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【 CASE REPORT 】

Multiple Placental Infarcts in a Pregnant Woman with Essential Thrombocythemia

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Abstract:

Myeloproliferative neoplasms (MPNs), including polycythemia vera, essential thrombocythemia (ET), and primary myelofibrosis, mainly occur in older patients, but have also been reported in younger patients. A "second peak" occurs in female patients in their thirties, particularly in ET; thus, the management of pregnancy is often discussed.

We herein present the case of a 33-year-old woman with a high platelet count and multiple placental infarcts during delivery who was subsequently diagnosed with ET. Although there are no worldwide guidelines for the management of MPNs in pregnancy, the risk of thrombosis is markedly increased in these patients, and antithrombotic therapy should be considered.

Key words: myeloproliferative neoplasms, essential thrombocythemia, pregnancy, placental infarcts, aspirin, low-molecular-weight heparin

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Introduction

Philadelphia chromosome-negative myeloproliferative neoplasms (MPNs), including polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF), are clonal disorders characterized by an overproduction of terminally differentiated hematopoietic cells. MPNs mainly affect the elderly, but can also occur in women of childbearing age, especially concerning ET. The risks of miscarriage and other complications during pregnancy in patients with MPNs are higher than those in the general population. Therefore, management of MPNs during pregnancy may require special considerations.

We report a 33-year-old woman with high platelet counts showing multiple placental infarcts upon delivery, and subsequently diagnosed with ET. Administration of aspirin or heparin in pregnant ET patients has been reported to improve live birth rates. Our report reconfirms the need of antithrombotic therapy in ET patients during pregnancy.

Case Report

A 33-year-old woman at 32 weeks of gestation was referred to our hospital with a high platelet count. The medical record from her first pregnancy, which occurred six years previously, showed a normal platelet count, protein C activity, and antithrombin III level. The levels of total protein S antigen and free protein S antigen were slightly below normal, presumably because of pregnancy (1, 2), and lupus anticoagulant and anti-cardiolipin antibodies were both negative. However, two months prior to her second pregnancy, a medical examination revealed a high platelet count that was not treated. Since the non-stress test (NST) showed a loss of variability, she was immediately admitted to our hospital. The patient also had high blood pressure and proteinuria, and was diagnosed with hypertensive disorders of pregnancy. A hematogram showed a platelet count of 1,002×

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Table. **Laboratory Findings on Admission.**

Peripheral blood		Blood chemistry		Serological test	
WBC	8.5 $\times 10^9$/L	TP	6.8 g/dL	CRP	0.5 mg/dL
Neu	77 %	Alb	3.1 g/dL	Fe	109 μg/dL
Lym	18 %	AST	22 U/L	TIBC	533 μg/dL
Mono	4 %	ALT	17 U/L	ferritin	39 ng/mL
Eosi	1 %	ALP	639 U/L	Epo	6.8 mIU/mL
RBC	4.3 $\times 10^{12}$/L	γGTP	16 U/L		
Hb	13 g/dL	LDH	202 U/L	Urinalysis	
Hct	36.8 %	T-Bil	0.4 mg/dL	Protein	(3+)
Plt	1,002 $\times 10^9$/L	BUN	23 mg/dL	Sugar	(-)
Reti	22 ‰	Cre	0.7 mg/dL	Occult blood	(-)
		Na	135 mEq/L		
PT(INR)	0.91	K	4.7 mEq/L		
APTT	40.7/36.0 sec	Cl	103 mEq/L		
FIB	546 mg/dL				
FDP	5.7 μg/mL				
vWF	177 %				

Reti: reticulocyte, vWF: von Willebrand factor, Epo: erythropoietin

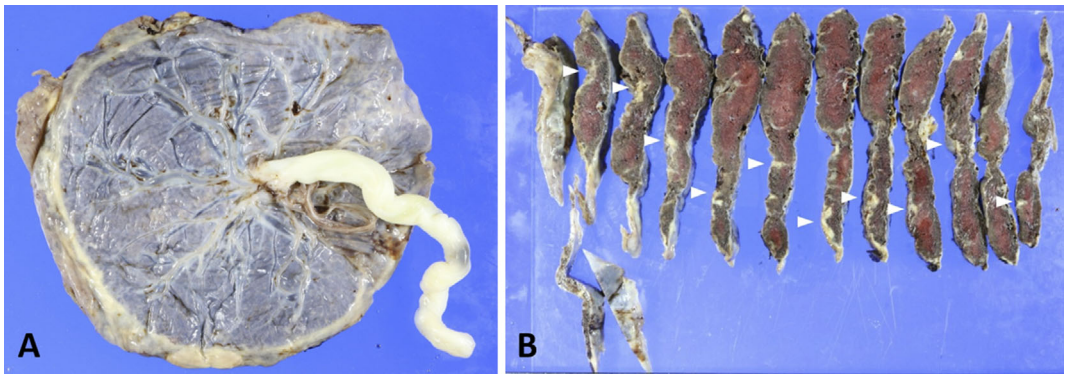

Figure 1. **A gross view of the placenta. The fetal side of the placenta (A) showed collapsed amniotic vessels and a cut section (B) showed multiple infarcts (arrow heads).**

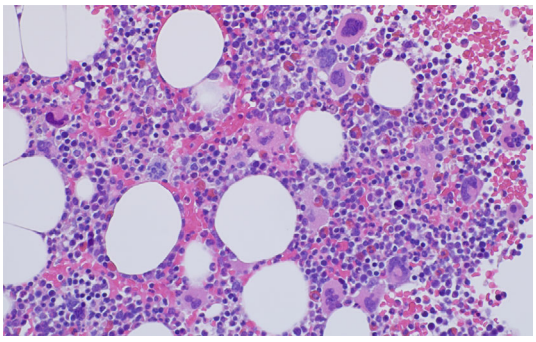

Figure 2. **A histopathological view of the bone marrow (aspiration biopsy) showed slightly hypercellular bone marrow with scattered enlarged megakaryocytes.**

10^9/L, a white blood cell count of 8.5×10^9/L, and a hemoglobin level of 13.0 g/dL (Table). Treatment with heparin (10,000 U/day) was initiated in order to prevent microthrombosis. At three days after her admission, fetal variability disappeared and NST showed late decelerations. A non-reassuring fetal status was diagnosed and emergency cesarean section was performed. The baby weighed 1,580 g and had Apgar scores of 5 and 7 at 1 and 5 minutes, respectively, and was therefore admitted to the neonatal care unit. Multiple placental infarcts were observed (Fig. 1). After delivery, the patient was treated with low-molecular-weight heparin (4,000 U), followed by heparin (10,000 U/day) for 6 weeks.

At two months after delivery, a bone marrow assessment revealed an elevated number of enlarged megakaryocytes with a slight increase in reticulin fibers, which was classified as the MF-1 grade (Fig. 2). No genetic mutations of *JAK2*, *MPL*, or *CALR* were detected; thus, the patient was diagnosed with triple-negative ET.

Discussion

The incidence of hemorrhagic and thromboembolic complications is high in patients with MPNs; thus, the main treatment strategy aims to prevent these events. Cytoreduc-

tion therapy using hydroxyurea, anagrelide, or other drugs is recommended for high-risk ET patients, defined by >60 years of age and/or a history of a previous thrombotic event. Cytoreductive therapy is also recommended for patients with platelet counts of $>1,500\times10^9$/L because they have a high risk of bleeding. In contrast, young patients with no cardiovascular risk factors and a low risk of thrombosis, such as the patient in the present case, are often not treated. However, a systemic review showed that the risk of developing thrombotic events was two-fold higher in patients with the *JAK2* V617F mutation (3); thus, antithrombotic therapy has recently been applied to the treatment of young patients with *JAK2* mutations.

We previously conducted a retrospective analysis of Japanese patients with MPNs and the findings obtained showed that the mean ages of MPN patients with PV, ET, and PMF were 66.4, 57.2, and 66.3 years, respectively, suggesting that MPNs mainly occur in elderly patients (4). However, MPNs have also been reported in young patients; we found a "second peak" in female ET patients in their thirties (4). Thus, an increase in the risk of ET with pregnancy has frequently been discussed.

Among patients with ET, 50-60%, 15-30%, and 5% harbor the *JAK2* V617F, *CALR*, and *MPL* mutations, respectively. The remaining patients are referred to as triple-negative ET patients because they do not carry *JAK2*, *CALR*, or *MPL* mutations. More than 30% of young ET patients in the "second peak" have been found to be triple-negative (5). These triple-negative ET patients have been reported to have lower hemoglobin levels, a lower leukocyte count, and longer survival (6). The risk of thrombotic events in triple-negative ET patients was shown to be significantly lower than that in patients with *JAK2* mutations, even in a multivariable analysis adjusted for age and a history of thrombosis (7).

Recent reports have shown the increased risk of maternal and fetal complications, including hypertensive disorders, in patients with MPNs (8-11). The risk of fetal loss in pregnant ET patients was previously reported to be 3- to 4-fold higher than that in the general population (10). Studies conducted in the USA, Italy, and Finland showed that the rate of live births was approximately 60%, while abortion in the first trimester occurred in approximately 33% of pregnancies (10). The presence of the *JAK2* V617F mutations in ET patients was identified as an independent risk factor for pregnancy complications (10). In contrast, the findings of a study by the Mayo Clinic demonstrated that *JAK2* V617F-positive and -negative patients had a similar rate of pregnancy loss (12). Indeed, the present patient with triple-negative ET developed multiple placental infarcts, suggesting the need for antithrombotic therapy, not only for patients with *JAK2* mutations, but also for pregnant *JAK2*-negative patients.

Although there are currently no worldwide guidelines for pregnant MPN patients, the European LeukemiaNet guidelines recommend the use of low-dose aspirin for patients with low-risk pregnancies, and low-molecular-weight heparin for those with high-risk pregnancies with a previous history of a major thrombotic event and/or severe pregnancy complications (13). Alimam et al. reported the outcomes of 58 pregnant women (56 singleton pregnancies and 1 twin pregnancy) with MPNs, among whom 88% received aspirin during the index pregnancy and 41% were additionally prescribed low-molecular-weight heparin (14). Fifty-eight pregnancies resulted in live births, one in miscarriage, and one in a stillbirth. The rate of miscarriage was 1.7%, which was lower than that previously reported, and may have been due to the high rate at which aspirin was administered. The findings of another study conducted in the USA revealed that the rates of pregnancy loss among patients who received aspirin was 21%, while that among patients who did not receive aspirin was 75%, indicating a salutary role for aspirin therapy among pregnant ET patients (12). Niittyvuopio et al. also reported that all 13 pregnancies treated with aspirin exhibited no complications during pregnancy, whereas 18 out of 27 pregnancies (67%) without any treatment had at least one pregnancy-related complication and 15 resulted in miscarriage (15).

High rates of placental infarction due to thrombosis in ET patients have been reported (16), and this seems to be the most consistent pathogenesis of the pregnancy failures (17). Additionally, in the present case, the patient's condition was also complicated by hypertensive disorders of pregnancy, which is a major cause of placental infarction.

In conclusion, we presented the case of a pregnant ET patient. Delivery resulted in a live birth; however, the patient was complicated by placental infarction and the infant was born with a low birth weight. The use of aspirin or heparin has been reported to increase the live birth rate among ET patients; thus, we strongly recommend the administration of antithrombotic therapy to ET patients during their pregnancy, even if the patient's condition is categorized as low-risk.

The authors state that they have no Conflict of Interest (COI).

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