Aluminum induced bone and joint disease overview and current perspective

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Abstract: Aluminum is ubiquitous in nature. With constant exposure to it abnormally high concentrations can accumulate in human tissues and organs. Patient's most prone to toxic aluminum levels are those with chronic renal failure undergoing dialysis and those who are treated with oral doses of compounds high in aluminum content. The toxic effects of this metal lead to development of important bone and joint diseases. Imaging techniques including plain film or digital radiography, radionuclide imaging and MR imaging are crucial in correct diagnosis and therapeutic management of these diseases.
Abnormalities of the skeletal system include low bone turnover rate osteoporosis, osteomalacia, and multiple non-healing-fractures. The spectrum of joint diseases developing during long-term dialysis includes erosive arthropathy of the hands and feet, spodyloarthropathy mimicking infectious spondylitis, periarticular and tendonous calcifications. Chondrocalcinosis with crystal deposition and beta2-microglobulin can also occur with the arthropathy.
With tighter control of aluminum concentration in dialysis fluid, and avoidance of oral intake of aluminum containing compounds, aluminum toxicity and its osteo-articular manifestations should be a rare occurrence in the future.

ALUMÍNIUM-OKOZTA ÍZÜLETI ÉS CSONTBETEGSÉGEK ÁTTEKINTÉSE ÉS JELENLEGI MEGÍTÉLÉSE

Az alumínium mindenütt előfordul a természetben. Állandóan hat az emberi szervezetre, ezért kórosan nagy koncentrációban halmozódhat fel annak szöveteiben és szerveiben. Az alumínium-mérgezés veszélye az idült vesebetegség miatt dialysáló kezelésben részesülő, valamint a magas alumínium tartalmú perorális készítményeket szedő betegeket fenyegeti a leginkább. E fém toxikus hatásai nagy jelentőségű csont- és ízületi betegségeket idézhetnek elő. Az utóbbiak kórismézésének és kezelésének nélkülözhetetlen eszközei a képalkotó eljárások (natív röntgenfelvétel, digitális radiográfia, izotóp-szcintigráfia, és MRI). A csontozat alumínium-okozta betegsége például a lassú csontanyagcseréjű osteoporosis és az osteomalacia; többszörös, nem gyógyuló csonttörések is bekövetkezhetnek. Hosszú távú dialysáló kezelés során erosiv arthropathia alakul ki a kéz és a láb ízületeiben. Fertőzéses spondylitist utánzó spondyloarthropathia is felléphet, továbbá mészlerakódások keletkezhetnek az ízületek körül és az inakban. Az arthropathiához kristálylerakódással járó chondrocalcinosis és β_2-microglobulinaemia társulhat. A dialysáló folyadék alumíniumszintjének gondosabb ellenőrzése és az alumínium tartalmú készítmények szedésé-nek mellőzése esetén aligha kell az alumínium toxicitásától és annak csont-ízületi szövődményeitől tartani.

Aluminum comprises close to 8% of the earth's crust thus humans are constantly exposed to this element. Little has been known about it's metabolism and toxicity until the mid twentieth century. Aluminum is present in all tissues and organs in the body and when there is excessive accumulation multiple organ systems are effected by this metal (1).

The important diseases induced by aluminum toxicity include dementia, anemia, myopathy, bone and joint disease (2-5).

The potentially fatal encephalopathy of aluminum toxicity causes lethargy, seizures, speech difficulties, coma and eventually death. The dementia is caused by neurofiabrillary changes with degeneration of neurons in the brain with amyloid deposits, resembling the changes seen in Alzheimer disease, however there is no evidence that Alzheimer disease is caused by toxic levels of aluminum. The myopathy results in loss of coordinated movement, tremors and muscle spasms. The anemia is microcytic and is often the first sign of aluminum toxicity.

ALUMINUM BONE DISEASE

The most important alteration in aluminum toxicity occurs in the skeletal system of patients on dialysis for endstage renal disease receiving excessive aluminum from the dialysate fluid, and oral intake of Aluminum hydroxide taken as a phosphate binder to prevent hyperphosphatemia. Another group of patients with aluminum bone disease are those treated with high doses of aluminum containing antacids for peptic ulcer disease. Parkinson (6) and Ward (7) first showed direct evidence that there is a linkage between aluminum and the bone mineralization process with increase in under-mineralized osteoid volume and increased bone aluminum content. Alfrey (8) described that aluminum loading of bone occurred when untreated water was used from a municipal water sources with a naturally occurring high aluminum content, or aluminum was used as an addative in attempts to purify water. Aluminum even in minute amounts crosses the dialyzing membrane causing gradual accumulation in patients undergoing dialysis. With the addition of orally administered aluminum containing compounds as phosphate binders in the gastrointestinal tract, the excessive aluminum is deposited in bone (9-10). The identical process occurs in peptic ulcer disease patients with high aluminum intake from antacids (11).

The kidneys and the gastrointestinal tract control the metabolism of aluminum. The normal oral intake of aluminum from food and water is approximately 5-10 mg/day. Of this intake 8-10 microgram is absorbed in the small intestine. The kidney is the major organ for elimination of aluminum: the gastrointestinal tract excretes most of the remaining excess (12). Any retained aluminum is bound to the protein transferrin in the plasma and carried to all organs in the body. Strict control of aluminum level in the dialysate, replacing aluminum hydroxide with calcium carbonate for phosphate binding and monitoring blood aluminum levels regularly prevent the toxic effects of aluminum. During the last few years these measures have been implemented in most dialysis centers worldwide, limiting dialysate aluminum levels to the maximum of 3 micrograms/liter decreasing aluminum related diseases yet a recent study found wide variation in dialysate aluminum content in some countries in Europe and South America (13).

The diagnosis of aluminum toxicity can be made by measuring plasma aluminum levels, the deferoxamine test and by bone biopsy. Using intravenous deferoxamine injection of this agent removes aluminum from bone and other organs elevating blood aluminum levels. However elevated aluminum levels may be found without presence of bone disease, therefore the only specific test to prove bone involvement is bone biopsy (19). Iliac crest biopsies are stained with aluminum stain (aurine tricarboxilic acid) which stains aluminum bright red. Accumulation of aluminum on the trabecular bone surface at the mineralization front is diagnostic of aluminum bone disease (20, 21), [Fig 1].

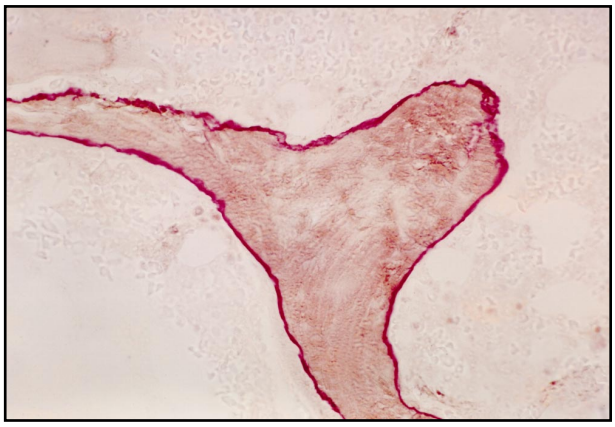


Figure 1. Photomicrograph of iliac crest bone biopsy, with aluminum stain and low power. Deposition of aluminum (red) on the surface of trabecular bone at the mineralization front.

The spectrum of bone diseases resulting from the toxic effects of aluminum include osteoporosis, osteomalacia, low rate of bone formation and development of non-healing fractures. The fractures are usually insufficiency fractures with Looser zones and occur at multiple sites. The most common locations include the ribs.

[Fig 2a, and b] verebral column, pelvis, femoral neck and proximal tibia (14,15,16). The fractures are readily diagnosable on plain films, however some of the fracture lines are not always identifiable. Occasionally MRI maybe helpful in demonstrating several intramedullary extensions of the fracture lines, [Fig 3a, b and c]. Bone scintigraphy is used to identify multiple fracture sites and to monitor effectiveness of treatment [Fig 4a, b, and c].

Treatment of aluminum toxicity consists of renal transplantation or deferoxamine therapy. This agent mobilizes aluminum from bone, tissue deposits and from the dialysate during dialysis when it is infused one hour prior to dialysis (22). However deferoxamine is toxic and in high doses it can exacerbate encephalopathy, cause auditory neurotoxicity and even fatal bacterial and fungal infection with Rhizopus pneumonia and Mucormycosis (23, 24).

ALUMINUM INDUCED JOINT DISEASE

The increasing survival of patients with chronic renal failure and long duration of dialysis often for 10 to 15 years resulted in increasing recognition of dialysis related articular abnormalities. Kuntz first reported progressive destructive arthropathy in the hands and wrists (25). Subsequently Naidich noted that the arthropathy increases in frequency and severity as the duration of dialysis increases (26). Bedani found a number of articular and periarticular abnormalities including erosive arthropathy with cysts, spondyloarthropathy deposition of calcium in

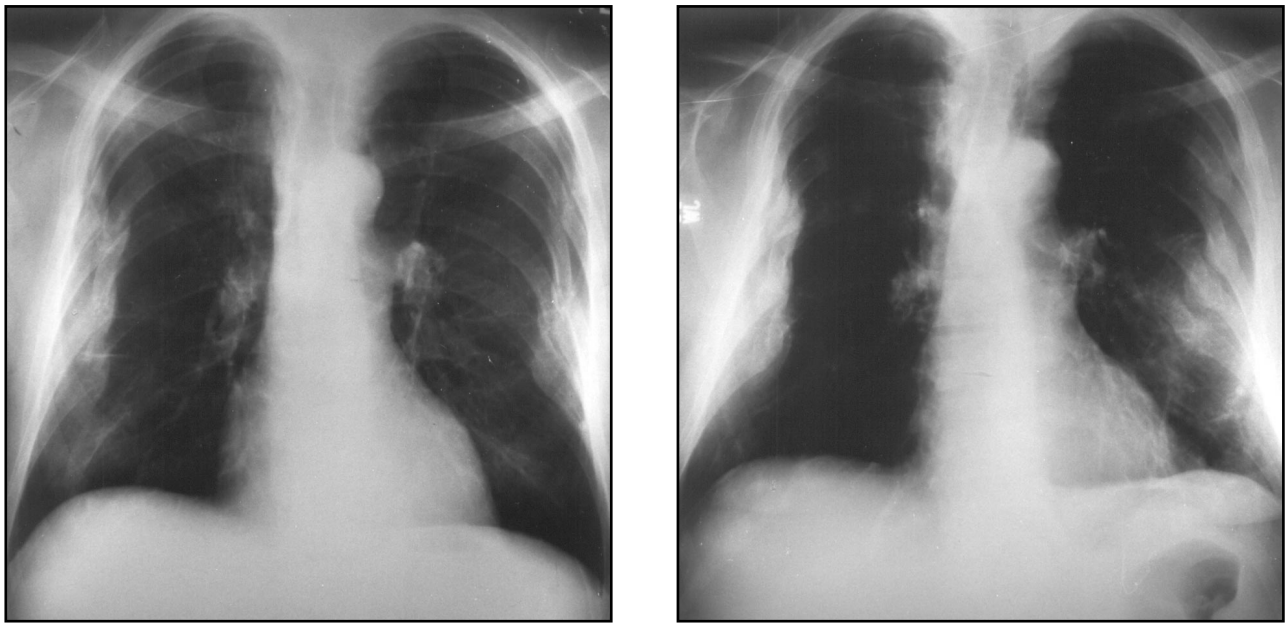


Figure 2. Chest radiographs of a 61-year-old male on hemodialysis for 7 years for chronic renal failure with markedly elevated serum aluminum level.
A) Bilateral painful rib fractures present for two years with no signs of healing.
B)14 weeks after initiation of deferoxamine theaapy. There is healing of the fractures with promínent bony callus.

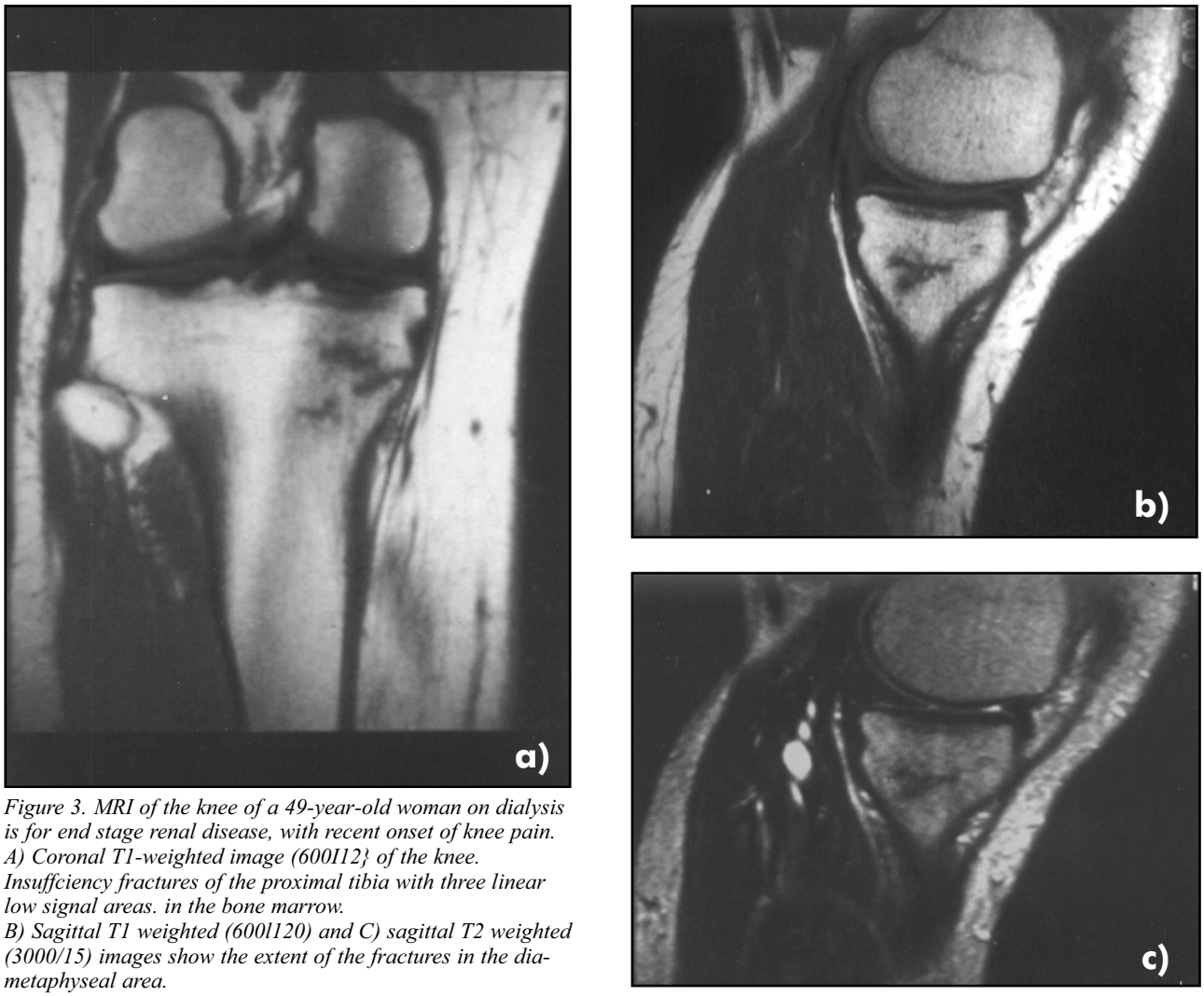
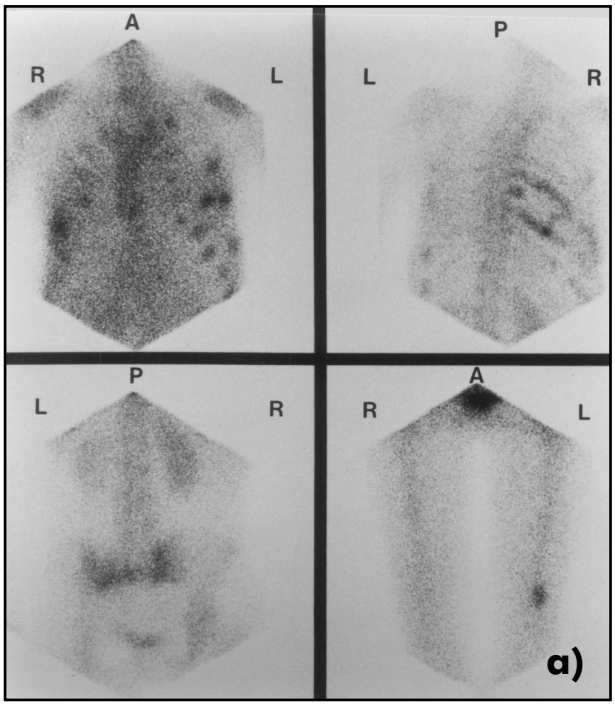
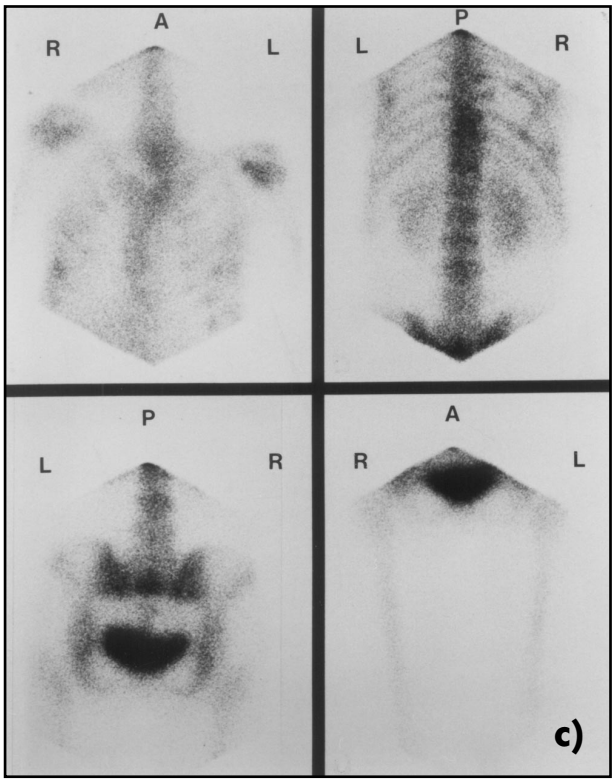


Figure 3. MRI of the knee of a 49-year-old woman on dialysis is for end stage renal disease, with recent onset of knee pain.
A) Coronal T1-weighted image (600I12} of the knee. Insuffciency fractures of the proximal tibia with three linear low signal areas. in the bone marrow.
B) Sagittal T1 weighted (600l120) and C) sagittal T2 weighted (3000/15) images show the extent of the fractures in the dia-metaphyseal area.





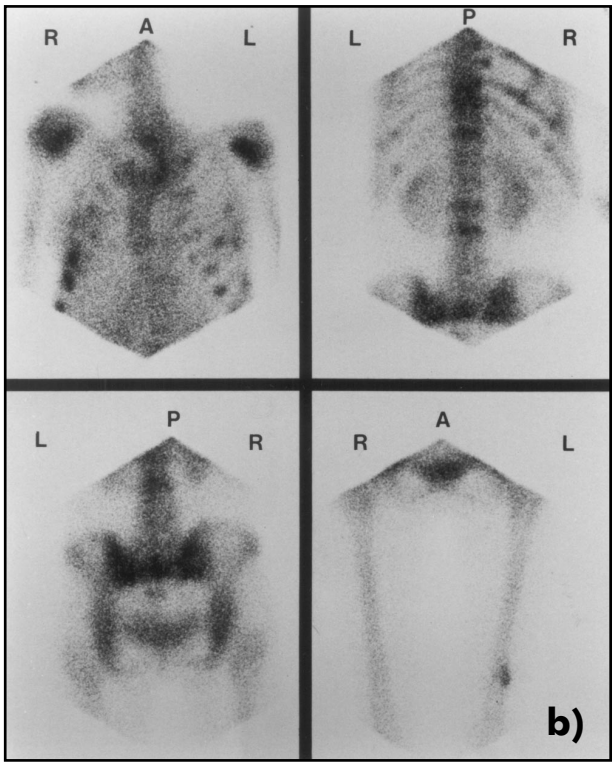


Figure 4.Tc -MDP radionuclide images of a 41-year-old woman, a chronic user of aluminum containing antacids for peptic ulcer disease and status post liver transplantation for sclerosing cholangitis with subsequent acute renal failure requiring dialysis for 4 weeks.
A) Initial scan. Multiple foci of increased uptake in rib fractures and a solitary abnormal focus in a stress fracture in the distal left femur. Poor bone uptake with high soft-tissue activity on all images.
B) Six weeks later on deferoxamine therapy Continued incaeased uptake in the rib fractures, linear increased uptake in multiple vertebral compression fractures, and no change in the distal femoral fracture. The bone to soft-tissue activity has improved.
C) Eight weeks after B. Decreased activity in rib fractures and compressed vertebrae indicating healing. No detectable activity in distal femur indicating healing of the stress fracture.

soft tissues, beta2-microglobulin amyloidosis and chondrocalcinosis in patients undergoing dialysis for 15 years or longer (27).

The erosive arthropathy in the hands has a predilection for the proximal and distal interphalangeal joints. Initially there is joint space narrowing and later marginal erosions and subluxations develop. The tapeziometacarpal joints reveal narrowing, sclerosis and cysts, mimicking erosive osteoarthritis. Some authors implicate multifactorial causes including degenerative and inflammatory etiologies (28). Others believe that hyperparathyrodism and dialysis amyloidosis cause the erosive joint disease (29).

Spondyloarthropathy develops after several years of dialysis most commonly in the cervical spine however any portion of the vertebral column may be involved. Radiographic manifestations vary from erosions of the endplates to ankylosis and progressive destruction of the vertebrae, simulating infectious spondylitis (30). Since dialysis patients are prone to develop infectious spondylitis the differentiation of the two conditions is important. MR imaging can be very helpful in differentiating dialysis spondyloarthropathy from infectious spondylodiscitis. When low signal is seen on both T1 and

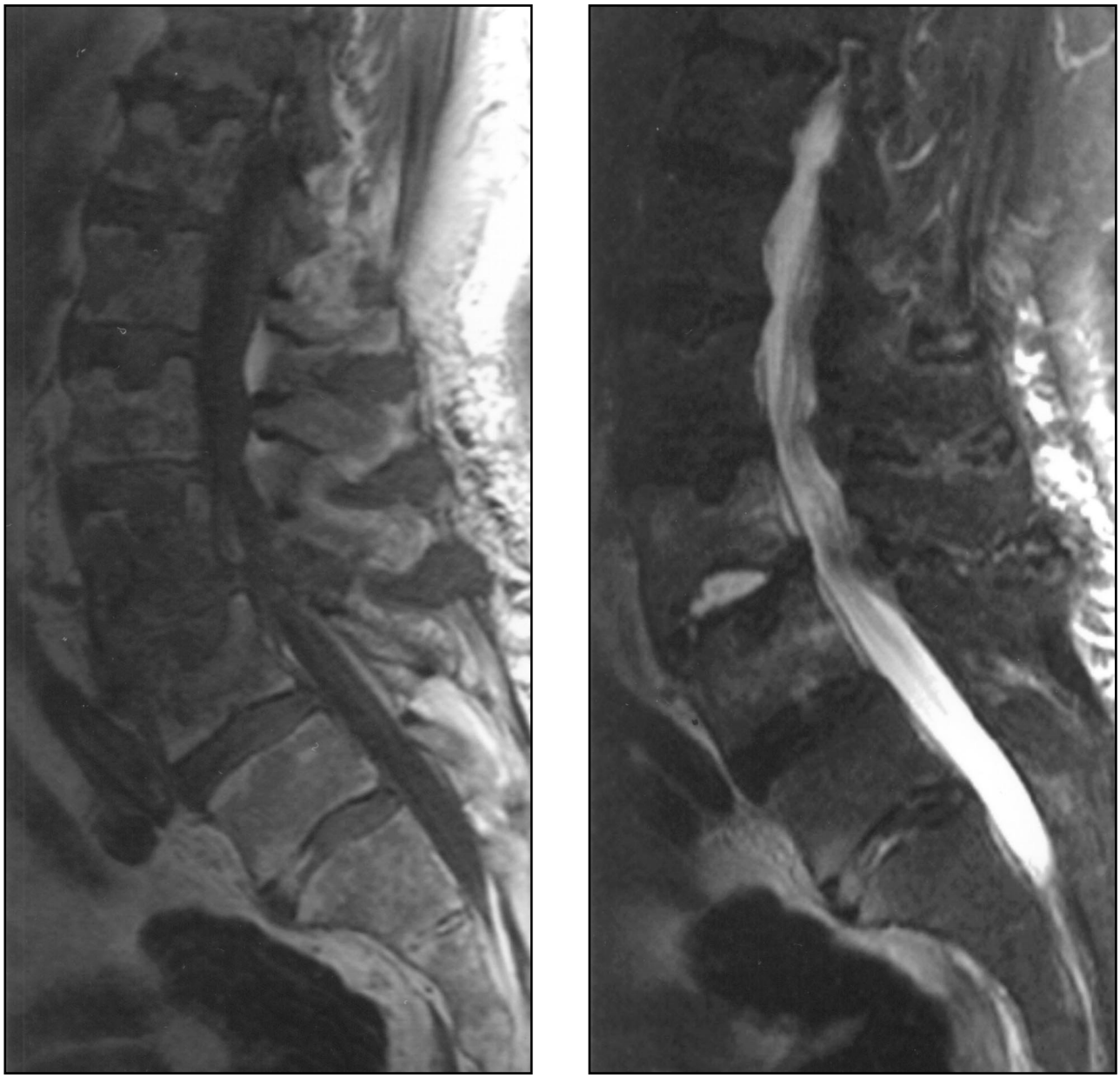


Figure 4. MRI of dialysis spondyloarthropathy. A) 67 year old male on hemodialysis for 11 years with no clinical or laboratory evidence of infection. The images show false positive fndings for spondylodiscitis. A. Sagittal T1 weighted feast spin-echo image (600/12) shows low signal intensity in the L3 and L4 vertebrae. B) Sagittal T2-weighted fast spin echo image (5000l18) marked enhancement of the L3-L4 disc and slightly creased signal in the L3 and L4 vertebrae.

T2-weighted images infectious etiology can be ruled out (30, 31), whereas in infectious spondylodiscitis there is decreased signal on T1-weighted images and increased signal on T2-weighting in the discs as well as in the end plates of the vertebrae (32, 33). However patients with no clinical or laboratory evidence of infection may also show bright signal on T2-weighted image [Figure 5a and b] and may reveal enhancement following injection of gadolinium making differentiating between the two conditions unreliable without clinical and laboratory correlation (33, 34).

The reason for the bright T2 signal and gadolinium enhancement in absence of infection is the result of the often deposited crystals in tissues at the annulus of the disk. While most of the areas of crystal deposition show low T1 and intermediate T2 signal, if there is increase in water content in the tissue from inflammatory changes or vascular granulation tissue there is increase in T2 signal and enhancement will be seen with gadolinium.

Crystal deposition and soft tissue calcifications are commonly seen in long-term dialysis patients. The type of crystals can be calcium pyrophosphate, hydrox-

yapetite, monosodium urate or calcium oxalate. Bedani found chonrocalcinosis in 13% and periarticular calcifications in 27% in his study of long-term dialysis patients (27). The presence of soft tissue calcific deposits however is not the direct result of aluminum toxicity and dialysis but results from the increase in the calcium/phosphorus ratio in the blood and extra cellular fluid in chronic renal failure patients (8,35).

The reason for development of amyloid arthropathy with soft tissue deposition of beta2-microglobulin amyloid is unknown. It has been shown that both hypercalcemia and hyperparathyroidism enhance the polymerization of beta2-microglobulin into amyloid fibrils and may cause accumulation of abnormally high amounts of this protein in cartilage, synovium and connective tissue (36). Since this form of amyloidosis often precedes hemodyalisis it is likely caused by renal failure and uremia rather than dialysis.

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