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## An Interesting Case: Sunitinib-Induced Microangiopathic Hemolytic Anemia and Nephrotic Syndrome

İlginç Bir Olgu: Sunutinib İlişkili Mikroanjyopatik Hemolitik Anemi ve Nefrotik Sendrom

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### To the Editor,

Sunitinib is a heterodimeric oral tyrosine kinase inhibitor that targets a large number of receptors, including VEGFR and PDGFR. Anti-VEGF treatments can cause hypertension, proteinuria, neutropenia, anemia, and thrombocytopenia [1]. It has been shown in animal experiments that vascular endothelial growth factor (VEGF) contributes to the repair of glomerular endothelium in experimental microangiopathia and anti-VEGF antibodies cause proteinuria by glomerular dissociation and downregulation of nephrin receptors [2]. The increase of VEGF levels in the blood 2-3 weeks after thrombotic microangiopathy (TMA) supports the idea of VEGF-mediated repair of the glomerular endothelium [3]. Anti-VEGF treatment may cause thrombosis due to the procoagulant phospholipids released as a result of the disruption of plasma membrane integrity and due to the decrease in the levels of nitric oxide and prostaglandin I<sub>2</sub>, which contributes to the production of VEGF [4].

A 54-year-old woman was receiving sunitinib for a metastatic gastrointestinal stromal tumor (GIST). She presented to the clinic 8 months after the initiation of therapy with

microangiopathic hemolytic anemia (MAHA) and nephrotic syndrome (NS). Proteinuria (3.5 g) was detected in the 24-h urine collection. The platelet count was 35000/mm<sup>3</sup>, white blood cell count was 6700/mm<sup>3</sup>, and hemoglobin was 7 g/dL. In the blood smear, normochromic normocytic anemia, diffuse schistocytes, and fragmented erythrocytes were present (Figure 1). Sunitinib was discontinued and methylprednisone was

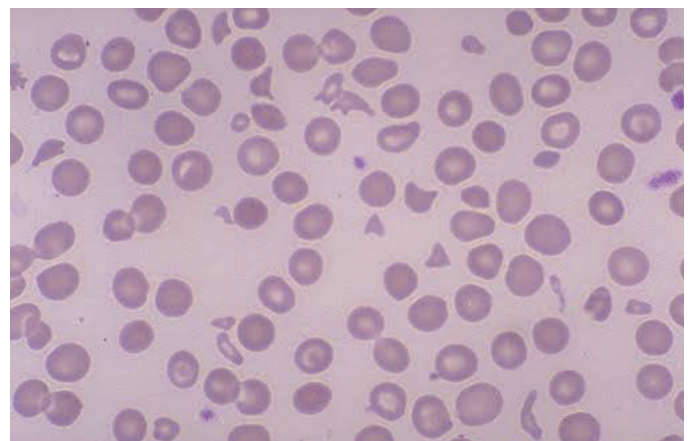


Figure 1. Peripheral blood smear showed rare schistocytes and mild thrombocytopenia.

started with the resolution of symptoms. MAHA and NS relapsed with re-challenge with sunitinib. Symptoms resolved after the discontinuation of sunitinib.

Bollee et al. published the case of a patient with malignant skin hidradenoma who developed hypertension and proteinuria. Renal biopsy showed microangiopathic anemia [5]. A second reported case involved metastatic renal cell carcinoma; hypertension, nephrotic proteinuria, azotemia, creatinine increase, oliguria, thrombocytopenia, and anemia developed and kidney biopsy showed focal segmental glomerulosclerosis and TMA. After the cessation of sunitinib, the patient recovered [6]. A third case involved hypertension and proteinuria; a kidney biopsy showed TMA. This patient improved with the cessation of sunitinib and steroids [7]. In a fourth case of metastatic GIST, the patient presented with hypertension, loss of vision, seizures, anemia, thrombocytopenia, acute renal failure, and posterior leukoencephalopathy with schistocytes in the blood smear. After the cessation of sunitinib, he improved [8]. A fifth case involved metastatic renal cell carcinoma with nephrectomy as well as nephrotic proteinuria. TMA was confirmed by kidney biopsy. Kidney functions and proteinuria almost entirely improved after stopping sunitinib and starting steroids [9]. In another case of metastatic renal cell carcinoma, three weeks after the start of sunitinib, hypertension, proteinuria, thrombocytopenia, and anemia developed. Schistocytes were noticed in the blood smear. The patient's symptoms improved after the discontinuation of sunitinib [10].

In contrast to many cases discussed, the case that we present here was not a case of renal cell carcinoma but rather metastatic GIST. Generally, sunitinib is used in the first line of treatment for renal cell carcinoma, but it is used after imatinib in GIST treatment, as we did for this patient. Therefore, it is interesting that this toxicity developed after the second tyrosine kinase inhibitor. In this regard, it is an infrequent phenomenon. Similar to other patients mentioned, hypertension was detected in our patient before the development of toxicity. As in most of the other cases, our patient's condition improved almost completely after stopping sunitinib. Our patient did not undergo a kidney biopsy because she had thrombocytopenia and therefore rejected the kidney biopsy. Furthermore, the diagnosis was made clinically, so a biopsy was not required.

The use of anti-VEGF drugs has become widespread and there are limited published data about such severe toxicities (Table 1). For this reason, we wanted to present this rare case that we found and we believe that it can contribute to the literature.

**Keywords:** Sunitinib, Nephrotic syndrome, Hemolytic anemia, Microangiopathic hemolytic anemia

**Table 1. Naranjo algorithm assessment.**

<b>Naranjo Algorithm</b>	
2020-03-03 11:30:14	
1. Are there previous conclusive reports on this reaction?	No [0]
2. Did adverse event appear after the suspected drug was given?	Yes [+2]
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	Yes [+1]
4. Did the adverse reaction appear when the drug was readministered?	Yes [+2]
5. Are there alternative causes that could have caused the reaction?	No [+2]
6. Did the reaction reappear when a placebo was given?	Do not know or not done [0]
7. Was the drug detected in any body fluid in toxic concentrations?	Do not know or not done [0]
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	No [0]
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	No [0]
10. Was the adverse event confirmed by any objective evidence?	Yes [+1]
→ Naranjo Score	8
→ Adverse Drug Reaction	PROBABLE

*Cut-off points include:*  
 ≤0 DOUBTFUL ADR  
 1-4 POSSIBLE ADR  
 5-8 PROBABLE ADR  
 ≥9 DEFINITE ADR

**Anahtar Sözcükler:** Sunitinib, Nefrotik sendrom, Hemolitik anemi, Mikroanjiyopatik hemolitik anemi

### Ethics

**Informed Consent:** Since the patient died, consent was not obtained.

### Authorship Contributions

Concept: V.H., S.P.; Analysis or Interpretation: V.H., S.P.; Literature Search: V.H., S.P.; Writing: V.H., S.P.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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## Kimura Disease Associated with Minimal Change Disease

### Minimal Değişiklik Hastalığı ile İlişkili Kimura Hastalığı

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#### To the Editor,

Kimura disease is a benign chronic inflammatory disease with unknown etiology, which usually presents with lymphadenopathies in the head and neck, peripheral blood eosinophilia, and elevated serum immunoglobulin E (IgE) levels. It is mostly observed in young males of Asian descent in the second and third decades of life, but sporadic cases in other ethnic groups have also been reported [1,2]. Here we present a patient with Kimura disease and concomitant nephrotic syndrome who presented with lymphadenopathies of atypical locations.

A 25-year-old male patient presented with new-onset hypertension, decreased urine output, and lower extremity swelling. His past medical history was unremarkable with no history of allergies. On examination, his blood pressure was 140/100 mmHg, heart rate was 90/min, and body temperature was 37 °C. He had bilateral 2+ pitting edema of the bilateral lower extremities and an enlarged, soft, nontender 3-cm left inguinal lymph node. Laboratory evaluation results were as follows: white blood cells, 6790/μL; eosinophils,

1280/μL (18.9%); normal hemoglobin level and platelet count; serum creatinine, 0.66 mg/dL; urea, 26 mg/dL; albumin, 2.4g/dL; triglyceride, 295mg/dL; erythrocyte sedimentation rate, 81 mm/h; total IgE, 3318 kU/L (<87). Urinalysis showed 3+ protein and the spot urine protein/creatinine ratio was 7819 mg/g. Viral serologies and rheumatologic markers were negative. Serum C3, C4, IgG, IgA, and IgM levels were also normal. A percutaneous renal biopsy was performed for nephrotic syndrome. Pathological examination of the specimen revealed no significant changes by light microscopy and was negative for immunofluorescence, indicating minimal change disease. The patient was started on low-dose perindopril with a gradual increase to 10 mg/day. Positron emission tomography-computed tomography (CT) performed to assess any associated malignancy showed hypermetabolic activity in the inguinal and right external iliac regions (SUV<sub>max</sub>: 2.5). The left inguinal lymph node was excised. The pathology was reported to be consistent with Kimura disease (Figure 1). During follow-up, his creatinine levels progressively increased to 2 mg/dL and he was started on methylprednisolone at 1 mg/kg. At week 1, his creatinine regressed to baseline. At week 3, complete remission of proteinuria was achieved and