Int J Clin Exp Pathol 2017;10(2):2255-2258
www.ijcep.com /ISSN:1936-2625/IJCEP0038737

Case Report

Thrombotic microangiopathy with ANCA-associated vasculitis in a child: a case report and review of literature

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Received August 25, 2016; Accepted December 6, 2016; Epub February 1, 2017; Published February 15, 2017

Abstract: We describe a case with acute renal failure, pulmonary bleeding, rashes and abdominal pain in a 9-year-old girl suffered from Thrombotic mircroangiopathy (TMA). The reason of TMA was ANCA-related vasculitis, which was seldom seen in pediatric patients. This type of patient is easily misdiagnosed as henoch-schoenlein purpura. The patient was given prednisone and mycophenolate mofetil (MMF) for the treatment of ANCA-related vasculitis. The renal function returned to normal and proteinuria decreased dramatically.

Keywords: Thrombotic mircroangiopathy, ANCA-related vasculitis

Introduction

Thrombotic microangiopathy (TMA) is an acute clinical syndrome, characterized by microangiopathic hemolytic anemia, thrombocytopenia, and multiple organ dysfunctions because of thrombogenesis. Hemolytic-uremic syndrome (HUS) is a typical phenotype of TMA in pediatric patients, which present with fever, diarrhea, dehydration, renal failure, and microangiopathic hemolytic anemia and mostly caused by gastrointestinal tract bacterial infection. In most cases, patients would remiss spontaneously after supportive therapy without complications. The typical pathology of TMA is thrombi and segmental fibroid necrosis in glomerular capillary, afferent glomerular arteriole and renal arteriole. In the present report, we showed a pediatric case of TMA with ANCA-associated vasculitis (AAV).

Case report

A nine-year old girl without significant past medical history characterized by two-week history of abnormal pain, vomiting, nausea, oliguria, gross hematuria and edema. There were rashes on her hypogastric zone and femoribus internus. Her tonsil was swelling without favor. There was tenderness around the navel with rebound tenderness. Proteinuria3+ and hematuria3+ were found in urine routine test. The red blood cells were 3.62×1012/L, white blood cells were 10.3×109/L. Neutrophils were 8.02×109/L, platelets were 122×109/L, hemoglobin was 98 g/L. Stool routine test was normal and the occult blood test was negative. Her creatinine was elevated quickly to 715.7 umol/L within 14 days. Testing for antineutrophil cytoplasmic antibody (ANCA) was weakly positive, complement C3 and C4 were decreased. The anti nuclear antibody was weakly positive. The anti-ds-DNA and extractable nuclear antigen were negative. Before the renal biopsy, the patient was received 0.25 g/d of intravenous methylprednisolone for three days, followed by another three-day course of 0.25 g/d of intravenous methylprednisolone after 3-day interval, since we thought there was the possibility of crescent nephritis. In the meantime, the patient was given antibiotics (ceftazidime, 1 g iv.drip, bid) because of acute tonsillitis, which might be another reason for acute renal injury.

After these treatments, the creatinine was trended down to 183 umol/L. The renal biopsy was performed (on Day 11 th admission) and results showed that multiple thrombi in glomer-

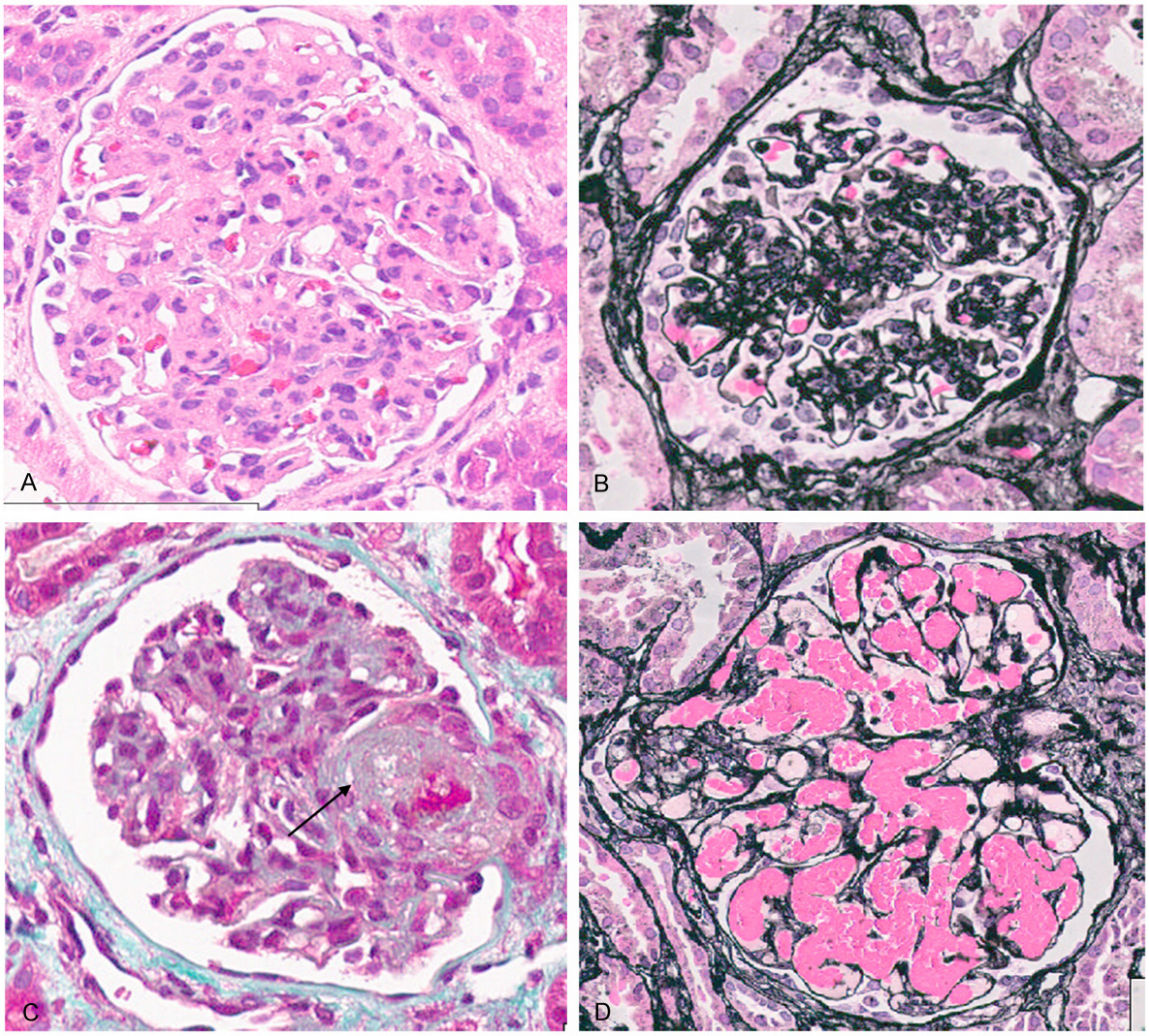

Figure 1. Renal biopsy photographs (digital scan): A. Haematoxylin and eosin stain. Capillary endothelial cells hyperplasia in glomeruli of kidney. B. Periodic acid-silver methenamine stain. Glomerular capillary compression. C. Masson's trichrome stain. Fibrosis and necrosis in afferent arteriole of glomerulus (arrow). D. Periodic acid-silver methenamine stain. Multiple thrombi in glomerular capillaies.

ular capillar, glomerular capillary endothelial cells hyperplasia, fibrosis and necrosis in interlobular arteries and afferent arterioles of glomerulus (see **Figure 1**). No crescents were found in glomerulus. Furthermore, 2% schistocytes were seen in the peripheral blood smears which was consistent with the diagnosis of TMA. Hemoptysis and hematuria were observed after kidney biopsy and developed Type one respiratory failure (SpO2 down to 70%). The patient was intubated and on SIMV mode for three days. The hemoptysis ceased and respiratory failure were resolved on Day 15th. Her SpO2 was back to 100% and hemoglobin kept stable. The rashes disappeared and the urine volume became normal. There were no pain in stomach, no cough and hemoptysis. We prescribed prednisone 1 mg/kg, mycophenolate mofetil (MMF) 20~30 mg/kg, dipyridamole for anticoagulation, gamma globulin intravenous drip for the treatment of TMA and vasculitis, nifedipine for hypertension. The creatinine level returned to 76 umol/L, the proteinuria dropped from 4.098 g/d to 1.67 g/d, following the next 2 months. The ANCA became negative. There were no schistocytes in the peripheral blood smears and the complement level back to normal.

Discussion

This patient suffered from purpura, acute renal failure, abnormal pain. These symptoms made

us sure she got henoch-schoenlein purpura at first, which is a common disease in children. The typical renal histology of henoch-schoenlein purpura is like IgA nephropathy. IgA stains in the glomerular mesangiums, capillary endothelial cells and epithelial cells. Crescentic glomerulonephritis can be one type of IgA nephropathy. In this patient the renal biopsy gave us a different result. There were no IgA stained, only weakly IgM and 2+ C3, which we thought were nonspecific. Inversely, multiple thrombi in glomerular capillaries, glomerular capillary endothelial cells hyperplasia, fibrosis and necrosis in interlobular arteries were seen in the biopsy result, which is consistent with the specific lesion of TMA. The schistocytes in peripheral blood smears confirmed the renal histological result. The most common tpye of TMA inpediatric patients is HUS. HUS in children have been classified as either diarrhea-positive versus diarrhea-negative or as typical versus atypical. Diarrhea-positive or typical HUS is casused by Shiga toxin (Stx) infection [1]. The typical clinical manifestations are bloody diarrhea, thrombocytopenia, hemolysis, fever, oligoanuria, neurological dysfunction, metabolic abnormalities and acute kidney injury. The treatments for typical Hus is supportive treatment, especially keep the balance of body fluid. More than 80-90% of patients with Stx infection have a self-limited course. Children atypical Hus is atypical HUS (aHUS) defined also as a microangiopathic anemia with thrombocytopenia and renal failure, however there is most often (though not exclusively) no classic enteric prodrome. aHUS is caused by abnormalities in the alternate complement pathway (AP), resulting in uncontrolled complement acivation and subsequent tissue damage [1]. Clinical manesfestions are fever, upper respiratory tract infection, and non-bloody diarrhea. Plasma exchange and anti complement treatment were recommended. There were no ANCA positive in both Hus and aHus patients.

There were no diarrhea, fever and special drugs intake in this case. Stool routine test was normal. The serological testing for antineutrophil cytoplasmic antibodies (ANCA) was weakly positive which is an evidence for ANCA-related vasculitis. AAV is uncommon in children. It is reported that a retrospective, single-center, cohort study of 40 children diagnosed AAV between 1987 and 2012 the biopsy specimens were categorized as focal in 13 patients (32.5%), crescentic in 20 (50%), mixed in two (5%), and sclerotic in five (12.5%) [2]. The AAV in children manefested as crescentic glmerulattis, tachypnea, hemoptysis, fever, headache, abodomonal pain [3]. There is no report that children with both TMA and ANCA-realted vascutis.

Vasculitis is injury and infiltration of vascular endothelial cells, which might be a reason for TMA. Low sC3 levels and histologic signs of TMA are associated with a poor renal prognosis in patients with AAV [4, 5]. According to one paper among the 220 adult patients with ANCA-associated glomerulonephritis, 30 were identified having concomitant renal TMA by pathologic evaluation. TMA was independently associated with all-cause mortality in patients with AAV [5]. Some case reports reported that the treatments for TMA with AAV were plasma exchange, intravenous methylprednisolone pulse therapy followed by oral prednisolone [6], daily oral cyclophosphamide [7], or rituximab [8].

This patient also got pneumorrhagia when we found microvascular thrombi in kidney. Pulmonary involvement was common in AAV but uncommon in TMA. Nokes Tetal reviewed 144 articles, only one of 74 patients had clinical important pulmonary involvement [9]. In patients with TMA, pulmonary vessels may be inherently resistant to the development of platelet microvascular thrombi and to the occurrence of endothelial injury. The paper analyzed the reasons, including low shear stress of the pulmonary circulation limit the formation of von Willebrand factor-mediated platelet thrombi [10]. Low pressure and high compliance system sustained the pulmonary circulation even microvacular thrombi develops [11].

There were a few case reports exhibited that a positive ANCA patient can get henoch-schoenlein purpura at the same time [12-14]. The reason might be that inflammatory cytokines make priming of neutrophils and up regulation of adhesion molecules on their surface as well as on the vascular endothelium. Then released PR3 can be processed and presented by antigen presenting cells to T-helper cells. PR3-stimulated Th cells act on B cells, enhancing the production of ANCA [15].

In conclusion, in our case, as purpura and acute renal injury were primary symptom, it was easily misdiagnosed as henoch-schoenlein purpura [16]. The renal biopsy and positive ANCA confirmed the patient got TMA and AAV. We adopted the treatment for both TMA and AAV, that is, first received methylprednisolone and subsequent prednisone plus mycophenolate mofetil. The patient got a good therapeutic result. Her renal function was back to normal and proteinuria decreased. This is the first report a pediatric patient got TMA and AAV at the same time.

Disclosure of conflict of interest

None.

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