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Pregnancy and childbirth after treatment with autologous hematopoietic stem cell transplantation for severe systemic sclerosis requiring parenteral nutrition. Ethical issues

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ABSTRACT

We report a pregnancy in a patient who had undergone autologous hematopoietic stem cell transplantation (AHSCT) for diffuse cutaneous systemic sclerosis (SSc). SSc onset was at age 25, with Raynaud phenomenon and evolved to include diffuse cutaneous, arthritis, pulmonary fibrosis and extensive gastrointestinal involvement. AHSCT (cyclophosphamide/ATG for conditioning) was performed four years later with improvement of all features apart from the gastrointestinal symptoms requiring parenteral nutrition (PN). Forty months after AHSCT, she had a spontaneous miscarriage necessitating curettage. Despite advice to avoid pregnancy because of poor nutritional status and recurring catheter infections from her PN, she fell pregnant one year later. The pregnancy proceeded normally and she delivered at 34 weeks, under cesarean section. The baby girl, (1990g and 4 APGAR score) after initial respiratory distress, is now 4 years old with normal growth and development. Unfortunately, the patient died early in 2008 due to severe disease progression terminating with gastrointestinal obstruction and pericarditis. This first report of a successful pregnancy in a patient with diffuse SSc treated by AHSCT illustrates that despite the possibility for a normal pregnancy, the decision to do so includes aspects of maternal prognosis.

Introduction

Systemic Sclerosis (SSc) is a connective tissue disease with female predominance (sex ratio 3 to 8:1) characterized by diffuse micro-vascular injury, fibroblast activation and increased collagen production leading to diffuse sclerosis (1). Although the mean age of disease onset is the mid-forties after most women have completed childbearing (1, 2), youngest patients may have legitimate questions on fertility and pregnancy. Pregnancy in women with active SSc is mostly possible, but considered to be "high risk" and should be planned (3). Thus, patients with early diffuse SSc should delay pregnancy due to the risk of renal crisis (2, 3) and have reduced life expectancy in case of visceral involvement (4). For them, treatment by autologous Hematopoietic Stem Cell Transplantation (AHSCT) shows promising results (5-6), but may be complicated by cyclophosphamide (CY) induced sterility (7).

Case report

We report a successful pregnancy after AHSCT in a 32-year-old black woman from the West Indies, who despite an initial good response to AHSCT, died from disease progression four years later, emphasising the medical and ethical complexity of such cases.

SSc began at age 21 with Raynaud phenomenon and progressed three years later to diffuse cutaneous involvement (modified Rodnan skin score 36), arthritis, pulmonary fibrosis and gastrointestinal involvement requiring transient parenteral nutritition (PN). Antinuclear and topoisomerase 1 antibodies were positive and renal and cardiac function normal. At age 25, she underwent AHSCT (5) with stem cell mobilisation using CY 4 g/m2 (5800mg total) and G-CSF, plus conditioning with CY 200mg/kg body weight (9200 mg total) followed by a CD34+ selected graft. No major toxicity occurred. Her clinical status improved (Fig. 1) apart from chronic intestinal pseudo-obstruction, which required 6 cycles of nocturnal home PN infusions weekly. Menses returned 12 months post transplant, and she was cautioned against pregnancy.

Forty months after AHSCT, she experienced a spontaneous miscarriage after six weeks of amenorrhea. One year later, she became pregnant again. Warfarin, octreotide and the ACE inhibitor were substituted with enoxaparin, erythromycin and amlodipine respectively. PN was adjusted to twice the daily caloric expenditure with 7 infusions weekly. The clinical course of the pregnancy was considered normal with monthly clinical review, foetal growth assessment by ultrasound as well as uteroplacental vascular resistance index on Doppler ultrasound without protodiastolic notches (9). At 33 weeks gestation, the patient was admitted for preterm labour, successfully treated with oral nifedipine (10). Subsequently, she developed hypertension of 130/95 mmHg with 1.8 g/24 hrs proteinuria. Twelve milligrams

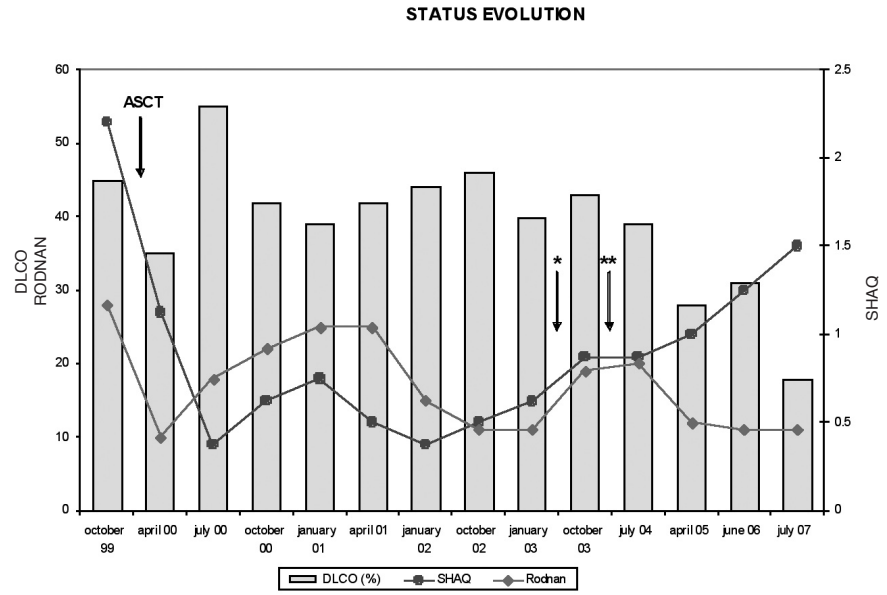

Fig. 1. Evolution of the functional and the clinical status, as assessed by the Scleroderma Health Assessment Questionnaire (SHAQ) (8) the modified Rodnan skin score (Rodnan) and the Diffusing Capacity of the Lung for Carbon Monoxide (DLCO) after Autologous Hematopoetic Stem Cell Transplantation (AHSCT, performed in January 2000) and during pregnancy. (*first miscarriage in May 2003; ** pregnancy started in May 2004).

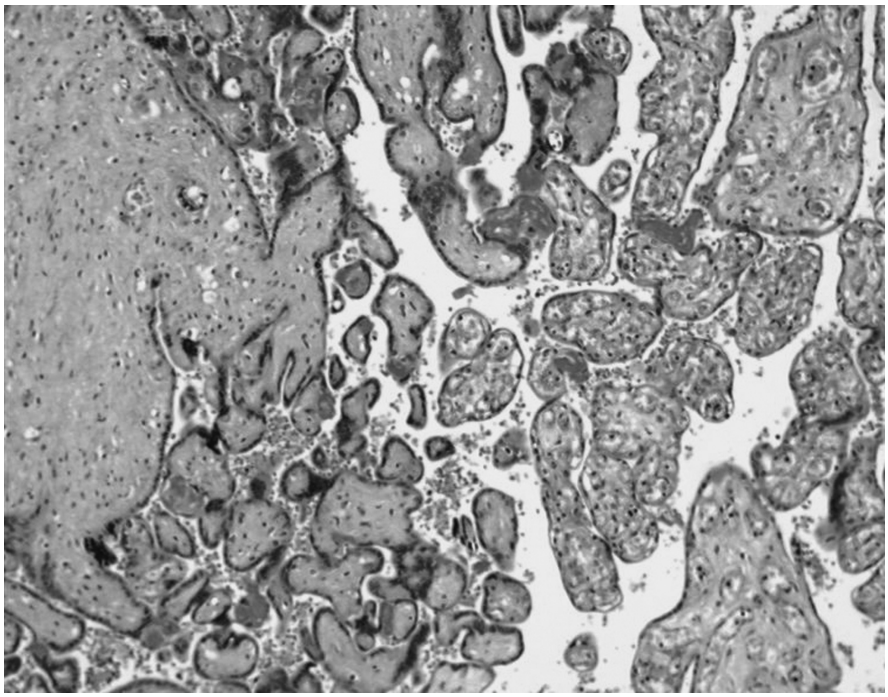

Fig. 2. Placenta analysis on histological examination (HES x 100) showing perivillous fibrin deposition and syncitial knots with some congestive and hypoxic terminal villi, as seen in chronic uteroplacental malperfusion. Left: Accelerated maturity with small fibrous terminal villi and numerous syncytial knots (Tenney-Parker change); Right: normal sized but congestive villi.

intramuscular betamethasone were administered for foetal pulmonary maturation to anticipate premature delivery. At 34 weeks gestation, decreased foetal heart rate required urgent caesarean delivery under spinal anesthesia after interrupting enoxaparin. A healthy girl, weighing 1990g (30th percentile) with an APGAR score of 4 and 10 at one and five minutes respectively was delivered and transferred to the neonatal unit for five days. Respiratory distress syndrome required 12 hours mechanical ventilation. Placenta analysis is shown in Figure 2. The postnatal course was uncomplicated and treatment initiated during pregnancy was continued three months during breastfeeding.

Four years later, the child is healthy with normal growth and development. The mother on PN for a total of 92 months, with yearly Caribbean holidays, underwent musculoskeletal and functional status deterioration necessitating nurse practitioner home care during the last six months. Despite sustained improved skin score, SSc lung fibrosis progressed 2 years after delivery. A new episode of gastrointestinal obstruction with pericarditis led to death from intractable cardiorespiratory failure at age 36.

Discussion

Both SSc and AHSCT raise special issues concerning pregnancy. In SSc, most women will experience normal pregnancy, although the associated risks are known: fetal loss, foetal growth retardation plus increased frequency of renal crisis in early diffuse SSc (2). Therefore, women are advised not to become pregnant during the acute early phase of the disease. Nonetheless, SSc female patients have normal fertility and may express the desire to conceive, especially when their functional status and general condition is improved after successful AHSCT (5, 6).

The use of alkylating agents for conditioning before AHSCT may be associated with gonadal dysfunction and infertility, but it does not constantly albeit fertility (11) or increase the risk of foeto-maternal complications in women becoming pregnant after AHSCT for haematological disease (12). As already solved for male patients with semen preservation, fertility preservation has become a practical issue in women eligible for ASCT. Information about the consequences of ASCT on fertility should be provided and ovarian tissue cryopreservation (13) or use of gonadotropin-releasing hormone agonists (14) may be an option in the near future.

SSc patients should be advised that their “high risk” pregnancy requires a multidisciplinary approach for close

monitoring of the SSc, the pregnancy and delivery, including weekly home monitoring of weight, BP, urinary sediment analysis and at least monthly hospital visits for clinical, ultrasonographic and biological examination. In case of renal crisis, ACE inhibitors are required despite their potential association with birth defects and infant kidney dysfunction (3). In our patient, acetylsalicylic acid to prevent placental vascular complications was contraindicated because of gastric telangiectasia. However, most previously reported SSc pregnancies had normal outcome (2, 3) without its use, which can be controversial. In preterm labour, calcium channel blockers have proven efficacy plus a vasodilatating effect (15). In this case, vaginal delivery was not considered because of severe atrophy due to SSc and local anesthesia was preferred to general one because of low mouth opening preventing intubation. As already reported (5, 6), AHSCT permitted rapid improvement of the patient's quality of life. It did not affect her fertility, nor her desire for pregnancy, despite reserves from the medical staff and need for PN again. Successful pregnancy with the birth of a normal child was achieved after previous treatment by high dose alkylating agents.

In conclusion, pregnancy following AHSCT for severe SSc is possible, but requires expert multidisciplinary management to provide individual therapeutic option and specific therapeutic consensus. However, pregnancy and the child's ultimate outcome depend on the mother's long-term prognosis raising difficult ethical issues.

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