RESEARCH HIGHLIGHT

Complete Response of severe idiopathic thrombocytopenic purpura after resection of bulky chromophobe renal cell carcinoma

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Idiopathic thrombocytopenic purpura (ITP) associated with renal cell carcinoma (RCC) is relatively rare. In almost all of these case reports, patients affected with ITP developed differentially-involved cancer, because resection of cancer could not improve thrombocytopenia and the treatment of ITP needed to be continued after surgery. We report the case of a 48-year-old woman with massive renal cell carcinoma, measuring approximately 20 × 14 × 14 cm, who presented with severe thrombocytopenia: platelet count, 2000 cells/μl. After confirming normal bone-marrow, she received high-dose dexamethasone and intravenous gamma globulin, which rose the platelet count to normal levels. She then underwent left radical nephrectomy. The pathological examination revealed chromophobe RCC. After the resection, the platelet count was maintained within the normal range without any treatments. The current case is the first report of chromophobe RCC causative of severe ITP and the second case who achieved a sustained complete remission of ITP after cancer surgery alone; moreover our case is only one patient without other causes of ITP.

Keywords: renal cell carcinoma; chromophobe; idiopathic thrombocytopenic purpura; high-dose dexamethasone; gamma globulin therapy

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Introduction

Renal cell carcinoma (RCC) has been the 15th most common cancer in the world for the past several decades, the seventh most common cancer in men and the ninth most common in women, with an estimated over 200000 new cases by 2008, representing 2-3% of all new cancers. Incidence in males is higher than in females. There were 116000 deaths (1.5% of the total) in 2008 [1, 2]. The most common histology subtype of RCC is clear cell carcinoma (70-80%). Conversely, the frequency of chromophobe in RCC is 3-5%, which subtype is derived from the cortical collecting ducts. [2] In clear cell carcinoma, biallelic VHL inactivation caused by allelic deletion or loss of

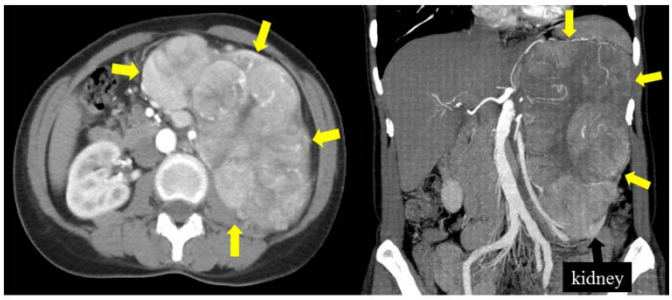

Figure 1. Contrast enhanced CT. CT scans showed the homogeneous enhancement tumor of left kidney, of which maximum diameter was 20cm, with no metastatic disease.

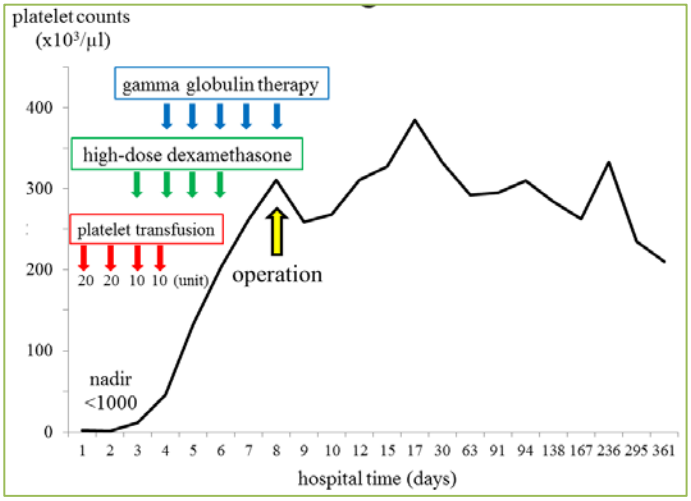

Figure 2. The platelet count and treatment. Infusion of platelet concentrates failed to raise the platelet count. The platelet count rose after the treatment with corticosteroids and intravenous immunoglobulins and was never less than 200000cells/μl without medication.

heterozygosity (LOH) on chromosome 3p (>90%) [3] along with gene mutation (~50%) [4, 5] or promoter hypermethylation (5–10%) have been described. On the other hand, the genetic alterations in chromoohobe are losses of chromosomes 2, 10, 13, 17 and 21, 93%, 93%, 87%, 90% and 70%, respectively [6]. Incidence of metastatic disease in chromophobe RCC is only about 0.6%. Chromophobe RCC has a favorable prognosis and a 5-year survival rate of 80-100%, compared with 20% for most RCC cases. [7]

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disease, which is caused by autoantibody production resulting in the destruction of platelets and thrombocytopenia [8]. Diagnosis of ITP requires a platelet count of less than 100000/μl [9]. An incidence of ITP is about 3.9 cases per 100000 person-years [10]. The etiology of primary ITP is currently unknown, while the causes of secondary ITP include other autoimmune disorders, infections, vaccinations, lymphoproliferative disorders,

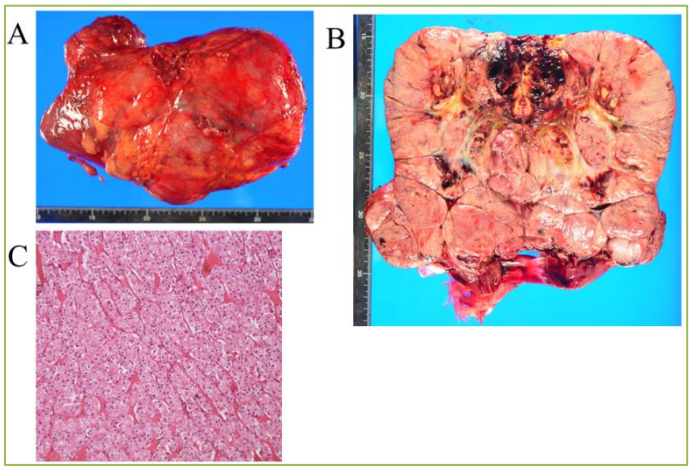

Figure 3. Gross specimen and Photomicrograph. A: The tumor size was over 20cm and the weight of the resected tumor was1920g. B: The cut surface of the resected tumor appeared homogeneously light tan and the tumor presented as a large solitary solid compact mass without necrosis or calcification. C: Microscopic examination revealed a renal cell carcinoma, chromophobe type, which consist of large polygonal cells with transparent slightly reticulated cytoplasm with prominent cell membranes in a stone paving pattern.

congenital immune deficiencies, and medications. The incidence of ITP in patients with malignancies is unclear. The mechanism affecting these patients is unknown but may be related to tumor infiltration of bone marrow, chemotherapy-induced or radiation-induced bone marrow hypoplasia, or platelet consumption due to disseminated intravascular coagulation [11].

Here, we report a case of a patient with idiopathic thrombocytopenic purpura caused by bulky chromophobe RCC who presented with severe thrombocytopenia.

Case report

A 48-year-old woman visited our hospital with a chief complaint of sudden generalized petechial hemorrhage since the morning. She had complained of left back pain for some time. There was nothing significant about her past personal history and family history. She had no fever and no history of medication. Physical findings were generalized petechiae and extensively palpable mass in the left lateroabdominal region. Computed tomography (CT) showed a large left renal tumor, measuring approximately 20 × 14 × 14cm (Figure 1) with no metastasis and without splenomegaly. Therefore she was diagnosed as having left renal cancer (cT2bN0M0) with severe thrombocytopenia: platelet count, 2000 cells/μl. Other hematological values except for the platelet counts were within the normal limit. In addition, platelet-associated immunoglobulin G level was high at 63.2 ng/10^7 cells (reference value, < 27.6 ng/10^7 cells). Immunoglobulin G and M levels were within the normal limit at 1537.0 mg/dl

Table 1. Patient characteristics in who reported 6 cases of RCC with ITP

Age	Gender	Pretreatment platelet count (cells/μl)	Primary focus side of kidney	Maximam size (cm)	Diagnose with metastasis	Pathology	Splenectomy	Period of CR (days)	Citation
68	F	7000	left	18		RCC	yes	140	*Enright H, et al.:* ***Br J Urol****, 1989*
58	F	18000	left	7.8	vigina, lung, brain	clear cell type		unknown	*Allard JE, et al.:* ***Gynecol Oncol****, 2004*
29	F	12000	left	4		clear cell type	yes	unknown	*Yoshinaga A, et al.:* ***Hinyokika Kiyo****, 2005*
69	M	2000	left	8		RCC	yes	8	*Klimberg I, et al.:* ***Urology****, 1984*
59	F	51000	right	8	lymph nodes	sarcomatoid type		21	*Hasegawa J, et al.:* ***J Cardiovasc Surg****, 2002*
68	F	7000	right	5		clear cell type		210	*Kamra D, et al.:* ***J Urol****, 2002*

(reference value, 870-1700 mg/dl) and 68.0 mg/dl (reference value, 46-260 mg/dl), respectively. Anti-platelet antibody levels were negative.

On the following day, her platelet count decreased to less than 1000/μl despite being treated with platelet transfusion. Bone marrow puncture revealed no abnormalities, such as a normocellular marrow with adequate megakaryopoiesis and no evidence of metastatic tumor.

She was treated with a high-dose dexamethasone (40 mg/day) for four days and intravenous gamma globulin for five days. As a result, the platelet count increased to 311000 cells/μl (Figure 2). Finally, left radical nephrectomy was performed uneventfully. The pathological examination revealed chromophobe RCC (weight: 1920g, pT2b, G1, INF alpha, v0, ly0, pN0) (Figure 3). Her condition became better spontaneously and her platelet count has not declined (Figure 2).

Discussion

We reported a case of massive chromophobe RCC with severe thrombocytopenia. Thrombocytopenia is caused by ITP or thrombotic thrombocytopenic purpura (TTP) which is due to cancer-associated thrombotic microangiopathy (TMA), erythropoietin production of RCC, autoimmune disorders (e.g., systemic lupus erythematosus, systemic sclerosis, antiphospholipid syndrome), bone marrow transplantation, pregnancy, medication use or infection. TTP is characterized by TMA, in which autoimmune hemolytic anemia or kidney failure are prominent abnormalities [12]. We considered what in this case Thrombocytopenia was not associated with TTP, because other hematological values except for the platelet counts, e.g. the Red-cell count, Hemoglobin, Hematocrit, LDH, Creatinine, CRP, serum complement level, antinuclear antibody, anti-double stranded DNA IgG antibody, prothrombin time, activated partial thromboplastin time, were within the normal limit and CT did not revealed splenomegaly. Consequently, unknown mechanisms of cancer immunity might have been involved in the ITP in our case.

The first-line treatment for RCC without metastasis is to radically resect the tumor. The standard first-line agents for ITP are steroids and intravenous immunoglobulin, or a combination of both. Therapeutic options for refractory ITP include a splenectomy, as well as biologic agents such as rituximab, romiplostim, and eltrombopag [9]. Splenectomy is the most effective second-line treatment and has a success rate of 66% [13]. Many cases of ITP complicated with several cancers including RCC have been reported. [11, 14] However, in almost all of these case reports, patients affected with ITP developed differentially-involved cancer, because resection of cancer could not improve thrombocytopenia and the treatment of ITP needed to be continued after surgery. Krauth MT *et al*. reported 35 cases, including 6 cases of RCC, in whom ITP was concurrent with the diagnosis of cancer (within 6 months before or after cancer diagnosis). Six patients, all with renal cell cancer, underwent nephrectomy and achieved at least a short term CR of ITP after resection of the tumor (Table 1). Furthermore, only two of the six patients achieved long term CR (over 3 months), one patient with Evans syndrome was performed tumor resection alone and the other patient was performed splenectomized simultaneously [14]. In the current case, the platelet count was restored with steroids and intravenous immunoglobulins, allowing for uneventful resection of the chromophobe RCC solid tumor. Thus, the clinical course of

this case suggests that ITP could result from massive chromophobe RCC, since ITP was completely resolved after radical nephrectomy. In addition, this is the second case who achieved a sustained complete remission of ITP after cancer surgery alone; moreover our case is only one patient without other causes of ITP.

This is the first case, to our knowledge, where ITP could be caused by massive chromophobe renal cell cancer. Furthermore, the platelet count in our case showed a lower level than past reports. Extirpation of the tumor should be done in ITP cases with co-existing malignancy (after appropriate and prompt pretreatment).

Conflicting interests

The authors have declared that no conflict of interests exist.

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