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Recurrent Pregnancy Loss Linked to Elevated Levels of Perinuclear Anti - Neutrophilic Cytoplasmic Antibodies: A Rare Yet Triumphant Tale!

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1. Introduction

Recurrent pregnancy loss (RPL) and autoimmunity are known to be associated. In many instances of RPL, there is a failure in normal control mechanisms that prevent an immune reaction against self, resulting in an autoimmune response. Autoantibodies to phospholipids, thyroid antigens, nuclear antigens and others have been investigated as possible causes for RPL. We report a rare instance of RPL linked to severe immunological thrombocytopenia, chronic high - titer positivity for perinuclear antineutrophilic cytoplasmic antibodies (pANCA), hypertension, diabetes (Type 1), and negative antinuclear antibodies (ANA), Antiphospholipid antibodies (APLA) and anti - dsDNA antibodies. In our case, all three cases of pregnancies resulted in fetal death, despite the fact that our patient features did not fit any serological and clinical manifestations/criteria of any systemic autoimmune (vasculitic or non - vasculitic) disease except that her p - ANCA titers remained elevated. She successfully delivered a healthy baby when she was put on immunosuppression throughout her fourth pregnancy despite persistent high titer - pANCA levels.

2. Case Report

Our patient, a 39 - year female, house maker with Type - 1 diabetes (controlled on insulin) reported to our clinic with throbbing headache of 2 weeks duration. She had no fever, oral ulcers, rash, hair fall, sicca, Raynaud phenomenon, and her joint examination were normal. Her blood pressure was 190/110 mmHg and sugars were normal. Ophthalmology examination, chest and cardiac evaluation were not significant. Her liver and renal functions were within normal limits. Her acute phase reactants were high with an ESR of 90 mm/hour. Immunological investigations showed negative anti - nuclear antibody (ANA) and antiphospholipid antibody (APLA) with normal complement levels. Thyroid function test was normal with negative anti - thyroid peroxidase (anti - TPO) antibodies. Using an indirect immunofluorescence assay for antimyeloperoxidase antibody, p - ANCA was found in high titers while cytoplasmic ANCA was negative. Her clinical and serological characteristics, however, were not consistent with the diagnosis of any specific autoimmune vasculitic or non - vasculitic diseases. At the time of this presentation, she was not pregnant. We used antihypertensive drugs to manage her blood pressure. Over the course of one week, her headache and blood pressure subsided. Her obstetric history was noteworthy since she had two unexplained miscarriages at 12 and 14 weeks of pregnancy. Other than the ultrasonographic evidence suggesting absent heart activity in well - formed babies at 12 and 14 weeks of her two prior pregnancies, no other information about the prior pregnancies was documented. A review for recurrent pregnancy loss was conducted, but the results did not pinpoint a particular reason. The antiphospholipid antibody syndrome (APLA) was ruled out again by repeating the test. She was always compliant with insulin and sugars were always under control. Thrombophilia workup was also negative. Her subsequent pregnancy was complicated by recurrent thrombocytopenia (platelet range: 20, 000 - 30, 000/ml) and a bone marrow biopsy suggestive of peripheral destruction of platelets. She was started on high dose oral corticosteroids. She again tested negative for ANA, anti - dsDNA and anti - platelet antibodies, but p - ANCA was detected at high titers. Platelet stabilized at 45, 000/ml without bleeding and therefore corticosteroid therapy was gradually tapered and discontinued. However, fetal death was diagnosed at 10 weeks. Manual vacuum aspiration was performed after stabilizing the platelet count to 60, 000/ ml with platelet transfusion and oral corticosteroids. The placenta showed no signs of vasculitis. Thrombocytopenia resolved completely after 4 months. She did not develop any other symptoms related to her positive p - ANCA on her 6 months follow up. For her persistent high titer p - ANCA levels, we put her on oral steroids and hydroxychloroquine for the entire period of her subsequent pregnancy and she delivered a healthy baby (2.5 kg) at 38 weeks of gestation by caesarean section with no evidence of thrombocytopenia.

3. Discussion

A few autoantibodies like APLA antibodies [lupus anticoagulant (LA), anti - cardiolipin (ACL) and anti - β 2 glycoprotein I (β2GP1)], thyroglobulin (TG), thyroid peroxidase (TPO), antibodies to nuclear antigens (ANA), anti - laminin, anti - prothrombin antibodies (aPTs) and anti -

sacchromyces cerevisiae antibodies (ASCA) have been reported to be associated with RPL or as possible factors involved in infertility pregnancy complications related with RPL (1). Nonetheless, testing for autoantibodies other than APLA is not suggested at present as their affiliation has not been consistent (2). Our patient had RPL, unrelated autoimmunity manifestations and significantly raised p - ANCA which is related with vasculitic and non - vasculitic immune system problems. Systemic necrotizing vasculitides (SNVs) are known to cause pregnancy complications such as miscarriage, preterm labor, vasculitis flare - ups and, in rare cases, life - threatening complications in the mother (3). Yet, in our patient clinical and serological elements didn't fit into any of the SNVs or other immune system illnesses where p - ANCA is known to be elevated. Based on literature, there have been two case reports of microscopic polyangiitis (MPA) in which transplacental exchange of p - ANCA has been reported (4, 5). In one of them, these autoantibodies led to lung and kidney issues in the infant, and this has been thought of as immediate clinical proof that this antibody is pathogenic. Nonetheless, in the subsequent case, the infant was unaffected in spite of a high titer levels of p - ANCA. The subsequent case underlines that p - ANCA alone may not be pathogenic without other cofactors causing disease. Relationship of high titers of p - ANCA with RPL is not consistently been reported till now. In a prospective, controlled trial of 59 women with recurrent abortion, ANCAs occur more frequently in patients with recurrent miscarriage patients than in controls (6). In this cohort of 59 patients, p - ANCA occurred in 2, and c - ANCA in 6 of 59 case patient; c - ANCA levels were significantly higher in patients than in controls ($P = 0.028$) (6). This is in contrast to the results published by Bustos D et al, in which the authors did not find significant differences for ANCA antibodies between RPL and control group (7). Nevertheless, they studied ANCA by an immunoassay (antimyeloperoxidase and antiproteinase - 3) in contrast to Bustos D et al who studied ANCA by the gold standard method of Immunofluorescence (7). Notwithstanding, it is uncertain whether these autoantibodies are exclusively responsible for our patient RPL. Extreme thrombocytopenia reflects worsening of her autoimmunity during pregnancy, which in turn might be answerable for the fetal loss. That's what we concluded that consistent immunosuppression with corticosteroids and hydroxychloroquine might be helpful in her next pregnancy, regardless of the way that she doesn't fit into the conclusion of a specific immune system issue which led to a successful outcome. Uncommon autoantibodies might be related with pregnancy loss, even without clinical indication of the immune disorder with which the autoantibodies are typically related. Screening a board of autoantibodies may be helpful in unexplained RPL as uncommon autoimmunity might be related with RPL (8). We believe that further research could be helpful to study the relationship of uncommon autoantibodies like p - ANCA with RPL including treatment regimens which may incorporate immunosuppression.

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