

CASE REPORT

Nephrotic syndrome after autologous hematopoietic stem cell transplantation: a case report

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Abstract

Nephrotic syndrome (NS) is a rare complication of hematopoietic cell transplantation (HCT) and is thought to represent a renal manifestation of chronic graft-versus-host disease (cGVHD). Glomerulopathies occur less often in recipients of autologous as compared to allogeneic HCT and, in this setting, renal pathology is less well characterized. This case report describes a 54-year-old man admitted for the evaluation of a nephrotic-range proteinuria. His past medical history included a λ light-chain secreting multiple myeloma (MM) for which he underwent autologous HCT. Prior to admission, the level of proteinuria on successive check-ups was over 3.5 g/day, while on treatment with Losartan for the past six months for mild arterial hypertension. At the time of admission, the clinical examination was unremarkable and there were not any signs of cGVHD. Initial testing showed a nephrotic-range proteinuria (5.6 g/day) with normal renal function, while excluding secondary causes of NS. The patient underwent a kidney biopsy that revealed the classic variant of focal and segmental glomerulosclerosis (FSGS). The patient was started on Cyclosporine 5 mg/kg/day and, after nine months, he experienced a partial remission (proteinuria 1.2 g/day). This is the first report of FSGS as the etiology of autologous HCT-associated NS.

Keywords: glomerular sclerosis, autologous hematopoietic cell transplantation, nephrotic syndrome.

Introduction

Multiple myeloma (MM) is a plasma cell dyscrasia accounting for approximately 10% of all hematological cancers [1, 2]. The mechanism of renal disease in MM can be subdivided in immunoglobulin-dependent and immunoglobulin-independent, with cast nephropathy, monoclonal immunoglobulin deposition disease and light-chain (AL) amyloidosis being the most common in the former category [1, 2]. However, cases of cryoglobulinemic and crescentic glomerulonephritis, minimal-change disease (MCD) or a membranous pattern of glomerular lesion have been described [1–4]. Hematopoietic cell transplantation (HCT), either allogeneic or autologous, is being increasingly used as treatment for a whole range of malignant and nonmalignant conditions, including MM, with various complications related to HCT being recognized over the past few years [5–8]. Nephrotic syndrome (NS) after allogeneic HCT has been attributed to chronic graft-versus-host disease (cGVHD) with kidney biopsy showing features of MCD or membranous nephropathy (MN) and rarely focal and segmental glomerulosclerosis (FSGS) [9–13]. Nevertheless, glomerulopathies occur less often in recipients of autologous as compared to allogeneic HCT and, therefore, renal pathology in this setting is less well characterized [6, 9].

We describe here a rare histopathological finding in a patient with a history of multiple myeloma and autologous HCT.

Case presentation

A 54-year-old man was transferred from the Department of Hematology for the evaluation of a nephrotic-range proteinuria. His past medical history included a λ light-chain multiple myeloma diagnosed four years ago. The initial therapeutic regimen consisted of Thalidomide and Dexamethasone followed by Bortezomib in association with high-dose Dexamethasone. Two years ago, the patient underwent autologous HCT. In this period of time, the serum creatinine was normal and there were no signs of proteinuria. Two months before the admission to the Department of Nephrology, a relapse of the disease was suspected that was ruled out by a subsequent bone marrow biopsy. In the past two months, the level of proteinuria on two successive check-ups was over 3.5 g/day, despite being on treatment with Losartan for the past six months for mild arterial hypertension (Figure 1).

At the time of admission, the patient was otherwise well and the clinical examination revealed no remarkable findings. There were no edemas, his blood pressure was 130/90 mmHg and diuresis of 2000 mL/day. In addition, our patient did not have any signs of cGVHD.

Initial testing showed mild inflammation, with ESR (erythrocyte sedimentation rate) of 40 mm/h, C-reactive protein (CRP) of 2.4 mg/dL, nephrotic range-proteinuria (5.6 g/day) and normal serum albumin. In addition, the λ and κ light-chain levels in serum were 15 mg/L and 13 mg/L, respectively (with a normal κ/λ ratio), and λ

light-chains were undetectable in urine. Urinalysis was unremarkable and the serum creatinine was normal. Additionally, the immunological and virological markers were within the normal range and there were no signs of active multiple myeloma. A kidney biopsy was performed that revealed under light microscopy segmental consolidation of the glomerular lobules with adherence to Bowman's capsule. Electron microscopy (EM) showed diffuse foot process effacement, hyalinosis and accumulation of foam cells. These histopathological findings are characteristic for the classic (NOS – not otherwise specified) variant of FSGS (Figure 2).

The patient was started on Cyclosporine (5 mg/kg/day – with dose adjustment in order to obtain a plasma level of 125–175 ng/mL) for nine months, in addition to Losartan 100 mg/day. After six months of immunosuppressive (IS) treatment, the patient experienced a partial remission (proteinuria 2.6 g/day), with no subsequent relapses. At nine months after the diagnosis, the serum

creatinine level was normal and the proteinuria was 1.2 g/day (Figure 1).

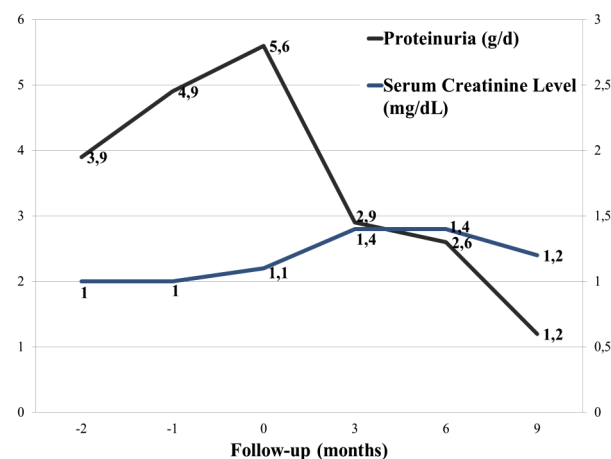


Figure 1 – Evolution of the patient's proteinuria and renal function after the start of IS therapy.

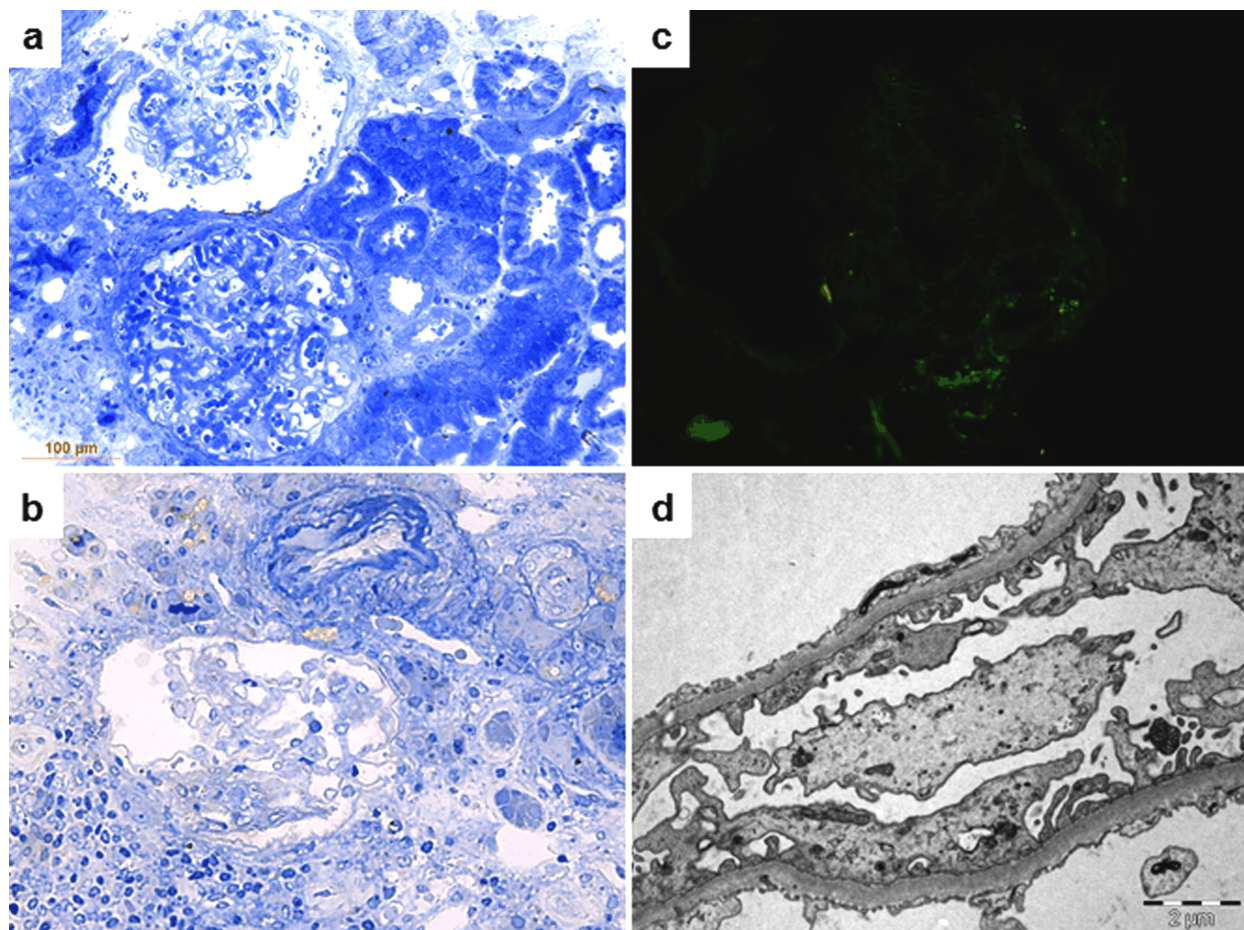


Figure 2 – Kidney biopsy. Light microscopy showing glomeruli with slight mesangial proliferation (a) and tuft adhesion to Bowman's capsule (b). Additionally, periglomerular inflammatory cells and amorphous deposits in arterial wall are identified (b). The immunofluorescence was positive for C3 in vascular walls (c). Electron microscopy showed foot process effacement (d).

Discussion

Our patient had nephrotic-range proteinuria, with a gradually increasing level in the past two months prior to the admission to the Department of Nephrology, but no other signs of nephrotic syndrome. The nephrotic-range proteinuria in addition to undetectable λ light-

chains in the urine indicated a glomerulopathy. Given the patient's past medical history of multiple myeloma and autologous HCT, our first suspicion was of AL amyloidosis associated with the neoplastic disorder, which usually presents as a nephrotic syndrome or nephrotic-range proteinuria. However, the kidney biopsy revealed FSGS NOS variant.

FSGS in the context of multiple myeloma was reported in a minority of cases [3, 4]. MM is usually associated with cast nephropathy, monoclonal immunoglobulin deposition disease, AL amyloidosis, fibrillary and immunotactoid glomerulonephritis, with each of these entities being a possible cause of nephrotic-range proteinuria [1, 2]. However, the fact that the multiple myeloma was in a remission for the past two years and the histopathological proof excluded a myeloma-related disorder.

Nephrotic-range proteinuria has been recognized as a rare complication of HCT and it seems to be a glomerular manifestation of cGVHD [14]. cGVHD is a frequent complication of allogeneic HCT and involves mainly the skin, eyes, liver, gastrointestinal and respiratory tracts [5, 6, 12]. The pathogenic mechanism is related to the formation of antigen–antibody complexes secondary to immune reactions initiated by the allogeneic grafts in which recipient and donor T-cells recognize foreign antigens [7, 12]. Similar to our case, the clinical manifestations usually appear after one year following the HCT and kidney involvement consists mainly of nephrotic-range proteinuria with a normal renal function [9, 11, 14]. Although the majority of patients diagnosed with glomerular disease show signs of overt GVHD, nearly one third of cases occur in the absence of concomitant GVHD [5, 6], as was the case with our patient who did not have any extrarenal involvement. Nevertheless, the majority of renal biopsies revealed membranous nephropathy or minimal-change disease as the etiology of the nephrotic syndrome, with FSGS being reported only in a couple of cases [10, 14]. In the case of membranous nephropathy, subepithelial deposits are thought to be antigen–antibody complexes that prove the GVHD in the kidney of allogeneic transplant recipients [5]. Additionally, glomerulopathies occurring after allogeneic HCT reveal a close temporal relationship between the onset of NS, the diagnosis of cGVHD and the cessation of IS therapy, indicating a possible pathogenic link [6, 7]. Nevertheless, up to 40% of patients still developed a glomerular disease while on IS therapy [6]. Initially, it was thought that a glomerulopathy can occur only in patients receiving an allogeneic HCT, because only in this case a classic cGVHD is possible. However, it seems that autologous HCT recipients also develop glomerular diseases and, as a GVHD cannot be responsible for the development of renal disease, it was proposed that an immune dysregulation similar to autoimmune syndromes could explain these findings [5, 6, 12]. A form of “autologous GVHD” involving the skin, gastrointestinal tract and liver has been described in some patients after autologous HCT [12] but, as seen with post-allogeneic HCT-associated glomerulopathy, not all patients show signs of “autologous GVHD”, thereby explaining the absence of extrarenal manifestations in our patient [5]. Also, FSGS could represent a scar of thrombotic microangiopathy (TMA), another possible complication of HCT [11]. However, EM did not show mesangiolysis and the loss of endothelial cells typical of TMA and the fact that there were not any renal or systemic signs in the period following the HCT make this possibility unlikely. Review of the literature

reveals several cases of membranous nephropathy and MCD occurring after autologous HCT, but, to our knowledge, FSGS in this setting was not described before [9, 12, 14]. Whether there is a pathogenic link between autologous HCT and the development of FSGS remains debatable.

Conclusions

Despite that cGVHD has been shown to affect many systems, the effect of GVHD on the kidney has only been recently recognized. Glomerular lesions that occur after autologous or allogeneic HCT could therefore represent the renal manifestation of GVHD, but further studies are needed to better delineate the pathophysiology of this complication.

Conflict of interests

The authors declare that there are no conflict of interests.

Consent for publication

Written consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this Journal.

References

- [1] Heher EC, Rennke HG, Laubach JP, Richardson PG. Kidney disease and multiple myeloma. *Clin J Am Soc Nephrol*, 2013, 8(11):2007–2017.
- [2] Singhal S, Mehta J. Multiple myeloma. *Clin J Am Soc Nephrol*, 2006, 1(6):1322–1330.
- [3] Paueksakon P, Revelo MP, Horn RG, Shappell S, Fogo AB. Monoclonal gammopathy: significance and possible causality in renal disease. *Am J Kidney Dis*, 2003, 42(1):87–95.
- [4] Valizadeh N, Makhdomi K, Noroozinia F, Behzadi F. Multiple myeloma presenting with focal segmental glomerulosclerosis. *South Asian J Cancer*, 2013, 2(3):168.
- [5] Hingorani S. Renal complications of hematopoietic-cell transplantation. *N Engl J Med*, 2016, 374(23):2256–2267.
- [6] Hu SL. The role of graft-versus-host disease in haematopoietic cell transplantation-associated glomerular disease. *Nephrol Dial Transplant*, 2011, 26(10):2025–2031.
- [7] Beyar-Katz O, Davila EK, Zuckerman T, Fineman R, Haddad N, Okasha D, Henig I, Leiba R, Rowe JM, Ofran Y. Adult nephrotic syndrome after hematopoietic stem cell transplantation: renal pathology is the best predictor of response to therapy. *Biol Blood Marrow Transplant*, 2016, 22(6):975–981.
- [8] Angelo JR, Hingorani S. Chapter 9: Hematopoietic stem cell transplant-related kidney disease. In: *ASN online curricula. Onco-nephrology curriculum*. American Society of Nephrology, 2016, 1–7. <https://www.asn-online.org/education/distancelearning/curricula/onco/Chapter9.pdf>.
- [9] Troxell ML, Pilapil M, Miklos DB, Higgins JP, Kambham N. Renal pathology in hematopoietic cell transplantation recipients. *Mod Pathol*, 2008, 21(4):396–406.
- [10] Lopes JA, Martins C, Jorge S, Melo MJ, Resina C, Moreno R, do Carmo JA. Focal segmental glomerulosclerosis: a very unusual complication of allogeneic hematopoietic cell transplantation (HCT). *Bone Marrow Transplant*, 2011, 46(7):1019–1020.
- [11] Hingorani S. Chronic kidney disease in long-term survivors of hematopoietic cell transplantation: epidemiology, pathogenesis, and treatment. *J Am Soc Nephrol*, 2006, 17(7):1995–2005.
- [12] Abudayyeh A, Truong LD, Beck LH, Weber DM, Rezvani K, Abdelrahim M. Membranous nephropathy in autologous hematopoietic stem cell transplant: autologous graft-versus-host disease or autoimmunity induction? *Clin Kidney J*, 2015, 8(4):440–444.

- [13] Oliveira JSR, Bahia D, Franco M, Balda C, Stella S, Kerbaux J. Nephrotic syndrome as a clinical manifestation of graft-versus-host disease (GVHD) in a marrow transplant recipient after cyclosporine withdrawal. *Bone Marrow Transplant*, 1999, 23(1):99–101.
- [14] Bruckamp K, Doyle AM, Bloom RD, Bunin N, Tomaszewski JE, Cizman B. Nephrotic syndrome after hematopoietic cell transplantation: do glomerular lesions represent renal graft-versus-host disease? *Clin J Am Soc Nephrol*, 2006, 1(4): 685–694.

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Received: November 1, 2016

Accepted: November 28, 2017