Navigating Fertility Challenges: A Case Report on Immune Thrombocytopenia and Antiphospholipid Antibodies in a Woman Pursuing Pregnancy

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Immune thrombocytopenia (ITP), driven by autoantibodies targeting platelet antigens, is an acquired disorder posing considerable challenges, particularly in pregnancy, where its prevalence escalates to 1–3 per 10,000 women, a tenfold increase compared to the general population [1]. Predominantly characterized by a heightened risk of bleeding, particularly during pregnancy, the incidence of significant hemorrhagic events stands at approximately 18%, mostly non-severe [1]. Despite its rarity, thrombosis can manifest as a complication, especially when accompanied by antiphospholipid antibodies, which amplify the propensity for arterial and venous thrombotic events alongside obstetric complications and thrombocytopenia [2,3].

In this case report, we present the case of a young female with primary unexplained infertility, complicated by ITP and antiphospholipid syndrome (APS), predisposing her to increased bleeding and thrombotic risks. During a multidisciplinary consultation, the medical staff navigated the intricate landscape of fertility treatments and pregnancy options, carefully considering the delicate balance between risks and benefits to optimize patient outcomes.

PATIENT DESCRIPTION

A 30-year-old woman with primary infertility presented to our outpatient clinic planning to conceive. Her medical history revealed a complex array of conditions, including a history of ITP, thrombocytopathy of glycoprotein VI, triple positive antiphospholipid antibodies without clinical manifestation other than thrombocytopenia, positive antinuclear antibodies (ANA), and mild asthma.

ITP initially presented at the age of 17 years, manifesting over time with symptoms such as purpura, ecchymoses, mucosal involvement, and nosebleeds. The patient did not have a history of significant surgeries or dental procedures. Blood tests revealed platelet values ranging from 70,000 to 80,000. Extensive investigations were conducted with evidence of anti-platelet immunoglobulin-G type autoantibodies targeting integrin αIIbβ3 (fibrinogen receptor) on the platelets and antiphospholipid antibodies identified. The patient's platelet counts were moderately reduced, but symptoms were investigated, including platelet aggregation tests that revealed a diminished response to collagen and reduced reactivity to epinephrine. A fluorescent-activated cell sorting (FACS) test yielded positive results for an acquired defect in glycoprotein VI. In addition, exome sequencing was conducted, targeting mutations known to cause human diseases. However, no findings indicative of a platelet disorder were identified.

A therapeutic trial commenced raising the platelet count before conception, initially with prednisone (at a dose of 20 mg) that was only modestly effective but was discontinued due to adverse effects, namely sleep disturbances as well as abdominal and facial swelling. Subsequently, a second-line treatment with intravenous immunoglobulin (IVIG) (at a total dose of 70 g) was attempted but proved ineffective, as there was no improvement in the platelet count.

As part of her medical evaluation, the patient consistently tested positive for antiphospholipid determinants, including immunoglobulin-G anti-cardiolipin, immunoglobulin-G anti-beta-2-glycoprotein-I, and lupus anticoagulant, which all exhibited high titers. The patient had no history of arterial or venous thrombosis or pregnancy complications associated with APS.

Furthermore, the patient presented with ANAs at a titer of 1:320. These antibodies display a nucleolar pattern, characteristic of autoimmune diseases, mainly systemic lupus erythematosus. A thorough clinical and laboratory investigation was conducted, but no findings supporting a specific autoimmune disease were identified.

Following 18 months of unsuccessful attempts to conceive spontaneously, the patient was first admitted to our reproductive endocrinology and infertility (REI) outpatient clinics and was diagnosed with unexplained infertility. Following a thorough investigation and multidisciplinary deliberation involving specialists from hematology, endocrinology, and immunology, it was decided to proceed with in vitro fertilization (IVF) with oocyte retrieval during hospitalization.

The patient underwent an IVF cycle using the multi-dose gonadotropin releasing hormone (GnRH) antagonist (cetrorelix 0.25 mg daily) ovarian stimulation (OS) protocol. OS included a combination of follicle-stimulating hormone (FSH; follitropin alfa 112.5 IU) and FSH + luteinizing hormone (LH) (follitropin alfa/lutropin alfa 112.5 IU/56.25 IU) with a GnRH agonist trigger (triptorelin 0.2 mg) for final oocyte maturation. Throughout the stimulation cycle and 5 days post-trigger, the patient received prednisone (10 mg) for immune modulation and enoxaparin (20 mg) for anticoagulation.

Platelet levels before oocyte retrieval were 72,000 per microliter. Hemoglobin was 13 grams per deciliter, and hematocrit was 39.7%. The sperm analysis was normal (volume of 2 milliliters, concentration of 150 million per milliliter, with 70% motility). Thirteen oocytes were retrieved, and an intracytoplasmic sperm injection (ICSI) was planned for half of them. As two oocytes were at the germinal vesicle (GV) stage, ICSI was performed on four oocytes, and all four were successfully fertilized. Of the other seven oocytes that were planned for insemination, only one was normally fertilized, although six of the seven were mature. The patient was hospitalized following retrieval with no evidence of bleeding and no need for additional platelet transfusion. This cycle resulted in the successful cryopreservation of four embryos (one blastocyst and three at the cleavage stage). A second cycle followed a similar OS protocol with a few adjustments. Cetrorelix administration began on day 6 of stimulation, and the FSH+LH dosage was initiated earlier and gradually increased to a maximum daily dose of 175 IU. Platelet levels on the day of retrieval were 53,000 per microliter, hemoglobin was 13.2 grams per deciliter, and hematocrit was 40%. The day after oocyte retrieval, platelet levels decreased to 37,000 per microliter, hemoglobin to 11.3 grams per deciliter, and hematocrit to 33.4%. As there were no signs of internal bleeding on ultrasound scans, no platelet transfusion was administered. Platelet levels spontaneously increased to 49,000 per microliter the following day. This cycle yielded 11 frozen embryos (2 blastocysts and nine cleavage-stage).

Subsequently, the patient expressed interest in pursuing pregnancy through IVF. However, given the complexity of her medical history, which included a heightened risk of both clotting and significant bleeding, a comprehensive multidisciplinary discussion involving specialists from the hematology, immunology, high-risk pregnancy, and fertility departments convened.

After considering various complexities and challenges in the pregnancy with a significant risk to the pregnant mother from both bleeding risks and coagulation risks, we recommended surrogacy. In addition, the insertion of an intrauterine device is recommended as a means of preventing spontaneous pregnancy in the future.

COMMENT

ITP can manifest in primary or secondary forms, with the latter often associated with APS [2]. Predictors for significant bleeding include a platelet count below 10,000 to 20,000, previous minor bleeding episodes, female sex, and chronic ITP lasting over 12 weeks [1]. The patient exhibited several risk factors for severe bleeding. In cases of declining platelet counts during pregnancy without acute conditions like childbirth, standard treatments for non-pregnant ITP, including steroids, intravenous immunoglobulins, and rituximab, may be administered [1]. Glycoprotein VI thrombocytopathy often manifests as an acquired form and is associated with ITP. While glycoprotein VI deficiency does not play a significant role in hemostasis, patients typically experience minor bleeding symptoms [4]. However, when ITP is compounded with a defect in glycoprotein VI, the patient faces a heightened risk of severe bleeding, particularly during pregnancy.

APS is an autoimmune systemic disease [3]. The primary risk factors associated with venous or arterial thrombosis and adverse obstetric outcomes include the presence of LAC and triple positive antiphospholipid antibodies, both of which were present in our patient [3]. The patient also exhibited positive ANA, which, in conjunction with positive antiphospholipid antibodies, elevated the risk of thrombosis and obstetric complications [5]. APS is also associated with mild and typically benign thrombocytopenia [2]. Individuals with ITP and positive antiphospholipid antibodies face an increased risk of future coagulation events. Pregnant women with ITP and positive antibodies to antiphospholipids are at increased risk of thrombosis and obstetric complications [2,3]. Although the patient only showed laboratory signs of APS without clinical manifestations other than thrombocytopenia, the severity of their phenotype was significant. This finding included high levels of antibodies to type G antiphospholipids, ANA, and thrombocytopenia, which posed a heightened risk during pregnancy and the postpartum period.

The combination of thrombocytopenia and positive antiphospholipid antibodies complicates the administration of treatment during pregnancy to prevent coagulopathy, typically involving enoxaparin and acetylsalicylic acid. This scenario raises critical questions about managing pregnancy complications, whether the primary concern is bleeding or excessive clotting, and how to respond with appropriate treatments in each situation.

Despite these challenges, a notable success for the patient was the completion of IVF with oocyte retrieval during hospitalization. This procedure preserved her fertility despite the significant risks of bleeding and coagulopathy. Consequently, this achievement provides the option of surrogacy if carrying a personal pregnancy proves unfeasible. Looking forward, advancements in medical treatments may enable such patients to use their own IVF cycles for pregnancy, potentially offering better outcomes and more tailored responses to their complex medical conditions.

CONCLUSIONS

The patient's case depicts a complex scenario involving heightened risks of both bleeding and thrombosis. Given the scarcity of literature on this matter, a personalized decision for the patient was imperative. Initially addressing primary infertility, a tailored protocol for oocyte retrieval was necessary. After a multidisciplinary discussion, a unique pre-retrieval treatment protocol was devised. Due to the substantial risks of severe bleeding and thrombosis, pregnancy was not recommended, and surrogacy was advised as a safer alternative.

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References

1. Gonzalez-Porras JR, Palomino D, Vaquero-Roncero LM, Bastida JM. Bleeding complications associated with pregnancy with primary immune thrombocytopenia: a meta-analysis. *TH Open* 2022; 6 (3): e230-7.
2. Tomasello R, Giordano G, Romano F, et al. Immune thrombocytopenia in antiphospholipid syndrome: is it primary or secondary? *Biomedicines* 2021; 9 (9): 1170.
3. Barbhaiya M, Zuily S, Naden R, et al; ACR/EULAR APS Classification Criteria Collaborators. The 2023 ACR/EULAR Antiphospholipid Syndrome Classification Criteria. *Arthritis Rheumatol* 2023; 75 (10): 1687-702.
4. Ahmed MU, Receveur N, Janus-Bell E, et al. Respective roles of glycoprotein VI and FcγRIIA in the regulation of αIIbβ3-mediated platelet activation to fibrinogen, thrombus buildup, and stability. *Res Pract Thromb Haemost* 2021; 5 (5): e12551.
5. Ricard L, Laurent C, Papo M, et al. Clinical and prognostic significance of antinuclear antibodies in primary antiphospholipid syndrome: a multicenter retrospective study. *Joint Bone Spine* 2022; 89 (2): 105297.

Capsule

Resolution of squamous-cell carcinoma by restoring T-cell receptor signaling

Cutaneous squamous cell carcinoma (SCC) is primarily caused by oncogenesis mediated by ultraviolet radiation, and β-human papillomavirus (β-HPV) is believed to be a mere facilitator that is dispensable for the maintenance of cutaneous SCC. **Ye** et al. described a woman with benign and malignant HPV-related diseases that include a recurrent, unresectable, invasive cutaneous SCC with β-HPV19 genomic integration in the context of germline pathogenic mutations in *ZAP70*, an adapter required for T-cell receptor (TCR) signal transduction. Restoration of the integrity of TCR signaling by allogeneic hematopoietic-cell transplantation led to the resolution of all HPV-related diseases, thereby revealing a direct role of β-HPV in skin carcinogenesis in hosts with defective adaptive T-cell responses.

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