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Kidney allograft disfunction eleven years after transplantation – A challenging diagnosis

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CASE REPORT

A 65-year-old male with chronic kidney disease secondary to acquired polycystic kidney disease.

Start of renal replacement therapy – peritoneal dialysis – on 14/9/2001.

Kidney transplantation with an organ from a deceased donor on 11/02/2003.

PRA 0%; HLA compatibilities – 1A, 1B, 1DR

Induction immunosuppression: daclizumab, MMF, sirolimus and prednisolone.Discharge from hospital on the 12th day after surgery with a serum creatinine of 1.7 mg% and medicated with MMF, sirolimus and prednisolone.

Increase in creatinine from 1.7 to 2.0 mg/dl on the 30th day after kidney transplantation.

Kidney biopsy revealed a borderline acute cellular rejection, treated with pulses of methylprednisolone. The patient remained relatively stable over the next 10 years and without significant complications, maintaining a serum creatinine below 2.0 mg/dl.

Prednisolone was suspended in 2010.

In 2014, a progressive deterioration of the allograft dysfunction was witnessed, with an increase in creatinine from 1.6 to 2.7 mg/dl in July of 2014 and onset of proteinuria: 24-hour proteinuria of 2.9gr.

CMV antigenaemia and BK virus in the blood and urine – negative.

Presence of donor-specific anti-HLA 65 and 11 antibodies.

Complement components – normal.

HBsAg, anti-HCV and anti-HIV 1 and 2 – negative.

A kidney biopsy was performed:

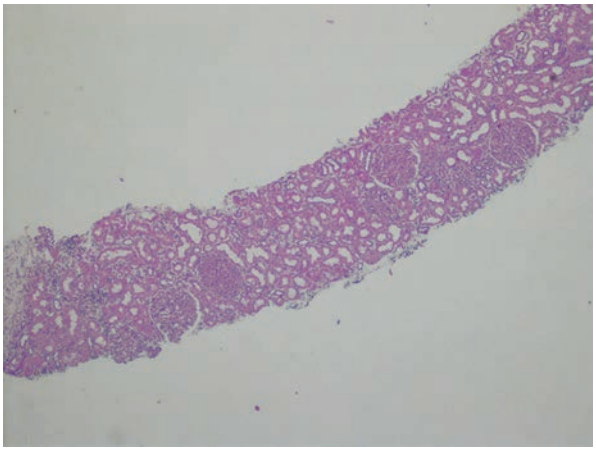


Figure 1

Fragment with 11 glomeruli, one of which obsolescent (H&E, x40).

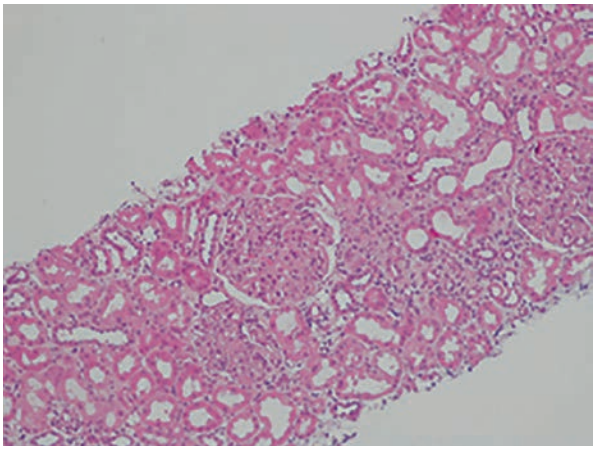


Figure 2

Glomeruli with thickened capillary walls with the presence of some mononuclear and polymorphonuclear cells (H&E, x100).

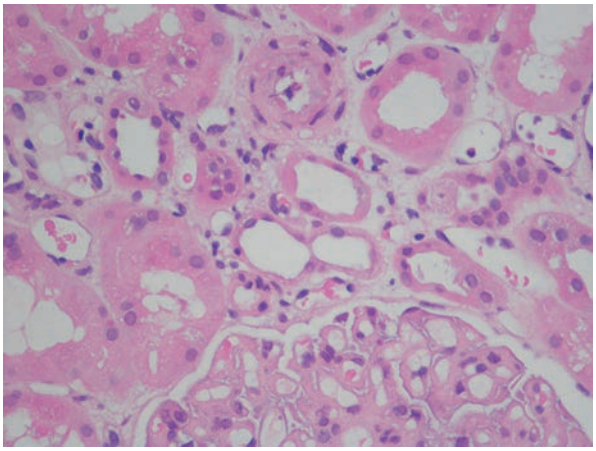


Figure 3

Peritubular capillaries with capillaritis: presence of mono- and polymorphonuclear cells, thickened glomerular capillary walls. Arteriolopathy (H&E, x200).

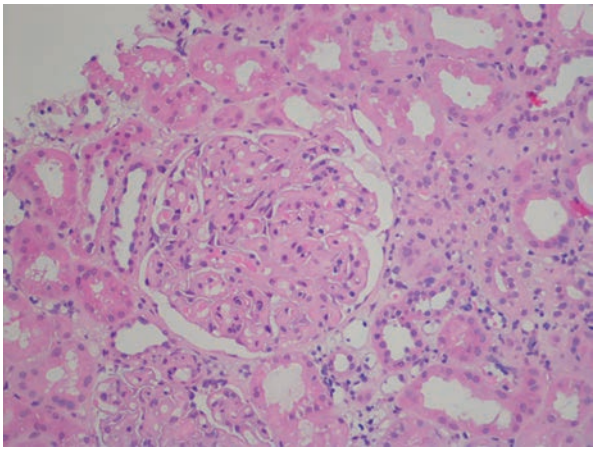


Figure 4

HE, x 200 – Glomerulus with thickened walls and mild glomerulitis, peritubular capillaries with some polymorphonuclear and mononuclear cells (H&E, x200).

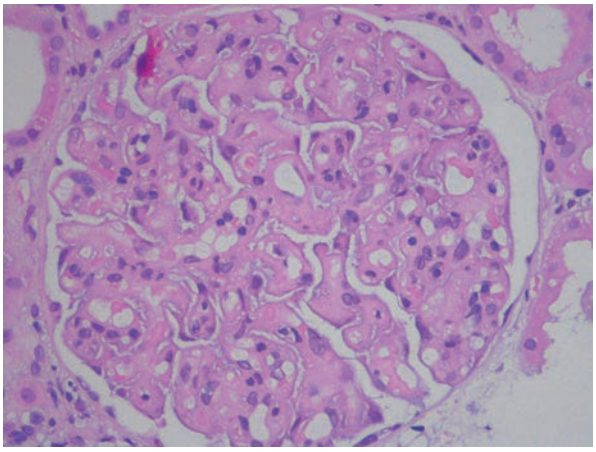


Figure 5

Glomerulus with thickened walls and the presence of some polymorphonuclear cells (H&E, x400).

DIAGNOSIS

Transplant glomerulopathy, with no signs of acute T-cell-mediated rejection and with positivity for C4d in the peritubular capillaries.

Chronic antibody-mediated rejection

Immunosuppression was altered to tacrolimus, MMF and prednisolone, and the patient was discharged with a serum creatinine of 2.3 mg/dl.

COMMENTS

Transplant glomerulopathy (TG) is a morphological entity that generally affects the renal allograft at a later stage and is mainly characterized by duplication of the glomerular basement membrane of the glomerular capillaries and absence of detectable immune complex deposits by immunofluorescence/immunocytochemistry. Morphological changes are similar to the classical pattern of membranoproliferative glomerulonephritis, but in which cell proliferation is usually less intense.

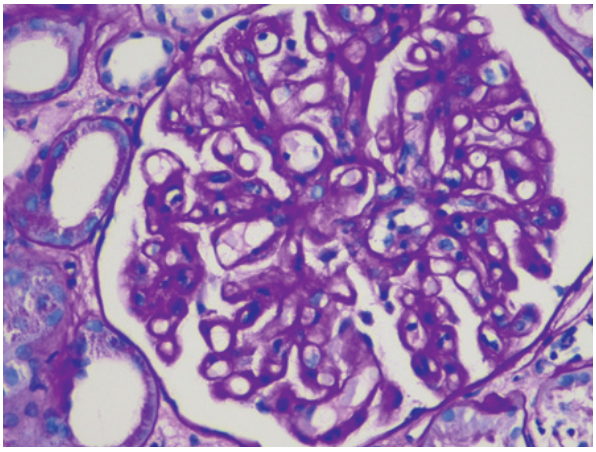


Figure 6

Glomerular capillaries with thickened walls (PAS, x400).

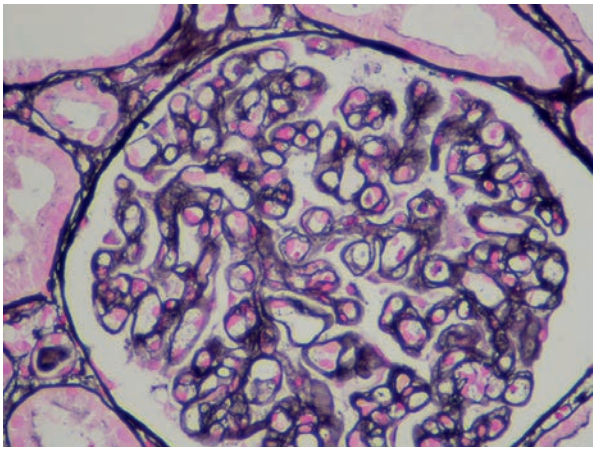


Figure 7

Glomerular capillary walls with double contours (Marinozzi, x 400).

These morphological features were first described in the sixties[1] and the designation of transplant glomerulopathy was first used by Zollinger *et al.*[2].

Its pathogenesis has been the subject of numerous controversies and interpretations: since its association with infectious diseases, namely CMV in the early eighties[3] and most recently hepatitis C virus, and thrombotic microangiopathies[4]; to autoimmune phenomena[5] and to its characterization as a result of alloreactivity to the donor in the context of chronic antibody-mediated rejection.

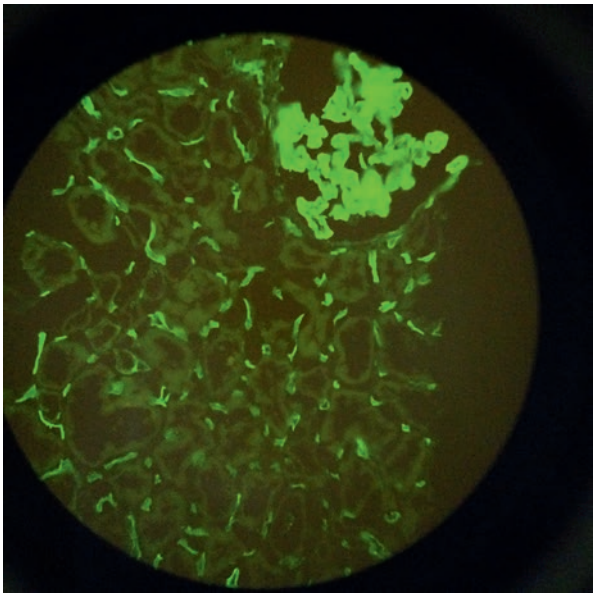


Figure 8

Positive staining for C4d in the glomerulus and peritubular capillaries; IgG, IgA, IgM, C3 and C1q – negative (IF).

In 1997, the Banff conference defined the morphological characteristics of transplant glomerulopathy[6] and, in its 2005 update[7] included TG as a feature of chronic antibody-mediated rejection, which was defined as[8]:

Banff criteria for chronic antibody-mediated rejection (CHR)[a]

Morphological features
– Duplication of glomerular basement membrane (cg1–3)
– Multilaminated PTC basement membrane
– Arterial intimal fibrosis without elastosis
– Interstitial fibrosis with tubular atrophy with or without PTC loss
Diffuse C4d positivity along PTC
Presence of donor-specific antibody

Abbreviations: CHR, chronic humoral rejection; PTC, peritubular capillary.

[a] All three major criteria are required. These parallel those that are used in the Banff schema for acute antibody-mediated rejection.

(Adapted from: Colvin RB, Hirohashi T, Farris AB, Minnel F, Collins AB, Smith RN. Emerging role of B cells in chronic allograft dysfunction. Kidney Int Suppl 2010; 78(Suppl 119):S13-S17[8]).

Transplant glomerulopathy, which normally appears at later stages, can affect about 4% of kidney allografts at the end of one year and 20% at 20 years, although it is often under-diagnosed, and in 50% of cases it may not show evident clinical and laboratory changes and the diagnosis is only made resorting to protocol biopsies[9]. Its clinical manifestations are characterized

by progressive renal dysfunction, initially sub-nephrotic proteinuria and hypertension[10], and is a poor prognostic factor with graft losses that can attain 40-70% of affected patients[11]. This prognosis is substantially worsened when the TG is associated with the presence of C4d deposits in peritubular capillaries in the context of chronic antibody-mediated rejection[12].

Although, as aforementioned, TG may be associated with different pathologies[4,5], in the case report we have described, the presence of donor-specific anti-HLA antibodies and clearly evident C4d deposits in the peritubular capillaries allow for the diagnosis of TG in the context of chronic antibody-mediated rejection.

When TG is diagnosed with coexisting obvious morphological changes by light microscopy and accompanied by important clinical and laboratory manifestations, there is no effective treatment and not even the optimization of maintenance immunosuppression appears to contribute to alter its poor prognosis[13].

There appears to be some evidence that when TG is diagnosed early, and only with detectable ultrastructural changes on electronic microscopy, high doses of immunoglobulin, plasmapheresis and rituximab may have some efficacy[14].

Even randomized trials for the treatment of acute and chronic antibody-mediated rejection with new immunomodulators, such as bortezomib[15] and eculizumab[16], do not seem very promising in preventing TG.

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