CASE REPORT

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Management of myelofibrosis during pregnancy: A case report

Lečenje mijelofibroze tokom trudnoće

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Abstract

Introduction. Primary myelofibrosis (PMF) is a clonal myeloproliferative neoplasm that occurs most commonly in the decade six of life and it is very rare in the young persons. **Case report.** We reported a 28-year-old female patient with primary myelofibrosis who had a normal pregnancy and delivery in the week 40 of pregnancy without any complications. Two years before the diagnosis of PMF she had normal pregnancy. The patient was treated with interferon-alpha and low dose aspirin during the whole pregnancy and with low-molecular-weight heparin a week before delivery and 6 weeks after. The patient had no complications during pregnancy. She delivered in term with healthy, normal baby weight. **Conclusion.** Decision about treatment strategy of pregnancy associated hematologic malignancies should be made for each patient individually.

Key words:
myeloproliferative disorders; primary myelofibrosis; pregnancy; interferon-alpha; treatment outcome.

Apstrakt

Uvod. Primarna mijelofibroza je klonsko mijeloproliferativno oboljenje koje se najčešće javlja u šestoj deceniji života, a vrlo retko kod mladih osoba. **Prikaz bolesnika.** Prikazana je 28-godišnja bolesnica sa primarnom mijelofibrozom, koja je imala normalnu trudnoću i porođaj u četrdesetoj nedelji trudnoće bez komplikacija. Tokom cele trudnoće bolesnica je lečena interferonom alfa i niskim dozama aspirina, a nedelju dana pre i 6 nedelja nakon porođaja primenjen je i niskomolekularni heparin u profilaktičkim dozama. Bolesnica nije imala komplikacije tokom trudnoće i rodila je zdravu bebu normalne težine. **Zaključak.** Odluka o strategiji lečenja trudnica sa prisutnim hematološkim malignitetima treba da bude doneta posebno za svaku bolesnicu.

Ključne reči:
mijeloproliferativni poremećaji; primarna mijelofibroza; trudnoća; interferon-alfa; lečenje, ishod.

Introduction

Primary myelofibrosis (PMF) is a clonal myeloproliferative neoplasm chacterized by a proliferation of megakariocytes and granulocytes in the bone marrow, associated with reactive deposition of fibrous connective tissue and with extramedullary hematopoises [1, 2]. It occurs most commonly in the decade six of life and it is very rare in the young ones [1, 2]. Pregnancy is a high-risk event in women with thrombocytosis, especially in patients with essential thrombocythemia and PMF. The risk of spontaneous abortion is 2.5-fold higher than in the control population, while the incidence of maternal complications is lower, 3% for major thromboembolic and 2% for major bleeding event [3]. We reported a 28-year-old female patient who had a normal pregnancy and delivery, treated with interferon-alpha, low-dose aspirin and low-molecular-weight heparin (LMWH).

Case report

A 28-year-old woman was sent to the hematologist in November 2011, due to asymptomatic thrombocytosis (platelet count 1,040 × 10^9/L). Her previous medical history was unremarkable, excluding conization of uterine cervix because of cervical intraepithelial neoplasia diagnosed in 2007. Two years before admission she had a normal pregnancy and delivery. Physical examination did not show peripheral lymphadenopathy, hepatosplenomegaly or signs of skin and mu-

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cosal bleeding. Laboratory findings (sedimentation rate, biochemistry and hemostatic findings) were normal. Except for elevated platelet count, the rest of the full blood count was within normal limits. Chest radiology was normal, too. Ultrasonography of the upper abdomen showed slightly enlarged spleen (130 × 60 mm in diameter). The bone marrow trephine biopsy showed 60% bone marrow cellularity with moderate proliferation of megakariocytes, which were mostly enlarged, hyperlobulated, polymorphic, forming clusters of variable size. Reticular fibrosis was moderate, gradus I. Kariotype was normal, 46-XX. Janus kinase 2 (JAK2) (V617F) mutation was not identified, as well as bcr-abl rearrangement. Pattern of *in vitro* growth of hematopoietic progenitors from bone marrow and peripheral blood did not speak in favor of the myeloproliferativne disease, so the revision of pathological findings of the marow trephine biopsy was done in the University of Cardif, Wales. These findings confirmed the diagnosis of prefibrotic phase of primary myelofibrosis (MF-1) with no evidence of CD34/CD117 blasts. Considering low International Prognostic Scoring System and Dynamic International Prognostic Scoring System (both 0) we decided to follow the patient with low-dose aspirin as the only treatment.

Soon after the diagnosis of PMF, the patient became pregnant. Interferon alpha therapy (3 MIU, 3 times a week) was given immediately, together with low-dose aspirin. After three weeks of therapy platelet count was reduced to normal value and sustained within normal limits during the whole pregnancy. Two weeks before delivery low-dose aspirin was stopped and LMWH was given before delivery and 6 weeks after. Fetal growth and placental circulation were monitored frequently and were normal all the time of pregnancy. The delivery was spontaneous, without complications and with normal baby weight. Stem cells from umbilical cord are saved for eventual stem cell transplantation. After six weeks, interferon therapy was stopped. One year after delivery, the platelet count of the presented patient was about 750×10^9/L. The treated with low-dose aspirin only was continued. In view of planning further therapy and possible need for allogeneic stem cell transplantation, HLA typing for her and her closest relatives (brother and sister) was done. Unfortunately, compatible donor was not found.

Discussion

PMF is at least prevalent of all myeloproliferative neoplasms in women of child bearing age – the prevalence is 0.023–0.06/100.000 in this age-group [4]. There are only a few literature data about pregnancy, complications in pregnancy, recommended treatment and delivery in these patients. Taylor et al. [5] and Gotić et al. [6] described one patient each with previous thrombosis and fetal loss with one successful pregnancy and child birth, while Tulpule et al. [7] in 2008 described two patients with 4 pregnancies. The first patient had no previous history of thrombosis and was treated with low-dose aspirin only and despite the complication (disseminated TBC infection) had the full-term normal delivery. The second woman had a history of previous thrombosis, so she was treated with LMWH and low-dose aspirin during the whole pregnancy. Despite the therapy, she had two fetal losses and one full-term normal delivery. Later on, it was shown that pregnancy in patients with chronic myeloproliferative disease has many risks [8–11], particularly increased risk for thrombosis. Harrison [12] shows that such risk is similar to risk in patients with thrombophilia and antiphospholipid syndrome. The most frequent complication in pregnant women with Philadelphia negative myeloproliferative neoplasms is abortion, while other maternal complications are relatively low with 3% for major thromboembolic and 2% for major bleeding events [3]. The presence of JAK2 mutation seemed to be an independent predictor of pregnancy complication [3]. This study also improved benefit from an intensive therapy including interferon-alpha with (out) LMWH throughout pregnancy and at least for six weeks after delivery. Fetal safety of interferon-alpha was also confirmed in the study of Yazdani Brojeni et al. [10]. Their results suggest that interferon-alpha have a protective effect against pregnancy loss and does not significantly increase the risk of major malformations, miscarriage, stillbirth and preterm delivery above general population rates [10].

Having in mind all these studies we decided to treat the presented patient with interferon-alpha and low dose-aspirin during the whole pregnancy and with LMWH two weeks before and six weeks after the delivery. We suggest such therapeutic approach as the best for patients with PMF, although the nature of the disease itself (low DIPSS score and negative JAK2 mutation) maybe contributed to good outcome of pregnancy.

The question of further treatment of our young PMF patient still remains. HLA typing of her sister and brother have been done, but no HLA-matched sibling donor was found. The only curative treatment of PMF is allogeneic hematopoietic stem cell transplantation [13]. According to French authors factors affecting favorable engraftment are splenectomy before HSCT, HLA-matched sibling donor, peripheral blood use as a source of stem cells and the absence of pre-transplant thrombocytopenia [13]. Tefferi [2] modified risk stratification of patients with PMF for further management that could be useful for patients like the presented. However, having in mind that the presented patient is still very young (at this moment 30 years) and in excellent condition with low International Prognostic Scoring System, the risk of allogeneic hematopoietic stem-cell transplantation in the light of the lack of family matched donor remain significant, particularly in innovative drug era. New drugs such as JAK2 inhibitors, mTOR (target of rapamycin) inhibitors, histone deacetylase inhibitors and pomalidomide show encouraging results in treatment of patients with PMF [14, 15]. Interferon-alpha also showed some promising results in reducing the fibrosis in Philadelphia-negative chronic myeloproliferative neoplasms [16], and it can possibly be used in combination with new drugs.

Conclusion

This case is the first reported pregnancy in primary myelofibrosis patient without the previous history of abortions, with no complications during pregnancy and normal, in term delivery with healthy, normal weight baby.

Decision about treatment strategy of pregnancy associated hematologic malignancies should be made for each patient individually.

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