Why does post-transplant osteonecrosis develop?

Sirs,

We read with interest the article by Ekmekci et al. [1], on the association of thrombophilia and osteonecrosis (ON) of the femoral head in renal transplant recipients. We previously reported a case with diffuse ON and severe osteoporosis which was unusual in its presentation in the early post-transplant period, focusing on pre-transplant hormonal changes [2]. Following our report, Dr. Weinstein drew our attention to their research supporting glucocorticoid (GC)-induced ON involved in osteocyte apoptosis, by personal communication. They demonstrated that osteoblasts and osteocytes were the direct targets of GC action in vivo, and that excess levels of steroid hormone directly induced apoptosis of these cell types.

Ekmekci et al. [1] reported that factor V Leiden and prothrombin gene mutations might be an important risk factor for the development of ON of the femoral head. They observed no difference in the cumulative doses of GCs and ciclosporin A between the ON and control groups, whereas Celik et al. [3] found that the 3, 6 and 12 month treatments with cumulative GC doses were significantly higher in the ON group and that there was no correlation between ON and genetic mutations of factor V Leiden, prothrombin and 5,10-methylenetetrahydrofolate reductase (MTHFR). Our case had MTHFR C677T heterozygous mutation but not factor V Leiden G1691A and prothrombin G20210A mutations. In the non-transplant population, there are different reports on the relation of genetic mutations predisposing to coagulation and ON [3,4].

A recent hypothesis emphasizes the fact that vascular thrombosis is the major pathogenetic event leading to osteocyte necrosis and eventual collapse of the femoral head in ON [5]. Exogenous and endogenous factors lead to endothelial dysfunction, thrombus formation and ischemia, finally inducing apoptosis in osteocytes and osteoblasts. Thrombophilia, particularly impaired fibrinolysis, can play a potential role in thrombus formation. Decreased fibrinolytic activity through elevated plasminogen activator inhibitor (PAI)-1 levels can be associated with the subsequent development of ON and transient osteoporosis of the hip [6]. Glueck et al. [7] first ascribed a role to the PAI-1 genotype in association with ON. Ferrari et al. [6] demonstrated a strong association between the 4G/4G genotype of PAI-1 and ON in GC-treated renal transplant recipients. However, a significant correlation of the incidence of ON with PAI-14G/5G or MTHFR C677T polymorphisms was not observed in Japanese renal transplant recipients [8]. Osteocyte apoptosis may be an important mechanism in the GC-induced loss of bone mineral density and microarchitectural deterioration predisposing to fractures. It has been found that bisphosphonates inhibit osteoblast and osteocyte apoptosis induced by GC [9]. Furthermore, impaired osteoblastogenesis and early osteoblast apoptosis may play important roles in the pathogenesis of post-transplant osteoporosis by possible mechanisms such as post-transplant hypophosphataemia, GC usage and pre-existing bone disease [10]. Ekmekci et al. [1] did not report osteoporosis status in their study. Perhaps they could evaluate whether the pre-existing osteoporosis was related to the development of ON and whether bisphosphonate or statin usage, if present, affected the outcome in patients with osteoporosis, especially in those with thrombophilia.

ON can be the end result of a process that starts as osteoporosis [2]. Although the aetiologies of post-transplant osteoporosis and ON are multifactorial, there can be a complex pathogenic relationship between both processes. The state of bones in the pre-transplant period, the effect of uraemic milieu, post-transplant medications and other cofactors on haemostatic alterations, and individual genetic differences can determine the outcome. More evidence is needed to better comprehend the role of these parameters for future prevention and treatment of ON.

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Increasing incidence of severe encapsulating peritoneal sclerosis after kidney transplantation

Sirs,

Encapsulating peritoneal sclerosis (EPS) is a life-threatening complication of peritoneal dialysis (PD). Since the first report in 1980 [1], the reported overall prevalence of EPS has
varied between 0.7% in Australia [2], 2.5% in Japan [3] and 3.3% in a single-centre study in Great Britain [4]. The diagnosis of EPS is difficult, mainly because a uniformly used definition is lacking. Most clinicians use the criteria defined by the Ad Hoc Committee of the International Society of Peritoneal Dialysis (ISPD) [5]. This committee defined EPS as: ‘A clinical syndrome with persistent, intermittent or recurrent presence of intestinal obstruction with or without the existence of inflammation parameters and the existence of peritoneal thickening, sclerosis, calcifications and encapsulation confirmed by macroscopic inspection or radiological findings’. It is our distinct impression that in recent years we are witnessing a marked increase in the incidence of EPS. In order to investigate whether this suspicion is justified, we initiated an analysis of the occurrence of EPS in two university hospitals in The Netherlands (Erasmus Medical University Centre in Rotterdam and the Utrecht Medical Centre in Utrecht). Both centres serve as regional transplantation centres and are comparable in patient population. Cases were identified by retrospective investigation of the medical records of both PD populations in the period 1998–2005. Patients at risk for developing EPS were defined as either having previous PD treatment or patients with a history of PD having undergone renal transplantation no more than 3 years ago. Encapsulating peritoneal sclerosis was defined according the criteria developed by the ISPD [5].

Eighteen cases (13 males/five females, age 39.8 ± 10.2 years) of severe EPS were identified. Twelve of these patients were treated at the Erasmus Medical Centre and six patients at the Utrecht Medical Centre. Thirteen patients were not on PD at the time of diagnosis and were either on haemodialysis or had received a functioning kidney graft.

The PD population, treated in the period 1998–2005, comprised of 418 patients (206 patients in Rotterdam and 212 in Utrecht). In both 1998 and 1999, there was one EPS case each year, in 2002 one case and in 2003 two cases. However, in 2004 and 2005 we observed three and 10 cases respectively. The number of patients on PD did not change significantly in time throughout the whole period in both the centres. Although there was a steady increase in patients alive with functioning kidney graft and a history of PD, the increasing incidence of EPS exceeded the increase in patients at risk (Figure 1, \( P = 0.038 \), using a Pearson’s chi-square test for trend analysis).

Patients had a mean time on PD of 71.8 ± 44.9 months at the time of EPS diagnosis. Seventeen patients used icodextrin and the mean time on icodextrin was 34.2 ± 22.2 months. Seven patients were treated with icodextrin within the period between November 2001 and July 2002, when an outbreak of icodextrin-associated peritonitis occurred [6]. In these patients, there was no history of aseptic peritonitis.

Fifteen patients (83%) had a history of kidney transplantation. The mean time from the last kidney transplantation to the diagnosis of EPS diagnosis was 39.3 ± 71.1 months.

The overall mortality was 50%. In eight patients death was attributable to EPS.

This study shows that in two Dutch university hospitals the incidence of severe EPS has increased significantly in the period from 1998 to 2005 in stable PD populations. Earlier reports also appeared to indicate an increased incidence of EPS [2,7]. In these retrospective surveys the apparent increase was related to the duration of PD treatment, with substantial increased prevalence after 5 years of PD [2]. However, in our study the majority of patients were on PD for a considerably shorter period than 5 years when they developed EPS.

The pathophysiology of EPS is unknown, but it appears that EPS is not solely the result of progression of peritoneal remodelling that happens with PD. A second hit, has been postulated to aggravate the damage to the peritoneum and to induce the further development of EPS [8]. Although limited by the retrospective nature of this study, we investigated whether infection [2] or type of dialysis solution [9–11] could be such a second hit.

However, the mean number of peritonitis episodes was only 0.54 ± 0.73 for every year of PD and we found no increase of specific micro-organisms in the EPS population. Almost all of the patients developing EPS used icodextrin. Since half of our patients were treated with icodextrin during the period in which the outbreak with icodextrin-related aseptic peritonitis [12,13] occurred, a possible contribution of icodextrin to the development of EPS cannot be entirely excluded and has to be evaluated.

![EPS cases and the population at risk for EPS in Rotterdam centre in 1998–2005. Population at risk is defined by patients with a kidney transplant and a history of PD (open boxes). EPS cases are shown (lined boxes) in Rotterdam. Significant trend of increase of EPS independent of the increase in the defined population at risk (\( P = 0.038 \), chi-square trend analysis).](image-url)
As the majority of EPS patients underwent a kidney transplantation at some point in time, transplantation, with subsequent immunosuppressive treatment, could also be considered as the second hit in the development of EPS. This suggestion is strengthened by the fact that, in some patients, EPS developed shortly after kidney transplantation. It remains unclear whether the transplantation procedure itself or the concomitant medication is responsible. Cessation of peritoneal lavage after transplantation could lead to diminished clearance of fibrin and may thus contribute to peritoneal fibrosing. Also, the known profibrotic effects of calcineurin inhibitors (CNIs) may have had an effect on the development of EPS [14,15].

In conclusion, this study confirms our impression that the incidence of EPS has increased in the last few years. The design of this study precludes conclusions on the cause of the increased incidence, but the remarkable preponderance of EPS patients with a functioning renal allograft may point towards a pathogenetic role of kidney transplantation. A multicentre study is urgently needed to address this increasing threat to the patients on PD.

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