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Extreme Thrombocytosis Presenting in Anti-Neutrophil Cytoplasmic Autoantibodies-Associated Crescentic Glomerulonephritis with Immune Complex Deposits: A Case Report

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Abstract

Introduction: We describe a female patient with extreme reactive thrombocytosis (RT) in anti-neutrophil cytoplasmic autoantibodies (ANCA)-associated crescentic glomerulonephritis (CGN) with immune complex deposits, which has never been reported before. **Case Presentation:** A female adolescent with symptoms of oliguria and gross hematuresis had serious renal function impairment (crescent formation and immune complex deposits in renal pathology examination with positive serum ANCA) and extreme thrombocytosis. We made a diagnosis of CGN and RT. After treatment with Prednisone, Cyclophosphamide, and plasmapheresis, the symptoms of oliguria and gross hematuresis were relieved remarkably and the serum creatinine and platelet count declined significantly. **Conclusions:** The diagnosis of thrombocytosis is not easy in all cases. The coexistence of ANCA and the immune complex in CGN may cause a severe inflammatory state, leading to extreme RT. The roles that the immune complex and ANCA play on the effect of the platelet count and function in CGN need further research.

Keywords: Thrombocytosis, Immune Complex Diseases, Glomerulonephritis

1. Introduction

Thrombocytosis is commonly classified as reactive and essential. There are various causes of reactive thrombocytosis (RT), including acute infection or inflammation, iron deficiency, malignancy, and splenectomy. The diagnosis of essential thrombocytosis (ET) is principally based on platelet count, histopathological features, and evidence of clonality (1). Anti-neutrophil cytoplasmic antibodies (ANCA) have been known to be closely related to ANCA-associated vasculitis, including microscopic polyangiitis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, and single-organ ANCA-associated vasculitis, which often cause renal limited pauci-immune complex crescentic glomerulonephritis (CGN) and moderate thrombocytosis (2). Whereas there are studies reporting immune deposits in ANCA-associated CGN (3, 4), which is consistent with our case, there are no relative studies reporting extreme thrombocytosis (platelet count > 1000×10^9 /L) (5, 6) in the immune complex and ANCA-associated CGN. Our case illustrates extreme thrombocytosis secondary to ANCA-associated CGN with immune complex deposits.

2. Case Presentation

A 15-year-old previously well girl (ethnic Han, high school student) presented with oliguria and gross hematuresis of 20 days' duration after catching a cold. The daily urine volume was about 100 mL without urinary irritation or dermal ecchymosis. She said that she had always been in good condition without any allergic erythra or arthralgia history and never had undergone hospitalization or surgery. Her parents were healthy and denied any family history. On admission to our hospital, her pulse was 78 beats per minute, respiratory rate was 20 breaths per minute, temperature was 36.7°C, and blood pressure was 145/81 mmHg. She had a pale appearance without erythema, joint gall, or enlarged nodules. Serological examination demonstrated severe impaired renal function (serum creatinine = 1071 μmol/L); p-ANCA (titer = 1:10) with positive myeloperoxidase 8.7 (normal range > 1.0); slightly declined C3 (0.673 g/L in a normal range of 0.785 to 1.52 g/L) with anti-basement membrane, anti-nuclear, anti-extractable nuclear antigen; anti-keratin antibodies; and negative rheumatoid factors. Routine blood test showed slight leukocytosis (white blood cell = 11.74×10^9 /L), extreme thrombocytosis (platelet = 1389

$\times 10^9$ /L), and anemia (hemoglobin = 92 g/L). Urine routine test showed severe hematuresis (red blood cell = 1529 /HP) and severe proteinuria (protein = 6.0 g/L). Fecal occult blood was negative. Renal ultrasound examination demonstrated enlarged kidneys with enhanced echo of bilateral renal parenchyma. Renal biopsy was done, which showed cellular and fibrous-cellular crescents accounting for 90% under light microscopy with C3 (focal and segmental: +-++); C1q (focal: -/+-+); IgA (focal: +); and negative IgG, C4, and FN (on a 0 to 4+ scale). The bone marrow aspiration specimen showed an increased megakaryocyte count, and the gene test of BCR-ABL and JAK2-V617F mutation was negative. Hepatitis virus B antigens and hepatitis virus C antibody were negative. Moreover, serum tumor markers, including alpha fetal protein, carcinoembryonic antigens, and tumor-associated carbohydrate antigens, were in the normal range.

Based on the clinical, laboratory, and pathological evidence, we made a diagnosis of ANCA-associated CGN with the immune complex deposits while the origin of thrombocytosis was unknown. The diagnoses of systemic lupus erythematosus, rheumatoid arthritis, allergic purpura, and other immune diseases were excluded considering the negative serological testing and relevant clinical symptoms and signs. JAK2-V617F is a clonal marker and is an important criterion in the diagnosis of ET (1), which was negative in our patient. The bone-marrow aspiration showed the active cellular proliferation of megakaryocytes, which can be seen in both primary and secondary thrombocytosis. The results of the bone-marrow aspiration and the absence of BCR-ABL excluded the diagnosis of hematological tumors such as chronic myelogenous leukemia, primary myelofibrosis, and polycythemia vera. Negative serum tumor markers to some extent assist in excluding other malignancies which may cause thrombocytosis. According to the latest revision of the World Health Organization's diagnostic criteria for ET (1), the current evidence was not enough to confirm the diagnosis of ET. Moreover, the positive serum ANCA persistently existed during the patient's hospitalization (p-ANCA titer keeping level of 1:10 with positive myeloperoxidase 8.7 - 9.8) with impaired renal function due to CGN. We, therefore, could not ignore the possibility of RT.

The patient received intermittent hemodialysis 3 times a week, pulse therapy with Methylprednisolone (800 mg/day, 3 days/course for 2 courses) and Cyclophosphamide (0.4 mg/day), and plasma exchange (2000 mL/day) for 7 times in conjunction with other supportive treatments such as blood pressure control and gastric mucosa protection. However, the platelet count was found extremely high during the course of the disease and the reason was still indefinite. When the patient was discharged, her serum creatinine fell to 313.8 μmol/L with a platelet count of 439 $\times 10^9$ L. To confirm that the serum platelet level did fall to almost normal range, we did a follow-up of 6 months. She continued pulse therapy with Cyclophosphamide at regular intervals for 3 times and until now, her platelet count has not gone beyond 500 $\times 10^9$ L (Figure 1). The diagnosis of RT was finally confirmed.

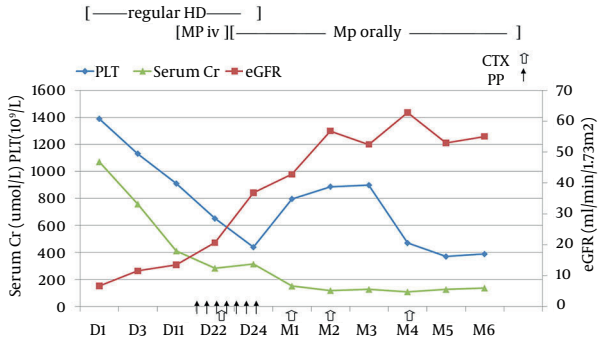

Figure 1. Clinical Course of the Patient: the Platelet Count Decreased with the Recovery of the Renal Function

3. Discussion

We presented a case of ANCA-associated CGN with the immune complex deposits and extreme thrombocytosis. The extended duration of the patient's disease complicated the differentiation between RT and ET. When the platelet count almost recovers to the normal range without the need for the administration of Hydroxycarbamide, the diagnosis of ET can be definitely excluded.

There are strengths in the management of the patient described herein. The bone marrow examination and the gene test of BCR-ABL and JAK2-V617F mutation were necessary and thorough and they excluded possible hematological disorders. Hydroxycarbamide was not administered given that the diagnosis of ET was not confirmed. Thrombocytosis was asymptomatic in this case, which precluded the possible side effects of Hydroxycarbamide when the patient was in a critical condition. It is known that ANCA-associated CGN may lead to chronic renal insufficiency and even death due to infection and uremia complications. The treatments were appropriately intense and effective inasmuch as the renal function almost recovered to the normal range and there was no occurrence of severe complications during the treatment course. In addition, we performed a 6-month follow-up to administer regular tests and timely treatments so as to ascertain that the diagnosis was accurate and complete. The limitation is that we did

not detect inflammatory factors such as C-reactive protein (CRP) and interleukin (IL-6) and discontinued the regular ANCA serology test after the patient's discharge, which reflects the inflammatory state to some extent.

Secondary thrombocytosis usually has a platelet count of fewer than 800 $\times$ 10^9 L (5). Although extreme thrombocytosis usually appears in ET, caution should be exercised regarding the diagnosis given that the morbidity of ET is much lower than that of RT (6). We searched several studies (7-9) reporting extreme RT in which the primary diseases were splenectomy, iron deficiency, and infection including respiratory syncytial virus bronchiolitis and pneumonia (mostly in infants). A study on Chinese people indicated that RT is not rare in ANCA-associated vasculitis patients and it has an occurrence rate of about 20% (10). Nevertheless, no further studies have systematically reported the range of thrombocytosis. Among the cases which we found relating to immune complex and ANCA-associated CGN, no one reported the occurrence of extreme thrombocytosis. Inversely, there were cases reporting a probable association between thrombocytopenia and ANCA (3, 11).

Some studies have reported that the immune complex acts synergistically with ANCA to produce more severe glomerulonephritis, as is manifested by heavier proteinuria and inferior kidney function (12, 13). That means that the coexistence of ANCA and the immune complex may cause a far more active immune and inflammatory state, leading to an extremely high platelet count. There have been a considerable number of articles researching the association between thrombocytosis and cytokines such as IL-6, IL-11, and thyroperoxidase (TPO) in inflammatory conditions such as infection and rheumatoid arthritis. With respect to CGN, however, there are only a few animal studies contradictorily showing a relation between the platelet count and nephritis and failing to mention ANCA (14, 15). More clinical and basic studies are needed to uncover the association between extreme RT and the immune complex in ANCA-associated CGN and further reveal the possible mechanism.

Reaching a definite diagnosis of thrombocytosis is not as easy as expected in some cases. The coexistence of ANCA and the immune complex may cause severe CGN, leading to extreme RT. The roles that the immune complex and ANCA play in the effect of the PLT count and function on CGN need further studies.

Footnote

Authors' Contribution: Zhang Xuemei and Diao Yongshu performed equally in the data collection and the writing of the manuscript. Zhang Ling contributed significantly to analysis and manuscript preparation. Yang Yingying helped perform the analysis with constructive discussions. Fu Ping contributed to the conception of the study and collection of original data.

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