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CASE REPORT

A pregnancy-associated nonfamilial case of PAPA (pyogenic sterile arthritis, pyoderma gangrenosum, acne) syndrome

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Key Clinical Message

Little is known about the influence of pregnancy on pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA) syndrome. We experienced a rare case of pregnancy complicated with PAPA syndrome. The patient had various histories of skin and joint disorders and experienced subarachnoid hemorrhage during pregnancy; however, her skin lesion was unaffected.

Keywords

Arterial dissection, PAPA syndrome, pregnancy, subarachnoid hemorrhage.

Introduction

Pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA) syndrome is an extremely rare, autosomal-dominant, hereditary auto-inflammatory disease. Elevated production of interleukin (IL)-1β and tumor necrosis factor (TNF)-α induced by proline–serine–threonine phosphatase-interacting protein 1 gene *PSTPIP1* (also known as CD2-binding protein 1) mutations has been reported as the cause of this systemic inflammatory disorder. *PSTPIP1* mutations have been observed in familial cases; however, sporadic-onset cases without gene mutations have also been reported.

We experienced a case of pregnancy complicated with PAPA syndrome in a female patient without *PSTPIP1* mutations. She had subarachnoid hemorrhage (SAH) after undergoing posterior inferior cerebellar arterial dissection for the treatment of cerebral aneurysm in the second trimester of pregnancy.

Case

The patient was a 31-year-old, primiparous woman with PAPA syndrome. She had the history of various skin lesions (pyoderma gangrenosum and severe cystic acne) and joint inflammation that first appeared when she was 3 years old. Her joint inflammation progressed, and joint deformity became prominent from age 15 years. When she was 19 years old, she underwent artificial joint replacement of the third finger of her left hand. However, the artificial joint was infected by methicillin-resistant *Staphylococcus aureus*. Thus, the artificial joint was removed, and bone autotransplantation was performed. Her facial acne became worse up to age 20 years. Her skin lesions and arthritis became stable at the age of 26 years. At age 30 years, she was suspected to have an autoimmune disorder. Considering her clinical course and an elevated serum level of IL-1β (21 pg/mL; normal, < 10 pg/mL), a diagnosis of PAPA syndrome was made.

However, *PSTPIP1* gene mutation associated with familial PAPA syndrome was not observed, and she had no family history of the syndrome. Thereafter, she had been followed for PAPA syndrome at our internal medicine division. She eventually became pregnant and was referred to our obstetrics outpatient ward at 7 weeks of gestation. Her height was 164 cm and body weight was 56 kg (body mass index, 20.8 kg/m^2). Her blood pressure at the initial visit was 113/75 mmHg. Distal interphalangeal joint deformities and restrictions of movements were observed on the first, second, third, and fourth fingers of both hands. Furthermore, rigidity was present in the interphalangeal joint of the second finger of her left foot. She also had skin pigmentation on the lower extremities and buttocks (Fig. 1).

At 13 3/7 weeks of gestation, she complained of mild headache and underwent a medical examination. Her symptom was diagnosed as common cold. However, 2 days later, she was admitted to our hospital because of severe headache and vomiting. She had alert consciousness with no motor dysfunction or loss of sensation. The deep tendon reflexes were all normal. Her blood pressure was 142/103 mmHg, and her pulse rate was 69/min with normal respiration. Her blood tests were all normal except for a slight decrease in prothrombin time to 11.6 sec and a slight increase in D-dimer level to 1.3 μg/mL. At 13 week 6 days of gestation, an emergency stent-assisted coiling procedure for cerebral aneurysm treatment was planned. Before the operation, the risk of serious postoperative complications (including cerebrovascular ischemia) was explained to her family. Coil placement was performed successfully. However, after the procedure, symptoms of cerebrovascular ischemia (dysphagia and impaired limb movement) appeared, and SAH was diagnosed. Thus, physical training and tube feeding were started. At 21 weeks of gestation, she was discharged from the referring hospital after recovery and administered with acetylsalicylic acid after the operation until 22 weeks of gestation. Thereafter, she had been followed at our outpatient ward, and her pregnancy course was uneventful.

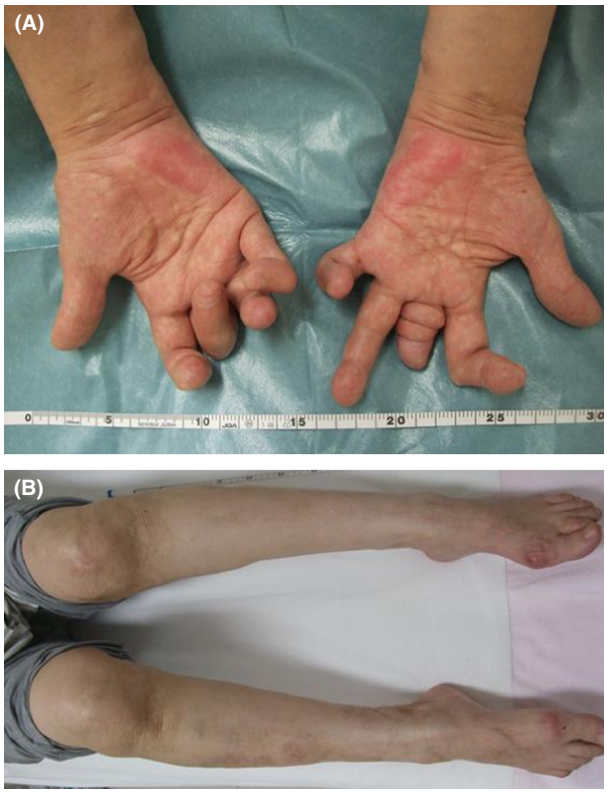

Figure 1. Physical examination findings. (A) Distal interphalangeal joint deformities in the first to fourth fingers. (B) Skin pigmentation on the lower extremities.

After a discussion with neurosurgeons, we made the following basic plans to prevent the recurrence of SAH (or artery dissection): (i) maintain her systolic blood pressure at <120–130 mmHg and (ii) deliver the fetus through a planned cesarean section near term. At 35 weeks of gestation, her blood pressure increased to 135/84 mmHg. Thus, she was readmitted to control her blood pressure. At 36 weeks 0 days of gestation, elective cesarean section was performed and she delivered a healthy male infant (weight, 2552 g; Apgar score, 8 and 9 at 1 and 5 min, respectively). Her postpartum course was uneventful, and she was discharged from the hospital with her infant at 7 days after the delivery. At present, her symptoms of PAPA syndrome had been stable and she had completely recovered from the complication of coil intervention.

Discussion

We experienced a rare case of pregnancy complicated with PAPA syndrome, which is known to be an autoinflammatory disease [1]. PAPA syndrome has been reported in five families, mostly in the autosomal-dominant type associated with mutations of the PSTPIP1 gene. The PSTPIP1 protein binds pyrin, which is an inhibitor of the inflammatory process that recruits caspase-1. The mutation of PSTPIP1 in PAPA syndrome increases binding to pyrin, which, in turn, causes a decrease in free pyrin. Thus, the increased recruitment of caspase-1 induces an increase in IL-1β production [1, 2]. Thereby, PSTPIP1 gene mutation results in neutrophil infiltration in arthritis, acne, pyoderma gangrenosum, and other neutrophilic dermatoses. Hong et al. reported a case of pregnancy with PAPA syndrome in a woman who developed exacerbation of arthritis at 31 weeks of gestation;

administration of an IL-1 receptor antagonist dramatically improved her symptom [3]. However, nonfamilial PAPA syndrome cases had been reported without a point mutation in the *PSTPIP1* gene [4]. There may be gene point mutations other than that of the *PSTPIP1* gene in nonfamilial PAPA syndrome [1, 3].

In our case, the patient's symptom (skin lesion) had been unaffected during pregnancy. There was only one case report in which the symptoms of PAPA syndrome (pyoderma gangrenosum and acne) became worse during pregnancy [1]. Thus, the effect of pregnancy on the symptoms in PAPA syndrome needs further investigation. There are few published cases of cerebral arterial dissection even in hereditary connective tissue diseases during pregnancy (e.g., Ehlers–Danlos syndrome and Marfan syndrome) [5, 6]. Mizutani reported that cerebral arterial dissection has a low frequency of causing SAH (3.2%) [7]. In our case, elevation of IL-1β was observed, and we speculated that it might be related to the cause of aneurysm formation in the cerebellar artery. Inflammatory cytokines, such as TNF-α and IL-1β, are known to induce the proliferation of smooth muscle cells in vascular tissue [8]. In addition, administration of anakinra, an inhibitor of IL-1β, or deletion of the IL-1β coding gene has been shown to increase the diameter of aortic aneurysms in animal models [9].

Conclusion

We report a case of pregnancy with PAPA syndrome and SAH after posterior inferior cerebellar arterial dissection in the second trimester of pregnancy. The symptoms of PAPA syndrome had been stable without any medications during pregnancy and postpartum. However, the risk of cardiovascular events associated with pregnancy in PAPA syndrome needs further investigation.

Conflict of Interest

The authors declare that there are no conflict of interests.

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