Sunitinib-Induced Microangiopathic Hemolytic Anemia: A Case Report

Serdal Korkmaz¹, Saadettin Kılıçkap², Hatice Terzi³, Mehmet Sencan¹

ABSTRACT

Thrombotic thrombocytopenic purpura (TTP) is a particular form of thrombotic microangiopathy typically characterized by thrombocytopenia, microangiopathic hemolytic anemia, fever, neurological abnormalities, and renal dysfunction. TTP requires a rapid diagnosis and an adapted management in emergency. Daily sessions of therapeutic plasma exchange (TPE) remain the basis of management of TTP. Also, TTP is a rare disease that is fatal if it is not treated. We describe a case of a 60-year-old woman who complained of hematuria and right lumbar pain and was diagnosed clear cell renal carcinoma. The patient progressed with interferon-alpha (IFN-α) therapy, and she was treated with sunitinib. At 8 weeks after the therapy, the patient presented with pallor, weakness, and widespread ecchymosis. After evaluation of clinical and laboratory findings, the patient was diagnosed as TTP. The drug was discontinued, and her symptoms improved.

Key words: Renal cell carcinoma, sunitinib, hemolytic anemia

INTRODUCTION

Renal cell carcinoma (RCC) is the most common cancer of the kidney. Most patients who are diagnosed with RCC present with metastatic disease (1). Immunotherapy has been the standard treatment in advanced RCC during the past two decades. But, targeted therapies have changed the treatment landscape for patients with metastatic RCC. One of them, sunitinib, is an orally administered multitargeted tyrosine kinase inhibitor that was approved as first- and second-line treatment of metastatic RCC (2).

Sunitinib inhibits not only vascular endothelial growth factors (VEGF) but also other tyrosine kinases, including platelet-derived growth factor receptors (PDGFR-α and PDGFR-β), stem cell factor receptor (KIT), and FMS-like tyrosine kinase-3 receptor (3). The most common side effects of sunitinib treatment are fatigue/asthenia, anorexia/loss of appetite, hypothyroidism, hand-foot syndrome, stomatitis, taste changes, diarrhea/abdominal pain, myelosuppression, and hypertension. Herein, we reported a case that developed thrombotic thrombocytopenic purpura (TTP) under sunitinib.

CASE REPORT

A 60-year-old woman was admitted with hematuria and right lumbar pain to our clinic. Physical examination revealed a mass on the right lumbar region. Serum biochemistry was unremarkable. The level of her hemoglobin was 12.2 gr/dL. Her abdomen ultrasonography showed a mass with a diameter of 10x13x14 cm on the right kidney. Radical nephrectomy was carried out, and she was diagnosed as clear cell RCC. The patient was treated with interferon-alpha (IFN-α) 10 mu/m² three times in a week. After 3 months, she complained of non-productive cough, loss of appetite, and weight loss. Her chest computed tomography revealed multiple nodules with a diameter of 2.5 cm on bilateral pulmonary parenchyma and pleura, and there was also pleural effusion on the right hemithorax in a 2-cm width. Her complete blood count was within the normal range (hemoglobin 13 g/dL, white blood cell count 6.87×10³/µL, and platelet count 354×10³/µL). The treatment was changed with sunitinib 50 mg once daily for 4 weeks followed by a 2-week rest.

At 8 weeks after the therapy, the patient presented with pallor, weakness, and widespread ecchymosis. There were no any neurological symptoms. She did not receive any concomitant medications during the treatment period. Serum biochemistry and complete blood count revealed hemoglobin as 9.4 g/dL, hematocrit as 27.4%, white blood cell count as 3.8×10³/µL, platelet count 55×10³/µL, lactate dehydrogenase (LDH) as 530 IU/L, indirect bilirubin as 1.9 mg/dL, and reticulocyte count as 8.2%. Mean platelet volume was 8.5 fL (normal range: 6.85–11 fL). Both direct and indirect Coombs tests were negative. Also, these laboratory findings have been summarized in Table 1. Peripheral blood film reflected thrombocytopenia, with evidence of schistocytosis (Figure 1). Other laboratory

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investigations yielded normal renal and liver function tests, a normal coagulation screen, and a normal electrolyte profile. She was diagnosed as TTP. There were no any to use of another medical drugs, and diagnosis viral and bacterial infection disease. Sunitinib was withdrawn. After 5 days, all laboratory parameters rapidly improved and returned to baseline values.

**DISCUSSION**

RCC is accounts for 85% of all renal neoplasms and 3% of all adult malignancies (4). Currently, the standard therapy for metastatic RCC is multitargeted therapy, including sunitinib and sorafenib or mTOR inhibitors, such as temsirolimus.

Hematologic toxicity is the most common toxicity of many chemotherapeutic agents and targeted therapy. But, it usually appears due to myelosuppression. Microangiopathic hemolytic anemia is, however, a very rare toxicity. Although the majority of cases has no evident triggering event, several etiologic causes (especially drugs) have been identified. The toxicity was described for many chemotherapeutic agents, including mitomycin C, bleomycin, cisplatin, and gemcitabine (5, 6). But, very rare case reports are available about sunitinib-induced microangiopathic hemolytic anemia (7).

In our case, the patient displayed microangiopathic hemolytic anemia after sunitinib (Sutent; Pfizer medical, Istanbul, Turkey) therapy. Until now, the exact mechanism(s) of sunitinib-induced hemolytic anemia was not well understood. One of the possible mechanisms may be due to impaired circulating and/or coagulation system. Because sunitinib inhibits both VEGF and PDGFR, the inhibition may result in endothelial dysfunction due to subendothelial collagen damage (8, 9). The other mechanism may be explanation with a mild/moderate deficiency in circulating ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin-type 1 motif, member 13) activity levels due to the inhibition of the protease’s activity by IgG antibodies after the drug administration (10). But, we could not evaluate ADAMTS-13 activity in our case. Merely, the Naranjo adverse drug reaction probability scale revealed that it was probable that sunitinib might be responsible for this clinical situation (11).

In the literature reporting TTP-HUS associated with anti-VEGF agents, there are only three sunitinib-related TTP-HUS cases. Two of them were RCC (7, 12), and one was a gastrointestinal stromal tumor (13). The drug-related common side effects were hypertension, azotemia, and edema. But, our patient did not display any of these side effects but only had widespread ecchymosis. ADAMTS13 activity had been measured in two of these cases but not in the other one, as in our case. The medication had been ceased, and plasma exchange had been performed in all of them; recovery was the outcome. In our case, we had withdrawn sunitinib and had planned plasma exchange. Since improvement was very rapid both clinically and by laboratory tests, we decided to monitor the patient closely. As mentioned above, she became normal after 5 days of follow-up.

**CONCLUSION**

Thrombotic thrombocytopenic purpura may cause fatal outcomes, and sunitinib is a popular drug that is being used widely by oncologists currently. We presented a sunitinib-related TTP case and should confess that every clinician and patient might not be so lucky. So, physicians should consider this side effect in patients treated with sunitinib.

**Table 1. Laboratory test results of the patient**

<table>
<thead>
<tr>
<th>Tests</th>
<th>Pre-treatment</th>
<th>Under treatment</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (14-18 g/dL)</td>
<td>13.2</td>
<td>9.4</td>
<td>11.3</td>
</tr>
<tr>
<td>Hematocrit (42-52%)</td>
<td>39.8</td>
<td>27.4</td>
<td>34.5</td>
</tr>
<tr>
<td>Leukocyte (4-11×10^3/µL)</td>
<td>6.28</td>
<td>2.85</td>
<td>5.88</td>
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<tr>
<td>Platelet (150-400×10^3/µL)</td>
<td>194</td>
<td>55</td>
<td>276</td>
</tr>
<tr>
<td>LDH* (125-240 IU/L)</td>
<td>159</td>
<td>585</td>
<td>169</td>
</tr>
<tr>
<td>Total bilirubin (0.3-1.2 mg/dL)</td>
<td>1.2</td>
<td>2.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Indirect bilirubin (0.1-1.1 mg/dL)</td>
<td>1.0</td>
<td>1.8</td>
<td>0.9</td>
</tr>
<tr>
<td>Reticulocyte (0.5-2.5%)</td>
<td>Not performed</td>
<td>8.2</td>
<td>1.7</td>
</tr>
<tr>
<td>Direct /indirect Coombs tests</td>
<td>Not performed</td>
<td>-/-</td>
<td>-/-</td>
</tr>
</tbody>
</table>

*LDH: Lactate dehydrogenase
Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

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