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ORIGINAL ARTICLE

Sonographic features suggestive of amyloidosis in hemodialysis patients: Relations to serum beta2-microglobulin

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Abstract *Aim of the work:* To determine sonographic features suggestive of amyloidosis in hemodialysis patients complaining of shoulder pain, and to study their relations to serum beta2-microglobulin (β2M).

Patients and methods: Clinical examination, skeletal survey, musculoskeletal ultrasonography of the shoulder joints, and serum β2M were done for 32 patients with end stage renal disease, who were regular on hemodialysis.

Results: Serum β2M levels were markedly raised in all patients, and increased with increasing duration of dialysis ($r = 0.91$, $p < 0.001$). Twenty-five patients had a non homogeneous thickening of the supraspinatus tendon >7 mm, and thickening of the biceps tendon >4 mm, 30 had synovial deposits, 27 had subdeltoid bursa effusion, 25 had thickened subacromial bursa, 7 had supraspinatus tendon tear, and 17 had bony erosions. Serum β2M levels significantly correlated with thickened supraspinatus tendon (>7 mm) and supraspinatus tendon tear ($r = 0.41$, $p = 0.03$ and $r = 0.42$, $p = 0.01$ respectively). Long time on hemodialysis was the significant independent determinant for supraspinatus tendon tear and humeral head erosions ($p = 0.001$ for each).

Conclusion: Elevated serum β2M levels and sonographic features suggestive of dialysis-related amyloidosis (DRA) were found in all hemodialyzed patients complaining of shoulder pain either with or without clinical and/or radiological features suggestive of DRA. So, for diagnosis of DRA, sonographic features should correspond to the presence of clinically or radiologically evident β2M amyloid, and we should exclude other causes of non-amyloid changes.

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1. Introduction

Dialysis-related amyloidosis (DRA) is a disorder caused by tissue deposition of beta2-microglobulin (β2M) as amyloid fibrils [1]. The tissue deposition of amyloid detected histologically occurs much earlier than any clinical or radiographic manifestations of the illness. A prospective postmortem study found joint amyloid deposition in 21% in patients receiving hemodialysis for less than 2 years, 50% at 4–7 years, 90% at 7–13 years, and 100% at more than 13 years [2].

The pathogenesis and pathophysiology of DRA are probably multifactorial and have been associated with the duration of renal failure, patient's current age, patient's age at initiation of hemodialysis, duration of hemodialysis, bioincompatibility of dialysis membranes [3], less residual renal function, and the coexistence of high-turnover renal osteodystrophy [4].

Heparin is widely used as an anticoagulant in hemodialysis. Yamamoto et al. [5] have suggested that heparin could exert a subtle effect on the development of β2M amyloidosis under some clinical conditions. Also, Uji et al. [6] have suggested a possible association of β2M with glycosaminoglycans (GAGs) containing a sulfate moiety, including heparin, in hemodialyzed patients.

Dialysis-related amyloidosis is characterized by painful stiff joints, usually first involving the shoulder, and less commonly the hands, wrists, knees, and other large joints. Involvement tends to be bilateral and symmetrical, and is frequently associated with the carpal tunnel syndrome (CTS) and tenosynovitis [7].

As clinical symptoms of DRA are nonspecific, they may easily be misinterpreted as other joint diseases [8]. Typical specific radiological amyloid bone cysts are a late event. Different studies observed that capsulosynovial swelling precedes the development of characteristic bone cysts [9,10]. They are hypothesizing that amyloid infiltration of synovial membrane and tendons [11–13] might be accessible to ultrasonographic assessment [14].

Ultrasonography (US) has been suggested as the modality of choice in evaluating DRA of the shoulder. Thickening of the supraspinatus tendon greater than 7 mm and thickening of the long head of the biceps tendon greater than 4 mm, both in the appropriate clinical setting, have correlated excellently with DRA of the shoulder [9,15,16].

Biopsy is nearly always required for definitive diagnosis. However, because histologic confirmation is not always possible and increased serum β2M level is not diagnostic, imaging findings combined with history and clinical findings are usually used for the assessment of musculoskeletal involvement by DRA [17].

The aims of the study were to determine sonographic features suggestive of amyloidosis in hemodialysis patients complaining of shoulder pain, and to study their relation to serum β2M.

2. Patients and methods

2.1. Study subjects

The study was conducted at the renal unit of Minia University Hospital, Minia governorate, Egypt. All patients with end stage renal disease (ESRD), who were regular on hemodialysis were included. All patients had persistent shoulder pain lasting for more than 6 weeks. They were 32 patients, 18 males (56.2%) and 14 females (43.8%). Fifteen healthy age and sex matched subjects served as controls. Informed consent was taken from all participants in the study. The study was approved by the ethics committee of the Faculty of Medicine, Minia University.

All study patients were undergoing hemodialysis with low-flux hemodialyzers. All patients were dialyzed 3 times/week. The duration of each session was 4 h.

Patients having any evidence of autoimmune deficiency syndrome, lymphoproliferative disorders, inflammatory disorders like systemic lupus erythematosus, rheumatoid arthritis, Crohn's disease, and liver cirrhosis, which lead to rise in β2M were excluded from the study. Patients with chronic infections like tuberculosis, chronic osteomyelitis and patients with primary amyloidosis were also excluded.

2.2. Clinical diagnosis

Patients were examined clinically to show if they completed the characteristic triad of DRA or not. The triad included flexor tenosynovitis of the hand with diminished extension of the fingers, signs or symptoms of CTS and shoulder pain with diminished range of motion [18,19].

2.3. Laboratory investigations

Serum β2M was estimated by ELISA technique (pre hemodialysis) using ORG 5BM beta2-microglobulin kit, the normal range: 0–3.0 μg/ml [20]. Serum parathyroid hormone (PTH) was assayed in all patients by the Intact Parathyroid Hormone ELISA Kit, normal range: 15–55 pg/ml [21].

Blood urea and creatinine were measured in all patients. The normal plasma concentration of urea was 20–40 mg/dl, and the normal range of creatinine was 0.6–1.2 mg/dl for male and 0.5–1.1 for female.

2.4. Imaging

Skeletal survey involving X-rays of the shoulders, pelvis, cervical spine, lumbar spine, knees and wrists were taken to look for subchondral bone erosions and cysts, bone fractures, destructive arthropathy and spondyloarthropathy – characteristic of amyloidosis [22]. A radiological diagnosis of renal osteodystrophy was made if any of the following were present: subperiosteal resorption, tuft resorption, distal clavicular erosions, Rugger–Jersey spine or other typical bony sclerosis, or coarse bony trabeculation [23].

All patients underwent musculoskeletal ultrasonography of the shoulder joints to assess features suggestive of amyloidosis. Ultrasonograms were obtained and interpreted by one researcher (F.A., rheumatologist) using conventional grey-scale ultrasound machine with a 7.5–12 MHz linear transducer. In the shoulders: tendons were examined, evaluating changes of their sonographic appearance, alterations of their margins, modifications of their thickness and the presence of peritendinous fluid collection; sonographic signs of bursitis were searched for [24]. Bony erosion should be specifically noted during shoulder sonography as a sign of arthropathy [16]. The normal supraspinatus tendon thickness was