<td>Progressive vascular disease leading to heart failure, ESRD**, S.V.A†, with death in early adulthood</td>
</tr>
<tr>
<td>Treatment</td>
<td>Colchicine prophylaxis to prevent attack and amyloidosis</td>
<td>Carbamazepine/diphenylhydantoin to prevent painful attacks, enzyme replacement therapy (experimental)</td>
</tr>
</tbody>
</table>

† S.V.A: Cerebrovascular accident, ‡ LVH: Left ventricular hypertrophy, *ESRD: End-stage renal disease, **HSP: Henoch-Schönlein purpura.

788