## CASE REPORT

# Sunitinib-induced endocapillary proliferative glomerulonephritis with IgA2 deposit in addition to thrombotic microangiopathy: a case report

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## Abstract

**Background**  Sunitinib, a multi-targeted tyrosine kinase inhibitor, is used as a second-line therapy for gastrointestinal stromal tumors (GIST) resistant to imatinib. However, its impact on the vascular endothelial growth factor (VEGF) pathway can lead to significant toxicities, including hypertension and thrombotic microangiopathy (TMA).

**Case presentation**  This case report describes a unique instance of a patient with metastatic GIST who developed endocapillary proliferative glomerulonephritis (EPGN) with IgA2 deposits and TMA following sunitinib treatment. The patient presented with severe hypertension, nephrotic syndrome, and acute kidney injury. Renal biopsy confirmed the diagnosis, revealing IgA2 deposits, which are not commonly associated with TMA. Discontinuation of sunitinib led to a rapid improvement in renal function and proteinuria. The potential mechanisms underlying sunitinib-induced glomerular injury may involve the blockade of VEGFR-1, affecting immune cell recruitment and function, and the disruption of the nitric oxide and endothelin systems, leading to endothelial damage and immune dysregulation. Management of these toxicities requires a personalized approach, with options ranging from symptomatic relief to drug discontinuation. The use of endothelin receptor antagonists and other therapeutic alternatives for GIST management is discussed.

**Conclusions**  This case highlights the complex interplay between the therapeutic effects of sunitinib and its potential renal and cardiovascular toxicities, emphasizing the need for close monitoring and effective management strategies to optimize patient outcomes.

**Keywords**  Sunitinib, Vascular endothelial growth factor blockade, Thrombotic microangiopathy, IgA2 deposit, Case report

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## Background

Sunitinib, a multi-targeted tyrosine kinase inhibitor (TKI), is commonly used as a second-line therapy for patients with gastrointestinal stromal tumors (GIST) who have developed resistance to imatinib [1]. While it has shown efficacy in prolonging progression-free survival, sunitinib's impact on the vascular endothelial growth factor (VEGF) signaling pathway can lead to a variety of toxicities, most notably hypertension and thrombotic microangiopathy (TMA) [2–4]. This report presents a comprehensive analysis of a case where sunitinib induced both endocapillary proliferative glomerulonephritis (EPGN) with IgA2 deposit and TMA, emphasizing the complex interplay between the drug's therapeutic effects and its potential side effects.

## Case presentation

A 59-year-old male was initially diagnosed with GIST in 2012. He underwent subtotal gastrectomy and initiated treatment with imatinib, which he tolerated well for seven years. In 2019, with the detection of GIST metastasis, the patient underwent splenectomy and radiofrequency ablation of the liver metastases. Subsequently, the patient was switched to sunitinib as a second-line therapy. Three years into sunitinib treatment, the patient developed severe hypertension (180/120 mmHg) and rapidly progressive lower limb edema, which eventually generalized to the entire body. He exhibited no fever and signs of infection in the respiratory tract, gastrointestinal tract, or skin before the onset of edema. Further clinical examination revealed effusions in the pericardial, pleural, and abdominal cavities, indicative of a severe nephrotic syndrome, and acute kidney injury stage 2 (AKI).

Laboratory tests at the time of presentation revealed a white blood cell (WBC) count of $2.2 \times 10^9$/L, hemoglobin level of 6.6 mg/dL, platelet count of $180 \times 10^9$/L, serum albumin of 1.75 mg/dL, and serum creatinine of 2.59 mg/dL. The urinary protein level was elevated at 8.33 g/day, with red blood cells (RBCs) in the urinary sediment at 36.8/HP. Peripheral blood schistocytes were present at 1.7% of total RBCs, Serum complement levels were as follows: C3 at 0.671 g/L and C4 at 0.243 g/L. Further laboratory results showed a C-reactive protein level of 2.08 mg/L, complement factor H level at 442.2 mg/L, lactate dehydrogenase (LDH) at 459 U/L, and von Willebrand factor collagen-binding activity measured at 71%. Notably, no monoclonal protein bands were detected in serum and urine immunofixation electrophoresis. The patient underwent a comprehensive autoimmune disease screening, including tests for antinuclear antibodies (ANA), anti-double-stranded DNA (anti-dsDNA) antibodies, antineutrophil cytoplasmic antibodies (ANCA), anti-glomerular basement membrane (anti-GBM)

antibodies, and anti-phospholipase A2 receptor (anti-PLA2R) antibodies. All these tests yielded negative results. The results of the viral illness screening showed the presence of EBV-IgG and CMV-IgG with EBV-IgM and CMV-IgM testing negative. Then patient was positive for antibody to hepatitis B surface antigen, suggesting immunity or vaccination, while all other markes were negative. The patient exhibited negative hepatitis C antibody, normal liver function test results, and no signs of cirrhosis. The serum cryoglobulin testing was negative. Renal biopsy immunofluorescence staining showed $IgA_2$ 3+, $C_3$ 2+, with negative $IgA_1$, IgG and its subtypes ; both kappa and lambda staining positive with strong intensity 3+ (Supplemental Fig. 1). Light microscopy showed segmental mesangiolysis, double contours of the glomerular basement membranes, endocapillary and mesangial deposits with 'pseudo-thrombi'; electron microscopy showed mesangial and sub-endothelial deposits with expansion of the lamina rara interna, no substructual deposits were observed, all leading to a diagnosis of TMA and EPGN with $IgA_2$ deposit which is associated with sunitinib (Fig. 1).

Sunitinib was discontinued, and the patient's progression-free survival (PFS) with sunitinib was 3 years. Supportive therapies were administrated to alleviate edema and hypertension. An angiotensin receptor neprilysin inhibitor was initiated three months after hospital discharge. During the six-month follow-up period, there was a rapid recovery of proteinuria and renal function (Fig. 2).

Unfortunately, despite the decrease in urinary total protein to 0.39 g/24 h with no hematuria, the reduction in serum LDH and creatinine levels to 169 U/L and 121 μmol/L (estimated GFR of 52.3 ml/min per 1.73m$^2$), respectively, along with the increase in albumin concentration to 37.6 g/L, a recurrence of GIST was detected during routine CT examination. Whole exome sequencing revealed the presence of mutations in both the KIT and PDGFR genes. The patient underwent another liver interventional ablation procedure and resumed treatment with imatinib, which led to a reduction in the size of the GIST. After he resumed imatinib, his kidney function and proteinuria remained stable within 12-month follow-up.

## Discussion and conclusions

The use of sunitinib in the treatment of metastatic GIST and other malignancies (e.g. renal carcinoma and advanced pancreatic endocrine tumor) has been well-established, particularly in patients who have developed resistance to imatinib. By targeting c-Kit and PDGFR, sunitinib also exerts its effects by inhibiting the VEGF pathway (mainly via blockade of VEGFR-2), which is
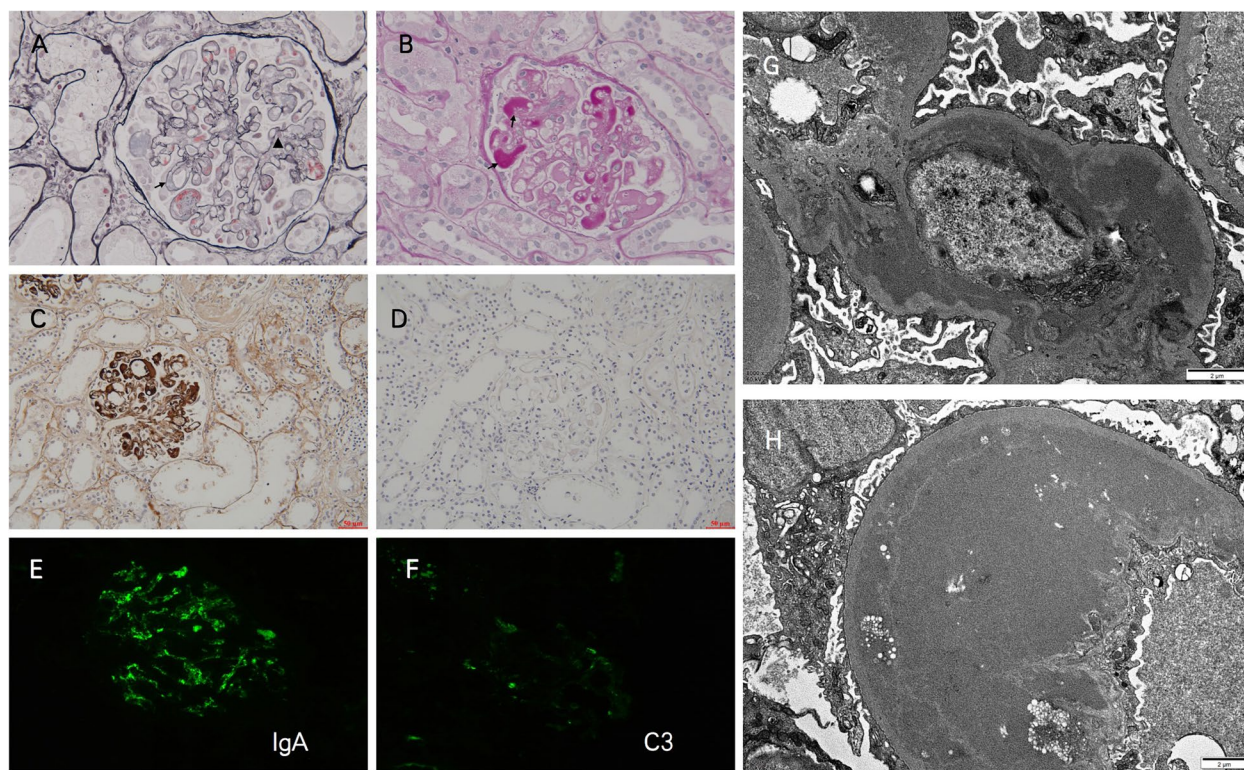
**Fig. 1** The kidney biopsy results of the patient. **A** PASM-Masson (200X) stain shows segmental mesangiolysis (triangle) and double contours (arrow) of the glomerular basement membranes. **B** PAS (200X) stain shows endocapillary and mesangial PAS positive deposits with 'pseudo-thrombi'(arrow). C&D. IgA subtype immunohistochemical stain: The endocapillary and mesangial deposits were positive for IgA2 (**C**) but negative for IgA1 (**D**). E&F. Immunofluorescence microscopy shows strong (+++) IgA (**E**, 200X) and moderate (+~++) C3 (**F**, 200X) mesangial and peripheral capillary loop elongated segments of deposits. G&H. Electron microscopy shows mesangial (**G**, 8000X) and sub-endothelial deposits (**H**,8000X) and expansion of the lamina rara interna (**H**, 8000X)

crucial for maintaining vascular permeability and blood pressure regulation. This dual action is beneficial for controlling tumor growth and angiogenesis; however, it can also lead to a spectrum of renal toxicities, including TMA which has been well-documented [5–7]. Additionally, histological evaluations of renal biopsies from patients undergoing VEGF-targeted therapy have revealed a range of glomerular lesions, including minimal change disease, collapsing-like focal segmental glomerulosclerosis, immune complex-associated focal proliferative glomerulonephritis, and cryoglobulinemic glomerulonephritis [3, 4, 8]. These findings underscore the multifaceted impact of VEGF inhibition on renal function and structure. In this report, we describe a unique case of a patient who developed EPGN with IgA2 deposit alongside TMA as a result of sunitinib treatment. The diagnosis was confirmed through renal histopathology. Notably, the patient experienced a swift resolution of proteinuria and improvement in renal function following the discontinuation of sunitinib.

In the context of sunitinib-induced glomerular injury, the blockade of VEGFR-1 may also play a significant role in the observed pathology. VEGFR-1, also known as FLT1, is expressed on various cell types, including monocytes and macrophages, and its inhibition by sunitinib could potentially influence the recruitment and function of inflammatory cells within the kidney [9, 10]. This disruption in the immune response to glomerular injury may contribute to the development of IgA2 deposits observed in the case. The presence of IgA2 deposits in the patient's glomeruli could indicate an immune-mediated component or a secondary phenomenon related to the endothelial injury caused by sunitinib. The co-occurrence of TMA and these immune complex deposits suggests a complex interplay between the drug's vascular effects and the patient's immune system. The exact mechanisms by which VEGFR-1 inhibition leads to such immune dysregulation and subsequent IgA2 deposition require further investigation but could involve alterations in the local renal environment that promote the interaction between immune cells and the glomerular basement membrane, resulting in the formation of immune complexes and subsequent inflammation and injury. IgA deposits are a key component in the pathology of infection-associated
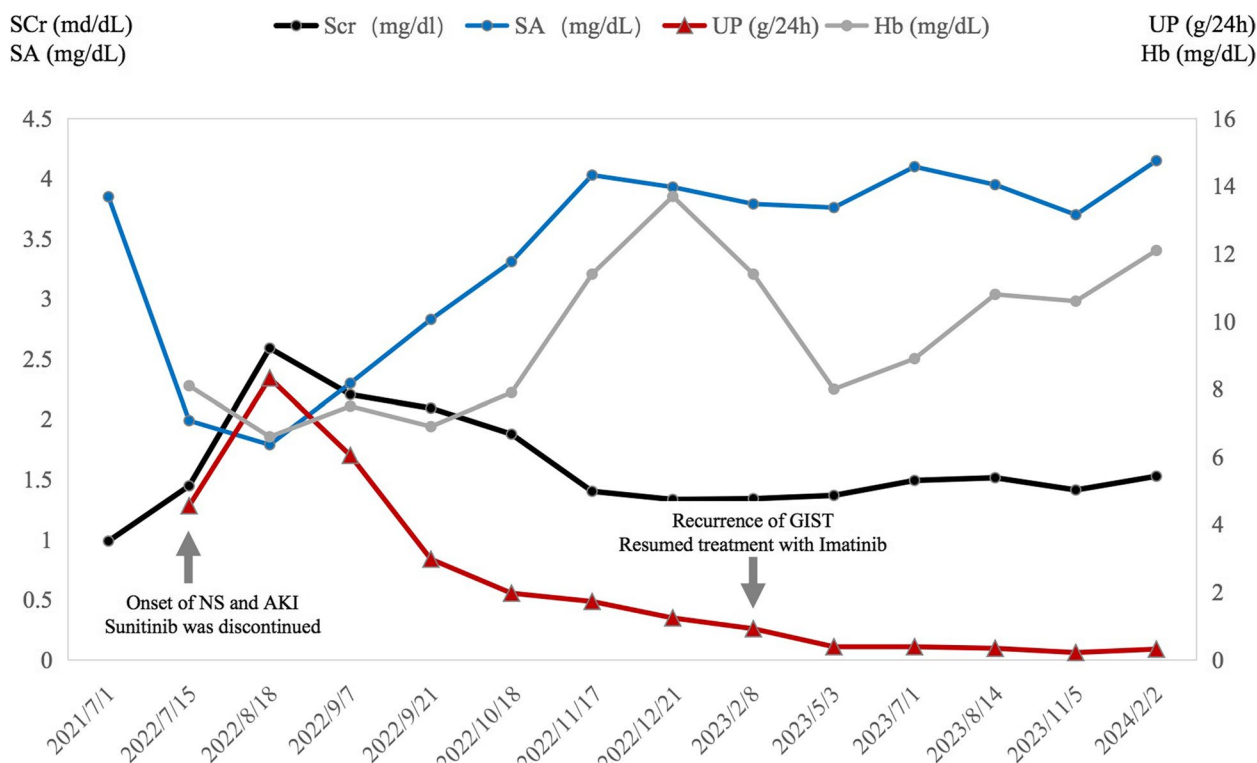
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**Fig. 2** The clinical trajectory of proteinuria, serum albumin, kidney function and hemoglobin level following sunitinib discontinuation, demonstrating significant improvement. After resume with imatinib, the clinical condition remained stable

glomerulonephritis (GN), especially when IgA predominates as the immunoglobulin involved. While primary IgA nephritis (IgAN) is marked by the presence of galactose-deficient IgA1 due to its serum predominance, IgA2 is notably more abundant in secretions and the colon, existing primarily as dimeric secretory IgA. In contrast, both monomeric IgA1 and IgA2 are commonly found in the serum. A comprehensive proteomic analysis of IgAN revealed that IgA1 was associated with heightened levels of complement activation, increased severity of mitochondrial damage, and considerable accumulation of extracellular matrix, while IgA2 subtype displayed proteome expression patterns akin to those of normal controls [11]. Notably, patients with post-MRSA infection GN exhibited substantially higher levels of IgA2 against *S. aureus* cell membrane antigens than those with primary IgAN [12].

Sunitinib is thought to reduce nitric oxide availability, potentially harming endothelial cells. This process disrupts the balance with the endothelin system, where endothelin-1 (ET-1) levels may rise, affecting renal function. ET-1 influences the reabsorption of sodium and water in the renal tubules, leading to volume expansion and increased blood pressure. It also interacts with the renin-angiotensin-aldosterone system, further regulating blood pressure and fluid balance [13]. Sunitinib exposure has also been observed to link to the downregulation of glomerular proteins crucial for kidney health in a dose-dependent manner, such as the expression of glomerular nephrin, Neph1, podocin, and endothelin-converting enzyme gene [5, 14]. This suggests that sunitinib may affect blood pressure at lower doses than those causing renal impairment, with functional changes in the glomerular filtration barrier contributing to proteinuria. Endothelin receptor antagonists, such as Bosentan and Ambrisentan, can block ET-1's effects, reducing vasoconstriction and blood pressure, and mitigating organ damage in kidney diseases such as IgA nephropathy and diabetes,. The potential use of endothelin receptor antagonists in mitigating these sunitinib associated toxicities is an area that warrants further exploration.

In managing sunitinib-associated toxicities, a personalized approach is essential. For patients with mild to moderate symptoms, symptomatic relief or temporary dose adjustment may be sufficient. However, in severe cases, discontinuation of sunitinib may be necessary to prevent further complications [17, 18]. The availability of other therapeutic options, such as ripretinib and avatrombopeg, the primary target of which are not VEGFR but a switch pocket of c-Kit and PDGFRα and the PDGFRα

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with the D842V mutation, respectively, offering alternative strategies for GIST management albeit with their own set of considerations [1].

The case presented in this report highlights the intricate relationship between the therapeutic benefits of sunitinib and its potential to induce renal and cardiovascular toxicities. The rapid improvement following sunitinib withdrawal underscores the drug's role in the observed pathologies. As the search for novel therapeutics continues, so too does the need for strategies to alleviate the side effects of current treatments. Close monitoring of renal function and vigilant management of sunitinib-associated toxicities are essential for optimizing patient outcomes. Further research is crucial to elucidate the mechanisms of sunitinib-induced toxicities and to identify potential therapeutic interventions that can improve the quality of life for patients with GIST.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-024-03732-6.

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Supplementary Material 1.

Supplementary Material 2.

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### Availability of data and materials
All data supporting the findings of this study are available within the paper and its Supplementary Information.

### Data availability
No datasets were generated or analysed during the current study.

## Declarations

### Ethics approval and consent to participate
The study was approved by the Ethics Committee of Peking University First Hospital (2017[1280]). The authors declare that they have obtained consent from the patient reported in this article for publication of the information about him that appears within this case report.

### Consent for publication
Informed consent was obtained in both written and verbal format from the patient to publish this case report and any accompanying images.

### Competing interests
The authors declare no competing interests.

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