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Incidental Finding of Panhypogammaglob-ulinaemia in Pregnancy-an Extremely Rare Condition

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Summary- A 22 year old lady, G2P0 presented at a 311 weeks of gestation with an abnormal group and antibody test found incidentally during routine 28 week blood testing. She reported no past medical history apart from medication controlled gestational diabetes and denied any family history of autoimmune diseases. She was subsequently diagnosed with panhypogam-maglobulinemia. After consultation with an immune-ologist, a number of blood investigations were undertaken, all of which were negative, except for an MRI which showed a possible small thymoma. All fetal ultrasounds were unremarkable. Given the importance of transplacental immunoglobulin (Ig) transfer in the third trimester and the concern of serious infection during pregnancy she has was commenced on intravenous immunoglobulin (IVIg). After a loading dose of IVIg (0.6mg/kg) and a subsequent dose (0.4mg/kg) her Ig level was 10. She was administered a third dose and it was decided that her Ig levels be monitored weekly and IVIg only administered should her levels drop below 7. Since her Ig levels dropped to 6.9g/L at 37 5 weeks of gestation, she received another dose (0.4mg/kg). She underwent a normal delivery at 391 weeks and was diagnosed with a thymoma postnatally.

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I. Background

This case is particularly interesting not only because it is very rare but presents an interesting clinical challenge. Although panhypogammaglobulinemia is a well described condition, only a few published cases of it occurring in pregnancy exist. Additionally, among the few cases published there is a disagreeance as to whether treatment is required.

II. Case Presentation

The patient is a 22 year old woman of subcontinental Indian origin who at the time of diagnosis was 30 weeks pregnant with her second pregnancy. She has no past history of any significant infections, neither recently nor in her childhood and denied any past operations or hospital admissions. After a routine 28 week oral glucose tolerance test during her second pregnancy she was diagnosed with gestational diabetes. After a trial of diet control, she was started on metformin at 34 weeks maintained adequate control of her blood sugar levels. Apart from her recent gestational diabetes and a first trimester miscarriage in the first trimester of her first pregnancy, she has no significant past medical history of note. There is no significant family history of note and prior to pregnancy she denies any abnormal weight loss, fevers, fatigue and night sweats. There is no history of consanguinity and she is a non-drinker and non-smoker. She has no known drug allergies and apart from metformin she also took a pregnancy multi-vitamin,

Her pregnancy was the result of spontaneous conception and and all antenatal ultrasounds were unremarkable. At 223 weeks a morphology revealed no abnormalities and a cephalic lie with a posterior placenta. Her 45 week routine blood tests revealed she was rubella non-immune and had low globulins (16g/L (20–36). Urinalysis performed showed no abnormalities.

III. Investigations

At 311 weeks her blood tests showed undetectable levels of Igs (IgG <1 g/L(7 -16); IgA <0.06 g/L(1 – 4); IgM 0.07 g/L(0.4 – 2.3)).

MRI (323 weeeks) showed a mass within the anterior mediastinum in the expected location of the thymus measuring 37mm in width by 18mm in maximal AP dimension. The appearance is somewhat non-specific, with a differential line between a thymic remnant and a thymoma. There are no overly aggressive features to suggest a thymic carcinoma.

Ultrasound (322 weeks) did not show any placental oedema or other obvious placental pathology demonstrated.

A postnatal CT confirmed the presence a thymic mass which intraoperative histology demonstrated to be a thymoma.

Other investigations (FBC/ELFTs, Urine Protein, Serum EPP/Urine EPP, ANA/ENA C3/C4, Lymphocyte subsets, CRP/ESR, HIV, Faecal a1anti-trypsin, urinalysis for EPP and the presence of Bence-Jones proteins) performed to exclude SLE, Leukaemia, Lymphoma, Multiple Myeloma and nephritic syndrome are all negative.

IV. Differential Diagnosis

- Good Syndrome (thymoma with immunodeficiency)
- CVID
- Primary or secondary nephrotic syndrome.

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V. Treatment if Relevant

After discussing the treatment options with the immunologist it was decided that the patient would undergo intravenous administration of Ig. Given her extremely low levels of Ig, a loading dose of 0.6mg/kg was administered at 331 weeks. Apart from the patient suffering from tachycardia and shivering, the infusion continued uneventfully. Three more infusions were administered at a lower dose of 0.4mg/kg at 343, 351 and 385 weeks with no adverse effects noted. The fourth dose was administered at approximately 39 weeks since her Ig level fell below 7. Peripartum antibiotics were prescribed for seven days and the newborn's Ig levels were checked postnatally. These were all normal. As per instruction of an immunologist the patient was administered a tetanus vaccine postnatally and tetanus antibody levels were measured four weeks later to see if an immune response was mounted. Surgical removal of the thymoma discovered on MRI and CT was undertaken with no complications.

VI. Outcome and Follow-up

Four days after the admission the loading dose of IVIg the patient's blood tests revealed a significant improvement in plasma Ig levels (IgG 8.0, IgA <0.06, IgM <0.05). After the second dose her bloods showed further improvement (IgG 10.0, IgA <0.06, IgM <0.05). However, her Ig levels dropped to 6.9g/L at 37 5 weeks of gestation hence she received another dose (0.4mg/kg).

After delivery the infant's Ig levels were monitored and found to be progressing as expected of a normal child. The patient was followed up by an immunologist and a CT scan confirmed to diagnosis of a thymoma. This was removed surgically and histologically confirmed as a thymoma. The patient has recovered well from the procedure and has had no long term side effects.

VII. Discussion

Good syndrome is an exceptionally rare condition characterised by a combination of B and T cell immunodeficiency and the presence of a thymoma. As a result of their immunodeficiency patients are susceptible to bacterial infection with encapsulated organisms as well as opportunistic viral and fungal infections (1). The presence of such a condition during pregnancy presents a unique challenge for treating conditions. Additionally there are very few published cases regarding thymoma related immunodieficncy in pregnancy with only one other case noted in the literature (2).

After confirming the presence of hypogam-maglobulinaemia in our patient, a number of common causes such as HIV, myeloma and nephrotic syndrome were ruled out before a literature search for rarer causes was undertaken. Although there are very few cases of hypogammaglobulinaemia reported on, some potentially treatable causes were identified. A 1977 case report describes three conditions related to placental oedema which may be responsible for Ig deficiency (3). These conditions, fetal transfusion syndrome, hydrops fetalis and congential hepatic disease, and indeed placental oedema were ruled out by a normal ultrasound performed at 322 weeks. (2). To rule out the presence of a thymoma, an MRI scan was performed which demonstrated a small mass unable to be defined as either a thymoma or a thymic remnant. The presence of a thymic carcinoma was however ruled out.

Although cases exist where a hypog-ammaglobulaemic mother was untreated during pregnancy and delivered a healthy neonate, a number of cases have demonstrated treatment with IV Ig is desirable as individuals are prone to serious infections and fetal loss (4-9). As demonstrated in a case published by Laursen and Chistensen (1973) neonates born to hypogammaglobulinaemia mothers are typically deficient in Ig (5). Given that it can take infants up to four months to produce adequate levels their own Ig, it is often necessary to provide IV Ig therapy to newborns as well(10). Despite being deficient in Ig at birth it seems likely from previous cases that the newborn will go on to produce normal levels of Ig once its own immune system become functional during the first six months of life (5).

Postnatally, mothers require further investigation of the cause of hypogammaglobulinaemia and may require ongoing IV Ig therapy. In our case a thymoma was discovered and surgical removal was undertaken. As expected from prior cases the delivery of the fetus was uncomplicated we do not believe her condition will have any lasting effect on the infant's health.

VIII. Learning Points/take Home Messages

- Any abnormalities found in routine blood tests during pregnancy need to be investigated and treated seriously
- There is a need for more cases of a similar nature to be published so that the best treatment can be determined.
- Currently, IVIg therapy is the mainstay in order to optimise fetal/neonatal outcome.

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