

Coexistence of essential thrombocythemia, iron-refractory iron deficiency anemia and renal cell carcinoma

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Abstract

Essential thrombocythemia (ET) is a Philadelphia chromosome (Ph)-negative myeloproliferative neoplasm. It is characterized by thrombocytosis and megakaryocytic hyperplasia of the bone marrow with *JAK2V617F* mutation. Iron-refractory iron deficiency anemia (IRIDA) is an autosomal recessive disorder, which is mainly characterized by iron deficiency anemia not responding to oral iron intake, but partially responding to parenteral iron therapy. Recently, it has been shown that IRIDA has stemmed from mutations in the gene *TMPRSS6*, which encodes a transmembrane serine protease (matriptase-2) expressed by the liver. Renal cell carcinoma (RCC) accounts for 2-3% of all cancers. As the most common solid lesion in the kidneys, it represents approximately 90% of all renal malignancies. Approximately 30% of patients with symptomatic RCCs seem to display paraneoplastic syndromes. The symptom that may result from erythrocytosis is the most well-known paraneoplastic hematological event. Here, we report a patient who presents with coexistence of RCC and thrombocytosis, which hasn't been caused by hormonal factors that are produced in tumor cells. This patient has been therefore diagnosed with ET. The patient who was expected to display RCC with polycythemia, conversely present with IRIDA.

Introduction

Essential thrombocythemia (ET) is a Philadelphia chromosome (Ph)-negative myeloproliferative neoplasm (MPN). It is characterized by thrombocytosis and megakaryocytic hyperplasia of the bone marrow with *JAK2V617F* mutation in 50-60% of patients. ET transforms into myelofibrosis in a minority of cases, while evolution to acute leukemia is uncommon and increases with the use of certain therapies. Survival of ET patients does not

substantially differ from that of the general population.

Iron-refractory iron deficiency anemia (IRIDA) is an autosomal recessive disorder. It is mainly characterized by iron deficiency anemia that is not responding to oral iron intake, but partially responding to parenteral iron therapy. Recently, it is shown that IRIDA has stemmed from mutations in the gene *TMPRSS6*, which encodes a transmembrane serine protease (matriptase-2) expressed by the liver. IRIDA patients indicate inappropriately increased levels of hepcidin which is a hormone delivered by the liver inhibiting iron absorption from the intestine and iron release from macrophage stores. According to recent studies, *TMPRSS6* down-regulates hepcidin expression by cleaving hemojuvelin, a membrane-bound protein which triggers hepcidin signaling in hepatocytes.¹

Renal cell carcinoma (RCC) accounts for 2-3% of all cancers.² RCC, as the most common solid lesion in the kidney, represents approximately 90% of all kidney malignancies.³ Many renal masses are asymptomatic and non-palpable till the late phases of the disease.⁴ Currently, more than half of the RCCs are identified incidentally through imaging while investigating some non-specific symptom complexes.⁵⁻⁷ The classic triad of flank pain, gross hematuria and palpable abdominal mass is uncommon (6-10%).^{8,9}

Paraneoplastic syndromes are found in approximately 30% of patients with symptomatic RCCs. A few symptomatic patients present with symptoms due to metastatic disease, such as bone pain or persistent cough.^{4,10} Ten to forty percent of patients with RCC experience paraneoplastic phenomena over the span of the disease. The symptom that may result in erythrocytosis is the most well-known paraneoplastic hematological event. Erythrocytosis is reported in 1 to 8% of the patients.¹¹ Modest granulocytosis and thrombocytosis appears in approximately 20% of the patients and is seen as part of a systemic inflammatory reaction as it is typically interrelated with anemia, fever, weight loss, and increased serum levels of CRP and interleukin-6.¹² Here, we report a patient who presents with coexistence of RCC and thrombocytosis, which hasn't been caused by hormonal factors that are produced in tumor cells. This patient has been diagnosed with ET. The patient, who was expected to display RCC polycythemia, conversely had IRIDA. We could not find similar cases previously reported and this may be the first documentation of such a case in literature.

Case Report

A 56-years-old male presented with weakness

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and weight lose. Physical examination was unremarkable. His blood counts were: white blood cells: $9500 \times 10^9/L$; hemoglobin: 6.9 g/dL; mean corpuscular volume 58 fl.; platelets count: $1.423.000/mm^3$; C-reactive protein: 0.9 mg/L; serum iron: $5 \mu mol/L$ (normal range: 15-30 $\mu mol/L$); total iron-binding capacity: 505 $\mu g/dL$ (normal range: 110-350 $\mu g/dL$); transferrin saturation: 1% (normal range: 20-45%); ferritin: 3.1 ng/mL (normal range: 20-330 ng/mL); sedimentation rate 23 (normal range: 0-20). The peripheral blood smear showed hypochromic and microcytic cells, anisopoikilocytosis and thrombocytosis while his liver and kidney tests were normal.

Endoscopy and colonoscopy was applied to the patient in order to determine the etiology of iron deficiency anemia and no pathological signs were found.

According to the etiology of thrombocytosis, *JAK2V617F* mutation was found as positive and Ph chromosome was negative in our patient. Serum erythropoietin level was 11.9 (normal range: 3.5-17.6).

Bone marrow biopsy showed megakaryocytic hyperproliferation, in which megakaryocytes are increased in size with mature hyperlobulated with abundant cytoplasm and grouped. Standard cytogenetic studies showed a normal male karyotype (46 XY) and FISH (fluorescence *in situ* hybridization) analysis for deletion 5q [del (5q)] was negative.

Abdominal computed tomography was applied to the patient to investigate the presence of other malignancies and a 35×32 mm. solid renal mass was diagnosed. The biopsy of

this mass showed clear cell RCC (cRCC).

During the examination of patient, oral iron treatment was used both to correct anemia. The hemoglobin concentration, serum iron level and ferritin level didn't increase enough after four weeks. This failure is usually due to poor compliance, misdiagnosis, continued blood loss, or malabsorption but none of these reasons were present in our patient. Starch block electrophoresis of the hemoglobin was applied to him to investigate the underlying thalassemia, and the hemoglobin electrophoretic pattern was found normal. We suspected that the patient may have IRIDA, because all of its typical features as microcytic anemia with low serum iron, no response to oral iron, and only a partial response to intravenous iron therapy were present in our patient; however, we couldn't identify mutations of the *TMPRSS6* gene and high plasma levels of hepcidin due to technical difficulties.

As a result of all these investigations, the patient was found to have coexistence of RCC, ET and IRIDA.

Radical nephrectomy operation was planned for the patient by urologists. Before the operation cytoreductive therapy with hydroxyurea was administered to the patient until his platelet count is reduced below 400 000/mm³ and parenteral (intravenously) iron treatment was applied to the patient until the hemoglobin level increased at least above 10 g/dL.

Discussion and Conclusions

Platelet count can increase in a variety of conditions, such as anemia, reduced iron

stores, inflammation, the absence of a spleen, and primary proliferative disorders. Of all these conditions, malignant neoplasms are one of the most frequent causes of thrombocytosis. Here we report a patient who presented with coexistence of RCC and thrombocytosis, but it hasn't been caused by hormonal factors that are produced in tumor cells. He has been diagnosed with ET. This patient, who was suspected to have RCC polycythemia, conversely had IRIDA.

We aimed to show that coexistence of malignant neoplasms and thrombocytosis may not only arise from the production of humoral factors produced by the tumor, but concomitant MPN must be also considered.

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