Nephroquiz 10: A 16-Year-Old Patient With Thrombocytopenia and Kidney Failure

Maryam Ghazizadeh,[1] Matin Ghazizadeh,[2] Mohsen Nafar[3]

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[1]Department of Hematology and Oncology, Modarres Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Department of Otorhinolaryngology, Head and Neck Surgery, Taleghani Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3]Chronic Kidney Disease Research Center, Shahid Labbafinejad Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

CASE

A 16-year-old boy was admitted because of thrombocytopenia, proteinuria, and progressive kidney failure. He also had a history of recurrent epistaxis, ophthalmologic problems, and sensorineural hearing loss since childhood. Family and drug history were unremarkable. His hematologic abnormalities were erroneously diagnosed as idiopathic thrombocytopenic purpura. He had received prednisone for 6 months without any response. Physical examination was unremarkable. Complete blood count revealed thrombocytopenia and anemia. Urinalysis showed proteinuria (3+). Serum creatinine was raised up to 10 mg/dL. Kidney biopsy was not performed because of severe thrombocytopenia.

On the following days, serum creatinine was further raised. Despite adequate hydration, uremic symptoms appeared, and therefore, hemodialysis was initiated via a central vein catheter. Macrothrombocytopenia and neutrophil inclusion bodies were detected in his peripheral blood smear (PBS). Coagulation tests were normal. Bone marrow biopsy was done. Erythroid hyperplasia was shown in the bone marrow examination. Megakaryocytes count was adequate. Laboratory tests including erythrocyte sedimentation rate; C-reactive protein; completements C3, C4, and CH50; antineuclear antibodies, double-stranded DNA, and anti-Ro were done considering systemic lupus erythmatosus, but all of them were negative. Anticardiolipin antibodies, anti-β2 microglycoprotein, and lupus anticoagulant were negative, so antiphospholipid antibody syndrome was ruled out.

On the following days, the condition was complicated by generalized seizure and loss of conciseness. The detected schistocytes in the PBS were 1%. The lactate dehydrogenase level was normal primarily; but thereafter, it increased to 850 U/L. He underwent plasma exchange in order to manage thrombotic thrombocytopenic purpura (TTP), but it was not effective. In addition, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) level was normal, verifying that the patient was not complicated by TTP.

Later, alveolar hemorrhage occurred and the patient died. The last laboratory study was molecular genetic test. *MYH9* mutation was detected, so the diagnosis of Fechtner syndrome was confirmed.

QUIZ
What are the Differential Diagnoses of Thrombocytopenia and Kidney Failure?

One of the differential diagnoses of thrombocytopenia and kidney failure is TTP. It is described as thrombi in the small blood vessels, microangiopathic hemolytic anemia, thrombocytopenia, kideny failure, central nervous system dysfunction, and fever. Microangiopathic hemolytic anemia in TTP is associated with schistocytes in the PBS. The etiology of TTP can be ADAMTS13 deficiency or antibody directed against ADAMTS13; it may be hereditary or acquired.[1] Plasma exchange is effective in more than 90% of TTP patients.[2-3]

Drug-induced thrombotic microangiopathy (DITMA) is another differential diagnosis of thrombocytopenia and kidney failure. Some drugs may induce TTP or hemolytic uremic syndrome (HUS). The most common drugs that are responsible for DITMA include quinine, cyclosporin, sirolimus, tacrolimus, and interfrone. Drug-induced thrombotic microangiopathy is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and kidney failure, but ADAMTS13 activity is normal. Kidney biopsy is not necessary in DITMA.

Another differential diagnosis is cancer-related microangiopathic hemolytic anemia that is a paraneoplastic syndrome associated with solid cancer such as stomach, breast, lung, and prostate. Disseminated intravascular coagulation and pulmonary symptoms were more common in cancer-related microangiopathic hemolytic anemia. Plasma exchange is not effective except of prostate cancer and HUS.

Hemolytic uremic syndrome should be considered as another possible diagnosis. Patients with HUS suffer from vascular lesions similar to the lesions in TTP, but vascular involvement in HUS is more prominent in the kidney than the central nervous system. Thrombocytopenia, microangiopathic hemolytic anemia, and acute kidney dysfunction are the significant clinical features in HUS.[4]

Systemic lupus erythmatosus is another possible diagnosis. Clinical manifestations are neuropsychiatric symptoms, renal involvement, thrombocytopenia, and hemolytic anemia. Thrombocytopenia in systemic lupus erythmatosus is caused by antiplatelet antibodies. Also, it can be due to thrombotic microangiopathic hemolytic anemia, which is characterized by the presence of schistocytes in the PBS.[5] Vasculitis is the main pathogenesis of thrombotic microangiopathic hemolytic anemia.[6-7]

Antiphospholipid antibody syndrome (APS) should be considered in the differential diagnosis of kidney failure and thrombocytopenia. Hypertension, proteinuria, hematuria, hematologic abnormalities, and acute or chronic kidney failure are usually observed in APS. The most common hematologic feature of APS is thrombocytopenia (22% to 42%).[8] Renal involvement is seen in both primary and secondary APS,[9] with the frequency of 25%. Renal arterial thrombosis, infarction, and end-stage renal disease usually occur in APS.[10] Increased intimal thickness and medial hyperplasia are the consequence of thrombotic lesions.[11]

Another differential diagnosis is advanced liver disease and hepatorenal syndrome. Thrombocytopenia is a current manifestation of advanced liver disease, especially cirrhosis. Thrombocytopenia in cirrhosis is mild to moderate and occurs due to hypersplenism. Kidney failure is not frequent in the advanced liver disease except for the hepatorenal syndrome. This syndrome occurs in 40% of patients with cirrhosis and is described by oliguria in the absence of proteinuria.

The definite diagnosis of the reported case is Fechtner syndrome which is an autosomal dominant variant of Alport syndrome. It is manifested by nephritis, sensorineural hearing loss, cataract formation, macrothrombocytopenia, and polymorphonuclear inclusion bodies. It belongs to a group of hereditary macrothrombocytopenia including Sebastian syndrome, Fechtner syndrome, May-Heglin anomaly, and Epstein syndrome.[12] The common genetic finding in all of these syndromes is mutation in the gene encoding the heavy chain of nonmuscle myosine-9.[13] Macrothrombocytes and neutrophils with prominent dohle-like bodies are demonstrated in the PBS of patients with May-Hegglin anomaly, Fechtner syndrome, and Sebastian syndrome.[14] Renal abnormalities such as hematuria and proteinuria are manifested in Fechtner syndrome and Epstein Syndrome.[14] Histopathologic examination of the kidney reveals hyalinization of glomeruli and proliferation of mesangial cells.[15] Severe seizures and thrombotic events have been described in May-Hegglin

anomaly. [16]

Renal manifestations of Fechtner syndrome range from microscopic proteinuria, hematuria, hypertancion, and chronic kidney disease that may lead to the need for kidney transplantation. Fechtner syndrome can progress to end-stage renal disease by the age of 20 to 40 years, due to hereditary nephritis. Hematologic manifestations of Fechtner syndrome include recurrent epistaxis, gingival bleeding, easy bruising, menorrhagia, and extensive bleeding associated with surgical procedures. Platelet aggregation test and bone marrow biopsy are normal in Fechtner syndrome. Platelet count ranges from 50×10^9/L to 91×10^9/L.[15] High frequency sensory neural hearing loss usually is identified by the 3rd decade. Ophthalmic abnormalities including glaucoma and cataract can appear at the early childhood.

There is no general suggestion consept the management of Fechtner syndrome. Corticosteroids and splenectomy are ineffective. Desmopressin is helpful in patients with moderate bleeding, but platelet transfusion may be needed in cases with severe bleeding.[17] Also, eltrombobag, a kind of thrombopoiten receptor agonists, has been effective in Fechtner syndrome.[18]

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Correspondence to:
Matin Ghazizadeh, MD
Department of Otorhinolaryngology, Taleghani Hospital, Arabi St, Yaman Ave, Chamran, Hwy, Tehran, Iran
Tel: +98 21 2303 1317
Fax: +98 21 2243 2570
E-mail: matinghazizadeh@hotmail.com