


## Case Report

# Secondary immune thrombocytopenic purpura with renal cell carcinoma

Shigeaki Nakazawa,<sup>1,2</sup>  Masataka Kawamura,<sup>1,2</sup> Kosuke Nakano,<sup>1,2</sup> Norichika Ueda,<sup>1,2</sup> Hidefumi Kishikawa,<sup>1</sup> Hirokazu Kashiwagi,<sup>3</sup> Motohide Uemura,<sup>2</sup> Ryoichi Imamura,<sup>2</sup> Kenji Nishimura<sup>1</sup> and Norio Nonomura<sup>2</sup>

<sup>1</sup>Department of Urology, Hyogo Prefectural Nishinomiya Hospital, Nishinomiya, Hyogo, <sup>2</sup>Department of Urology, Osaka University Graduate School of Medicine, Suita, and <sup>3</sup>Department of Hematology and Oncology, Osaka University Graduate School of Medicine, Suita, Osaka, Japan

### Abbreviations & Acronyms

GPIIb/IIIa = glycoprotein IIb/IIIa  
ITP = immune thrombocytopenic purpura  
PA-anti-GPIIb/IIIa = platelet-associated anti-GPIIb/IIIa  
PLT = platelet  
RCC = renal cell carcinoma

**Correspondence:** Shigeaki Nakazawa M.D., Department of Urology, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan. Email: shigeakinakazawa@gmail.com

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

Received 5 February 2019; accepted 7 May 2019.  
Online publication 2 August 2019

**Introduction:** Several types of cancers are reported to induce secondary immune thrombocytopenia resembling immune thrombocytopenic purpura-like syndrome. However, renal cell carcinoma-induced immune thrombocytopenic purpura is an extremely rare phenomenon.

**Case presentation:** A 73-year-old male with right renal tumor and multiple enlarged lymph nodes presented severe thrombocytopenia, without bone or hepatic metastasis. Although platelet transfusion and high-dose immunoglobulin treatment were refractory, surgical resection of the tumor and lymph nodes promptly improved thrombocytopenia. After recurrence, he presented thrombocytopenia again. Tyrosine kinase inhibitor treatment was ceased due to uncontrollable hemorrhagic gastric ulcer. The patient eventually died of cancer 4 months after surgery. Flow cytometry analysis revealed the presence of integrin glycoprotein IIb/IIIa, which is a fibronectin/fibrinogen receptor on platelets and as an antigen in immune thrombocytopenic purpura.

**Conclusion:** To the best of our knowledge, this is the first reported case of renal cell carcinoma-induced immune thrombocytopenic purpura that demonstrates the presence of platelet-autoantibody glycoprotein IIb/IIIa.

**Key words:** cancer-induced immune thrombocytopenic purpura, platelet-autoantibody GPIIb/IIIa, renal cell carcinoma.

## Keynote message

Surgical resection of RCC promptly improved secondary ITP.

## Case presentation

A 73-year-old male was referred to the former hospital with complaints of gross hematuria and general fatigue. Laboratory tests revealed severe thrombocytopenia (PLT count  $16 \times 10^3/\mu\text{L}$ ) with mild anemia (hemoglobin 9.5 g/dL), normal prothrombin time, activated partial thromboplastin time, and fibrinogen degradation products. Contrast-enhanced computed tomography imaging revealed a right renal tumor measuring  $8 \times 7 \times 5$  cm and multiple lymphadenopathy without intravenous thrombus and hepatic metastasis (Fig. 1). Upon diagnosis of ITP, a total of 40 units of PLT were transfused to the patient, and a 5-day course of high-dose intravenous immunoglobulin was administered. However, these treatments were totally ineffective for the thrombocytopenia. The patient was transferred to our institution for further examination and treatment.

Upon hospitalization, laboratory tests revealed a low PLT count of  $28.0 \times 10^3/\mu\text{L}$  with elevated levels of lactate dehydrogenase (268 IU/L), creatinine (1.09 mg/dL), and C-reactive protein (12.9 mg/dL). Bone marrow aspiration and biopsy results revealed a normocellular marrow with megakaryocytic overgrowth and no signs of neoplastic infiltration or myelodysplasia. Bone scintigraphy was also normal.

On suspicion of cancer-induced ITP (i.e. secondary ITP or ITP-like syndrome), we decided to perform right nephrectomy and lymph node dissection. Since PLT count remained at a low level of  $12 \times 10^3/\mu\text{L}$ , 20 units of PLT were transfused on the day before surgery. However, on the day of



**Fig. 1** Contrast-enhanced computed tomography imaging reveals right renal tumor with multiple lymphadenopathy. Arrows indicate the right renal tumor and lymphadenopathy.

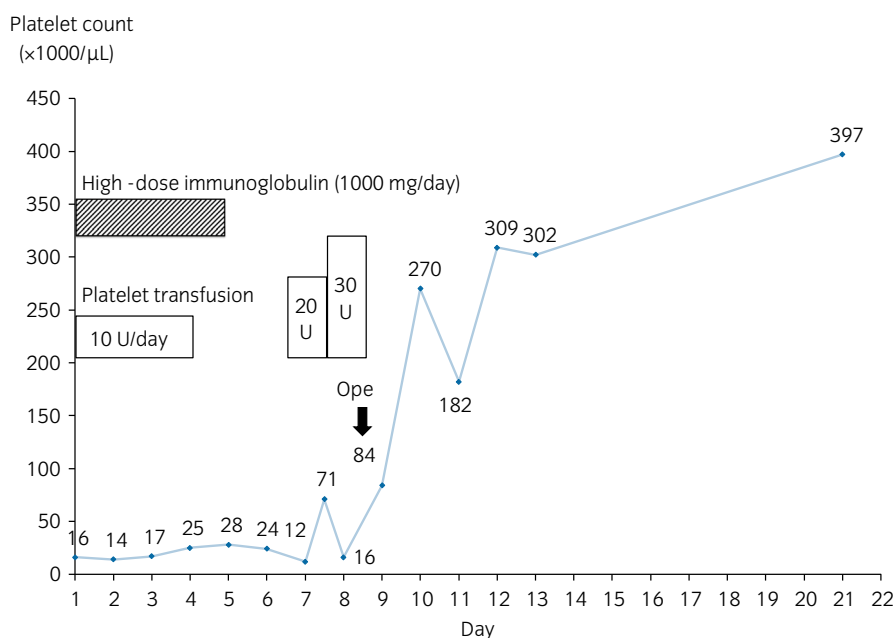
surgery, PLT count was still  $16 \times 10^3/\mu\text{L}$ , and an additional 30 units of PLT were transfused. Tumor resection and lymph node dissection were subsequently performed. The operation took 347 min, with intraoperative blood loss of 3250 mL.

Histopathologic examination revealed clear cell carcinoma (pT3a, grade 3) and metastatic cancer in the lymph nodes. Without additional PLT transfusion, PLT count dramatically improved to  $84.0 \times 10^3/\mu\text{L}$  and  $270.0 \times 10^3/\mu\text{L}$  at postoperative days 1 and 2, respectively (Fig. 2). The patient was discharged without any complications 14 days after surgery. However, lymph node recurrence appeared 2 months after surgery. PLT count decreased again as the tumor volume increased. Tyrosine kinase inhibitor treatment was administered but was discontinued due to hemorrhagic gastric ulcer. Eventually, the patient died of cancer 4 months after surgery.

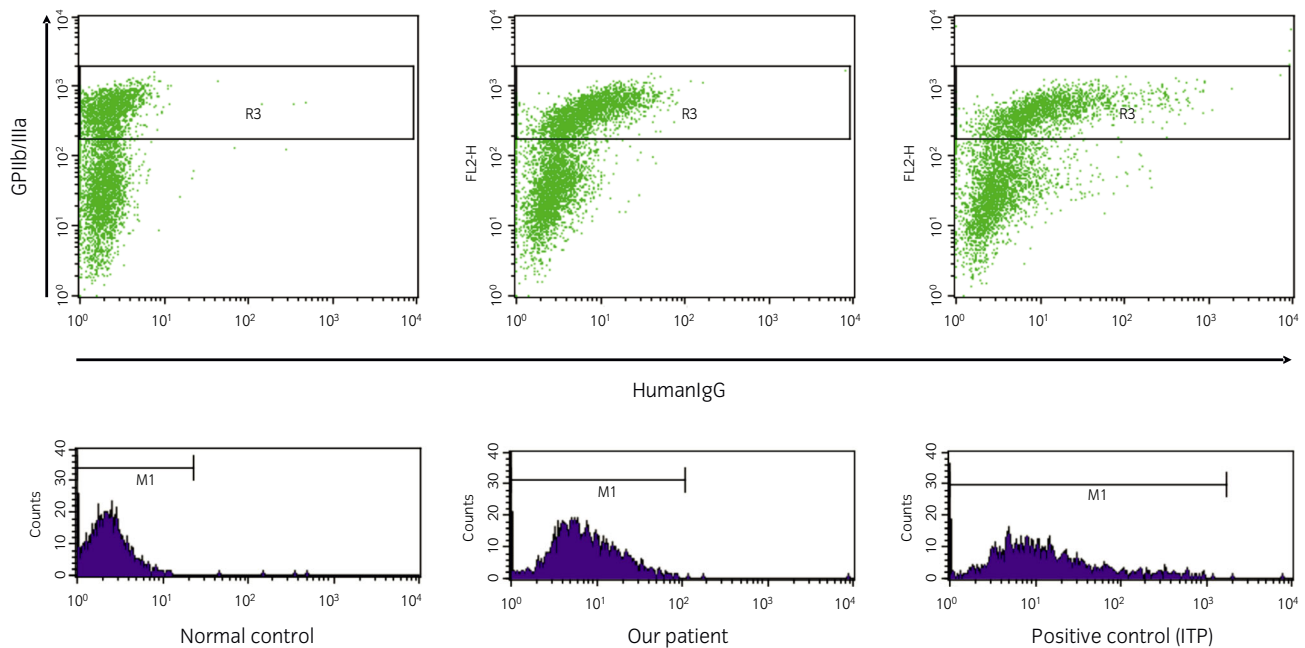
## Discussion

Primary ITP is an autoimmune disorder characterized by isolated thrombocytopenia due to accelerated PLT destruction and impaired PLT production.<sup>1,2</sup> Thrombocytopenia is frequently encountered in patients with cancer. This is commonly caused by bone marrow infiltration of malignant cells, cancer-induced disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, and intratumor hemorrhage. Secondary ITP (ITP-like syndrome) is rarely associated with cancer. Its etiology is associated with cancer-triggered immune-mediated PLT destruction.<sup>2</sup> There have been only 30 case reports of cancer-induced ITP-like syndrome, predominantly in cases of breast, gastrointestinal, ovarian, and lung adenocarcinoma.<sup>3,4</sup> Several cases of RCC-associated ITP have been reported in the medical literature.<sup>5–7</sup> High-dose corticosteroids and high-dose immunoglobulins are commonly used as initial treatments for ITP. Although these treatments are also effective for cancer-induced ITP-like syndrome, thrombocytopenia recurrence of thrombocytopenia occurs in approximately 60% of patients.<sup>3</sup> However, it is extremely rare that drug refractory thrombocytopenia is improved by tumor resection.<sup>7,8</sup>

Recent studies revealed that autoantibodies against PLT surface glycoproteins, such as GPIIb/IIIa and GPIb/IX complexes, play important roles in both PLT destruction and impaired PLT production. PA-anti-GPIIb/IIIa antibodies have been found in 43–57% of patients with ITP.<sup>9</sup> After lymph node recurrence, PA-anti-GPIIb/IIIa antibody was measured, as previously described (Fig. 3).<sup>10</sup> Briefly, washed PLTs were obtained by differential centrifugation and PA antibodies were eluted by diethyl ether. PLT eluates were mixed with GPIIb/IIIa-transfected 293T cells for 30 min on ice. After washing, the cells were incubated with fluorescein isothiocyanate-conjugated anti-human IgG and phycoerythrin-conjugated anti-GPIIIa antibodies and were analyzed on a flow cytometer.



**Fig. 2** PLT count variations in relation to various therapies.



**Fig. 3** Flow cytometry analysis of PLT-associated anti-GPIIb/IIIa antibodies. Lower histograms show IgG binding in GPIIb/IIIa-highly expressing 293T cells, which are indicated in square regions of upper dot blots. MFI, mean fluorescence intensity.

Figure 3 shows that our patient had anti-GPIIIa antibodies similar to patients with ITP.

The present case is unique in several aspects. Firstly, the patient showed severe thrombocytopenia without any findings of intravascular tumor embolus, intrarenal bleeding, bone metastasis, and disseminated intravascular coagulation. Secondly, this thrombocytopenia was refractory to high-dose immunoglobulin. However, it was dramatically improved after surgical resection of renal tumor and lymph nodes. Thirdly, PA-anti-GPIIb/IIIa, which is specific for ITP, was detected. These findings suggest that thrombocytopenia in our patient was associated with RCC-induced ITP (ITP-like syndrome). To the best of our knowledge, this is the first case report of RCC-induced ITP with confirmed presence of PA-anti-GPIIb/IIIa.

## Conflict of interest

The authors declare no conflict of interest.

## References

- 1 Kiyomizu K, Kashiwagi H, Nakazawa T *et al*. Recognition of highly restricted regions in the beta-propeller domain of alphaIIb by platelet-associated anti-alphaIIb beta3 autoantibodies in primary immune thrombocytopenia. *Blood* 2012; **120**: 1499–509.
- 2 Cines DB, Blanchette VS. Immune thrombocytopenic purpura. *N. Engl. J. Med.* 2002; **346**: 995–1008.
- 3 Horvath M, Fekete B, Rahoty P. Investigation of circulating immune complexes in patients with breast cancer. *Oncology* 1982; **39**: 20–2.
- 4 Tsoussis S, Ekonomidou F, Vourliotaki E, Karalis I, Dermizakis A. Successful treatment of idiopathic thrombocytopenic purpura-like syndrome in a cancer patient with low-dose interferon: case report and review of the literature. *Am. J. Hematol.* 2004; **76**: 353–9.
- 5 Klimberg I, Drylie DM. Renal cell carcinoma and idiopathic thrombocytopenic purpura. *Urology* 1984; **23**: 293–6.
- 6 Cho EJ, Lee HJ, Park KU, Kim UY, Lee HJ, Bang SM. Immune thrombocytopenic purpura in a patient with renal cell carcinoma. *Korean J. Intern. Med.* 2014; **29**: 671–4.
- 7 Kamra D, Boselli J, Sloane BB, Gladstone DE. Renal cell carcinoma induced Coombs negative autoimmune hemolytic anemia and severe thrombocytopenia responsive to nephrectomy. *J. Urol.* 2002; **167**: 1395.
- 8 Nonami Y, Yamashiro T, Yamamoto A *et al*. Double lung cancer combined with idiopathic thrombocytopenic purpura. A case report. *J. Cardiovasc. Surg.* 1999; **40**: 889–92.
- 9 Tomiyama Y, Kosugi S. Autoantigenic epitopes on platelet glycoproteins. *Int. J. Hematol.* 2005; **81**: 100–5.
- 10 Kuwana M, Kurata Y, Fujimura K *et al*. Preliminary laboratory based diagnostic criteria for immune thrombocytopenic purpura: evaluation by multicenter prospective study. *J. Thromb. Haemost.* 2006; **4**: 1936–43.