

# Minimal-change nephrotic syndrome in a hematopoietic stem-cell transplant recipient

Benjamin D Humphreys\*, Vijay K Vanguri, Joel Henderson and Joseph H Antin

## SUMMARY

**Background** A 61-year-old woman received standard immunizations, including *Haemophilus influenzae* type B, diphtheria, tetanus toxoid, and unconjugated 23-valent pneumococcal vaccine (Pneumovax®, Merck & Co., Inc., Whitehouse Station, NJ), 1 year after undergoing nonmyeloablative hematopoietic stem-cell transplantation for acute myelogenous leukemia. After 5 days, she developed fatigue with progressive weight gain and edema, and 14 days after immunization she presented with anasarca and was found to have acute renal failure and nephrotic proteinuria.

**Investigations** Physical examination, serum chemistry, examination of urine sediment, renal ultrasound using Doppler scanning, 24 h urine collection, and renal biopsy.

**Diagnosis** Minimal-change nephrotic syndrome with acute tubular injury.

**Management** Aggressive diuresis and oral corticosteroid therapy.

**KEYWORDS** acute renal failure, bone-marrow transplant, immunization, minimal-change disease, nephrotic syndrome

## CME

This article offers the opportunity to earn one Category 1 credit toward the AMA Physician's Recognition Award.

## THE CASE

Two years before presentation, a 59-year-old woman developed fatigue and pancytopenia and bone-marrow biopsy revealed acute myelogenous leukemia (AML). She had normal cytogenetics and entered remission after induction chemotherapy with anthracycline and cytarabine. Subsequently, she received consolidation therapy with high-dose cytarabine and did well until 1 year later, when pancytopenia recurred and her marrow showed relapsed AML. Soon thereafter, the patient underwent nonmyeloablative hematopoietic stem-cell transplantation (HSCT) from an unrelated donor. The patient had no pretransplantation proteinuria. Conditioning included fludarabine phosphate and busulfan,<sup>1</sup> and graft-versus-host disease (GVHD) prophylaxis consisted of methotrexate, sirolimus, and tacrolimus.<sup>2</sup>

The patient's post-transplantation course was uneventful. Immunosuppression was tapered and then discontinued after 6 months. One year after HSCT she received routine, recommended immunizations, including *Haemophilus influenzae* type B, diphtheria, tetanus toxoid, and unconjugated 23-valent pneumococcal vaccine (Pneumovax®, Merck & Co., Inc., Whitehouse Station, NJ). Her serum creatinine level at this visit was 71 µmol/l (0.8 mg/dl). After 5 days, she began to experience fatigue and progressive weight gain, and 14 days after immunization she had gained 10 kg and had generalized edema. She had a serum creatinine level of 301 µmol/l (3.4 mg/dl), hypoalbuminemia of 0.28 mg/l, proteinuria of 4+, and no hematuria. Examination of urinary sediment showed fine granular casts (Figure 1A). The patient was admitted to hospital for kidney biopsy and further evaluation. A Doppler renal ultrasound showed normal-sized kidneys, normal vascular flow, and no hydronephrosis. A 24 h urine collection contained 14 g of urine protein.

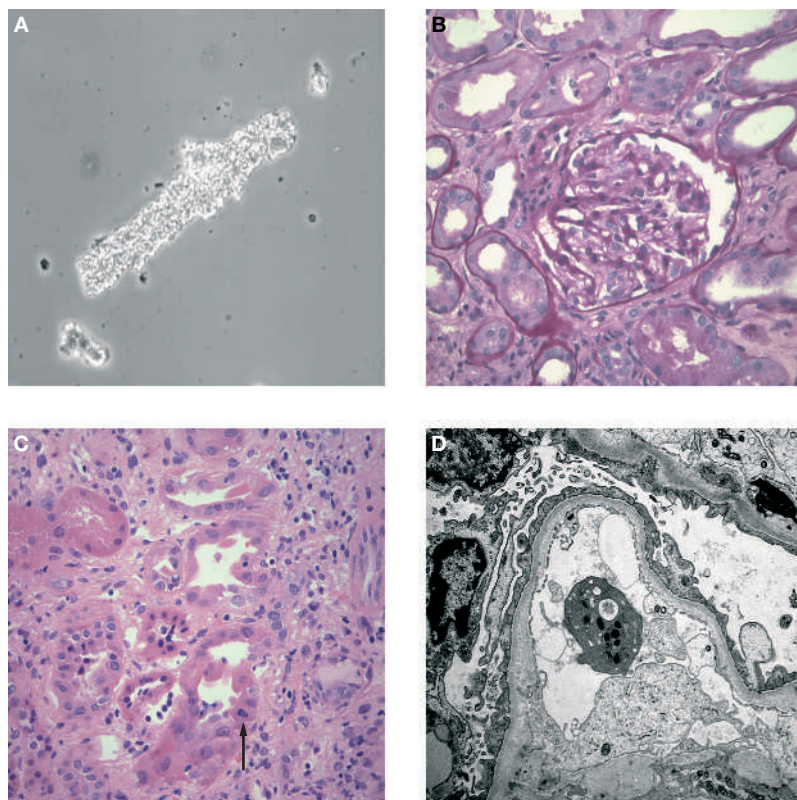
*BD Humphreys is an instructor at Harvard Medical School, and Staff Nephrologist in the Renal Division at Brigham and Women's Hospital, Boston, MA, USA. VK Vanguri is a renal pathology fellow and J Henderson is Staff Pathologist at the Department of Pathology, Brigham and Women's Hospital. JH Antin is Professor of Medicine at Harvard Medical School, and Chief of the Stem-Cell Transplant Program in the Department of Medical Oncology at the Dana Farber Cancer Institute, Boston, MA, USA.*

## Correspondence

\*Harvard Institutes of Medicine Room 550, 4 Blackfan Circle, Boston, MA 02115, USA  
bhumphreys@partners.org

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**Figure 1** The patient's urinary sediment and kidney biopsy findings. (A) Fine granular cast in the urinary sediment 14 days after vaccination. (B) Unremarkable glomerulus by light microscopy (periodic acid-Schiff reaction). (C) By light microscopy, tubules show evidence of injury, with mild vacuolization, epithelial atypia, and scattered mitotic activity (arrow). The interstitium appears expanded with a mild increase in mononuclear inflammatory cells. (D) Ultrastructural evidence of glomerular visceral epithelial cell injury, including effacement of foot processes. The capillary endothelium does not appear injured, because the fenestrations are well preserved and there is no evidence of glomerular basement-membrane remodeling or subendothelial expansion. No dense deposits are present.

Light microscopy of the kidney biopsy (Figure 1B,C) showed evidence of tubular injury and a mild, but diffuse, interstitial inflammatory infiltrate consisting of mononuclear cells and scattered eosinophils. It also showed 15 glomeruli without evidence of segmental or global sclerosis, active inflammation, basement-membrane changes, or thrombosis. No immune deposits or fibrin thrombi were identified by immunofluorescence and electron microscopy. Ultrastructural evaluation (Figure 1D) revealed severe injury of the glomerular visceral epithelial cells, including microvillous degeneration and diffuse foot-process effacement. The fenestrations of the glomerular capillary endothelium were well preserved and there was no significant

basement-membrane remodeling. Minimal-change disease (MCD), acute tubular injury, and mild active interstitial nephritis were diagnosed. The patient was diuresed and started on oral prednisone (60 mg/day). The proteinuria and acute renal failure (ARF) resolved rapidly. The urine protein:creatinine ratio decreased from 19.8 to 0.2 within 2 months of starting therapy (Figure 2). Within 3 weeks of the renal biopsy, the patient developed mildly elevated transaminases, dry eyes, and oral ulcerations. Mild chronic GVHD was diagnosed. Steroids were tapered and, ultimately, discontinued after 10 weeks. After 9 months, the patient remains in clinical remission from AML and the nephrotic syndrome. Her oral chronic GVHD responded to topical steroids, and her elevated transaminases have normalized.

#### DISCUSSION OF DIAGNOSIS

HSCT is the most common nonrenal transplantation, with 18,000 procedures performed annually in the US alone. The renal complications of this procedure can be divided into early and late events. Late events usually begin about 3 months after transplantation. The main causes of late renal disease in this population are summarized in Box 1.<sup>3</sup> At least 20% of survivors develop chronic kidney disease (CKD), and this is most commonly caused by either bone-marrow transplant nephropathy or chronic calcineurin inhibitor toxicity. Independent risk factors for the development of CKD in nonmyeloablative HSCT recipients include peritransplantation ARF, previous autologous HSCT, long-term use of calcineurin inhibitors, and chronic GVHD.<sup>4</sup>

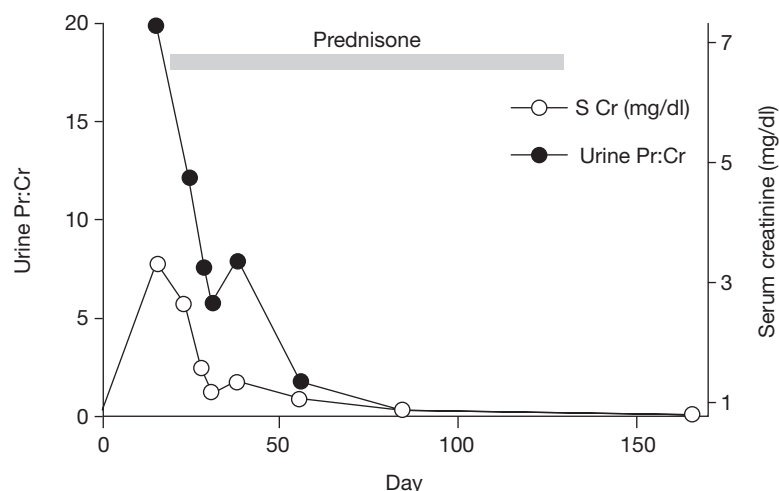
Glomerular disease is a less common late complication of HSCT than CKD. Membranous nephropathy predominates, usually in the setting of chronic GVHD. Proteinuria can be in the nephrotic range and hematuria is often present. In the case presented here, the abrupt onset of massive proteinuria argued against membranous nephropathy, and renal biopsy subsequently showed MCD. MCD is less common than membranous nephropathy in HSCT recipients and has never been described after nonmyeloablative HSCT.<sup>5,6</sup> Although the precise incidence of glomerular disease after HSCT has not been rigorously examined, an increasing number of reports indicate that both membranous nephropathy and MCD might be more common in HSCT recipients, compared with the general population. Other glomerulopathies also occur

in HSCT recipients occasionally, including focal and segmental glomerulosclerosis, IgA nephropathy, and immune-complex glomerulonephritis; however, it is not clear whether the risk of development of these complications is any higher in HSCT recipients than nontransplanted patients.

Most cases of MCD are idiopathic, but a variety of secondary causes are recognized and a partial list is presented in Box 2. The MCD in the case presented here was associated with an allergic reaction to vaccination. Various vaccines have been linked to MCD, including influenza, pneumococcal, and hepatitis B vaccines.<sup>7–9</sup> A circulating factor produced by activated T lymphocytes might be involved in the pathogenesis of MCD. Following injection in rats, T-cell hybridomas or the supernatants of concanavalin A-stimulated mononuclear cells from patients with MCD induce proteinuria and podocyte foot-process fusion.<sup>10</sup> MCD is also associated with atopy and lymphoproliferative diseases, such as Hodgkin's disease, and usually responds rapidly to corticosteroids.

ARF often co-exists with the nephrotic syndrome. Many patients with ARF and the nephrotic syndrome have active tubulointerstitial nephritis in the setting of a hypersensitivity reaction, with signs of tubular injury typical of ischemic or toxic insults. History and temporal associations with the onset of symptoms reveal that nonsteroidal anti-inflammatory drugs, angiotensin-converting-enzyme inhibitors, and diuretics are the most frequent causative agents. The patient in the case presented here had neither fever nor eosinophilia at diagnosis and was not taking any medication around the time of vaccination. A drug-associated type I hypersensitivity reaction is, therefore, unlikely to account for her tubulointerstitial nephritis or tubular injury. We speculate that vaccination itself triggered the hypersensitivity reaction.

Two other causes of ARF in the setting of massive proteinuria should be considered. The prothrombotic state of the nephrotic syndrome can cause bilateral renal vein thrombosis, presenting with flank pain and hematuria. In the case presented here, bilateral renal vein thrombosis was excluded by renal ultrasound using Doppler scanning. Patients with massive proteinuria might additionally develop ARF as a consequence of intrarenal edema with impairment of glomerular hemodynamics.<sup>11</sup> A hallmark of this syndrome of 'nephrosarca' is improvement in ARF with diuresis. The renal biopsy of the patient



**Figure 2** Time course for development and resolution of proteinuria after vaccination. Spot urine protein:creatinine ratio is plotted against time from vaccination (day 0). Prednisone therapy was started on day 16 and tapered after 8 weeks. The serum creatinine concentration is also indicated. Abbreviations: S Cr, serum creatinine concentration; Urine Pr:Cr, urine protein:creatinine ratio.

**Box 1** Late renal complications after hematopoietic stem-cell transplantation.

**Chronic kidney disease**

Bone-marrow transplant nephropathy/thrombotic microangiopathy syndrome  
Chronic calcineurin inhibitor toxicity

**Glomerular disease**

Membranous nephropathy  
Minimal-change disease

in the case presented here lacked significant interstitial edema, excluding this etiology of ARF.

Several factors support vaccination as the cause of both MCD and ARF in the case presented here: symptoms began 5 days after vaccination, MCD has previously been associated with both vaccination and HSCT, and recent data indicate that the nephrotic syndrome might be more common than previously thought in nonmyeloablative HSCT recipients. In a report of one HSCT recipient, MCD developed after withdrawal of ciclosporin immunosuppression but resolved after ciclosporin was reintroduced.<sup>12</sup> In the case presented here, we propose that simultaneous immunization with three different vaccines might have resulted in hyperstimulation of the recovering immune system, leading to dysregulated T-lymphocyte activation and, subsequently, MCD. The fact that the patient developed chronic GVHD soon

**Box 2** Some secondary causes of minimal-change nephropathy.

**Drugs**

Nonsteroidal anti-inflammatory drugs  
Ampicillin  
Gold

**Allergens**

Hymenoptera stings  
Food  
Pollen  
Poison ivy and poison oak  
Immunization

**Infection**

Viral

**Cancer**

Hodgkin's disease

after MCD was diagnosed indicates that MCD might be an unusual manifestation of GVHD in HSCT recipients. Nevertheless, we cannot rule out the possibility that the association between vaccination and MCD is co-incidental, because almost all HSCT recipients receive immunizations after successful engraftment and, to our knowledge, no other case of MCD has been reported in this context.

It is not known whether nonmyeloablative HSCT recipients are at greater risk of development of the nephrotic syndrome than myeloablative transplant recipients. Patients in both groups might develop chronic GVHD, which is itself associated with heightened risk of development of the nephrotic syndrome. In a consecutive series of 163 nonmyeloablative HSCT recipients, Srinivisan *et al.* reported an unexpectedly high incidence of the nephrotic syndrome.<sup>13</sup> They found seven cases of the nephrotic syndrome, and biopsy findings revealed that four of these patients had membranous nephropathy. Although MCD was not diagnosed, the remaining three cases were not biopsied. The majority of these patients with the nephrotic syndrome also had limited chronic GVHD. The reasons for a possibly higher risk of development of the nephrotic syndrome in nonmyeloablative HSCT recipients than myeloablative transplant recipients are speculative. Earlier withdrawal of immunosuppression in nonmyeloablative protocols could heighten susceptibility to immune-mediated glomerular disease. Host/donor marrow chimerism is

another important difference between the two types of HSCT. Whether persistence of host lymphocytes that survive conditioning alters susceptibility to either membranous nephropathy or MCD is not yet known and certainly warrants further study.

**TREATMENT AND MANAGEMENT**

The cornerstone for therapy in MCD is corticosteroid treatment, such as prednisone, usually at a daily dose of 1 mg/kg of body weight up to 80 mg. We recommend *Pneumocystis carinii* pneumonia prophylaxis for patients receiving daily doses of prednisone of 60 mg or greater.

Although 90% of children respond within weeks, approximately 75% of adults with MCD are steroid-sensitive and achieving remission takes longer, usually 1–3 months.<sup>14</sup> In adult patients with corticosteroid-resistant or frequently relapsing MCD, alternative immunosuppressive agents, such as cyclophosphamide, ciclosporin, or mycophenolate mofetil, are often required. The precise role of these agents has not yet been defined by trial data, however.

Control of edema in MCD is important and diuretics, combined with a low-salt diet, are the mainstays of therapy. Angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers can be used to reduce proteinuria, particularly in patients with heavy proteinuria or who have a slow response to corticosteroid therapy. In the case presented here, angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers were not prescribed because the patient had ARF and a rapid response to corticosteroid therapy. The thrombotic tendency in the nephrotic syndrome can be treated with aspirin (325 mg/day).

**CONCLUSION**

This report describes a case of minimal-change nephrotic syndrome associated with vaccination in a nonmyeloablative HSCT recipient. The benefits of vaccination in HSCT recipients are clear,<sup>15</sup> and this report should not alter current practice. Because of the expanding indications and growing numbers of HSCTs performed worldwide, combined with improved survival, nephrologists must be familiar with the renal complications of this life-saving procedure. Further study is needed to determine the incidence of both MCD and membranous nephropathy after HSCT, and to explore their association with GVHD and nonmyeloblastic transplantation protocols.

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## Competing interests

The authors declared they have no competing interests.