Massive hematuria in rheumatoid arthritis: An unusual manifestation of reactive amyloidosis

Sirs,

Secondary (AA) amyloidosis is a complication of rheumatoid arthritis (RA) reported in 2 – 23% of patients (1). It commonly becomes manifest when there is renal involvement; however, some cases with deposition of amyloid fibrils in various organs may remain silent (2). Only 20 RApatients with symptomatic bladder amyloidosis have been reported (3, 4). We present 3 RA patients who presented with gross hematuria and had bladder amyloidosis.

Case 1. A 73-year-old patient with seropositive, erosive RAfor 18 years was using sulfasalazine. Twelwe years ago he developed proteinuria and his rectal biopsy revealed AA-type amyloidosis. He was started on methotrexate and colchicine. In 1996 he had massive hematuria. His hematocrit was 20%; leucocytes 9000/mm^3, and platelets 100000/mm^3. The biochemistry, bleeding time, PT, and aPTT were normal. Urinary cultures remained sterile. On cystoscopy, the bladder was fragile and bleeding profusely. Clot evacuation and fulguration did not stop the bleeding, and an attempted biopsy resulted in perforation. The patient developed shock and transfused massively. The bladder was sutured. The histopathology revealed AA-type amyloid deposition mainly in the interstitial layers of the bladder. Today, the patient is well with no urological problems.

Case 2. A 56-year-old male came to us in 1988 with a 20-year history of seropositive, erosive RAand was given sulfasalazine. In 1992 he had proteinuria; rectal biopsy revealed AA-type amyloidosis; and methotrexate, prednisolone and colchicine were given. In 1996, he had massive hematuria. The whole blood count, biochemistry, bleeding time, PT, and aPTT were normal; urinary cultures were sterile. On cystoscopy, the bladder wall resembled that of hemorrhagic cystitis and fulguration and clot evacuation were performed. The patient had prostatic hypertrophy and underwent transurethral resection. The histopathologic examination revealed spotty AA-type amyloid deposition mainly around the vessels (Fig. 1). The patient at present shows no urological symptoms.

Case 3. A 44-year-old male with seropositive, erosive RAfor 24 years was on D-penicillamine and gold salts. In 1984 he developed proteinuria and rectal biopsy showed AA-type amyloidosis. The patient was given colchicine and placed on hemodialysis in 1987, but in 1992 had to undergo

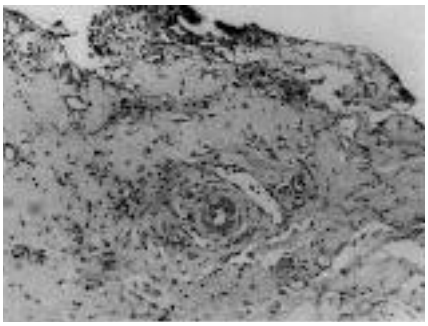

Fig. 1. Homogenous infiltration in a vessel wall of the lamina propria.

renal transplantation was started on immunosuppressives. In 1996 he had microscopic hematuria and in 1997 presented to us with macroscopic hematuria and hypotension. USG revealed a 71 x 59 mm mass in the bladder. Cystoscopy showed one thrombus and diffuse bleeding foci. As the peritoneal fluid increased during bladder irrigation, perforation was diagnosed and the bladder was sutured. On histopathology there was diffuse AA-type amyloid deposition around the vasculature of the bladder. Immunohistochemistry confirmed the presence of AA-type amyloid. The patient was administered massive transfusions and antibiotics. During the follow-up, he become febrile and *E. coli* were isolated from his urinary cultures. The patient developed septic shock under antibiotic therapy and died of urosepsis.

We have presented here 3 RApatients with symptomatic bladder amyloidosis. All 3 were males with at least a 20-year history of RA and amyloidosis for at least 4 years. Other reported cases also generally had RA of long duration (3). Patients with bladder amyloidosis generally present with massive, painless hematuria (3-5) and all of ours had gross hematuria.

In AA amyloidosis patients biopsies of the bladder can cause hemorrhage or even bladder perforation (6, 7). In case 1, perforation occured after cystoscopy and in case 3 during cystoscopy. Cystoscopic findings in bladder amyloidosis usually resemble infiltrating neoplasms; however, an ulcerated mucosa and beefy, edematous lesions may also be seen (4, 5). In case 2 the cystoscopic appearance was that of hemorrhagic cystitis; signs of bleeding were present in cases 1 and 3.

The pathogenesis of bleeding in amyloidosis may be infection (7), a bleeding diathesis caused by AL amyloidosis (8), or amyloid infiltration of the vessel wall preventing normal constriction (6). Vasoconstriction together with increased intravesical pressure might be important since case 2 also had prostatic hypertrophy. The infection in case 3 developed after cystoscopy-surgery. There was amyloid infiltration in the vessel walls in two of our patients. The anti-platelet effect of the NSAIDs frequently used in RA is well known. However, none of our patients were using these drugs. The treatments for bladder amyloidosis are transurethral fulguration, cystoscopy or cystectomy with clot evacuation, alum irrigation, temporary urinary diversion by percutaneous nephrostomy and ligation of the hypogastric arteries (3, 9). In case 2, bleeding was controlled by cystoscopy; in cases 1 and 3, surgery was performed after perforation. Although our patients were on colchicine, bleeding associated with bladder amyloidosis occurred in all three. Colchicine has shown promising results in experimental AA amyloidosis, but is not very effective clinically (10). The mortality rate in patients with gross hematuria is quite high (3) and one of our patients died of urosepsis.

In conclusion, massive hematuria is a rare manifestation that can complicate AAamyloidosis in RA patients. Extreme caution is needed in its management since it may result in serious complications.

M.R. ALTIPARMAK[1], *MD*
Ö.N. PAMUK[2], *MD*
I. FRESKO[3], *MD*

Departments of Nephrology[1] and Rheumatology[3], Cerrahpasa Medical Faculty, University of Istanbul, Istanbul; Department of Rheumatology[2], Trakya Medical Faculty, University of Trakya, Edirne, Turkey.

Address correspondence to: Dr. Mehmet Rıza Altıparmak, Rasimpasa Mah. Taslibayir Sok. No: 14 Daire: 10, Kadiköy – Istanbul, Turkey. E- mail: onpamuk80@hotmail.com

References

1. PAI S, HELIN H, ISOMAKI H: Frequency of amyloidosis in Estonian patients with rheumatoid arthritis. *Scand J Rheumatol* 1993; 22: 248-9.
2. HUSBY G: Amyloidosis. *Semin Arthritis Rheum* 1992; 22: 67-82.
3. NURMI MJ, EKFORS TO, PUNTALA PV: Secondary amyloidosis of the bladder: a cause of massive hematuria. *J Urol* 1987; 138: 44-5.
4. OKA N, FUKUMORI T, TAKAHASHI M, KANAYAMA H-O, KAGAWA S: Secondary amyloidosis of the bladder causing macroscopic hematuria. *Int J Urol* 2001; 8: 330-1.
5. FRAYHA RA, KULEILAT M, MUFARRIJ A, MUFARRIJ W: Hemorrhagic cystitis and sicca syndrome secondary to amyloidosis in rheumatoid arthritis. *J Rheumatol* 1985; 12: 378-9.
6. DIXON PVW, MATTHEWS PN, WILLIAMS GB: Massive haemorrhage following biopsy of amyloidosis of the bladder. *Br J Urol* 1984; 71: 650.
7. ABRAMOVICI I, CHWATT S, NUSSENSON M: Massive hematuria and perforation in a case of amyloidosis of the bladder: case report and review of the literature. *J Urol* 1977;

118: 964-6.
8. GRIEPP PR, KYLE RA, BOWIE E: Factor X deficiency in amyloidosis. A critical review. *Am J Haematol* 1981; 11: 443-50.
9. CROCITTO LE, EASTHAM JA, SKINNER EC, HUFFMAN JL: Management and evaluation of localized amyloidosis of the bladder: two case reports. *Urology* 1994; 44: 282-4.
10. CATHCART ES: Amyloidosis. *In* KELLEYWN, HARRIS ED JR, RUDDYS, SLEDGECB (Eds.): *Textbook of Rheumatology*, Philadelphia, W.B. Saunders Co., 1993: 1413-28.

Familial adenomatous polyposis coli associated arthritis and vasculitis

Sirs,

The association between arthritis, mainly peripheral (20%) but also axial (10%), vasculitis and inflammatory bowel diseases (IBD) is well known and frequently reported in the literature (1, 2). To our knowledge, an association between arthritis, vasculitis and FAP has never been recognized. Here we illustrate a case in which these features were all present, as well as a precise coincidence of timing between polyposis relapses after endoscopic removal and arthritis outbreaks.

A 56-year-old woman came to our attention because of fever, arthritis of the wrists and hands, and vesiculopapular eruptions on the back and limbs. There was a family history of colorectal carcinoma and adenomatous polyposis, with a sister also affected by polyarthritis. Biological assessment demonstrated a neutrophilic leukocytosis, ESR 92 mm/h and CRP 16.10 mg/dl; ANA, native DNA, ENA, ANCA and RF were negative, as well as blood cultures. X-rays of the wrists and hands showed not erosive arthritis (Fig. 1). After 6 days diarrhoea presented. A colonoscopy was performed and revealed a widespread colic polyposis.

The patient was treated with 6-methylprednisolone, with partial remission of a symptoms. After endoscopic clearing of 29 polyps on the residual rectum, laparoscopic total colectomy was performed. Histological examination revealed the presence of an intra-epithelial adenocarcinoma *in situ* (pTis pN0 pM0, staging A sec. Astler Coller). The patient was discharged without steroid therapy.

At the first follow-up 6 months later a new polyp was identified; at the same time cutaneous lesions, fever and polyarthralgias reappeared. A skin biopsy revealed leukocytoclastic vasculitis; a second rectal-ileoscopy showed the presence of 3 adenomatous polyps in the residual rectum, which were endoscopically removed. The patient was discharged on a regimen of gradually decreasing steroid therapy. During the next 18 months she showed complete improvement of her symptoms, but at this time arthralgias reappeared. She was treated again with short-term 6-methylprednisolone therapy and a new endoscopy was immediately performed, revealing the presence of 11 polyps, which were removed. At present (7 months later) the patient is free of recurrences and completely asymptomatic.

Familial adenomatous polyposis is an autosomal dominant disorder characterized by the presence of hundreds of polyps throughout the colon (3). In 1991 the genetic deletion responsible was identified on chromosome 5-q21 and since then more than 200 mutations have been recognized spread along the whole length of the gene (4). There currently seems to be no correlation between these genetic mutations and the extra-colonic manifestations of the disease, such as polyposis of the upper gastrointestinal tract (5) and osteomas of the mandible with the potential presence of supernumerary teeth (6).

The possible association between arthropathy and pouchitis after proctocolectomy for inflammatory diseases of the bowel and for FAPis described; the suggested mechanism is the persistence of abnormally permeable intestinal membrane in the site because of phlogosis. The described clinical manifestations are confined to arthralgias, not arthritis (7, 8).

In this case, cutaneous biopsy showed a perivascular infiltrate mainly composed of neutrophils (and their fragments) and lymphocytes, and fibrinoid degeneration of the wall of some vessels, leading to a diagnosis of necrotizing venulitis. A paraneoplastic expression of colon carcinoma, which is rarely manifested in an *in situ* colon carcinoma, was considered, but the second and the third outbreaks of cutaneous lesions occurred without evidence of neoplastic degeneration. Erythema elevatum diutinum and Sweet's syndrome were clinically and histologically excluded.

Moreover, the precise coincidence of timing between the polyposis relapses and arthritis/vasculitis outbreaks was very striking; this could reasonably suggest a correlation between altered intestinal permeability and the development of phlogosis, perhaps mediated by inflammation triggers. An additional interesting reflection could be made regarding the clinical case of the patient's sister, who was in turn affected by FAP and developed arthritis at the same time and with the same characteristics. This finding could suggest a common pathological and genetic mechanism.

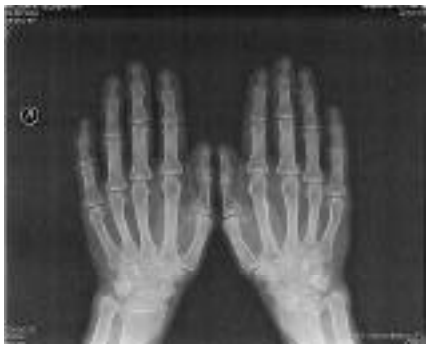

Fig. 1. X-ray showing non-erosive arthritis of the wrist and hands.

M. MATTIUZZO[1] A. SCAPINELLO[3]
R. BISCARO[2] G.F. FERRACCIOLI[4]

[1]School of Specialization in Internal Medicine, University of Udine; [2]Emergency Department and [3]Pathology Department, Ospedale di Montebelluna, Treviso; [4]Clinic of Rheumatological Diseases, University of Udine, Italy.

Address correspondence to: Dr. Renzo Biscaro, Director of Pronto Soccorso, Ospedale di Montebelluna, Via Montegrappa 32, Montebelluna (Treviso), Italy.
E-mail: muprs9@ulssasolo.ven.it

References

1. WOLLHEIM AF: Enteropathic arthritis. *In* RUDDYS, HARRIS ED, SLEDGE CB: *Kelley's Textbook of Rheumatology*. Philadelphia, W.B. Saunders 2001; 1081-8.
2. BONNET J, MODIGLIANI R: Manifestation systémiques des maladies inflammatoires chroniques de l'intestin. *In* KAHN MF, PELTIER AP, MEYER O, PIETTE JC: *Maladies et Syndromes Systémiques*. Flammarion 2000; 949-65.
3. BOLAND R, YOUNG SK: Poliposi gastrointestinale. *In* SLEISINGERMH and FORDTRAN JS: *Trattato di Gastroenterologia*. Piccin Ed., 1994; 778-9.
4. OLSCHWANG S, LAURENT-PUIG P: Polypose adénomateuse familiale. Epidémiologie, génétique et surveillance clinique. Ed. Techniques *Encyclopédie Médico-Chirurgicale* (Paris, France) Gastro-entérologie, 9-068-M-10, 1994, 5 p.
5. UTSUNOMIYA J, MAKI T, IWAMA T *et al*.: Gastric lesions of familial polyposis coli. *Cancer* 1974; 34: 745-54.
6. SONDERGAARD JO, BULOW S, JARVINEN HJ, WOLF J, WITT IN, TETENS G: Dental anomalies in familial polyposis coli. *Acta Odontol Scand* 1987; 45: 61-3.
7. ANDREYEV HJ, KAMM MA, FORBES A, NICHOLLS RJ: Joint symptoms after restorative proctocolectomy in ulcerative colitis and familial polyposis coli. *J Clin Gastroenterol* 1996; 23: 35-9.
8. THOMAS PD, KEAT AC, FORBES A, CICLITIRA PJ, NICHOLLS RJ: Extra-intestinal manifestations of ulcerative colitis following restorative proctocolectomy. *Eur J Gastroenterol Hepatol* 1999; 11; 1001-5.