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Case Report

The Relationship between Undifferentiated Connective Tissue Disorders (UCTD) and Thrombotic Thrombocytopenic Purpura (TTP): A Single Center Experience with a Review of Literature

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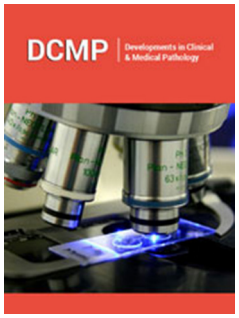

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Background

Thrombotic Thrombocytopenic Purpura (TTP) is a life-threatening syndrome characterized by thrombocytopenia and microangiopathic haemolitic anemia caused by deficiency (congenital or acquired) of ADAMTS 13, a proteinase that cleaves Von Willebrand Factor (VWF) in little multimers, in TTP we can observe antibodies against ADAMTS13. The presence of large VWF multimers brings microvascular platelets clumping in capillaries and arterioles of multiple organs (brain, kidney, hearts, bowel). TTP is classified in "congenital" or "acquired" and " idiopathic" and "secondary" to neoplasia's, infections, pregnancy, drugs, rheumatologic autoimmune disease (more frequently systemic lupus erythematosus or Sjogren syndrome, rarely with Undifferentiated Connective Tissue Disorders (UCTD) [1-9].

Aim

The coexistence of UCTD and TTP has been reported only in few cases in literature (14 in total); in 2012 was reported a sequential occurrence of TTP, ET and ITP diagnosis but only with empirical dates, without the confirm JAK2 molecular test and deficiency of ADAMTS 13. The immunological mechanism involved in this category of secondary TTP in not completely explained [10].

Methods

We analyzed in this retrospective study all patients with TTP admitted to our department in Dimiccoli Hospital of Barletta, from 2011 to 2021. The cases observed in these period were 8: 4 "idiopathic" (3 males and 1 female) and 4 "secondary" to collagenosis (4 females). The median age was 25 years (range 20-30) in "idiopathic group" and 37 years (range 30-45) in rheumatologic disease (1 systemic lupus erythematosus, 1 Sjogren's Syndrome in overlap with systemic lupus erythematosus, 2 undifferentiated connective tissue disorders).

In particular, we describe the case of a 29-year-old white Caucasian women admitted in our ward in April 2019 with normochromic normocytic anemia (9g/dl), severe thrombocytopenia (10x103 /microL), increased reticulocytes (10%). On physical examination she presented fever of uncertain origin (with negative cultural exams), headache, arthralgias, gradual

neurologic disorientation, paraestesias, arthralgies, Raynaud phenomenon. Biochemical analysis revealed normal epatorenal tests, normal Troponin I, but decreased plasma fibrinogen level (100), elevated levels of serum lactate dehydrogenase (1500U/L), Coombs tests negative and we observed several schistocytes in peripheral blood smear. Besides was documented the deficiency of ADAMTS 13 activity (<1%) and the presence of autoantibodies against ADAMTS13(2UB/microL) that leaded to a diagnosis of TTP. Computed tomography and angio magnetic resonance imaging not presented specific brain abnormalities. We started immediately daily plasmapheresis, fresh frozen plasma infusion and methylprednisolone (1mg/kg body weight). After 10 days of treatment, she showed a moderate improvement of anemia e thrombocytopenia, then the autoimmunity test were positive for ANA(1:1280) with speckled pattern and for anti U1_RNP(<240), reduction C3 (complement factor) level. Thus, the diagnosis was of UCTD associated to TTP. After 20 days of treatment, we observed a decrease of platelet count(10x103 microL) so the patient received 4 doses of rituximab (375mg/m2/week). Four weeks later the blood count become normal such as the level of ADAMTS 13 (83%); the autoantibodies against ADAMTS 13 were absent and we have not observed anymore schistocytes in peripheral blood smear. She was discharged with rheumatological therapy azathioprine 50mg/d and aspirin. We monitored the patient every three months and observed normal level of ADAMTS 13, normal biochemical parameters and good clinical conditions. After 2 years of hematological and rheumatological follow up, she presented persistent thrombocytosis (600x103/microL), she resulted "driven "Jak2 V617F mutation and the diagnosis of essential thrombocythemia was made on the basis of bone marrow histopathological examination and WHO criteria (February 2022).

Results & Discussion

Thrombocytopenia in "secondary TTP" by connective tissue disease has an immune pathophysiology associated with autoimmune disorders and the presence of rheumatological autoantibodies mediates platelets destructions. Autoimmunity involves the adoptive immune system with B and T cells that "play" a pivotal role in the complex immunology of connective tissue disorders with dysregulation of coagulation pathways until thrombosis. Activation of complement has been proven to be involved in systemic autoimmune diseases (low C3 levels indicates complements consumption), besides there is an important role of endothelial damage by endothelial inflammation and activation, the presence of anti-endothelial cells antibodies (ANA) and autoantibodies against ADAMTS13, ADAMTS 13 Hyperglycosilation and depressed plasma fibrinolytic action could explain their potential role in the pathogenesis of vasculitis, thrombocytopenia and thrombosis in "secondary TTP" in autoimmune disorders [1-9].

Conclusion

Autoimmunity may determine the loss of immune tolerance , among an imbalance between Treg and T cell effectors and the autoantibodies may create a disordered immune surveillance system, which permits the onset of malignant disease. Besides in connective tissue disease the release of proinflammatory cytokines could contribute to stimulate ROS related to precursors of JAK2 mutation, the onset of Clonal Hematopoiesis of Indeterminate Potential (CHIP) and, finally, the evolution in ET pathways.

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