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Subcutaneous Immunoglobulin Therapy in a Woman with Spontaneous Pregnancy Loss and Multiple Sclerosis

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Abstract

Background: Off-label use of intravenous immunoglobulin has been reported for the treatment of recurrent spontaneous pregnancy loss and selected cases of multiple sclerosis. However, the use of subcutaneous immunoglobulin has not been reported in these settings.

Methods and results: We report on tolerability and clinical efficacy of subcutaneous immunoglobulin therapy in a woman with the unusual association of IgG4 subclass deficiency, C4 hypocomplementemia, localized scleroderma, unexplained spontaneous pregnancy loss and multiple sclerosis. Weekly infusions of subcutaneous immunoglobulin were self-administered at home (6 grams/week, Hizentra®) during the next pregnancy after abortion. Interferon beta-1a for the treatment of relapsing-remitting multiple sclerosis was stopped before pregnancy. During pregnancy only subcutaneous immunoglobulin was administered. The patient was found to have 4% of CD3⁺CD16/CD56⁺ (Natural Killer (NK) /T cells). The patient delivered a healthy baby (Apgar score 9 at 5 minutes) at 37 weeks gestation. During pregnancy and 3 months follow-up after delivery no multiple sclerosis flare-ups were observed. NK-T cell percentages remained stable.

Conclusions: Our observation indicates that subcutaneous immunoglobulin therapy was well tolerated and efficacious in a selected case of unexplained abortion and multiple sclerosis.

Keywords: Immunoglobulin; Spontaneous pregnancy Loss; Multiple sclerosis

Introduction

Recurrent pregnancy loss is defined as two or more pregnancy losses before gestational week 20. Immunological abnormalities are hypothesized to play a role in recurrent miscarriage [1]. Distinct types of immune-based therapies have been evaluated

including intravenous immunoglobulins [2]. On the other hand pregnancy is associated with stabilization of autoimmune diseases, such as multiple sclerosis [3]. Although pregnancy in women with multiple sclerosis is not generally considered high risk, there are some associated therapeutic challenges. As an example, previous data suggest that pregnancy exposure to interferon-beta might result in lower mean birth weight and preterm birth [4] while other studies suggest the safety of this intervention [5]. We report on the tolerability and clinical efficacy of subcutaneous immunoglobulin therapy in a woman with the unusual association of IgG4 subclass deficiency, multiple sclerosis and unexplained spontaneous pregnancy loss.

Methods

NK and NK-T cell analysis was performed by four-color flow cytometry. IgG subclass and complement C4 assessment was done by nephelometry. Subcutaneous immunoglobulin: 20% liquid immunoglobulin therapy for subcutaneous use (Hizentra®, CSL Behring).

Case Report

A 30 year-old white woman presented with IgG4 subclass deficiency (0.04 g/L), C4 hypocomplementemia (12-15 mg/dL). IgG4 subclass deficiency was associated with recurrent respiratory infections, recurrent oral herpes, asthma and recurrent hidrosadenitis. The patient received intravenous immunoglobulin followed by self-administered subcutaneous immunoglobulin at home at a dose of 300 mg/kg/month. The change to subcutaneous injections was for patient convenience. The clinical course of the patient was complicated by localized scleroderma and later by relapsing/remitting multiple sclerosis. Interferon beta-1a was started. An unexplained spontaneous abortion presented at 11 weeks gestation. A study was performed to evaluate potential causes of recurrent spontaneous pregnancy loss including anatomical, chromosomal and endocrine factors. Antiphospholipid, antinuclear and anti-thyroid antibodies were negative. Peripheral blood natural killer cells expressing a T-cell marker (CD3⁺CD16/CD56⁺) were 4%. NK

cells (CD3⁺CD16⁺/CD56⁺) were below 12% in distinct determinations. During the next pregnancy after abortion, weekly infusions of subcutaneous immunoglobulin were self-administered at home with dose adjusted to 400 mg/kg/month: 6 grams/week. Interferon beta-1a for the treatment of relapsing-remitting multiple sclerosis was stopped before pregnancy. During pregnancy only subcutaneous immunoglobulin was administered. Subcutaneous infusions were administered in the abdomen, then in thighs or upper arms during the last weeks of pregnancy. A cesarean section was performed due to podalic presentation and premature rupture of membranes at 37 weeks gestation. The patient delivered a healthy baby (Apgar score 9 at 5 minutes). During pregnancy and 3 months follow-up after delivery no multiple sclerosis flare-ups were observed. A reconstitution of IgG4 levels was observed. NK-T cell percentages remained stable. Subcutaneous infusions were well tolerated and the patient did not have adverse reactions. The patient remains self-administering subcutaneous immunoglobulin at home.

Discussion

A cut-off value of 3.75% for the increased percentage of NK-T cells in the peripheral blood has been suggested as a potential biomarker of pregnancy failure [6]. It is well known that intravenous immunoglobulins might be useful to overcome recurrent pregnancy loss in women with immunological abnormalities including high NK cell counts [2], but the mechanisms at the base of a successful outcome are still unknown. It has been described that IVIG has the potential to alter cytokine profiles and NK activity [7]. Very interestingly, in a study performed by Manfredi et al. an association between IgG subclass deficiency and recurrent pregnancy loss was suggested and high rates of successful pregnancy were observed after therapy with intravenous immunoglobulin was used in these women. The authors speculated about restoring of the idiotype-antiidiotype network as a potential mechanism in these cases [8]. In another study performed by Wilson et al. lower levels of IgG subclasses were detected in women with recurrent pregnancy loss [9]. We have previously described a high prevalence of hypocomplementemia in the absence of autoantibodies in women with recurrent pregnancy loss [10]. IVIG is also a modifier of complement activation and injury [11]. We have recently reported that increased T-cell activation is associated with recurrent pregnancy loss [12]. It has been suggested that intravenous IgG and subcutaneous IgG preparations have comparable inhibitory effect on T cell activation [13].

For the first time we describe that subcutaneous immunoglobulin that was prescribed for IgG subclass deficiency was associated with a good outcome in the next pregnancy in a woman with distinct immunological abnormalities that have been associated with recurrent pregnancy loss. This could be an innovative approach to immunomodulation in women with recurrent pregnancy loss and immunological abnormalities, but the effectiveness of this intervention cannot be inferred based on a single case report. The safety and efficacy of subcutaneous immunoglobulin in this setting warrant evaluation in a clinical

trial. The most common adverse reactions that have been described in patients using SCIG are redness, swelling, itching, heat, or pain at the infusion site. Other common side effects that have been described are headache, vomiting, pain, and fatigue [14].

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