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Relapsing Acute Kidney Injury Associated with Pegfilgrastim

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Key Words

Pegfilgrastim · Glomerulonephritis · Renal dysfunction

Abstract

We report a previously unrecognized complication of severe acute kidney injury (AKI) after the administration of pegfilgrastim with biopsy findings of mesangioproliferative glomerulonephritis (GN) and tubular necrosis. A 51-year-old white female with a history of breast cancer presented to the hospital with nausea, vomiting and dark urine 2 weeks after her third cycle of cyclophosphamide and docetaxel along with pegfilgrastim. She was found to have AKI with a serum creatinine (Cr) level of 6.9 mg/dl (baseline 0.7). At that time, her AKI was believed to be related to prior sepsis and/or daptomycin exposure that had occurred 5 weeks earlier. She was dialyzed for 6 weeks, after which her kidney function recovered to near baseline, but her urinalysis (UA) still showed 3.5 g protein/day and dysmorphic hematuria. Repeat blood cultures and serological workup (complement levels, hepatitis panel, ANA, ANCA and anti-GBM) were negative. She received her next cycle of chemotherapy with the same drugs. Two weeks later, she developed recurrent AKI with a Cr level of 6.7 mg/dl. A kidney biopsy showed mesangioproliferative GN, along with tubular epithelial damage and a rare electron-dense glomerular deposit. Pegfilgrastim was suspected as the inciting agent after exclusion of other causes. Her Cr improved to 1.4 mg/dl over the next 3 weeks, this time without dialysis. She had the next 2 cycles of chemotherapy without pegfilgrastim, with no further episodes of AKI. A literature review revealed a few cases of a possible association of filgrastim with mild self-limited acute GN. In conclusion, pegfilgrastim may cause GN with severe AKI. Milder cases may be missed and therefore routine monitoring of renal function and UA is important.

Background

Acute glomerulonephritis (GN) generally presents as a pentad of proteinuria, hematuria, edema, hypertension and elevated creatinine (Cr). Most cases of GN occur due to immunological response to various triggers such as infections, drugs, cancers or systemic diseases such as lupus. In most cancer patients receiving chemotherapy, it is a common practice to administer granulocyte colony-stimulating factor (G-CSF) as a prophylaxis for anticipated febrile neutropenia. Two such G-CSF agents used are filgrastim and pegfilgrastim. Pegfilgrastim is a long-acting agent that has polyethylene glycol added to one end of filgrastim.

Adverse effects of pegfilgrastim range from mild headaches, peripheral edema, constipation, bone pain, arthralgias and myalgias to serious, although uncommon, events including acute respiratory distress syndrome, atraumatic splenic rupture, anaphylaxis, hematological malignancies and vascular complications [1–3]. While GN has rarely been reported, it is not a well-recognized complication. We hereby describe a case of mesangioproliferative GN and tubular necrosis with recurrent severe acute kidney injury (AKI) after administration of pegfilgrastim and its associated clinical course on two separate occasions.

Case Description

A 51-year-old female with a history of breast cancer presented to an outside facility with severe nausea and vomiting 2 weeks after her third cycle of chemotherapy with cyclophosphamide and docetaxel with pegfilgrastim. Five weeks prior to her presentation, she had had an episode of chest wall cellulitis around her central port site with associated methicillin-sensitive staphylococcus aureus bacteremia that was treated with daptomycin and port removal with resolution. Prior to the recent chemotherapy, her baseline serum Cr was 0.7 mg/dl and urinalysis (UA) had only a trace of blood and no protein. Upon admission to the outside hospital, she was found to have AKI with a serum Cr of 6.9 mg/dl. A routine UA by the lab reported 3+ proteins and 3+ blood, but no sediment or quantification was documented. She was started on hemodialysis with a presumptive diagnosis of acute tubular necrosis of uncertain etiology. She was dialyzed for 6 weeks when she sought a second opinion about her AKI at our facility. At that visit, it was noted that her kidney function had improved with a predialysis BUN of 18 and a Cr of 1 mg/dl (fig. 1). Dialysis was stopped. However, to our surprise, examination of her urine revealed 3+ proteinuria, red blood cell (RBC) casts and 3.5 g protein per day. An additional workup was sent, including complement levels, hepatitis serology, ANA, ANCA and serum protein electrophoresis that all returned normal. Repeat blood cultures were negative and transthoracic echocardiography was negative for vegetations. Renal biopsy was discussed but deferred as Cr had normalized; the patient was asymptomatic and still fully anticoagulated for a recent upper-limb deep venous thrombosis at the site of her old port. The possibility of a slowly resolving postinfectious GN was felt to be the most likely diagnosis at that time. After 4 weeks of stable kidney function and no signs of active infection, she was cleared to receive her fourth cycle of chemotherapy with the same agents along with pegfilgrastim. Two weeks later, she developed recurrent nausea and back pain as well as dark urine. She was found to have a serum Cr level of 6.7 mg/dl, UA again showed 3+ proteinuria and 3+ blood, with dysmorphic RBCs and RBC casts. A renal biopsy was then performed (anticoagulation had been discontinued at that time). The biopsy revealed mesangioproliferative GN, tubular epithelial damage, focal fusion of epithelial podocytes and lipid droplets in a visceral epithelial cell. A rare electron-dense, immune complex-like deposit was seen in the glomerular basement membrane and mesangium (fig. 2a–c). However, immunofluorescence was negative for IgA, IgG, IgM and complement. Her Cr level started improving spontaneously (without dialysis) and was back to baseline within 1 week. This time, her AKI was felt to be related to pegfilgrastim. Therefore, pegfilgrastim was eliminated from her fifth and sixth cycles of chemotherapy and the Cr level remained stable. On her last follow-up 6 months later, serum Cr was 1 mg/dl and the

spot urine protein/Cr ratio was 112 mg/g, although she still had some dysmorphic hematuria and 2 RBC casts.

Discussion

To our knowledge, this is the first reported case of severe AKI with biopsy-proven mesangioproliferative GN in a cancer patient receiving the G-CSF pegfilgrastim for chemotherapy-induced neutropenia. The pathophysiology of this injury may be related to the cytokine nature of G-CSF. G-CSF is a naturally occurring cytokine with levels that increase 10–30 times following physiological stimuli-like infections. After subcutaneous administration of 300 µg G-CSF, levels increase by 500–1,000 fold within 4 h and normalize over the next 48 h [4, 5]. G-CSF not only activates neutrophils but can also injure endothelial cells, modulate cytokine release and can potentially result in vasculitis in [4, 6]. G-CSF receptors are present on myeloid lineage cells as well as on subsets of monocytes, lymphoid cells, platelets and vascular endothelial cells [7–11]. G-CSF stimulation leads to mobilization of cells from the bone marrow microenvironment by release of metalloproteinases that cause shedding of adhesion molecules such as L-selectin, E-selectin and ICAM-1 [12, 13]. G-CSF also induces E-selectin expression on endothelial cells and E-selectin ligand expression on mobilized, circulating leukocytes. This has been postulated to lead to enhanced leukocyte-endothelial cell interactions and associated vascular complications [14]. This could result in glomerular and or renal tubular injury. Alternatively, hypersensitivity reaction to pegfilgrastin could also result in AKI.

A review of an international registry of 853 patients (during the years 1994–2003) receiving filgrastim for severe chronic neutropenia noted 25 cases of GN [1]. Twelve patients had underlying kidney disease while 13 patients had normal function at baseline. Seven out of the 13 patients had a kidney biopsy. Six patients had immune deposits and 1 patient had SLE. With a decreased dose or discontinuation of filgrastim, kidney injury resolved. However, a few cases had resolution of symptoms without any change in the dose of filgrastim.

Bonilla et al. [14] reported 1 case of mesangioproliferative GN out of 44 patients with severe congenital neutropenia receiving long-term filgrastim. Sotomatsu et al. [15] reported rapidly progressive GN in a 12-year-old male who had been receiving filgrastim for 7 years for severe congenital neutropenia. His filgrastim treatment was continued to prevent infections and he was treated with high-dose methylprednisolone followed by maintenance with prednisolone, cyclophosphamide, warfarin and dipyridamole. His Cr improved but proteinuria persisted. Another report was of a 44-year-old female with a history of hypertension and obesity who presented as a donor for peripheral blood stem cell transplantation. She developed macroscopic hematuria and proteinuria on the fifth day of filgrastim administration. Renal biopsy showed focal segmental proliferative GN with cellular crescents in 40% of the glomeruli. Immunofluorescence showed fine granular deposits of IgG, and kappa and lambda chains in mesangial areas. Her Cr remained stable and her urine gradually normalized over the course of 1 year after withdrawal of filgrastim [3]. Funakoshi et al. [16] described IgA nephropathy in a 7-year-old healthy donor for peripheral blood stem cell transplantation who developed hematuria and 3+ proteinuria 13 days after the first dose of filgrastim. Renal biopsy showed IgA deposition in the mesangium with

endocapillary and mesangial proliferation. This patient was treated with prednisone and azathioprine on day 75. His urine normalized by day 100 and remained normal at the 18-month follow-up.

In our case, the patient tolerated her first 2 cycles of chemotherapy with pegfilgrastim without any observed problems. However, it is possible that the renal manifestations could have been missed if she had had only asymptomatic proteinuria or hematuria. Alternatively, repeated exposure may have resulted in sensitization. With pegfilgrastim exposure during her third and fourth cycles of chemotherapy, she developed hematuria, proteinuria and severe renal insufficiency. Each episode of AKI occurred about 2 weeks after receiving pegfilgrastim. Both episodes were self-limiting over the course of the following few weeks without any active intervention, although dialysis was initiated at an outside institution with the first episode. The absence of proteinuria and a normal Cr before exposure speaks against any significant underlying kidney disease in our patient.

In conclusion, these findings suggest that pegfilgrastim may cause GN that can be severe enough to cause AKI requiring dialysis; however, the course is usually self-limited. Immune complex formation appears to play a role, but may not be a prominent or consistent feature on renal biopsy. Our case also had features of acute tubular injury. Abnormalities in urine sediment may persist for months, even after normalization of Cr. Though acute GN appears to be a rare occurrence, it is possible that milder cases are missed if the only manifestation is asymptomatic proteinuria or microscopic hematuria. Whether there are differences in occurrence with pegfilgrastim versus filgrastim is not clear yet. Routine monitoring of renal function and screening UA for hematuria or proteinuria for patients receiving G-CSF is indicated.

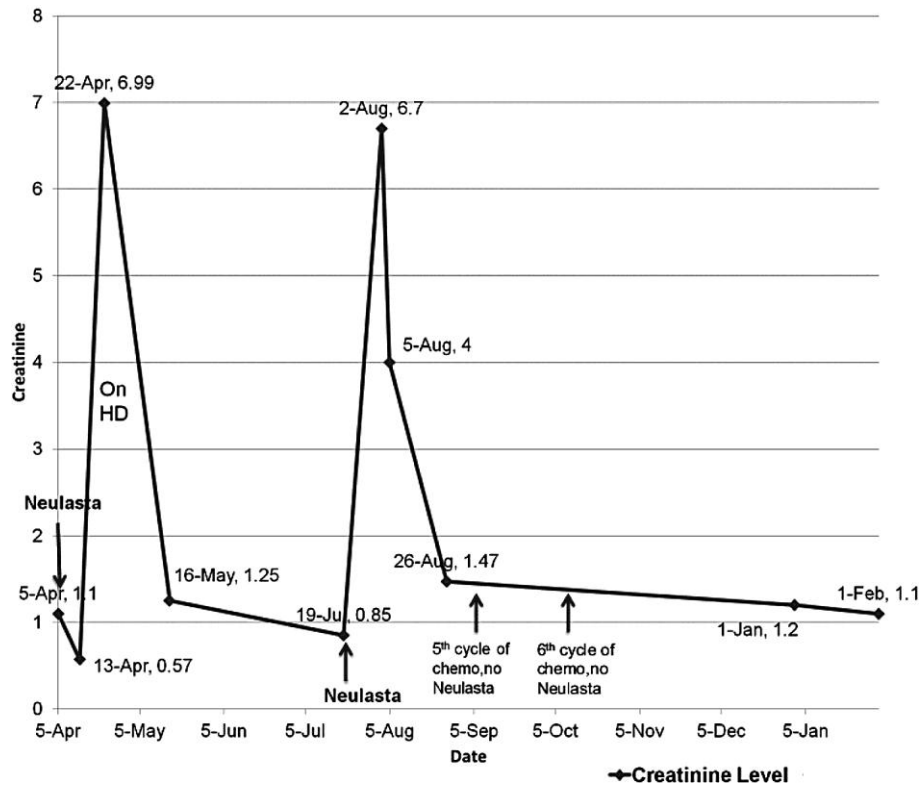


Fig. 1. Trend of serum Cr levels.

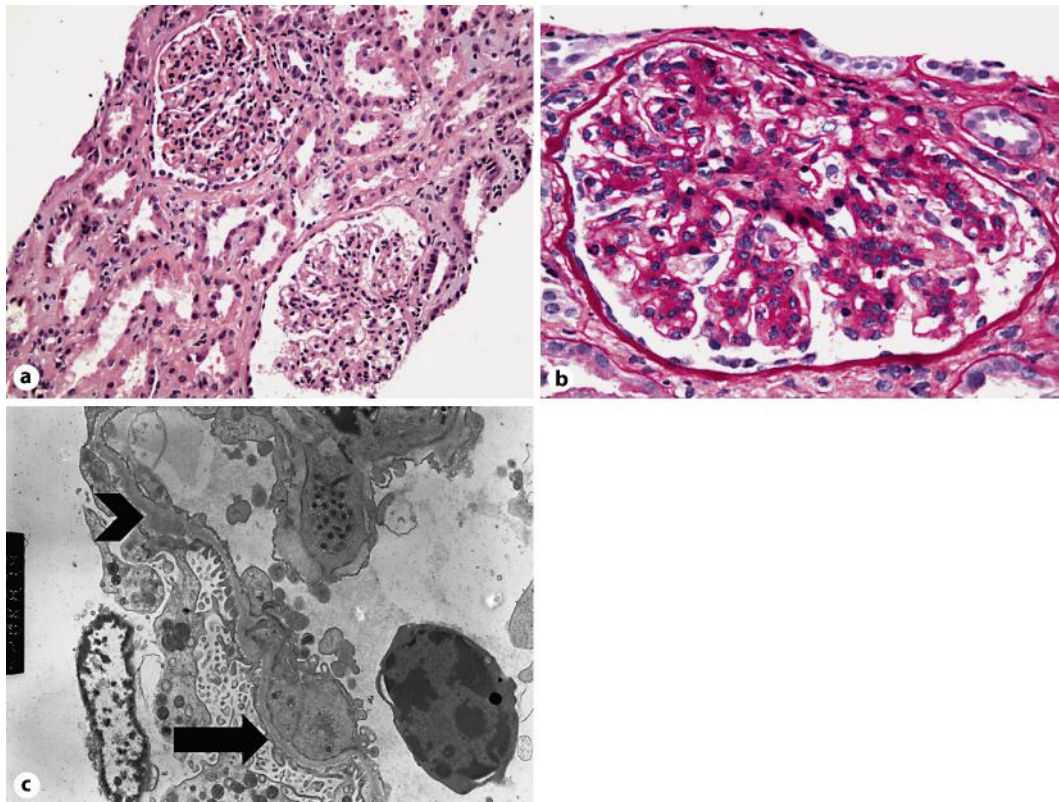


Fig. 2. **a** Light microscopy, $\times 340$. Hematoxylin and eosin stain. Two glomeruli with increased mesangial cellularity and tubular epithelial damage. **b** Light microscopy, $\times 690$. Periodic acid Schiff. Glomerulus with mesangial expansion and hypercellularity. **c** Electron microscopy, $\times 3,900$. Mesangial cells are prominent. Focal fusion of podocytes (arrow). Immune complex-like deposit (arrowhead).

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