Difficulties in Differentiating Hypertensive Disorders of Pregnancy With Polyarteritis Nodosa

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Abstract

Polyarteritis nodosa (PAN) is characterized by medium- or small-sized artery vasculitis with vessel wall inflammation and necrosis of muscular arteries, commonly presenting with fatigue, fever, weight loss, and joint pain. PAN in pregnancy is rare and is associated with worsening of vasculitis after delivery, resulting in myocardial infarction and heart failure which frequently lead to maternal death. We report a case of hypertensive disorders of pregnancy (HDP), which is difficult to differentiate from PAN. A 27-year-old multigravida was diagnosed with PAN 4 years prior after experiencing fever and lower extremity skin rash. During her PAN remission, she conceived her second pregnancy and opted to discontinue PAN medication and declined antihypertensive medications. At 22 weeks of gestation, her blood pressure was elevated to 200/100 mm Hg without proteinuria, for which she was admitted to our hospital. She was diagnosed with HDP-chronic hypertension without proteinuria, for which she was admitted to our hospital. Her blood pressure was immediately controlled using antihypertensive medication. Our case report highlights the importance of carefully managing HPD as a serious complication of PAN.

Keywords: Polyarteritis nodosa; Fibrinoid necrosis; Hypertensive disorders of pregnancy; Preeclampsia; Vasculitis

Introduction

Polyarteritis nodosa (PAN), first described in 1986, is necrotizing arteritis of medium or small arteries without glomerulonephritis, or arteriolar, venular, or capillary vasculitis [1]. It is not associated with antineutrophil cytoplasmic antibodies (ANCA) [2]. PAN can affect the whole body, manifesting as inflammation-induced constitutional symptoms, such as fever, fatigue, weight, loss, and hypertension. Additionally, it can cause ischemia or infarction-induced organ damage causing cardiac, respiratory, digestive, peripheral nervous, dermatologic, and musculoskeletal symptoms [3].

PAN is diagnosed based on the above clinical symptoms, according to the 1990 classification criteria of the American College of Rheumatology [4], the exclusion of ANCA-related vasculitis, and the histological confirmation of small- and medium-sized artery vasculitis. The most important component of the diagnostic process is to provide pathologic evidence regarding blood vessel inflammation of the affected organ, which necessitates biopsy of the affected area.

The difficulty in diagnosing and classifying vasculitis syndromes has led to uncertainties regarding the incidence of PAN. A previous study found that PAN affects approximately 31 individuals per 1 million [5], and has a predilection toward men aged 40 to 60 years [3]. Without accounting for pregnant women, the 5-year survival rate for PAN is 75-93% [6]. On the contrary, the 5-year survival rate is 88% when the following five prognostic factors are not considered: proteinuria >1 g/day, renal failure, cardiomyopathy, gastrointestinal tract involvement, and central nervous system involvement [6]. If more than two factors are present, the 5-year survival rate decreases to 54% [6, 7].

PAN in pregnancy is rare, with only three reported cases in the past decade [8-10]. Pregnancy outcomes are dependent on PAN severity during pregnancy [11]. It is rare for pregnancy to occur after PAN; most cases of PAN occur during pregnancy [12]. Pregnant women during the remission period have relatively good pregnancy outcomes; however, the prognosis is poor if PAN is first diagnosed during pregnancy, which may necessitate therapeutic abortion in 5-10% of patients [11, 12]. Regardless of the time of onset, approximately 40% of PAN in pregnancy is associated with hypertensive disorders of pregnancy (HDP), which can cause vasculitis in the maternal blood vessels of the placental bed [8]. Herein, we report a case of HDP, which was difficult to differentiate from PAN, and pre-
Polyarteritis Nodosa in Pregnancy

A 27-year-old, woman, *gravida 2 para 1*, visited the hospital for prenatal check-up. At 18 years of age, she was diagnosed with hypertension; at 19 years, she conceived and underwent normal spontaneous delivery of her first child. At 23 years of age, she experienced spontaneous high-grade fever (40 °C), joint pain, and leg rash, in addition to hypertension. She sought medical advice and was diagnosed with PAN because histological skin biopsy showed medium-sized artery vasculitis with fibrinoid necrosis. She was treated with oral corticosteroids (60 mg/day) and methotrexate (8 mg/day) as remission induction therapy; subsequently, at 25 - 27 years of age, remission maintenance therapy was initiated with oral corticosteroids (2.5 - 5.0 mg/day) and azathioprine (100 mg/day).

At 27 years of age, her second pregnancy was conceived during PAN remission. During the first trimester, she was diagnosed with chronic hypertension (CH) (blood pressure (BP), 160/90 mm Hg) by her previous doctor. She declined antihypertensive medication or to continue PAN medication. At 22 weeks of gestation, her BP was greatly elevated (200/100 mm Hg), which necessitated hospital admission. On admission, vital sign measurements revealed BP of 166/98 mm Hg and pulse rate of 82 beats per minute; however, physical examination revealed no leg edema. Her laboratory examinations are shown in Table 1. Liver and kidney functions were unremarkable with no proteinuria. Additionally, soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF) were 2,620 pg/mL and 45.8 pg/mL, respectively. Fetal ultrasound showed that the estimated fetal body weight was within the normal range (560 g ± 0.5 standard deviation (SD)) with normal amniotic fluid index (21.7 cm). Fetal monitoring with non-stress tests showed reactive tracings with no uterine contraction.

### Diagnosis

The patient was diagnosed with HDP (CH); PAN recurrence sent a review of related literature.

### Case Report

### Investigations

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### Diagnosis

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was excluded due to the absence of PAN-specific skin or joint symptoms indicated in the diagnostic criteria. To control BP, nifedipine (80 mg/day) and labetalol (150 mg/day) were initiated. Although we diagnosed HDP rather than recurrent PAN, we monitored her carefully, considering the possibility of recurrent PAN.

At 30 weeks of gestation, she was diagnosed with superimposed preeclampsia (SPE) because of severe hypertension (230/125 mm Hg), proteinuria of 4+ on dipstick testing (protein/creatinine 1.98 mg/dL ≥ 0.3 mg/dL), sFlt-1 of 12,600 pg/mL, and PlGF of 22.0 pg/mL, and the decision was made to deliver the baby.

Treatment

After hydrocortisone (100 mg) administration, the patient underwent cesarean section under combined spinal-epidural anesthesia. A single, 1,084 g (appropriate for gestational age infant) male neonate with Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score of 6/8 and an umbilical artery blood pH of 7.22 was delivered.

Follow-up and outcomes

After delivery, the patient’s BP was maintained at approximately 150/80 mm Hg with oral nifedipine (80 mg/day), amiodipine (2.5 mg/day), and candesartan (8 mg/day). Postoperatively, she tolerated the procedure well and she was discharged on the sixth postoperative day.

The pathology of the placenta showed fibrin deposition of the intervillous space and fibrinoid necrosis of terminal villus called placental circulatory failure with ischemic changes (black arrow heads). Fibrinoid necrosis was observed around the small maternal arteries in the decidua of the placental site (white arrow heads).

Discussion

PAN in pregnancy is associated with worsened vasculitis postpartum, which can lead to maternal death caused by acute renal failure and embolization or necrosis-induced acute myocardial infarction [13].

Since 1944, 17 cases of PAN during pregnancy have been reported (Table 2 [8-10, 13-17]). Until 1964, PAN was not diagnosed during pregnancy; hence all pregnancies resulted in postpartum maternal death. In 1973, a pregnant woman was diagnosed with PAN, which necessitated prednisolone administration, and resulted in the patient’s survival [18]. Currently, among the 18 reported cases (including the case reported herein) of PAN during pregnancy, seven have resulted in maternal death. Among the seven mortalities, six (85.7%) were due to the development of HDP, which was untreated. The maternal prognosis is poor if PAN is diagnosed during the pregnancy or postpartum period [19]. Additionally, recurrence may occur despite maintenance therapy [14]. PAN may cause vascular inflammation in various systemic organs, often resulting in severe hypertension and renal damage (elevated serum creatinine, proteinuria) [13]. HDP occurs in 40% of PAN in pregnancy [12]. Until 1980, six of eight cases (75%) were complicated with HDP, which was higher than its prevalence in 1989 (five of 11 cases, 45.5%). This decrease in incidence may be attributed to the high number of treated PAN patients during pregnancy (eight of 11 cases, 72.7%), leading to improved maternal survival and favorable prognosis. A limitation in the case review data is that the fatal cases are biased toward older publications when the recognition and treatment of preeclampsia (PE) and PAN may have been far from current standards.

No biomarker can determine the progression of PAN in pregnancy to SPE. Our patient developed CH during the non-
pregnant remission period, suggesting that the risk of SPE is increased by hypertension, even in remission. Generally, SPE occurs in 20-50% of CH and 75% of secondary hypertension, which necessitates the early detection of SPE [20]. sFlt-1 is a type 1 receptor for soluble vascular endothelial growth factor (VEGF). Increased maternal sFlt-1 leads to PlGF and VEGF inactivation, decreasing free PlGF and VEGF, resulting in vascular endothelial lesions [21]. Before clinical onset of PE, increasing sFlt-1 and decreasing PlGF levels are observed. Notably, a previous study found that sFlt-1/PlGF ratio > 38 is a predictive marker of developing PE within 4 weeks (positive predictive value of 36.7%) [22]. Our patient demonstrated a sFlt-1/PlGF ratio of 57 and 572 at 22 and 30 weeks of gestation, respectively. Vascular endothelial damage may have commenced at 22 weeks of pregnancy; however, sFlt-1 and PlGF levels were insufficient to differentiate between PAN and HDP.

PAN is a necrotizing vasculitis of medium- and small-sized arteries, without glomerulonephritis or arteriolar, capillary, or venular vasculitis [2]. Necrotizing vasculitis is characterized by pathologic neutrophilic infiltration of blood vessels, with nuclear dust of leukocyte origin, resulting in blood vessel destruction, and vessel wall and lumen eosinophilic substance deposition (fibrinoid necrosis or degeneration) [23]. Vasculitis is mainly characterized by pathologic necrotizing vasculitis, necessitating the presence of fibrinoid necrosis. Histologically, PAN is classified into four stages according to Arkin’s staging system: stage I, degenerative stage; stage II, acute inflammatory stage; stage III, granulation stage; and stage IV, scar stage [23]. Clinically, stage I and II lesions show severe blood vessel inflammation throughout the body, and stage III and IV lesions show ischemia in affected organs. In stage I, the tunica media and intima of blood vessels are edematous, with fibrinoid degeneration. In stage II, neutrophil, eosinophil, lymphocyte, and plasma cell infiltration occur in the tunica media and adventitia of blood vessels, with extension of fibrinoid necrosis to all layers [2]. The blood vessel wall has complete or partial fibrinoid degeneration, leading to the tearing and disappearance of the inner elastic plate [23]. These findings may indicate the development of thrombosis [5].

HDP needs to be differentiated from PAN. Histologically, HDP shows damaged vascular endothelium due to edema, thickening, thrombus formation, fibrinoid necrosis, and foam macrophage and lymphocyte infiltration. Additionally, vascular occlusion occurs due to multiple infarctions among the villus (Tenney-Parker change) [24]. There are some similar histological changes observed with both HDP and PAN. Histological examination of our patient showed fibrin deposition in the placental intervillus space and fibrinoid necrosis of terminal villus called placental circulatory failure. Moreover, ischemic changes and fibrinoid necrosis were observed around the small maternal arteries in the decidua (Figs. 1 and 2). Initially, our patient was diagnosed with CH, with no PAN recurrence. However, it is unclear whether PAN worsened the HDP due to the presence of fibrinoid necrosis in the maternal small

### Table 2. Reported Cases of Polyarteritis Nodosa in Pregnancy

| Case number | Age of patient (years) | Time of diagnosis | Treatment of PAN during pregnancy | HDP | Outcome | Gestation of weeks | Author | Year | Reference |
|-------------|------------------------|-------------------|-----------------------------------|-----|---------|-------------------|--------|------|-----------|
| 1           | 26                     | Autopsy           | -                                 | +   | Died    | VD                | Webb   | 1944 | [13]      |
| 2           | 28                     | Autopsy           | -                                 | -   | Died    | Artificial abortion | NA     | 1949 | [13]      |
| 3           | 33                     | Autopsy           | -                                 | +   | Died    | NA                | NA     | 1949 | [13]      |
| 4           | 23                     | Autopsy           | -                                 | +   | Died    | VD                | Talt   | 1955 | [13]      |
| 5           | 39                     | Autopsy           | -                                 | +   | Died    | CS                | Siegler | 1959 | [13]      |
| 6           | 39                     | Autopsy           | -                                 | +   | Died    | VD                | Varriale | 1964 | [13]      |
| 7           | 16                     | Prenatal          | +                                 | -   | Survived| VD                | DeBeukelaer | 1973 | [13]      |
| 8           | 32                     | Postpartum        | -                                 | +   | Died    | Spontaneous abortion | Reed  | 1980 | [13]      |
| 9           | 20                     | Prenatal          | -                                 | +   | Survived| CS                | Owen   | 1989 | [13]      |
| 10          | 22                     | Postpartum        | +                                 | +   | Survived| CS                | Antoine | 1996 | [14]      |
| 11          | 22                     | During pregnancy  | +                                 | +   | Survived| CS                | Fernandes | 1996 | [16]      |
| 12          | 32                     | During pregnancy  | +                                 | -   | Survived| VD                | Owada  | 2005 | [17]      |
| 13          | 26                     | Prenatal          | +                                 | -   | Survived| VD                | Pagnoux | 2010 | [8]       |
| 14          | 32                     | Prenatal          | +                                 | -   | Survived| CS                | Pagnoux | 2010 | [8]       |
| 15          | 27                     | Prenatal          | +                                 | -   | Survived| VD                | Pagnoux | 2010 | [8]       |
| 16          | 40                     | During pregnancy  | +                                 | -   | Survived| CS                | Joan    | 2018 | [9]       |
| 17          | 30                     | Postpartum        | -                                 | +   | Survived| CS                | Laura   | 2018 | [10]      |
| 18          | 27                     | Prenatal          | +                                 | +   | Survived| CS                | This case | 2021 | This case |

PAN: polyarteritis nodosa; HDP: hypertensive disorders of pregnancy; NA: not available; VD: vaginal delivery; CS: cesarean section.
arteries of the decidua.

Learning points

In this case, we found that PAN in pregnancy was difficult to differentiate from HDP. Our case report highlights the importance of carefully managing HDP as a serious complication of PAN.

Acknowledgments

None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

This study was approved by the institutional review board, and written informed consent was obtained from the patient.

Author Contributions

Emi Kondo and Eiji Shibata were responsible for drafting the manuscript. All authors read and approved the final version of the manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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