Gout and amyloidosis

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SUMMARY Two patients with gout and amyloidosis are reported. In contrast with other forms of chronic arthritis gout is apparently not associated with an increased incidence of amyloidosis. The possible reasons for this exception are discussed.

Amyloidosis is classically divided into 2 groups: the primary form, which is usually associated with a plasma cell dyscrasia and characterised by amyloid L protein (AL), and the secondary form, which is associated with chronic infections or inflammatory processes and characterised by amyloid A protein (AA).¹

Some forms of chronic arthritis are characterised by a prolonged and intense inflammatory response which may predispose to the appearance of amyloidosis. In fact amyloidosis is a major complication of rheumatoid arthritis, juvenile rheumatoid arthritis, and ankylosing spondylitis and may be associated with psoriatic arthritis and systemic lupus erythematosus.^{2–8}

The present report describes 2 patients with gout and amyloidosis and a search of the literature revealed only 5 additional cases.^{9–11} In most of these patients the amyloidosis either preceded the gouty attacks or could be attributed by coexisting chronic infections. Therefore it seems that gout in contrast to other forms of inflammatory arthritis is not associated with increased incidence of amyloidosis. The various possibilities for this exception are analysed and discussed below.

Case reports

Case 1. A male Jew of Sepharadi parentage, born in Morocco, was admitted to the Department of Medicine because of recurrent episodes of arthritis. His mother, brother, and maternal cousin suffered from early onset gout. The patient started to have typical attacks of gout at the age of 14. At first the disease affected the metatarsal joints, the ankles, and the knees. Later it progressed to the metacarpal

joints and the elbows. In the course of time the joints became extremely deformed, and multiple nodules, histologically diagnosed as tophi, appeared, mainly on the extensor surfaces of the extremities. Some of the tophi had secreting sinuses with long-standing secondary bacterial infection. The diagnosis of gouty arthritis was established by the demonstration of urate crystals in the nodules, serum uric acid levels of 580 $\mu\text{mol/l}$, and uricosuria of up to 5350 $\mu\text{mol/24 hours}$ on a low-purine diet.

The patient never adhered to any therapeutic regimen except for colchicine during acute attacks. At the age of 29 he was noted to have polyuria, the concentrating capacity of the kidney was decreased, blood urea rose to 11 mmol/l, creatinine to 230 $\mu\text{mol/l}$, and creatinine clearance was 36 ml/min. Urine analysis showed traces of protein and a few erythrocytes, leucocytes, and granular casts per high-power field. Kidney biopsy showed uric acid granulomas in the medulla and no changes in the glomeruli. Renal function remained satisfactory during the following 10 years. However, a gradual deterioration started at the age of 39, and the patient died of severe renal failure and terminal bronchopneumonia at the age of 46. Necropsy showed bronchopneumonia and amyloidosis of the kidneys, adrenals, and testicular blood vessels as evidenced by positive Congo-red staining and green birefringence. The kidneys were contracted because of amyloidosis, and uric acid crystals were found in the tubuli.

Case 2. A 39-year-old Jewish male was first admitted to hospital in the Department of Medicine because of a typical attack of gout affecting the first metatarsophalangeal joint of the right foot. The patient had a 3-month history of arthralgia affecting the knees and ankles. The family history was not significant. The patient was known to have a high erythrocyte sedimentation rate and massive proteinuria, which were detected in the course of a routine examination a year before admission.

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Physical examination gave no abnormal findings, and the pertinent laboratory data were: sedimentation rate 120 mm after one hour (Westergren), leucocytes $15 \times 10^9/l$, albumin/globulin 27/41 g/l, urea 10 mmol/l, uric acid up to 770 $\mu\text{mol/l}$, proteinuria up to 3 g/24 hours, uricosuria up to 3580 $\mu\text{mol}/24$ hours, and creatine clearance 54 ml/min. No paraprotein was detected in the serum or the urine. A bone marrow aspirate contained 5% plasma cells but was otherwise normal. Intravenous pyelography was also normal, and a kidney biopsy showed Congo-red and green birefringence, positive amyloid deposits, and interstitial inflammation. Arthrocentesis yielded uric acid crystals. The diagnosis of gouty arthritis associated with amyloidosis of the kidneys was made, and the patient was discharged on analgesics and probenecid.

During the next 2 years the patient felt relatively well except for infrequent attacks of gout. He was then readmitted with symptoms of severe renal failure, which culminated in death after 2 months. Permission for necropsy was not obtained.

Discussion

Amyloidosis occurs in about 15% of patients with rheumatoid arthritis. It is not infrequent in ankylosing spondylitis and may also complicate psoriatic arthritis.^{2-5 7 8} On the other hand the association of gout and amyloidosis is very rare. Talbott and Terplan,⁹ in their extensive review of the kidney in gout, mention only 3 such case reports published in 1876, 1901, and 1906. Talbott himself¹¹ found 4 patients with amyloidosis among 300 necropsies of patients with gout. The relevant clinical and pathological features of these cases and of our 2 patients are given in Table 1. We could find only 1 other report of gout associated with amyloidosis.¹⁰ This patient, a 53-year-old male, suffered from gout and died of renal insufficiency after 2 years. His kidneys showed pyelonephritis and deposits of an amyloid-

like material in the glomeruli and the cortical arterioles.

Gout has been estimated to affect at least 300 000 people in the United States.¹¹ In view of this high incidence and the small number of patients with amyloidosis reported so far it seems that gouty arthritis is not associated with an increased incidence of amyloidosis. In fact 2 of the 4 patients described by Talbott (nos. 2 and 3, Table 1), could have developed amyloidosis as a result of tuberculosis. In 1 of our patients (no. 6, Table 1), there is good reason to believe that amyloidosis manifested by a high sedimentation rate and massive proteinuria preceded the onset of gout. The other 3 patients (nos. 1, 4, 5, Table 1) suffered from long-standing severe tophaceous gout with discharging sinuses. Secondary infections of these tophi, well documented in one of our patients (no. 5) could have been the cause of secondary amyloidosis.

Current concepts on the pathogenesis of secondary amyloidosis suggest a dual mechanism. The amyloidogenic stimulus, chronic infection, or inflammation in man and endotoxin or casein administration in experimental animals, is believed to cause a persistent elevation of the serum precursor of amyloid, serum amyloid A (SAA), as well as an alteration of the degradation process of the precursor, presumably mediated by macrophages.

Gout, like rheumatoid arthritis, is characterised by a chronic, intense inflammatory response of the joints. Hence amyloidosis would be expected to complicate both diseases to a similar extent. The fact that amyloidosis is extremely infrequent in gout deserves comment. It may be argued that the inflammatory stimulus in this disease is too short to become an effective amyloidogenic stimulus. This argument, however, is not applicable in a substantial number of patients who suffer from protracted and severe inflammation. Alternatively, the inflammatory response in gout may be different from that in rheumatoid arthritis in that it is more

Table 1 Clinicopathological features in reported patients with gout and amyloidosis

Patient	Sex	Age		Serum uric acid $\mu\text{mol/l}$	Kidney stones	Family history	Severity of gout		Extent of amyloidosis	Cause of death
		Onset of gout	Death				Chronic tophaceous	Mono-arthritis		
1*	M	17	42	850	—	—	+		Generalised	Uraemia
2*	M	14	23	500	—	+	+		Kidneys	Tuberculosis
3*	M	28	32	410	—	—		+	Kidneys	Tuberculosis
4*	M	35	72	?	—	?	+		Kidneys	Arteriosclerotic heart disease
5**	M	14	46	590	—	+	+		Kidneys	Uraemia, pneumonia
6**	M	39	42	770	—	?		+	?	Uraemia

*Patient reported in Talbott.¹¹

**Patient reported in the present paper.

localised and limited. However, other localised infections and inflammatory processes, for example, osteomyelitis and Crohn's disease, are nevertheless known to trigger amyloidosis. Another possibility is that the inflammatory process in gout differs in nature from that in rheumatoid arthritis. Perhaps the inflammation and macrophage and polymorphonuclear activation induced by uric acid is specifically devoid of amyloidogenic properties. This hypothesis can be explored in gouty patients and in animal experiments. In patients one could monitor the serum amyloid precursor (SAA) level in correlation to disease activity. A positive correlation has already been detected in patients with rheumatoid arthritis. In animals one could follow SAA levels and amyloid deposition following chronic intra-articular administration of monosodium urate crystals.

Another factor which might possibly explain the low incidence of amyloidosis in gout is the administration of colchicine. This agent has been shown to prevent casein-induced amyloidosis in mice.^{12 13} Furthermore, a few patients with familial Mediterranean fever complicated by amyloidosis have shown regression of albuminuria during continuous, prolonged treatment with colchicine.¹⁴ However, since the large majority of patients with gout are treated with colchicine only during attacks and many patients take no colchicine at all, it is unlikely that the low incidence of amyloidosis in this disease is related to this drug.

In conclusion, it seems that gouty arthritis, in contrast to other forms of chronic arthritis, is not significantly associated with amyloidosis. The reasons for this exception are not clear, and further investigation is needed to unveil the mechanisms involved. A deeper insight into this problem may

possibly elucidate some of the pathogenic processes involved in secondary amyloidosis.

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