Post-transplant distal-limb bone-marrow oedema: MR imaging and therapeutic considerations

Gerd Rüdiger Hetzel¹, Jürgen Malms², Philip May², Peter Heering¹, Adina Voiculescu¹, Ulrich Mödder² and Bernd Grabensee¹

Departments of ¹Nephrology and Rheumatology and ²Diagnostic Radiology, Heinrich-Heine-University, Düsseldorf, Germany

Abstract

Background. In recent years a previously unrecognized pain syndrome of the distal lower limbs after organ transplantation has been noted. A relationship to cyclosporin A was suspected, but no clear aetiology and pathogenesis have been established.

Methods. During the last 30 months we diagnosed the pain syndrome in 10 patients after renal transplantation. We prospectively followed and evaluated the patients during their clinical courses and through pathological laboratory findings and magnetic resonance imaging (MRI).

Results. In all patients symptoms developed within 6 months of transplantation after otherwise uncomplicated clinical courses without graft rejection episodes. Impressive bone-marrow oedema on MRI as well as elevated serum alkaline phosphatase was seen in all patients, and often exceeded the duration of clinical symptoms. All patients were instructed to avoid stress to the extremities through immobility, and steroid doses were tapered down. Within 14 weeks, eight patients were free of symptoms. Two patients have not experienced remission after 3 and 4 months respectively. None of the patients developed signs of osteonecrosis.

Conclusion. Post-transplant distal limb bone-marrow oedema presents with distinct clinical findings and signs of bone-marrow oedema on MRI. Proven standard treatment does not exist. In our experience the elevation of the extremities, the strict avoidance of physical strain, and a stepwise withdrawal of steroids facilitates progressive disappearance of symptoms. Long-term damage to the affected osteal structures has not been seen, in contrast to avascular femoral-head necrosis.

Keywords: bone-marrow oedema; magnetic resonance imaging; osteonecrosis; reflex dystrophy syndrome; renal osteopathy; renal transplantation

Introduction

With the introduction of cyclosporin A (CsA) into the immunosuppressive therapy after renal transplantation, the incidence of avascular femoral head necroses and therewith the total number of osseous complications has markedly decreased [1]. It is generally accepted that this is due to lower doses of corticosteroids in therapy regimens including CsA.

In the last decade, symptoms of osteoarticular pain of a type unknown in the pre-CsA era have come to the attention of clinicians [2–8]. Episodes of pain in the distal lower limbs and knees are characteristically seen. The pain predominantly arises bilaterally and symmetrically within the first 2 years; however, most episodes occur several months after transplantation and can lead to a drastic limitation in a patient’s ability to walk. Worsening has been observed under stress and when standing, and occasionally a maximum pain intensity has been seen in resting states. Although long-term orthopaedic complications appear to be an exception, the episodes of pain may persist from weeks to months.

Within the last 30 months we have observed this pain syndrome with an increasing frequency in patients receiving kidney allografts at our institution. The aim of the current study was to report the results of different diagnostic imaging procedures as well as the clinical outcomes of a uniform therapeutic approach.

Subjects and methods

Between August 1997 and November 1999, 158 patients received a renal allograft at our transplantation centre. During routine follow-up we diagnosed the pain syndrome in 10 patients (mean age 48 years; five women after allogenic cadaver-renal transplantation; five men, two of them after allogenic living-donor transplantation). Initially the patients...
all had an uncomplicated course after transplantation. A spontaneous graft function was seen in all subjects postoperatively. Immunosuppression was achieved with a regimen including CsA (trough level 170–210 ng/ml), mycophenolate mofetil (1000 mg b.i.d.), and steroids (starting with 500 mg during the operation, tapering to 10 mg/day within 5 weeks). One patient was initially treated with antithymocyte-globulin for prevention of acute rejection. Since rejection episodes were not observed in any patient, the cumulative steroid doses were relatively low and no further antibody treatment was necessary. After the onset of symptoms, a detailed laboratory and diagnostic imaging work-up was performed. We prospectively followed and evaluated the patients during their clinical courses and through documented changes on magnetic resonance imaging (MRI), until remission.

**Therapy**

Upon diagnosis, all patients were instructed to avoid all physical stress and practise strict immobility for relief. Physical therapy as well as low-molecular heparin s.c. were prescribed as a prophylaxis against thrombosis. In cases of elevated CsA trough levels the dose was adjusted until a target level of 150–180 ng/ml was reached. Two patients were not able to follow the inactivity regimen for professional reasons (Table 1, patients 7 and 8); however, with increasing pain, one of them accepted inactivity as a therapy measure 5 months after the onset of symptoms (Figure 1). Steroid medication was tapered in all cases and subsequently withdrawn in eight patients. Rejection episodes did not occur. Furthermore, an attempt was made to treat the condition with calcium-channel blockers (nifedipine in seven cases, nitrendipine in three cases).

**Results**

**Clinical findings**

An overview of the most important clinical data is shown in Table 1. In all patients, symptoms developed within 6 months of renal transplantation while they were being treated with the above-mentioned triple immunosuppression (prednisone dose 5–10 mg/day at study time). All patients reported pain bilaterally and symmetrically at some point during the course in the areas of the forefeet, ankles, and/or knees. The chief complaint was described as a constant dull pain that led to a noticeable impairment in mobility. All patients described worsening pain when standing and under stress, and relief of symptoms upon elevating the legs to a horizontal position.

Except for mild soft-tissue swelling of the knees (two patients) and/or the dorsal side of the feet (three patients) combined with pain upon pressure, further clinical examination was unremarkable. In particular, there were no signs of acute arthritis, joint effusions, or trophic or vasomotor changes in the involved areas of the extremities.

**Laboratory data**

All patients had good transplant function with a mean serum creatinine of 1.5 mg/dl. The mean whole-blood trough level of CsA during the time from transplantation to the onset of symptoms was 211 ng/ml (range 171–257). In four cases persistent hyperparathyroidism was seen after transplantation. All patients showed an increase in levels of alkaline phosphatase with the onset of pain. Analysis of isoenzymes demonstrated a skeletal origin. The rise in alkaline phosphatase persisted for several months in all patients and exceeded the length of clinical symptoms (Table 1). As an example, Figure 1 shows the changes in alkaline phosphatase and the clinical course of a 30-year-old patient after living-related renal transplantation.

**Radiological findings**

The initial radiographs were unremarkable in seven cases. In three patients a marked and diffuse, blotchy osteoporosis was diagnosed.

**Nuclear medicine findings**

A three-phase skeletal scintigraphy was obtained during the initial onset of symptoms in eight patients. During the late phase an unusually symmetric and marked accumulation of the tracer substance was seen.

**Table 1. Clinical data of seven patients with distal-limb bone-marrow oedema after renal transplantation**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Years of dialysis</th>
<th>Steroid pulse therapy</th>
<th>PTH (ref &lt;5.5 pmol/l)</th>
<th>First symptoms (weeks after transplantation)</th>
<th>Average CsA trough levels before start of symptoms (ng/ml)</th>
<th>Duration of severe symptoms (months)</th>
<th>Duration of elevated AP levels (months)</th>
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<tr>
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<td>56</td>
<td>7</td>
<td>None</td>
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<td>8</td>
<td>229</td>
<td>2.5</td>
<td>8</td>
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<td>5</td>
<td>None</td>
<td>51</td>
<td>6</td>
<td>207</td>
<td>2</td>
<td>6</td>
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<tr>
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<td>186</td>
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<tr>
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<td>4</td>
<td>None</td>
<td>6.5</td>
<td>10</td>
<td>212</td>
<td>5</td>
<td>Still elevated</td>
</tr>
<tr>
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<td>42</td>
<td>6</td>
<td>None</td>
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<td>7</td>
<td>208</td>
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<td>230</td>
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<td>Still elevated</td>
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<td>4.3</td>
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<td>Still elevated</td>
</tr>
</tbody>
</table>

PTH, parathyroid hormone; CsA, cyclosporin; AP, alkaline phosphatase. No similarities concerning underlying renal disease, CMV status, or HLA constellation.
in the clinically affected areas of the knees, ankles, or forefeet. In four patients an additional accumulation in the early phase was noted in the same areas, indicating soft-tissue involvement. Because of the largely symmetrical distribution, the lack of prior examinations, and the unspecific findings, a correct interpretation was only possible retrospectively in conjunction with the striking MRI findings of the patients.

**Magnetic resonance findings**

The MRIs were made with either a 1 T-(Gyrosan Philips, Eindhoven, Netherlands) or a 1.5 T (Vision-Siemens, Enlangen, Germany) scanner. Short TR/TE (T1-weighted images) as well as long TR/TE (T2-weighted), and fat suppressed (STIR, T2 Spir) sequences were evaluated. In all patients a replacement signiﬁcant improvement but residual changes in six of fatty bone marrow with high intensity in T1 patients, complete remission in three patients, and morphological changes in one patient (low signal intensity in T1-images, high signal intensity in T2-images) was observed. As oedema contains more water molecules than the surrounding healthy bone marrow, the lesions became more evident on images obtained by fat suppression techniques.

The primary findings were thus seen as localized, patchy, oedematous changes, some of which included the entire bone (Figure 2). Neither a characteristic distribution nor a characteristic course of the oedematous changes was seen in the patients. No joint effusions were seen. In two cases an accompanying inﬂammatory reaction was visible in the surrounding soft tissue. A demarcation of localized areas by hypointense bands on T1- or T2-weighted images characteristic of avascular osteonecrosis or impaction within cancellous bone [9,10], possibly putting the patients at risk of long-term orthopaedic problems, was not observed in any case.

During the course of the symptoms an average of 3 (2–6) MRI scans were obtained in each patient. In the early follow-up period varying patterns in the distribution of the oedematous areas were particularly noticeable, i.e. regression was seen in the initially affected areas and newly affected areas were seen. Changes in MRI usually outlasted clinical symptoms. In seven patients residual bone-marrow oedema, though signiﬁcantly diminished, was seen on follow-up MRI scans even after complete remission of clinical symptoms and normalization of alkaline phosphatase. In one patient (Table 1, patient 2) residual oedema of the calcaneus was detectable up to 1 year after the bone pain had remitted.

After a mean interval of 9 months (3–24) from the first investigations, the final MRI scans to date showed significant improvement but residual changes in six patients, complete remission in three patients, and worsening of morphological changes in one patient (Table 1, patient 9), although his clinical symptoms have improved over a subsequent course of 3 months. None of the follow-up scans revealed changes suggestive of avascular osteonecrosis.

**Further clinical course**

Following the above-described measures, symptoms persisted in six patients (Table 1, patients 1–6) for an average of 13 weeks after the MRI diagnosis of post-transplant distal limb bone-marrow oedema was established. In the two patients who were not able to follow the inactivity regimen (Table 1, patients 7 and 8), the symptoms persisted for 5 and 6 months respectively. At this time, two patients (Table 1, patients 9 and 10) have experienced clinical improvement but not complete remission 3 and 4 months respectively after the beginning of their symptoms. In one of these patients
the bone-marrow oedema has worsened on MRI; both patients still have elevated levels of serum alkaline phosphatase. The other eight patients are followed regularly in our outpatient department. At the least follow-up visit, after a mean time of 23 months (3–36) from the onset of clinical symptoms, all of them are free of complaints except for one 57-year-old patient who reports mild pain in both knees after long-distance walking. Considering the clinical outcome and the results of the final follow-up MRI scans in these eight patients, which showed either significant improvement or complete remission without signs of avascular osteonecrosis, there is no evidence of irreversible osseous defects.

We did not see any effect from calcium-channel-blocker therapy. The exchange of tacrolimus (FK506) for CsA in one patient, due to adverse side-effects, had no influence on the symptomatic pain. In this patient, at a later point and after absolute avoidance of stress to the extremities, the pain subsided within 4 weeks (Figure 1).

Discussion

A pain syndrome of the distal lower limbs after organ transplantation has been previously described by several authors [2–8]. An elevation of alkaline phosphatase as a possible side-effect of CsA was known from the early use of this medication [11,12]. Williams and co-workers reported on 19 patients with pain symptoms that they termed ‘symptomatic renal osteodystrophy’ in 1987. The severe symptoms were limited exclusively to the lower extremities and worsened with physical stress. This is probably the first description of the pain syndrome in a larger group of patients [2].

The aetiology and pathogenesis of the pain syndrome was not understood, but most authors suspected a relationship to CsA [3–5,7,13,14]. Animal models have shown that dosage-dependent CsA use leads to an increase in bone metabolism with evidence of osteoclasts in the tibial area of the animals [15]. Although in vitro studies have led to contradictory results [16], there appears to be a general acceptance that CsA has some direct effect on bone metabolism. Our study patients initially showed slightly increased CsA trough levels. However, after lowering the levels (to 150–180 ng/ml) at the onset of symptoms, the pain did not subside. Even after exchanging CsA for tacrolimus in one patient because of gingival hyperplasia, the pain symptoms took several months to subside.

Goffin, Vande-Berg and co-workers [17,18] suggested that the pain syndrome was due to epiphyseal impaction of cortical bone, a hypothesis that could explain the character and length of clinical symptoms, the elevation of alkaline phosphatase, and the findings on diagnostic imaging. Many of our findings are comparable with the results reported by these authors, although we saw no linear bands of low-signal intensity on T1- and T2-weighted images consistent with occult fractures, and no progression towards avascular osteonecrosis. Therefore, in our opinion the pathogenesis of the syndrome remains to be elucidated.

MRI is the diagnostic measure of choice in affected patients. A higher sensitivity is achieved with MRI in comparison to the conventional plain film or skeletal scintigraphy. In all our patients severe bone-marrow oedema was documented. Considering the frequent
osseous symptoms among transplant patients, e.g. persistent renal osteopathy or steroid-induced osteopenia, and the lack of a common definition of these pain characteristics in the current literature, the evidence of our findings as seen by MRI should be conditional for establishing the diagnosis of the syndrome.

Nevertheless one must bear in mind that bone-marrow oedema is generally unspecific and has been seen in sympathetic reflex dystrophy syndrome of the foot [19], medial tibial pain in non-transplanted patients [20], transient osteoporosis of the hip [21], borderline necrosis or manifest avascular necrosis of the femoral head [9,22–24], and traumatic or stress fractures of the calcaneus, tibia, knee, or shoulder [25–27]. Therefore only the association of the MRI findings with bilateral lower limb pain, an almost normal physical examination, a rise in alkaline phosphatase, and possibly low cumulative steroid doses in post-renal-transplantation patients on CsA seems to be indicative of the syndrome. Thus, post-transplant distal-limb bone-marrow oedema can be seen as a distinct clinical entity and be separated from the above-mentioned conditions and especially from avascular osteonecrosis or reflex dystrophy syndrome.

Unlike avascular osteonecrosis [28], the total dose of corticosteroids does not seem to pose a specific risk. None of our study patients was treated for acute rejection with high-dose steroids. During follow-up significant improvement or even complete remission was seen on MR images along with clinical restitution in eight patients (Clinical outcomes in the other two patients is uncertain because of short follow-up period). Hyointense bands in T1-or T2-weighted images, indicative of avascular osteonecrosis and probably preceding the bone-marrow oedema in this entity [9] were not seen in any patient. In consideration of this finding and the clinical outcome of eight patients, it is our impression that in contrast to avascular osteonecrosis, long-term sequelae are at least unlikely in the majority of the patients. This impression is consistent with the reports in the literature [3–5,7,17,18,29], although progression to osteonecrosis in single patients cannot be excluded [6,8,17,18].

The overall benign clinical course as well as the findings on physical examination are inconsistent with the diagnosis of reflex dystrophy syndrome suggested by Munoz-Gomez and co-workers [13]. Although we were able to find very discrete soft-tissue swelling in the affected areas in four patients, the typical signs of the reflex dystrophy syndrome such as cool, moist, and partially cyanotic skin, and especially an episodic course overlapping with atrophic stages, were not seen in any of our cases.

No definitive therapeutic implications have been made. Some authors recommend lowering CsA levels [4,5,13]. We did not see a positive effect from this. No benefit was observed from application of non-steroidal anti-inflammatory drugs or the use of calcitonin [13,30]. Barbosa and co-workers [6] prospectively reported on 29 post-renal-, liver-, heart-, or lung-transplantation patients having a pain syndrome of the lower extremities. Since a few of these patients developed osteonecrosis, further discussion is needed to determine whether this syndrome is the same as post-transplant distal-limb bone-marrow oedema. The authors reported rapid symptomatic relief and a prophylactic effect of nifedipine and other calcium-channel blockers such as amlodipine, felodipine, and isradipine. Twenty-one of 22 patients (95%) became virtually symptom free, some of them within minutes of the start of calcium-channel-blocker therapy. We cannot confirm these findings, as none of our patients experienced relief from this medication. Our therapeutic strict avoidance of physical strain to the extremities in combination with the stepwise reduction of corticosteroids seemed reasonable because of patients’ reports of symptomatic relief with rest and reports in the literature that trauma-related epiphyseal trabecular bone impaction or insufficiency bone fractures may accompany this syndrome [8,17,18]. Symptomatic improvement as well as the lack of development of irreversible osseous lesions may be secondary to the complete avoidance of physical strain to the extremities with horizontal positioning as often as possible. Upon remission of symptoms only one patient was already steroid free; thus we do not attribute a clear effect to steroid reduction.

**Conclusion**

We report the occurrence of severe osteoarticular pain involving the distal lower limbs, mainly knee and ankle, that developed within 6 months after renal transplantation in 10 of 158 renal transplant patients. Increased uptake in long-bone epiphyses at scintigraphy and bone-marrow infiltration consistent with bone-marrow oedema at MRI were consistently observed in symptomatic areas. We achieved progressive disappearance of symptoms in eight of 10 patients at last follow-up through therapeutic decreased weight bearing and progressive lowering of steroid therapy.

**References**


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