Osseous metaplasia in a kidney allograft

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Abstract
Osseous metaplasia is defined by the presence of heterotopic normal bone tissue in a soft tissue. The bone matrix is associated with osteoblasts, osteoclasts, adipocytes and haematopoietic stem cells. Osseous metaplasia pathophysiology is not well known, but many factors have been incriminated including chronic inflammation and chronic ischaemia. We describe the second case of osseous metaplasia in a kidney allograft. Numerous factors might favour its development including factors linked to transplantation failure environment.

Keywords: bone; kidney; metaplasia; transplantation

Case report
A 21-year-old woman received a first renal transplant in 1995. The cause of end-stage renal disease was interstitial nephritis due to a vesico-ureteral reflux in her unique congenital kidney.

The transplant was from a 19-year-old cadaveric male donor dead from trauma. Cold ischaemia time was 19 h, and the number of HLA mismatches between recipient and donor was four. Donor and recipient were seropositive for cytomegalovirus and Epstein–Barr virus. Immunosuppressive regimen included cyclosporine, azathioprine and corticosteroids after an initial induction treatment with anti-thymocyte globulin. The patient required haemodialysis during the first week. Then, renal function improved, and at 1 year, mean serum creatinine was 150 μmol/L (MDRD 40 mL/min/1.73 m²).

Transplantation was complicated by several urinary tract infections including more than five graft pyelonephritis with classical urinary tract germs. Infections were favoured by a permanent vesico-ureteral reflux in the transplant. Despite macroplastic injection and ureteral surgical reimplantation in 1999, reflux was not corrected, and pyelonephritis episodes continued. She had no hypertension and no acute rejection. The native kidney reflux did not favour these infections since our patient was anuric at
transplantation and never presented native kidney pyelonephritis during transplantation.

Persistent graft vesico-ureteral reflux and iterative pyelonephritis led to chronic allograft failure, and the patient started haemodialysis in 2005, 10 years after transplantation. Despite a small urine output volume, permanent bacterial colonization was present and complicated by several other graft pyelonephritis episodes. Allograft nephrectomy was thus achieved on 18 November 2005.

During transplantation, phosphorus levels fluctuated between 1.0 and 1.8 mmol/L, except during the last 3 months during which they rose to >3.5 mmol/L. Serum calcium values were between 2.0 and 2.5 mmol/L, and PTH 1–84 levels were between 100 and 240 ng/L. Vitamin 25(OH)D3 deficiency at 52 nmol/L (normal range >63 nmol/L) and osteopaenia (T-score = −1.8 DS on osteodensitometry) led to oral supplementation with 1200 mg calcium carbonate and 800 UI cholecalciferol each day from 2003 to 2005.

Histological analysis revealed OM in the renal cortex (Figure 1). It consisted of osseous lamellas associated to osteocytes and adipocytes. A few haematopoietic stem cells were also present. von Kossa’s coloration confirmed that the osseous tissue was mineralized. The transplant contained two focal cortical OM areas of respectively 20 and 30 mm largest diameter. Calcium deposits were found in some glomeruli. Analysis of the rest of the graft showed diffuse cortical fibrosis associated with severe arteriolar intimal thickening as well as dense interstitial inflammation (lymphocytes and plasmocytes) with epithelial and endothelial injury.

No kidney biopsy was performed during transplantation. Ultrasound analysis of the transplant performed 72 h before nephrectomy showed three intraparenchymatous 5-mm-diameter calcifications that were not present on ultrasound analysis performed 19 months before.

**Discussion**

OM is the transformation of an adult tissue into bone tissue. This heterotopic osseous matrix can be mineralized, and is associated to osteoblasts, osteoclasts, adipocytes and haematopoietic stem cells. We report the second case of asymptomatic osseous metaplasia in a kidney allograft [3].

Several OM localizations have been reported in non-transplanted organs: gastric hyperplasic polyps, colon adenoma and polyps, endometrium and vagina in women, choroids plexus, nasal polyp, tympanum, labyrinth, parotid gland, kidney, skin (as during nephrogenic fibrosing dermopathy), aorta, abdominal wall, lung, lipoma, ischaemic myocardium, pituitary adenoma, melanoma and basal cell carcinoma [4]. Most localizations were asymptomatic and were discovered fortuitously.

OM pathophysiology is not well known, but many factors have been incriminated in its development: chronic ischae-
mia, trauma, chronic inflammation, non-resorbed haematoma, cancer, hypocalcaemia and hypervitaminosis D [4]. In a rat animal model, interstitial kidney cells can be transformed into osteoblasts in case of chronic ischaemia [5]. In humans, bone development in native kidney is associated with papillary necrosis, chronic pyelonephritis or chronic interstitial nephritis [2].

Extra-skeletal bone formation requires several steps. The first step is the differentiation of a mesenchymatous pluripotent cell into an osteoblast under the influence of paracrine osteogenic signal. The nature of this primary signal is unknown. Then, an osteogenic signal stimulates osteoblasts to induce bone matrix secretion. Finally, the local environment must be conducive to the continued production of the heterotropic bone [4,6].

The kidney transplant of our patient presented an environment-favouring OM: chronic inflammation (reflux, iterative infections and alloimmune conflict) and chronic ischaemia (severe arteriolar intimal thickening). Interestingly, the first case also reported interstitial inflammation and intimal artery fibrous narrowing, arguing for their implication in metaplasia. Kidney transplant might thus be a target of OM due to chronic inflammation and ischaemia secondary to infectious or immunological injuries.

Two cell types are described in OM: osteocytes and haematopoietic stem cells. Do these cells come from the recipient or from the donor? In the case of endometrial OM secondary to previous abortion, genetic analysis revealed that osteocytes are originally from local endometrial cells and not from fetal components [7]. OM is a local phenomenon since osteocytes might come from mesenchymatous local cells [1]. In our case, it is likely that bone cells were also derived from osteoblastic differentiation of local mesenchymatous cells. The origin of the haematopoietic stem cells found in this graft remains unclear. Although donor and recipient gender were different, we could not confirm whether chimerism was present or not with FISH analysis on Y chromosome because the transplantectomized kidney was not preserved in an appropriate solution for this type of analysis.

OM and ectopic calcifications are different entities: OM is a living tissue containing cells, while ectopic calcifications are apathetic calcium pyrophosphate deposits. OM is asymptomatic and probably often confounded with ectopic calcifications since their radiological aspects are identical. When allograft ultrasonography is performed, it is important for the physician to specify whether calcifications are in the renal pelvis (lithiasis) or intraparenchymatous. If they are intraparenchymatous, two entities are possible: ectopic calcification or osseous metaplasia. The physician should be aware of this entity since OM might be the evidence of chronic renal suffering.

Renal allograft OM is a rare entity but might often be confounded with intraparenchymatous calcification on ultrasonography. Numerous factors linked or not linked to the transplantation environment might favour OM development. It is probably not implicated in graft dysfunction but should alert physicians about kidney suffering.

Conflict of interest statement. None declared.

References

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