CASE REPORT

Focal Segmental Glomerulosclerosis with Acute Renal Failure Associated with Eltrombopag Therapy

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Eltrombopag, a small-molecule nonpeptide agonist of the thrombopoietin receptor, is used for treatment of thrombocytopenia of various causes, including chronic idiopathic thrombocytopenic purpura (ITP) and hepatitis C–related liver cirrhosis. During clinical trials, eltrombopag was discontinued in three patients due to ascites, neutropenia, and retinal exudates. Another recently reported major adverse event was reversible acute renal failure in a patient with antiphospholipid syndrome; nephrotoxicity caused by eltrombopag was highly suspected, but a kidney biopsy was not performed. We describe a 46-year-old woman with a history of mitral valve prolapse who had an incidental finding of an isolated low platelet count of 22 x 10^3/mm^3. A tentative diagnosis of ITP was made, and oral prednisolone 25 mg twice/day was started. Despite prednisolone dosage adjustments over the next several weeks, her platelet count remained at 15–40 x 10^3/mm^3, and oral eltrombopag 75 mg/day was begun. After seven doses, the patient came to the emergency department with persistent nausea and vomiting. Laboratory work-up revealed renal failure, and eltrombopag was discontinued. The patient was hospitalized, and on day 2, her renal failure had progressed, and proteinuria was detected. On day 6, emergency hemodialysis was begun. A complete blood count on day 21 revealed progression of anemia and thrombocytopenia. Splenectomy was performed on day 35, which successfully reversed her thrombocytopenia. She was discharged on day 39, and hemodialysis was discontinued on day 44. At follow-up on day 56, the patient's platelet count was within normal limits. On day 70, kidney biopsy results revealed a typical pattern of focal segmental and diffuse global glomerulosclerosis. By day 210, her ITP had resolved, and her renal function was stable. Use of the Naranjo adverse drug reaction probability scale indicated a probable relationship (score of 7) between the patient's development of acute renal failure and eltrombopag therapy. To our knowledge, this is the first case report of a patient who experienced acute renal failure and proteinuria concomitant with a pathology of focal segmental glomerulosclerosis after treatment with eltrombopag. This report of a serious case of reversible renal failure after treatment with eltrombopag may serve to inform clinicians about the possible severe renal adverse effects of eltrombopag before commencing with more extensive clinical use in the future.

Key Words: eltrombopag, idiopathic thrombocytopenic purpura, ITP, acute renal failure, focal segmental glomerulosclerosis, FSGS, adverse event.

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Eltrombopag, an orally available nonpeptide thrombopoietin receptor agonist, is used for the treatment of thrombocytopenia of various causes, including chronic idiopathic thrombocytopenic

Table 1. Laboratory Data During the Patient's Clinical Course

Laboratory Test	Normal Range	At Diagnosis of ITP	At Start of Eltrombopag Therapy	At Development of Acute Renal Failure
White blood cell count (x 10^3/mm^3)	4–11	6.8	7.9	19.8
Hematocrit (%)	36–48	36.3	42.2	43.5
Platelet count (x 10^3/mm^3)	150–400	22	11	136
Serum creatinine (mg/dl)	0.2–1.5	0.68	0.62	3.86
Serum lactate dehydrogenase (U/L)	< 250	241		1386
Serum IgG (mg/dl)	751–1560	961		893
Serum IgA (mg/dl)	82–453	319		315
Serum IgM (mg/dl)	46–304	26.9		51.7
Complement C3 (mg/dl)	79–152			143
Complement C4 (mg/dl)	16–38			36.7
Antinuclear antibody titer	Negative	Negative		Negative
Rheumatoid factor (IU/ml)	0–20			< 20.0
Anti–double-stranded DNA (IU/ml)	< 30			11
Anti–β_2-glycoprotein IgG (U/ml)	< 20			6.87
Antiphospholipid IgG (U/ml)	< 15			< 6.25
Anticardiolipin IgG (GPL units/ml)	< 15			5.01
C-ANCA (U/ml)	< 7			0.9
P-ANCA (U/ml)	< 7			1.6
Anti-GBM (U/ml)	< 7			0.8
Cryoglobulin	Negative	Negative		Negative

ITP = idiopathic thrombocytopenic purpura; Ig = immunoglobulin; GPL units = IgG phospholipid units; C-ANCA = classic antineutrophil cytoplasmic antibodies; P-ANCA = protoplasmic-staining antineutrophil cytoplasmic antibodies; GBM = glomerular basement membrane.

purpura (ITP) and hepatitis C–related liver cirrhosis.[1, 2] During clinical trials, eltrombopag was discontinued in three patients due to ascites, neutropenia, and retinal exudates.[2] Another major adverse event was recently reported in a 54-year-old man with a diagnosis of antiphospholipid syndrome based on the clinical scenario of two deep vein thromboses, a coronary artery thrombosis, and the following laboratory results: prolonged activated partial thromboplastin time, abnormal dilute Russel viper venom time, and high titers of anticardiolipin immunoglobulin (Ig) G and anti–β_2-glycoprotein IgG.[3] The patient experienced reversible acute renal failure after introduction of eltrombopag. Given the nature of antiphospholipid syndrome, where renal microvascular complication might have existed, the association between eltrombopag and nephrotoxicity in this patient was based on the result of eltrombopag rechallenge. However, the nephropathy caused by eltrombopag could not be confirmed without a kidney biopsy, which was not performed due to the patient's clinical condition of thrombocytopenia and ongoing anticoagulation.

We describe a 46-year-old woman who developed acute renal failure after treatment with eltrombopag, with the kidney biopsy results indicating a typical pattern of focal segmental glomerulosclerosis (FSGS) and diffuse global glomerulosclerosis. This may further clarify the kidney injury from eltrombopag that manifests with proteinuria and hypoalbuminemia through the destruction of renal podocytes.

Case Report

A 46-year-old Taiwanese woman with a history of mitral valve prolapse was referred for consultation with a hematologist because of an incidental finding of an isolated low platelet count

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of 22 x 10^3/mm^3 (normal range 150–400 x 10^3/mm^3). A primary screen with biochemistry tests and autoimmune profiles produced unremarkable results (Table 1). A bone marrow study revealed normal cellularity of 60% and increased megakaryocyte count with focal clustering. There was no evidence of dysplasia in three hematopoietic lineages. A tentative diagnosis of ITP was made, and oral prednisolone 25 mg twice/day (1 mg/kg/day) was begun.

One week later, the patient's platelet count recovered to 157 x 10^3/mm^3, so the same prednisolone dosage was continued for 1 more week, followed by tapering to 10 mg twice/day (Figure 1). Three weeks later, her platelet count decreased to 41 x 10^3/mm^3, and her prednisolone dosage was increased to 20 mg twice/day. Meanwhile, oral valsartan 80 mg/day was added for hypertension. Tapering of the prednisolone dose began when the platelet count recovered to 84 x 10^3/mm^3, and valsartan was continued at the same dose.

Two months later, the patient's platelet count decreased to 39 x 10^3/mm^3, then to 16 x 10^3/mm^3, remaining unresponsive to prednisolone dosage adjustments. She had also received oral diclofenac 25 mg 3 times/day for 10 days as pain relief for carpel tunnel syndrome. In the following weeks, her prednisolone dosage was adjusted to 5–10 mg/day; valsartan was maintained at 80 mg/day. However, her platelet count continued to range from 15–40 x 10^3/mm^3. After discussion with the patient, oral eltrombopag was chosen and begun at 75 mg/day instead of splenectomy.

At the start of eltrombopag, a complete blood count showed a white blood cell count of 7.9 x 10^3/mm^3 (normal range 4–11 x 10^3/mm^3), hematocrit 42.2% (36–48%), and platelet count 11 x 10^3/mm^3 (150–400 x 10^3/mm^3; Table 1). After seven doses of eltrombopag, the patient came to the emergency department because of persistent nausea and vomiting. Her body temperature was 37.9°C, heart rate 90 beats/minute, respiration rate 18 breaths/minute, and blood pressure 166/96 mm Hg. A complete blood count showed a white blood cell count of 19.8 x 10^3/mm^3 (segmented neutrophils 86% [normal range 45–75%], lymphocytes 8% [20–45%]), hematocrit 43.5%, and platelet count 136 x 10^3/mm^3. Her blood urea nitrogen (BUN) was 40 mg/dl (7–20 mg/dl), serum creatinine 3.86 mg/dl (0.2–1.5 mg/dl),

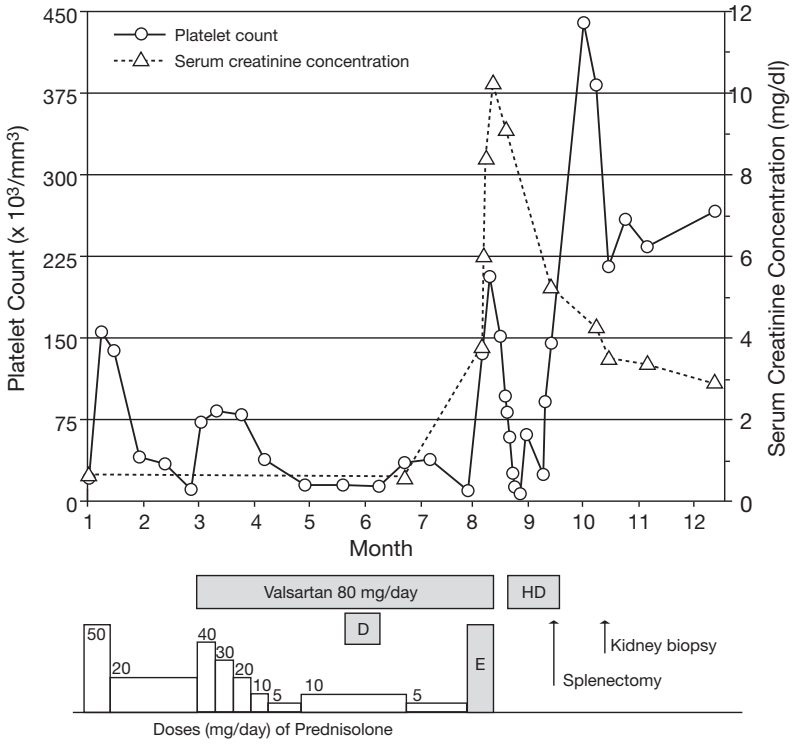

Figure 1. Time course of the patient's platelet count and serum creatinine concentration over time, with drug therapy (including prednisolone dosing) and clinical management shown. D = diclofenac 25 mg 3 times/day for 10 days; E = eltrombopag 75 mg/day for 7 days; HD = hemodialysis 3 times/week for 4 weeks.

sodium 132 mEq/L (135–147 mEq/L), potassium 4.2 mEq/L (3.4–4.7 mEq/L), and albumin 3.9 g/dl (3.7–5.3 g/dl). Urinalysis revealed microscopic sediments of 10–15 red blood cells/high-power field. Eltrombopag was discontinued, and the patient was admitted to the hospital and treated with adequate hydration (day 0).

On day 2, the patient's renal failure progressed with a BUN of 72 mg/dl, serum creatinine 8.44 mg/dl, and uric acid 11.9 mg/dl (normal range 1.8–6.2 mg/dl). A single-voided urine protein level was 123.4 mg/dl and urine creatinine level was 52.6 mg/dl, yielding a random urine protein: urine creatinine ratio of 2.35 (normal < 0.2). Her daily total urine output was 630 ml. Her BUN and serum creatinine progressed to peak levels on day 6 (102 mg/dl and 10.28 mg/dl, respectively), whereas her albumin decreased to 3.2 g/dl. Emergency hemodialysis using a temporary vascular access was arranged. During hemodialysis (days 6–38, 3 times/wk), neither eltrombopag nor prednisolone was used, and a complete blood count revealed progressive anemia and thrombocytopenia with a nadir hematocrit of 20.4% and a platelet count of 8 x 10^3/mm^3 (both on day 21). Corticosteroid-resistant ITP was considered, and a laparoscopic splenectomy was performed on day 35. After the operation, the patient's platelet count returned to 146 x 10^3/mm^3 and hematocrit to 28.7% (day 38). The patient was discharged on day 39, and hemodialysis was discontinued on day 44.

At follow-up on day 56, the patient's platelet count was 440 x 10^3/mm^3, which stabilized over the next 2 weeks (> 200 x 10^3/mm^3). Arrangements were made for the patient to undergo a kidney biopsy on day 70. At that time, her complete blood count revealed a white blood cell count of 11 x 10^3/mm^3, hematocrit 30.2%, and platelet count 216 x 10^3/mm^3; her BUN and serum creatinine levels were 54 mg/dl and 3.55 mg/dl, respectively. Her albumin level recovered to 4.2 g/dl. A single-voided urine analysis showed a protein level of 110 mg/dl and urine creatinine of 40.9 mg/dl, yielding a single-voided urine protein:urine creatinine ratio of 2.69.

The kidney biopsy result indicated a total of 26 glomeruli, with 20 of the 26 samples displaying global sclerosis obsolescence and 5 of 26 samples showing segmental sclerosis obsolescence (Figure 2). Wrinkle changes and "collapse" of glomerular basement membranes were also noted, but there was no glomerular proliferation, mesangial expansion, or mesangiolysis, and no evidence of microangiopathy. The tubulointerstitial tissue showed focal parenchymal fibrosis (estimated 40% of parenchyma involved), mononuclear cell infiltration, and atrophic tubular changes. The immunofluorescent examination showed no IgG, IgA, IgM, or C1q/C3/C4 deposition.

The features of the glomeruli on biopsy were typical for FSGS categorized as collapsing variant by the Columbia proposal.[4] On correlation with the patient's entire disease course, eltrombopag-induced FSGS was presumptively diagnosed. At follow-up on day 210, her ITP had resolved (platelet count 280 x 10^3/mm^3), and her renal function was stable, with serum creatinine levels ranging from 2.8–3.0 mg/dl and albumin levels above 4.0 g/dl.

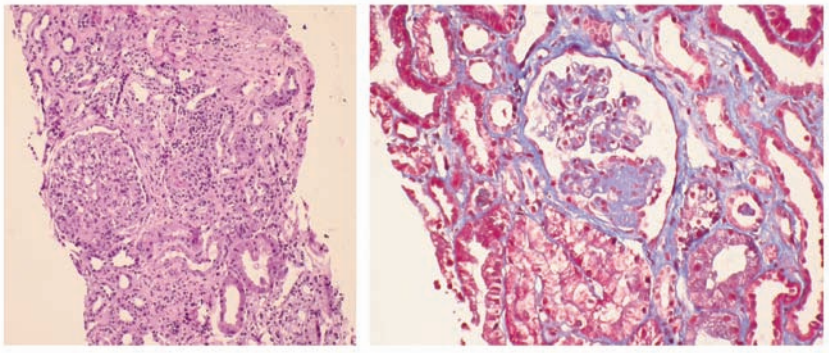

Figure 2. Photomicrographs of kidney biopsy specimens show global sclerosis obsolescence (left; original magnification x 40, hematoxylin-eosin stain), which appeared in 20 of 26 samples, and segmental sclerosis obsolescence (right; original magnification x 400, Masson trichrome stain), which appeared in 5 of 26 samples.

Discussion

In a phase I study of eltrombopag, reported adverse events merely consisted of some subjective discomfort such as headaches, abdominal pain, and sore throat.[5] In phase II studies, some nonspecific symptoms were reported such as influenza-like illness, arthralgia, myalgia, constipation, diarrhea, and pruritus.[1, 2] However, at doses of 30–75 mg used in clinical trials, eltrombopag therapy was discontinued in three patients because of abdominal pain and ascites (30 mg), neutropenia (50 mg), and retinal exudates (75 mg).[2] Another major adverse event was recently reported in a man who experienced reversible acute renal failure after introduction of and rechallenge with eltrombopag.[3] However, as mentioned earlier, a kidney biopsy was not performed. To our knowledge, our case report is the first report of a patient who experienced acute renal failure and proteinuria concomitant with a pathology of FSGS after treatment with eltrombopag.

The pathology of segmental sclerosis in kidneys was first described in autopsy specimens of children dying of nephrotic syndrome due to lipoid nephrosis.[6] By definition, a glomerular sclerosis obsolescence means hyalinosis and lipid deposits within the tuft and of some pseudotubules without affecting Bowman's space. In FSGS, some glomeruli have global sclerosis obsolescence and some have segmental sclerosis obsolescence. In 1970, FSGS was considered a distinct clinicopathologic spectrum for its manifestation of varying degrees of proteinuria, corticosteroid resistance, and progression of renal failure.[7] Drug-related FSGS was not common, and it was most notoriously reported with interferon,[8] lithium,[9] and pamidronate.[10] It is difficult to document eltrombopag-induced FSGS because eltrombopag is used in patients with thrombocytopenia, and some of them also have coagulopathy. Therefore, kidney biopsy cannot be performed. Our patient's case is rare and is valuable in helping elucidate the nephropathy of acute renal failure after eltrombopag use. In our patient, the morphologic features were consistent with collapsing variant FSGS, which was also noted in pamidronate-associated FSGS.[10]

Potential mechanisms of eltrombopag-related kidney injury remain speculative. Eltrombopag enhances proliferation and differentiation of megakaryocytes in human bone marrow by binding to the transmembrane domain of the thrombopoietin receptor with high specificity. It results in the activation of the Janus kinase–signal transducer and activator of transcription 5 (JAK-STAT5) pathway and augments the signals of downstream phosphoinositide-3 kinases (PI3K) and mitogen-activated protein kinases (MAPK)–extracellular signal-regulated kinases (ERK).[11] In animal models, the activated megakaryocytes release transforming growth factor-β,[12] which also activates MAPK-ERK and PI3K pathways in podocytes and leads to podocyte apoptosis and the development of glomerulosclerosis.[13] Massive proteinuria and FSGS follow. In our patient, massive proteinuria and a rapid clinical course of renal failure after administration of eltrombopag were consistent with a pathologic diagnosis of FSGS.

A thorough review of our patient's drug therapy revealed diclofenac and valsartan as possible agents causing her renal failure apart from eltrombopag. Diclofenac was used for only 10 days, and the interval between discontinuation of diclofenac and development of renal failure (> 2 mo) much exceeded its half-life (2–12 hrs). Furthermore, a normal serum creatinine concentration (0.62 mg/dl; Table 1 and Figure 1) was documented after 4 months of valsartan use. A rise in the serum creatinine concentration generally begins within a few days after initiation of valsartan[14]; however, a delayed effect on renal function has not been reported. More direct evidence was that the patient's serum creatinine concentration surged abruptly just after introduction of eltrombopag (taken for 7 days). Use of the Naranjo adverse drug reaction probability scale[15] indicated a probable relationship (score of 7) between the patient's development of acute renal failure and eltrombopag therapy. Evidence supporting our inference includes the temporal relationship between introduction of eltrombopag and development of acute renal failure, improvement of renal function after discontinuation of eltrombopag, exclusion of other causes of renal failure, similarity with a previous case report,[3] and confirmed nephropathy by renal biopsy.

Eltrombopag is absorbed rapidly after oral administration, with its peak plasma concentration within 2–6 hours.[16] It has a high plasma protein–binding rate (> 99%), is extensively metabolized in the liver, is eliminated in feces (59%) and kidneys (31%), and has a half-life of 26–35 hours in patients with ITP.[16] The thrombopoietin receptor is believed to be expressed in bone marrow and restricted to $CD34^+$ cells, megakaryocytes, platelets, and endothelial and dendritic cells,[17, 18] but it is not present in normal kidney tissue.

Thus, the underlying mechanism for eltrombopag-related renal failure remains unclear and needs further study. In our patient, however, the surgical intervention (splenectomy) eliminated her thrombocytopenia and required her to receive a kidney biopsy. This supports the idea that splenectomy remains an effective treatment for corticosteroid-refractory ITP, even in the critical clinical setting of renal failure, dialysis, and thrombocytopenia.

Conclusion

Our patient experienced acute renal failure, proteinuria, and hypoalbuminemia after treatment with eltrombopag. Although the mechanism for eltrombopag-related renal failure is unclear, discontinuation of the drug and temporary dialysis rescued this patient from end-stage renal disease. This case report may serve to inform clinicians about the possible severe renal adverse effects of eltrombopag before commencing with more extensive clinical use in the future.

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