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(CASE REPORT)

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Familial Mediterranean fever as a predictor of preeclampsia in pregnancy: Case report

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Abstract

Familial Mediterranean Fever (FMF) is an autosomal recessive auto inflammatory disorder characterized by recurrent fever and inflammation affecting the serosal membranes. Clinically, patients may experience attacks of recurrent fever and serositis, which can manifest with single or multiple simultaneous symptoms. While most patients are clinically diagnosed above the age of 2, cases diagnosed before 2 years of age, with an isolated fever clinical course, are believed to have a more severe course and an increased risk of developing amyloidosis.

Preeclampsia, a serious complication of pregnancy, is characterized by hypertension and organ damage, most commonly affecting the kidneys and liver. In this article, we present a case of a pregnant woman who was admitted during the 27rd week of pregnancy with rapidly developing preeclampsia and HELLP syndrome, despite having no previous history of complications. During the follow-up, we discovered the presence of FMF and certain thrombophilia gene mutations.

This case underscores the importance of considering specific diseases or syndromes under any presentation of preeclampsia. Timely identification of underlying conditions, such as FMF and thrombophilia, can aid in early intervention and appropriate management, potentially improving maternal and fetal outcomes

Keywords: Familial Mediterranean Fever; Preeclampsia; Maternal and perinatal morbidity

1. Introduction

Familial Mediterranean Fever (FMF) is an autosomal recessively inherited disorder caused by a mutation in the MEFV gene and manifests itself as recurrent 6–72-hour attacks of pyretic fever accompanied by the phenomena of aseptic peritonitis, pleurisy, arthritis, and inflammatory rash [1, 3, 12].

It is most prevalent in individuals of Turkish, Armenian, Middle Eastern and North African, Jewish and Arab descent. Among Armenians, the carrier rate for FMF is approximately one in seven, with an observed disease rate of roughly 1 in 500 [1]. In the Jewish population of Israel, the carrier rate varies from one in eight among those of Ashkenazi origin to one in four among those of Iraqi origin [9].

FMF, however, is not limited to these ethnic groups. It has also been reported at a lower prevalence in other populations such as Greece, Italy, Japan, and China [4, 9]. In the United States, FMF is frequently encountered in Ashkenazi Jews and

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immigrants from the Middle East and Armenia. The origin of FMF is hypothesized to date back more than 3000 years ago in Mesopotamia [8], with the disease spreading to Armenia and Turkey in the Ancient World. In the modern era, ease of transportation overseas and air travel contributed to its spread to countries beyond the Mediterranean basin.

Clinical symptoms of FMF include fever, abdominal, chest, or joint pain recurring with irregular intervals, erythema resembling erysipelas in the lower extremities, myalgia, orchitis, and aseptic meningitis [5, 12]. Notably, these symptoms show unresponsiveness to analgesics or antipyretics and typically resolve spontaneously within 24 to 72 hours. The course of an attack of FMF can be manifested by one symptom or several symptoms [9], and in most cases, symptoms appear before the age of 20 years, while in 60% of cases symptoms develop before 10 years, and in 90% of cases it occurs before the age of 20 years. [4, 6, 13]. FMF exhibits considerable variability in severity and clinical manifestations across different regions, likely influenced by variations in MEFV mutations, additional genetic modifiers, and environmental factors.

Preeclampsia is a significant cause of maternal and perinatal morbidity and mortality worldwide. Some studies have suggested a potential link between FMF and an increased risk of preeclampsia during pregnancy, but the exact mechanisms underlying this association remain unclear [7, 10, 11, 13]. There are inconsistent reports on whether there is an association between preeclampsia and maternal or fetal thrombophilia [2,14-16]

2. Case Presentation

In this clinical case, we are discussing a 20-year-old pregnant woman who was receiving antenatal care at the polyclinic department of the Erebouni Medical Center. During the 27th week of pregnancy, while on vacation in one of the regions of Armenia, the patient began to feel unwell. She urgently contacted her gynecologist, complaining of symptoms including edema (swelling), pain in the epigastric region, visual impairment, and elevated blood pressure (180/110 mm Hg). It's worth noting that her pregnancy had been progressing smoothly without prior complications, and her routine medical tests had shown normal results.

At the doctor's insistence, she promptly visited a nearby medical center. There, tests revealed that ALT was 23 and AST was 22. Her general blood test was normal, with only the general urine test showing a protein level of 2.5 ppm. In response to the doctors' request from Yerevan, the patient was transported to the Erebuni Medical Center using air ambulance services. The clinical and laboratory data obtained during her admission are presented in Table 1.

Table 1 Laboratory findings on admission of Ereboni medical center

Peripheral blood		**Blood chemistry**	
Red blood cells	$4.1x10^{12}$ /µL	Total protein	45.64 g/L (64-83)
Hemoglobin	126 g/L	Total bilirubin	45.07 µmol/L (<21)
Hematocrit	35.3%	Albumin	27.2 g/L (35–52)
PLT	$252x10^{9}$ /L	Glucose	7.13 mmol/L
WBC	$20.36 x10^{9}$/µL	Lactate	3.55
Neutrophil	$17.21x10^{9}$ /L	LDH	2225.66 IU/L (135–214)
Eosinophil	0	ALT	111.32 U/L (<33)
Monocyte	$1.47x10^{9}$ /L	AST	123.09 U/L (<32)
Lymphocyte	9%	Creatinine	102 µmol/L (44–84)
Baso	$0.03 x10^{9}$ /L	Blood urea	6.96 mmol/L (2.5–8.3)
Coagulation		Ca^{2+}	1.099 mmol/L (1.05–1.3)
PT	13.2	Na^{+}	131.8 mmol/L (138–145)
PT-INR	1.01	K^{+}	4.09 mmol/L (3.4–5.3)
APTT	29.5 sec	Fibrinogen	480 mg/dL

APTT = activated partial thromboplastin time, PT= prothrombin time.

However, within two hours of the laboratory tests, the patient's condition rapidly deteriorated, and she began to show signs of eclampsia—a severe complication associated with high blood pressure caused by pregnancy (preeclampsia). In response to this medical emergency, the healthcare team promptly conducted an emergency cesarean section to deliver the baby and address the eclampsia.

Table 2 Laboratory findings after admission of Erebouni medical center and during follow up

Duration	1 day after ICU	2 Day	3 Day	4 Day	1Week
ALT	124	544	477	289	118
AST	100	275	389	203	79
Blood urea	8.3	9.6	8.1	5.8	5.0
LDH	3201	2225	1008	680	215
PLT	59000	48000	37000	87000	160000
Albumin	25.3	22,1	21.7	25.8	33
WBC	22000	25000	26000	20000	13700
Hgb	102g/l	82g/l	78g/l	85g/l	100g/l

During the postoperative period, considering the patient's critical condition, elevated blood pressure (150/100 mm Hg), and deteriorating laboratory values, the decision was made to transfer the newborn to the intensive care unit for further treatment.

The newborn was born with a body weight of 700 g, necessitating immediate hospitalization in the premature newborn department. Laboratory tests (as shown in Table 1) indicated an elevated white blood cell (WBC) count (20.36 x 10^9/µl) with 17.21 x 10^9/L neutrophils, and a significant decrease in the mother's total protein (45.64 g/L). The mother exhibited heightened levels of ALT, AST, and LDH enzymes, as well as symptoms suggestive of thrombosis and HELLP syndrome. Moreover, molecular genetic testing confirmed the diagnosis of Familial Mediterranean Fever (FMF) due to the presence of two compound heterozygous mutations (MEFV E148/P3693 and SAA1 β/β) in the MEFV gene. Additionally, the patient was identified as homozygous for the PAI-1 4G gene and heterozygous for the thrombophilia genes MTHFR C677T and MTHFR A1298C.

The patient was prescribed colchicine, and after achieving stability in laboratory parameters over 2-3 days, she was transferred to the gynecological department. Following the normalization of the child's weight, both the mother and the child were discharged from the clinic.

3. Discussion

This clinical case report explores a unique scenario where signs of Familial Mediterranean Fever (FMF) were disguised as manifestations of eclampsia. FMF, a prevalent auto inflammatory disorder among Mediterranean populations, is characterized by recurrent polyserositis. The patient, a 20-year-old pregnant woman, presented with symptoms initially presumed to be eclampsia. However, further investigation prompted by the development of eclampsia led to the diagnosis of FMF and identification of thrombophilia gene carriership.

FMF, a genetically influenced condition, can present with diverse and often misleading symptoms, making accurate diagnosis challenging. Preeclampsia, on the other hand, is a serious complication of pregnancy characterized by high blood pressure and damage to other organs, most commonly occurring after 20 weeks of gestation. FMF may cause adverse pregnancy outcomes and may also increase perinatal and maternal complications through chronic effects and acute attacks. The rate of preterm labor and miscarriage was higher in patients not receiving colchicine therapy. Although colchicine crosses the placenta, Rabinovitch et al. reported its safety for pregnancy and fetus in a study after 10 years of follow-up, and they found fewer complications in those taking colchicine.

Most patients with chronic hypertension and FMF experience deterioration in kidney function during pregnancy and develop preeclampsia; and this situation led to premature birth.

Preeclampsia is more common in women of older maternal age. This situation is an independent risk factor for preeclampsia. In this case, the concurrent presence of eclampsia led to the realization of FMF, highlighting the importance of thorough evaluation and vigilance in clinical practice. The potential link between FMF and preeclampsia remains a subject of debate and warrants further investigation. The underlying pathophysiological mechanisms connecting FMF to the development of preeclampsia are yet to be elucidated. It is possible that chronic inflammation and deregulation of the immune system in FMF may contribute to the vascular changes observed in preeclampsia. However, more in-depth mechanistic studies are needed to establish a causal relationship.

As mentioned above, preeclampsia affects 2.5% to 3.0% of pregnant women [5] and stands as the leading cause of perinatal morbidity and mortality for both fetus and mother. It typically manifests itself in the second or third trimester of pregnancy [5]. While the mechanisms responsible for the pathogenesis of preeclampsia are not fully understood, there is consensus that it is associated with hypo invasion and failed conversion of maternal endometrial spiral arteries to the placenta, both of which are related to PAI-1 and PAI-1.2.

Maternal PAI-1 plasma levels are higher in patients with preeclampsia during the second trimester of pregnancy [14], and its mRNA level positively correlates with the severity of preeclampsia between 35 and 41 weeks of pregnancy [5]. Therefore, PAI-1 is considered a potentially useful predictor of preeclampsia.

Research data suggest that it remains unclear whether elevated PAI-1 levels are the primary mechanism leading to preeclampsia or a consequence of associated endothelial and placental damage [5]. One potential cause of impaired cytotrophoblast migration in preeclampsia is the lack of expression of the Raf kinase inhibitor protein (RKIP) in cytotrophoblasts, as loco statin (an RKIP inhibitor) induces PAI-1 expression while supporting NF-kB activation pathway, ultimately promoting inappropriate trophoblast invasion [14, 16].

Plasma PAI-1 expression increases after exposure to inflammatory cytokines, including interleukin 1β (IL-1β), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and fibroblast growth factor (FGF), or hypoxic conditions. Hypoxia can directly stimulate PAI-1 mRNA and protein expression [14] and can also stimulate hypoxia-inducible transcription factors (HIF-1α and HIF-2α) to induce PAI-1, both of which could be mechanisms of preeclampsia. When preeclampsia occurs in combination with elevated syncytial PAI-1 levels, intervillous fibrin deposition and infarction can reduce the flow of nutrients from mother to fetus, leading to intrauterine growth restriction (IUGR) [5].

However, there is controversy regarding the correlation between PAI-1 polymorphisms and preeclampsia. Gerhardt et al. (2005) found that women with the PAI-1 5G/5G genotype are at risk of early development of severe preeclampsia (17–35 weeks of gestation) [2]. In our case, the presence of FMF diagnosis can also induce PAI-1 and the development of preeclampsia.

Numerous studies have investigated the associations between methylenetetrahydrofolate reductase (MTHFR) gene C677T and A1298C polymorphisms and risk of recurrent pregnancy loss (RPL); however, the results remain controversial. No one about association with preeclampsia [15, 16].

4. Conclusion

In conclusion, the available evidence suggests a potential association between Familial Mediterranean Fever and an increased risk of preeclampsia during pregnancy. However, the current literature is limited, and further prospective, large-scale studies are required to determine the strength and nature of this relationship accurately. Clinicians should be aware of the possibility of preeclampsia in pregnant women with FMF and consider close monitoring and early intervention in such cases to improve maternal and fetal outcomes.

This case underscores the importance of considering specific diseases or syndromes under any presentation of preeclampsia. Timely identification of underlying conditions, such as FMF and thrombophilia, can aid in early intervention and appropriate management, potentially improving maternal and fetal outcomes.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

The present research work does not contain any studies performed on animals/humans subjects by any of the authors'.

Statement of informed consent

All participants involved in this study were provided with detailed information regarding the purpose, procedures, and potential risks and benefits of their participation. Written informed consent was obtained from each participant before their involvement in the study.

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