CASE REPORT

Hypergammaglobulinemic Purpura of Waldenstrom (HGPW) in Pregnancy: A Rare Case Report

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Introduction

Hypergammaglobulinemic purpura of Waldenstrom (HGP) is a rare skin condition first described by Waldenstrom in 1943. It presents as recurring purpura, elevated erythrocyte sedimentation rate, mild anemia, hypergammaglobulinemia and the presence of circulating immune complexes. It can be primary or secondary when associated with other autoimmune diseases, especially Sjogren's and lupus erythematosus. It usually affects females of reproductive-age group, i.e., between 18 to 40 years of age. It is usually a benign condition which does not require extensive investigation and treatment in its primary form. Limited literature is available of its occurrence in pregnancy in which case HGPW requires prompt diagnosis and treatment for better fetal and maternal outcome. The presence of anti-Ro antibodies in the maternal serum may lead to congenital

heart block in 1–2% of pregnancies, neonatal lupus rash in around 10–20% of cases with nine times risk of recurrence. Circulating immunoglobulins may lead to IUGR, preeclampsia, anemia or even IUD. Successful fetal and maternal outcome is possible in current and subsequent pregnancies if HGPW is diagnosed and managed on time [1, 2].

Case Report

A 22-year-old unbooked female primigravida reported to ANC clinic of DR RML Hospital on November 03, 2016, at 24 weeks of gestation with complaint of increasing non-pruritic rash over her body. Patient had similar episodes of skin eruptions for past one year which were non-pruritic and mostly on covered areas for which she took no medical consultation. There was no history of photosensitivity, allergy, bleeding disorders, joint pains and oral ulcer. There was no history of any dermatological or autoimmune disease in the family as well. On examination large purpuric rash was seen over her chest, upper abdomen and lower limbs, sparing her face and upper limbs (Figs. 1, 2, 3, 4). She had mild pallor and was normotensive with other general and systemic examination within normal limit. A dermatological consultation was sought where an autoimmune disorder was suspected in view of flaring up of skin lesions in pregnancy. Blood investigations revealed moderate anemia (7.6 gm% normocytic normochromic), raised erythrocyte sedimentation rate (129 mm in 1st hr), normal platelet count (1.8 lakhs), normal liver and kidney function tests, raised antinuclear antibodies (ANA), ds DNA were positive, raised anti-Ro antibodies and increased gamma globulins on protein electrophoresis, but anti-La antibody, beta 2 glycoprotein, lupus anticoagulant, anti-phospholipid antibodies (aPL) were negative. Her HbsAg, antiHCV, HIV were also negative. Urine routine and microscopic examination was normal with no evidence of proteinuria. Skin biopsy of the lesions revealed numerous dilated capillary channels with the presence of perivascular infiltrate and destruction of the wall by polymorphonuclear cells, endothelial swelling, karyorrhexis and focal extravasations of RBCs consistent with leukocytoclastic vasculitis (Fig. 5). On basis of this, a diagnosis of HGPW, secondary to lupus erythematosus was reached. Fetal echo was reported as increased PR interval in the fetus (first-degree heart block). Patient was started on hydroxychloroquine 200 mg twice daily and low-dose aspirin 75 mg once daily. She was regularly followed in antenatal O.P.D with serial fetal echo. She remained normotensive with no proteinuria or evidence of IUGR. Subsequent Fetal echo did not show prolongation of PR interval more than 95 percentile so steroids were not needed after consultation with fetal

medicine specialist. Patient was admitted at 38 weeks 6 days with leaking per vaginum and had an emergency LSCS because of fetal distress with PPIUCD insertion. A girl baby of 2.5 kg was delivered, and the neonate had no evidence of lupus. ECHO done later was reported normal. Patient was discharged from hospital and had partial remission of her rash in 4–6 weeks following delivery. She continued follow-up with the dermatologists and in rheumatic clinic and till now has no other sequela apart from skin rash.

Discussion

Effect of pregnancy on autoimmune disease depends upon whether the autoimmune disease is cellular or humoral in nature. Disease with strong cellular pathology like rheumatoid arthritis and multiple sclerosis is associated with remission, whereas diseases characterized by autoantibody production like SLE, Graves tend towards increased severity in pregnancy. Obstetrician should be familiar with common as well as rare manifestations of autoimmune disorders as they occur in women in reproductive age [1].

Jan Gosta Waldenström a Swedish physician first described the clinical entity of hypergammaglobulinemic purpura in 1943 which was then named “Waldenström’s” or “Benign” HGP. But it is not benign in pregnancy. HGP is a rare clinical syndrome usually affecting (80%) young females in reproductive-age group (18–40 years). It consists of a typical purpuric rash on dependent areas of the body and associated abnormal laboratory investigations (polyclonal IgG, increased ESR, positive RF/ANA/ENA and often a mild anemia and lymphopenia). The disorder may be primary or secondary to an underlying

Fig. 1 Macular rash over the upper abdomen and chest

Fig. 2 Face spared of any rash

Fig. 3 Purpuric macules on the lower limbs

Fig. 4 Purpuric macules on lower limb

Fig. 5 Skin biopsy showing leukocytoclastic vasculitis

inflammatory process, autoimmune disease (usually Sjögren's syndrome (SS) or systemic lupus erythematosus (SLE) or neoplasm. In younger patients, it is usually primary, but over time some patients develop evidence of an autoimmune connective-tissue disease, most frequently Sjögren's syndrome and occasionally rheumatoid arthritis or lupus erythematosus [2].

The presence of anti-Sjögren's syndrome A (SSA)/Ro antibodies (in the presence or absence of anti-SSB/La antibodies) in maternal sera has a 1–7.5% risk of having a child with third-degree CHB and neonatal lupus which occurs in up to 10% of babies in primigravida. The recurrence rate in subsequent pregnancies is about 2–3 times higher, i.e., around 20%. It can present as fetal bradycardia and cardiac failure, i.e., pericardial effusion and hydrops, after 16–24 weeks of gestation. A life-threatening cardiomyopathy may be present in 10–15% cases. Mothers with autoimmune antibodies should undergo regular fetal ultrasonographic assessments including fetal echocardiography as early as 16 weeks of gestation which can reveal varying degrees of AV block, and further fetal monitoring should be performed to look for bradycardia, fetal distress and hydrops fetalis. Regular and close monitoring for heart block and transplacental therapy with fluorinated steroids (dexamethasone) has shown satisfactory results at first evidence of heart block, and it is beneficial in first- and second-degree heart block, but once fetal third-degree block is detected, it is irreversible regardless of treatment. Prophylactic therapy is not currently indicated as they may have maternal and fetal side effects like osteoporosis, osteonecrosis, diabetes, hypertension, premature rupture of membranes, adrenal insufficiency of the fetus, intrauterine growth restriction (IUGR) and oligohydramnios [3, 4].

The etiology of the disorder is not clear, however, on skin biopsy; a leukocytoclastic vasculitis is usually seen. This suggests that the polyclonal increase in immunoglobulin's (many of which are autoreactive) is vital in the development of the clinical picture. Intrauterine growth retardation and renal insufficiency requiring pre-term delivery have been described due to hyper-viscosity associated with HGP. This hyper-viscosity is attributed to the increased level of IgG circulating in the plasma affecting the remodeling of maternal spiral arteries essential for adequate blood flow through the placenta [2, 4].

The literature concerning HGP and pregnancy is limited. Nonetheless, it is a vitally important clinical consideration since the disease has a marked preponderance in reproductive-age females. It is well recognized that anti-Ro antibodies can cross the placenta and cause complete heart block in the fetus. In a case report by Maeda-Tanaka M et al. in 2006, a 30-year-old primigravida woman with 14 years of HGP was found to have fetal bradycardia at 25 weeks' gestation [5]. Laboratory investigations demonstrated positive anti-Ro/SSA and anti-La/SSB antibodies in the maternal serum. Cesarean delivery was performed at 39 weeks, and a 2750-g female infant was born with complete atrioventricular block. Another case reported by Elaine C. Jolly et al. in 2008, a 22-year-old female primigravida presented at 25th week of her pregnancy with signs and symptoms of severe preeclampsia, non-pruritic purpuric coalescent rash. She had an IUD after 3 days. Placenta showed histological evidence of infarction. She was diagnosed with anti-Ro, La-positive HGPW [6]. Three cases reported by Kapur et al. in 2014 had positive anti-Ro (SSA) and anti-La (SSB) in pregnancy and were diagnosed with congenital heart block in fetus at various period of gestation [3].

Many patients, particularly those with primary HGP, will require no specific treatment, however, where attacks of rash and joint pains are frequent or debilitating successful therapy with colchicines, prednisolone, hydroxychloroquine, indomethacin, chlorambucil, rituximab and plasmapheresis have all been reported [4, 5, 7]. The antimalarial drug, hydroxychloroquine, appears to reverse platelet activation induced by human immunoglobulin aPL antibodies and decrease the thrombogenic properties of aPL antibodies and also appears to decrease aCL levels. No teratogenicity has been described with the use of hydroxychloroquine in pregnant women. This rare case report is being discussed, as it was diagnosed during late second trimester. Despite having SSA positive along with partial heart block, patient did not develop more complications in this pregnancy and the child did not need pace maker. The history of flare up in pregnancy and the wide spread skin lesions made us suspect autoimmune etiology, and the investigation and skin biopsy proved this rare disorder which is not seen in usual practice. Steroids were not given for the prevention of worsening

heart block as subsequent fetal ECG did not show PR interval beyond 95 percentile and steroids have significant associated side effects. A multidisciplinary approach is required to diagnose rare disorders of this kind. This patient would need more surveillance in her next pregnancy as the risk for CHB is more in second pregnancy and may require thromboprophylaxis as well. Contraception in these patients is best by copper or LNG IUCD. Estrogen-containing hormonal contraceptives may be used in stable, inactive SLE patients but are contraindicated in patients with positive aPL antibodies [7].

Conclusion

Obstetrician should be familiar with common and rare manifestations of autoimmune disorder as they occur in women in reproductive age and can have serious even life-threatening sequela in mother and child.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed Consent Written and informed consent was taken from patient for publication of case and photographs.

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