Massive hematuria due to bladder amyloidosis in patients with rheumatoid arthritis: Three case reports

Sirs,

Secondary amyloidosis is uncommon in rheumatoid arthritis (RA) (1). Amyloidotic involvement of the urinary bladder is very rare but severe, which is often revealed by macroscopic hamaturia (2). Once massive hamaturia occurs, it would trend to be fatal (3). We present three cases of the bladder amyloidosis (BA) secondary to RA who developed massive hematuria.

As shown in Table I, our cases had a long RA duration more than 16 years. Before massive hemorrhage, secondary amyloidosis was diagnosed histologically in another organ biopsy. Therefore, it was not difficult to postulate that bladder hemorrhage was attributed to secondary amyloidosis. Catastrophic hemorrhage from the bladder due to unrecognized secondary amyloidosis was reported (3). Cystoscopically, they showed hemorrhagic cystitis. The potential causes of hemorrhage cystitis are numerous and include chemical toxins, immune agents, radiation, viral-, bacterial-, fungal-infection, cancer, and amyloidosis in rheumatic diseases (4).

In Case 1, influenza-like symptoms prior to bladder bleeding and bacteriuria were proved to be present. An explanation would be that a kind of virus or bacterial infection causing influenza-like symptoms could be a trigger of stimulated bleeding. It is not clear why bleeding starts in patients in whom infection has been postulated as trigger. The usual clinical presentation of secondary BA is most frequently presenting with profuse, often painless, hematuria, thus masquerading as a tumor of genitourinary tract. Since they were female, dysfunctional uterine bleeding could be due to amyloid deposition and could mimic other common causes of vaginal bleeding. Although they had no problems in hemorrhagic diathesis, isolated factor X deficiency and abnormality of hemorrhagic diathesis in amyloidosis were described (5).

BA secondary to RA is not only one of the symptoms of systemic secondary amyloidosis simply but also an important prognostic factor of RA. Histologically, the amyloid deposits were found in stroma, muscle and arterioles in our cases. The bladder wall undergoes necrosis either spontaneously or after cystoscopy with biopsy.

In Case 2, after transurethral biopsy, it was estimated that the bladder wall which had been served for the punch biopsy would be fragile, and rupture of the bladder might arise leading to fistula formation in the peritoneal space. Careful consideration in transurethral punch biopsy in BA should be carried out because of danger to cause massive bleeding by the operation itself (6,7). Cystoscopic instrumentation has been reported to aggravate the hemorrhage and occasionally has provoked intractable bleeding. Since hemorrhage is usually refractory to fulguration and bladder irritation, we must be prepared to administer early aggressive intervention to arrest the bleeding. Cystostomy, bilateral ureteral catheterization and ligation of hypogastric arteries have been tried (6). Massive hematuria in RA patients with secondary amyloidosis must be considered as a premonitory sign of an advanced stage of the disease and of poor prognosis.

We have identified a novel polymorphism of serum amyloid A protein (SAA)1.3 and found the frequency of the SAA1.3 allele was markedly increased in amyloidosis in Japanese RA patients, suggesting this allele is a risk factor for amyloidosis secondary to RA (8). Two cases had SAA1.3 allele and Case 3 was homozygous for SAA1.3. Though Case 3 had the shortest RA duration, the time of amyloidosis diagnosed after RA onset was earliest. SAA1 genotype is suggested to relate with clinical severity in RA patients with amyloidosis (9).

Secondary BA should be considered as a possible cause of hematuria in patients with long-standing RA, especially with SAA1.3 allele in Japanese patients, and as an important prognostic factor of RA. Cystoscopy is possible to lead to intractable bleeding by itself. Rapid and vigorous treatment will be necessary under the sincere cooperation between rheumatologist and urologist.

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Table I. Clinical characteristics of three cases of massive hematuria in bladder amyloidosis secondary to RA.

Case/ Age/Sex	RA duration (yrs.)	Amyloidosis diagnosed after RA onset (yrs.)	Clinical* Stage	Class	SAA1 genotype	Amyloid deposition except bladder	Predated proteinuria	Painless hematuria	Passage of blood clots	Treatment	Outcome
1/52/F	28	22	IV	2	1.2/1.2	Stomach Kidney Heart	(+)	(+)	(+) Tamponade	Fulguration of bleeding vessel Clot evacuation	Alive Active
2/47/F	27	18	III	3	1.2/1.3	Stomach Kidney Elbow joint synovium	(+)	(+)	(+) Tamponade	Clot evacuation Fulguration Closure of perforation	Alive Hemodialysis
3/58/F	16	13	III	2	1.3/1.3	Stomach Kidney	(+)	(+)	(+)	Clot evacuation Fulguration Alum irrigation	Alive Active

*According to Steinbrocker's functional criteria (Steinbrocker *et al. JAMA* 1949 ; 140 : 659-62).

Letters to the Editor

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Iatrogenic Kaposi's sarcoma following immunosuppressive therapy for systemic lupus erythematosus

Sir,

Kaposi's sarcoma (KS) is a rare malignant tumour (incidence 0.01%) of endothelial and vascular smooth muscle cells. Four types of KS have been described: classic KS, which is an indolent disease predominently affecting the Ashkenazi Jews; African endemic KS; HIV-related KS; and iatrogenic KS appearing as a result of immunosuppressive therapy (1, 2). Recently, human herpesvirus 8 (HHV-8) was identified as the causative agent in almost all the cases of KS (3, 4).

A 39-year-old woman of Berber origin was admitted in our department for acute polyarthritis affecting the small joints of the hands and inferior legs oedema. Biological exams showed ESR 68 mm/h, CRP 26 mg/l, normal cells blood count, positive antinuclear antibodies (1/360), positive anti-DNA antibodies (1/160), negative rheumatoid factor. Urine proteins were 3.5 g/d and serum albumin 25 g/l. Serum urea and creatinine were in normal range. The diagnosis of SLE was made. Kidney biopsy showed proliferative glomerulonephritis. Treatment was started: monthly pulses (1 g) of cyclophosphamide with prednisone 60

Fig. 1. Typical cutaneous lesions of Kaposi's sarcoma affecting the forearm.

mg/d for 6 weeks followed by gradual dose reduction to 20 mg after 12 weeks. There was a marked clinical improvement associated with a fall in her ESR to 10 mm/h and normal renal tests within the second month. One week after the fourth cyclophosphamide pulse, she developed severe genital herpes infection which quickly disapeared after high doses of acyclovir (200 mg x 5/d). Two months later, she developed disseminated large purple nodules on the face, the dorsum of the forearm, the hands and the lower legs (Fig. 1). A skin biopsy showed typical KS lesions and blood investigations showed high-titre of IgG antibodies to Herpesvirus 1,2 (1/3500) and HHV-8 (1/5600). Prednisone was decreased gradually to 5 mg/d. Skin lesions showed partial regression but inflammatory markers and proteinuria raised once again. Three months later, The renal function tests worsned dramatically and the patient died suddenly after cardiac dysarythmia secondary to hypokaliemia.

Iatrogenic KS was first described among post-transplant patients on high-dose immunosuppressive therapy (5). It has also been observed in patients receiving immunosuppressive therapy for autoimmune diseases, including pemphigus vulgaris, dermatomyositis, polymyalgia rheumatica, rheumatoid arthritis, Sjögren syndrome, temporal arteritis, Crohn's disease, and SLE. Most of these patients were treated by steroids alone or in combination with cytotoxic drugs (e.g. cyclophosphamide, azathioprin and cyclosporin A). The first case of KS in SLE was reported by Klein *et al.* in 1974 (6) and since that, only 2 other cases were reported (7, 8). In 1994 Chang *et al.* (3) described a novel herpesvirus from a KS lesion which was named HHV-8. It was subsequently isolated from all types of KS lesions. Prior infection with HHV-8 is a requisite for the development of disease and it is likely in our case that infection was acquired by sexual route in the same time of the herpes infection. The question arises as to how immunosuppressive treatment can lead to the emergence of KS. Recent in vitro evidence supports the hypothesis that steroids have a direct role in stimulating tumour development and growth (9, 10).

Interrupting immunosuppressive therapy usually improves the KS lesions but can be followed by a flare of the underlying disease. Some kind of treatment without immunosuppressive effects and active on the underlying disease would be the best solution. Recently, Kötter and coll. (1) used interferon a in a iatrogenic KS during treatment of a severe ocular Behçet's disease and obtained complete remission of both disorders. The use of intravenous immunoglobulins would have been a possible alternative in our case. Our observation also suggest that clinicians should think to screeen patients for HHV-8 in autoimmune diseases when hign doses of immunosuppressive therapy are required.

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