The Interesting Case

Popliteal cysts from advanced amyloidosis in long-term haemofiltration/haemodiafiltration

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Introduction

Dialysis-related amyloidosis is termed Aβ2 m since the major protein component is β2-microglobulin [1]. The synovial tissues and nearby bones are predominant sites for Aβ2 m deposition. Carpal-tunnel syndrome, erosive and cystic bone lesions, as well as destructive arthropathy are recognized manifestations. Subchondral bone amyloid cysts are usually found in the non-axial skeleton, while the arthropathy can be fairly extensive involving the spine, shoulders, wrists, elbows, hips, knees, and/or ankles [2]. Pseudotumours resulting from amyloid deposition in soft tissues have been rarely described in proximity to joints [3,4].

In the last decade, a relationship between long-term haemodialysis and the appearance of Aβ2 m has been established, particularly with the use of cellulosic membranes [5]. Some centres have noted a lower incidence of Aβ2 m deposition in patients dialysed with highly permeable synthetic membranes. Beneficial effects seem consequent to an enhanced β2-microglobulin clearance from convection and membrane adsorption and possibly to a reduction in β2-microglobulin generation with more biocompatible membranes [6,7].

This report describes a case of severe Aβ2 m presenting with popliteal cysts associated with haemarthrosis episodes after long-term haemofiltration/haemodiafiltration.

Case Report

A 65-year-old white female with autosomal polycystic kidney disease has been on chronic renal replacement therapy since 1975. Until 1981 she was treated with conventional thrice-weekly haemodialysis using cellulosic membranes. Thereafter, she has been on intermittent haemofiltration from 1981 to 1993, and since then, on haemodiafiltration three times per week. For these two last modalities, high-flux synthetic membrane filters were used (HF80: 1.8 m² polysulphone membrane; Fresenius, Bad Homburg, Germany). Her dialysis regimen adequacy has been monitored on a regular basis and a Kt/V in the range of 1.2 (with haemofiltration) to 1.7 (with haemodiafiltration) per session has been delivered most of the time. Serum levels of β2-microglobulin measured on several occasions are presented in Table 1.

In 1985 the patient complained of dysaesthesia and thumb weakness in both hands, as well as bilateral shoulder pain. The nerve conduction velocity study demonstrated an impairment in the distribution of the median nerve supporting the diagnosis of bilateral carpal-tunnel syndrome. Plain radiographs of her shoulders were unremarkable. Surgical decompression of the entrapped median nerves was performed in 1986 with some symptomatic improvement. The microscopic examination of tissue specimens confirmed the presence of amyloid substance (Figure 1).

In 1990 the patient complained of lumbar pain and left sciatalgia. Spine and pelvic radiographs revealed diffuse osteopenia while the bone radionuclide scan was negative. One year later, a spontaneous fracture of the left femoral neck occurred; at that time, a bilateral hyperfixation at the femoral head and ischium level was observed on a repeated bone scan.

Failure of medical therapy for her secondary hyperparathyroidism prompted a sub-total parathyroidectomy in April 1992. A few months later, in February

<table>
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<th>Pre-session</th>
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<tr>
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<tr>
<td>1992</td>
<td>HF</td>
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<td>1993</td>
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<td>48.3</td>
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<tr>
<td>1995</td>
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<td>38.3</td>
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<td>1996</td>
<td>HDF</td>
<td>22.2</td>
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1993, a right knee haemarthrosis was found; 45 ml of bloody fluid removed by arthrocentesis produced some symptomatic improvement. On physical examination, bilateral popliteal masses and articular effusions were detected and later confirmed by ultrasonography (Figure 2). The size of the popliteal pseudotumours was $6 \times 5 \times 3$ cm on the right and $3 \times 3 \times 3$ cm on the left side; they were relatively firm or only mildly fluctuant, inducing pain on motion. No significant abnormalities except vascular calcifications were noted on plain radiography, osteoarticular structures and joint space being well preserved (Figure 3). Free amyloid fibrils were seen with Congo-red stain in the synovial fluid obtained by arthrocentesis. In June 1994, a new episode of haemarthrosis involved her right shoulder.

In March 1995 the patient presented with severe lumbar pain; on computed tomography, L4–L5 discopathy, infiltration of the yellow ligament and posterior vertebral articulations were reported as compatible with amyloid deposition. Again in July 1996 she developed suddenly a disabling left knee pain after squatting. Her knee was diffusely swollen and an amount of 25 ml of bloody fluid withdrawn by arthrocentesis was positive for $\beta_2$-microglobulin at a concentration of 14.5 mg/l. The computed tomography demonstrated bone cysts tibial plateaus and persistent popliteal masses consequent to $A\beta_2$ m accumulation (Figure 4). Interestingly, on both sides, the popliteal pseudotumour and the articular space were in communication with each other on the imaging studies. Systemic steroids were initiated (prednisolone 10 mg i.v. at each dialysis session) resulting in a partial functional recovery. A few months later, the patient is able to walk again.
Fig. 3. Radiography of right and left knees. Note the relatively well-preserved bone structures and articular spaces and the vascular calcifications.

Fig. 4. Popliteal cysts as seen on computed tomography; a communication with the articular space can be seen.

Discussion

As illustrated by this case, dialysis-related amyloidosis can be extremely disabling. Unfortunately, Aβ₂₅ usually gains the attention of the physician when skeletal damage has already occurred. Destructive arthropathy and pathological fractures are severe manifestations of Aβ₂₅ accumulation. Tumour-like subcutaneous masses from Aβ₂₅ deposition are extremely uncommon; they have been described at different sites, including the popliteal space, gluteal region, groin, and wrist [3,4]. Although disturbing from a functional and cosmetic standpoint, they are reported as being not painful nor inflammatory. However, as demonstrated by the present case, they can become painful with articular flexion. In fact, Aβ₂₅-related popliteal masses or pseudotumours should be called popliteal cysts, since they are in communication with the articular space (similar to Baker’s cysts). Indeed, the rupture of such cysts may lead to the development of an associated haemarthrosis, as observed on several occasions in our patient. We may thus speculate that Aβ₂₅ deposition induces some damage to the synovia.

The differential diagnosis of bone pain may be quite extensive in dialysis patients; however, when they have been on maintenance dialysis for over 5 years, the
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possibility of $A\beta_2$ m deposition should be kept in mind. Actually, after 5 years of long-term dialysis, annual bone survey is recommended, mainly to prompt any surgical intervention if necessary. A possible link between high-turnover osteodystrophy and $A\beta_2$ m accumulation has been suggested. In this regard, bioincompatibility has been proposed as further contributing to $A\beta_2$ m formation by enhancing bone resorption. In the present case, hyperparathyroidism could have created a favourable substrate for the development of $A\beta_2$ m.

The incidence of $A\beta_2$ m increases with time on dialysis; in some series, 100% of patients dialysed for over 20 years were found to be affected [5]. Likewise, our patient has been maintained on extracorporeal treatment for over 20 years. Age has also been shown to predispose to the development of $A\beta_2$ m [7]. One major aetiological factor remains the relative inability of renal replacement therapy to remove the $\beta_2$-microglobulin produced daily, and serum concentrations in uraemic subjects can reach 30–50 times normal. However, the degree of elevation of circulating $\beta_2$-microglobulin does not predict $A\beta_2$ m accumulation.

Following the introduction of high-flux high-efficiency modalities using synthetic membranes, there was considerable hope that $A\beta_2$ m could be prevented in dialysis patients. The use of synthetic membranes was viewed as particularly beneficial, since their cellulosic counterparts were considered as enhancing $\beta_2$-microglobulin generation. Since then, $\beta_2$-microglobulin synthesis has been shown to be only marginally increased with either low-flux or high-flux modalities as compared to healthy controls [8]. Nevertheless, bio compatible high-flux modalities remove more $\beta_2$-microglobulin [9], as reflected by relatively lower circulating $\beta_2$-microglobulin levels, but which still remain several times higher than normally [6]. In our patient, serum $\beta_2$-microglobulin concentrations have been significantly high despite a decreasing tendency over time. In any case, one would expect that the long-term combination of a high-efficiency convection-based modality, a biocompatible membrane, and an ultrapure dialysate [10] should reduce the incidence of $A\beta_2$ m deposition. The present case illustrates that $A\beta_2$ m can still occur under such desirable dialysis conditions.

In conclusion, the manifestations of $A\beta_2$ m deposits can be variable and fairly extensive after several years of renal replacement therapy. The formation of popliteal cysts is an extremely rare manifestation to be considered in the appropriate setting. Furthermore, $A\beta_2$ m should be included in the differential diagnosis of haemarthrosis; in other words, if haemarthrosis develops in a patient on long-term dialysis, $A\beta_2$ m should be specifically suspected.

References

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