Ochsner Journal 18:94–97, 2018

Polyarteritis Nodosa in Pregnancy

Laura Damian, MD, PhD,[1,2] Cristina Pamfil, MD, PhD,[2,3] Marius Fodor, MD, PhD,[4] Liliana Rogojan, MD, PhD,[5] Natalia Hagau, MD, PhD,[6] Simona Rednic, MD, PhD[1,2,3]

[1]Department of Rheumatology, Emergency Clinical County Hospital, Cluj-Napoca, Romania [2]Centre for Rare Musculoskeletal Autoimmune and Autoinflammatory Diseases, Cluj-Napoca, Romania [3]Department of Rheumatology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania [4]Department of Surgery, Emergency Clinical County Hospital, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania [5]Department of Pathology, Emergency Clinical County Hospital, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania [6]Department of Anesthesiology and Intensive Care, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

Background: Polyarteritis nodosa (PAN) is a rare disease that occurs predominantly in middle-aged males; its onset during pregnancy is exceptional.

Case Report: We present a case of PAN with peripartum onset in a patient with a twin pregnancy after ovarian stimulation for primary infertility. The pregnancy outcome was good in terms of the children's health. In the case of the mother, however, the presence of nonspecific signs and symptoms, a noncontributory ovarian biopsy, and mimics of a puerperal infection delayed the diagnosis of PAN. The emergence of a tender subcutaneous nodule on the forearm and its histopathologic findings were diagnostic. Treatment with pulse methylprednisolone and intravenous cyclophosphamide resulted in the patient's prompt recovery.

Conclusion: We present the case to stress the value of careful physical examination in unveiling the presence of a rare disease.

Keywords: *Polyarteritis nodosa, pregnancy, pregnancy outcome, vasculitis*

Address correspondence to Cristina Pamfil, MD, PhD, Department of Rheumatology, Iuliu Hatieganu University of Medicine and Pharmacy, Clinicilor 2-4, 40006, Cluj-Napoca, Romania. Tel: (+40) 747-030296. Email: cristinapamfil.umfcluj@gmail.com

INTRODUCTION

Polyarteritis nodosa (PAN) is a rare necrotizing vasculitis involving medium or small arteries that is sometimes associated with hepatitis B virus infection.[1] The clinical picture includes constitutional symptoms, such as fever and weight loss, as well as gastrointestinal, musculoskeletal, or neurologic features.[2] The serious complications of PAN are organ ischemia as a result of vessel occlusions, aneurysmal ruptures, or thrombosis. The onset of PAN during pregnancy is exceptional; to date only 19 cases have been reported.[3,4] The lack of specific immunologic tests and the presence of nonspecific biologic findings, such as fever and leukocytosis, make the differential diagnosis among a puerperal infection and systemic complications of pregnancy difficult.

We present a case of PAN with peripartum onset in a patient with a twin pregnancy that occurred after ovarian stimulation.

CASE REPORT

A 30-year-old female with euthyroid Hashimoto disease and polycystic ovary syndrome underwent ovarian stimulation with clomiphene, follitropin alfa, progesterone, and chorionic gonadotropin. The procedure was successful, resulting in a dizygotic twin pregnancy. After an uneventful pregnancy, the patient presented to the hospital in labor in the 38th week of gestation, with intact membranes and one fetus in cranial and the second in transverse presentation. Two babies of 2,200 g and 2,100 g, each with Apgar scores of 10, were delivered by cesarean section. Macroscopic examination of the mother's lower abdomen during surgery revealed enlargement of the left ovary and a slightly right-torsioned, purple-colored uterus, with significantly enlarged parauterine veins.

The patient's initial postoperative course was normal. However, 48 hours following delivery, the patient developed tachycardia, hypotension, infraumbilical abdominal wall pain, and fever (38.2°C). Abdominal ultrasonography revealed a minimal fluid collection in the abdominal muscles that was drained and interpreted as hematoma. Hemorrhagic fluid cultures were sterile, but the patient was nevertheless prescribed broad-spectrum antibiotic therapy (ceftriaxone 1 g intravenously [IV] twice daily, gentamicin 1.2 mg/kg IV every 8 hours, and metronidazole 7.5 mg/kg orally every 6 hours). Two days later, her fever recurred and the patient developed intestinal dynamic occlusion. Laboratory findings were remarkable for a white blood cell (WBC) count of 29,600 mm^3, C-reactive protein $>$100 mg/dL (reference range, $<$3 mg/dL), and persistent low serum potassium levels. Reintervention revealed 150 mL of

serohemorrhagic peritoneal fluid and a hypotonic uterus and myometrium. A subtotal hysterectomy was performed to prevent disseminated intravascular coagulation. Cultures from the uterine cavity and the peritoneal exudate were sterile. Antibiotic therapy was continued (ceftriaxone was replaced with teicoplanin 6 mg/kg every 24 hours), along with an anticoagulant (nadroparin 0.6 mL every 12 hours) and volemic support as required. Despite these measures, the patient's fever spiked again in the presence of tachycardia, dynamic intestinal occlusion, and a WBC count of 44,700 mm^3. Postoperative peritonitis and abdominal wall phlegmon were suspected. Reintervention could not confirm the diagnosis but revealed infiltrated abdominal walls and agglutinated intestinal ansae.

Persistent deterioration of the patient's condition led to another intervention that revealed ischemia of the left ovary with subcapsular hematoma and 500 mL of serohemorrhagic odorless fluid in the pouch of Douglas. Left adnexectomy was performed, but the biopsy findings were noncontributory to the diagnosis.

Extensive screening for infection was again negative (hemocultures, *Brucella* testing, and ultrasound imaging), although the patient had a 5-fold increase in procalcitonin level to 2.6 ng/mL (reference range, $<$0.5 ng/mL). Antinuclear antibodies and the antiphospholipid panel were negative; further, anti–double-stranded DNA and hepatitis C virus antibodies, hepatitis B surface antigen, antineutrophil cytoplasmic antibodies, rheumatoid factor, and antistreptolysin O titers were normal or negative. Because sepsis could not be ruled out, the patient was continued on broad-spectrum antibiotic therapy (imipenem/cilastatin 500 mg/500 mg every 6 hours, metronidazole 7.5 mg/kg orally every 6 hours, and moxifloxacin 400 mg orally daily). Clinical and biologic tests found arterial hypertension (140/100 mmHg), spiking fevers, leukocytosis (15,000-25,000 mm^3), increased fibrin degradation products, and persistent hypokalemia.

Finally, repetitive physical examination revealed several nodules on a vascular tract of the left forearm, suggesting PAN or infectious vasculitis. The histopathologic examination of a nodule biopsy was consistent with PAN, showing vasculitis with fibrinoid necrosis, intravascular thrombi, and lymphoplasmacytic intramural infiltrates with lesions in different stages of the disease (Figure 1).

Treatment with pulse methylprednisolone (500 mg/day IV for 5 days), cyclophosphamide (15 mg/day every 2-3 weeks for 6 months), and immunoglobulin therapy (total dose 0.5 g/kg) resulted in rapid resolution of the patient's fever and normalization of the inflammatory parameters. Notably, 3 months later, an abdominal bruit was perceived upon clinical examination. Computed tomography angiography revealed celiac artery stenosis (Figure 2), but because of the patient's lack of symptoms, stenting was postponed until completion of the cyclophosphamide therapy. At 1-year follow-up, the abdominal bruit has disappeared and the patient is in remission on azathioprine (2 mg/kg/day) and antiplatelet therapy (aspirin 75 mg/day).

DISCUSSION

PAN typically occurs in middle-aged men and is characterized by the lack of distinctive immunologic or biologic biomarkers such as antineutrophil cytoplasmic antibodies.[5]

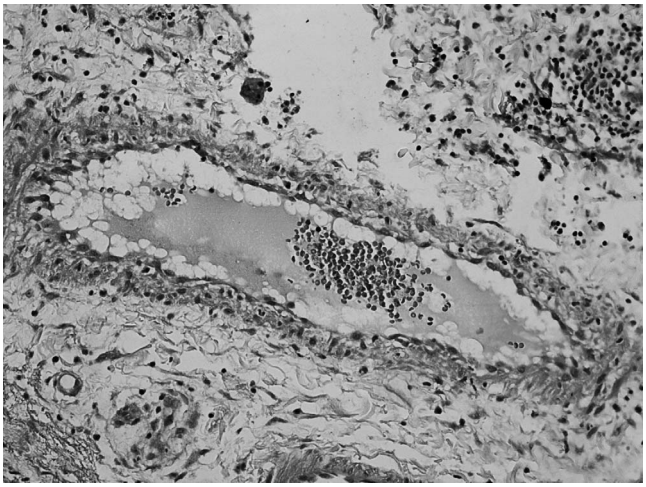

Figure 1. Intramural inflammatory infiltrate and fibrinoid necrosis with disruption of the vessel wall (hematoxylin and eosin stain, ×20). (To see this image in color, click to https://education.ochsner.org/publishing-services/toc/damian_17-0025_fig1.)

Presenting features include extensive livedo reticularis, severe hypertension that is responsive to glucocorticoids, acute abdomen as a result of vessel occlusion, rupture or organ perforation, acute genital inflammation (orchitis, epididymitis, or ovarian torsion), arthritis, myopathy, proteinuria, hypokalemia, renal failure, mononeuritis multiplex, skin purpura or necrosis, and subcutaneous nodules along the vessels.[2] For a diagnosis of PAN, the American College of Rheumatology requires meeting 3 of 10 criteria [6]; our patient had 4: new-onset hypertension, myalgia, arteriographic abnormalities, and a positive biopsy. Along with these symptoms and highly suggestive for the diagnosis were the presence of subcutaneous tender nodules, the ovarian involvement, and hypokalemia reflecting inflammation of the peritubular arterioles. The bloodstained peritoneal fluid likely resulted from the rupture of microaneurysms of visceral vessels.

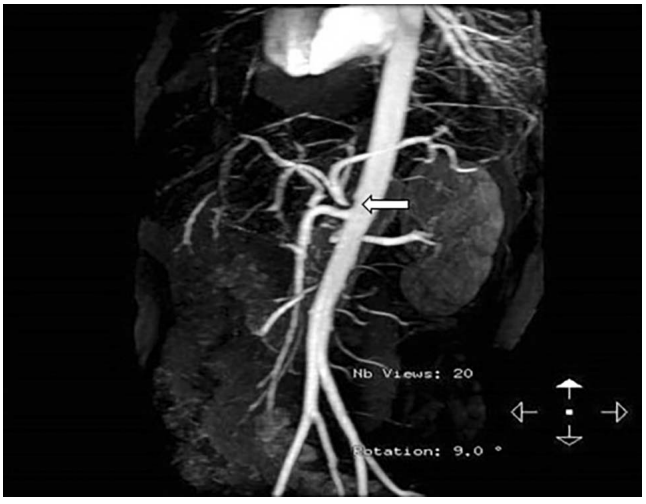

Figure 2. Computed tomography angiography of the abdominal aorta and branches shows circumferential stenosis of the celiac artery after its aortic branching (arrow).

Vasculitis in pregnancy is rare and likely underdiagnosed. To our knowledge, only 19 cases of PAN during pregnancy have been reported, resulting in 14 healthy babies and 5 abortions (2 therapeutic and 3 spontaneous).[3,4] In the case of PAN onset in advanced pregnancy, the prognosis is serious and associated with a high risk of maternal death. Gatto et al reported that in previously reported cases, 7 of 8 patients who had PAN onset during pregnancy died during gestation or within 42 days of delivery.[4] PAN can involve any organ or system and may manifest as severe hypertension, often with fatal outcome,[7] or with arterial ruptures that may precipitate cesarean section.[8] Factors associated with a severe outcome are elevated proteinuria and creatinine, cardiomyopathy, and gastrointestinal and neurologic involvement. The clinical picture may be complicated by the presence of the hepatitis B antigen in approximately 10% of cases.[4,9]

If PAN remains in remission during the pregnancy, the pregnancy may not induce a flare of the vasculitis.[4,10] Nevertheless, even in controlled disease, PAN relapses may occur.[9] In incipient pregnancy, therapeutic abortion is considered. In advanced pregnancy, high-dose glucocorticoids, and, when mandatory, cyclophosphamide during the third trimester may be lifesaving.[8]

PAN may also manifest postpartum, sometimes as a breast lesion, making it difficult to differentiate the vasculitis from an infectious mastitis or malignancy.[11] Our patient did not breastfeed and had no such recurrence.

In vitro fertilization (IVF) seems unlikely to have played a role in the occurrence of PAN in our patient. The few cases of necrotizing vasculitis reported after IVF or ovarian stimulation occurred early after the procedure, possibly through an allergic mechanism, as suggested by the presence of numerous eosinophils in the biopsy.[12]

Incidental isolated vasculitis of the genital tract has also been reported in the absence of autoimmune diseases. In all, approximately 50 cases of isolated PAN of the female genital organs have been uncovered during hysterectomy for other indications, primarily involving the cervix.[13] In tumor-like presenting vasculitis, ovarian involvement is frequent,[14,15] reaching 10% in a study of 46 cases.[16] In our patient, oophorectomy and hysterectomy may have had a favorable impact on the outcome through the removal of the visceral vasculitis. However, in our case, the genital tract vasculitis was not isolated, as tender celiac artery involvement was documented, and nodules were found on the patient's arm.

Our case is unusual in that the patient's pregnancy was uneventful and she carried twins successfully until term. For patients with PAN, the risk of preterm birth is high.[17] As an illustration of this point, the other published case report of a successful outcome of PAN with onset during pregnancy was complicated by premature rupture of membranes and premature delivery.[8]

CONCLUSION

A rare pathology such as PAN should be taken into account among other systemic complications of pregnancy in the presence of an inflammatory storm. Because PAN has no biologic pathognomonic red flags, severe hypertension, livedo reticularis, tender subcutaneous nodules, arterial bruits, and ovarian involvement should prompt the clinician to search for this almost-forgotten life-threatening pathology to allow timely institution of therapy. Multidisciplinary consultations with the gynecologist, neonatologist, rheumatologist, nephrologist, radiologist, and pathologist are crucial. Emergency cesarean section when necessary, infectious screening, pathologic examination of the available tissue, and prompt institution of glucocorticoids can be lifesaving.

ACKNOWLEDGMENTS

The authors have no financial or proprietary interest in the subject matter of this article.

The authors want to gratefully acknowledge the contribution of Dr Claudiu Damian for the interpretation and editing of the images. Funding: PN-II-RU-TE-2014-4-2708.

REFERENCES

1. De Virgilio A, Greco A, Magliulo G, et al. Polyarteritis nodosa: a contemporary overview. *Autoimmun Rev*. 2016 Jun;15(6): 564-570. doi: 10.1016/j.autrev.2016.02.015.
2. Forbess L, Bannykh S. Polyarteritis nodosa. *Rheum Dis Clin North Am*. 2015;41(1):33-46, vii. doi: 10.1016/j.rdc.2014.09.005.
3. Foster R, D'Cruz DP. Vasculitis in pregnancy. *Expert Rev of Obstet Gynecol*. 2007;2(5):681-688. doi: 10.1586/17474108.2.5. 681.
4. Gatto M, Iaccarino L, Canova M, et al. Pregnancy and vasculitis: a systematic review of the literature. *Autoimmun Rev*. 2012 May; 11(6-7):A447-A459. doi: 10.1016/j.autrev.2011.11.019.
5. Howard T, Ahmad K, Swanson JA, Misra S. Polyarteritis nodosa. *Tech Vasc Interv Radiol*. 2014 Dec;17(4):247-251. doi: 10.1053/j. tvir.2014.11.005.
6. Lightfoot RW Jr, Michel BA, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa. *Arthritis Rheum*. 1990 Aug;33(8): 1088-1093.
7. Reed NR, Smith MT. Periarteritis nodosa in pregnancy: report of a case and review of the literature. *Obstet Gynecol*. 1980 Mar; 55(3):381-384.
8. Pagnoux C, Le Guern V, Goffinet F, et al. Pregnancies in systemic necrotizing vasculitides: report on 12 women and their 20 pregnancies. *Rheumatology (Oxford)*. 2011 May;50(5): 953-961. doi: 10.1093/rheumatology/keq421.
9. Aya AG, Hoffet M, Mangin R, Balducchi JP, Eledjam JJ. Severe preeclampsia superimposed on polyarteritis nodosa. *Am J Obstet Gynecol*. 1996 May;174(5):1659-1660.
10. Owen J, Hauth JC. Polyarteritis nodosa in pregnancy: a case report and brief literature review. *Am J Obstet Gynecol*. 1989 Mar;160(3):606-607.
11. Trüeb RM, Scheidegger EP, Pericin M, et al. Periarteritis nodosa presenting as a breast lesion: report of a case and review of the literature. *Br J Dermatol*. 1999 Dec;141(6):1117-1121.
12. Amichai B, Grunwald MH, Halevy S. Allergic vasculitis induced by Decapeptyl: confirmation by macrophage migration inhibition factor (MIF) test. *Eur J Obstet Gynecol Reprod Biol*. 1993 Dec 30;52(3):217-218.
13. Fraenkel-Rubin M, Ergas D, Sthoeger ZM. Limited polyarteritis nodosa of the male and female reproductive systems: diagnostic and therapeutic approaches. *Ann Rheum Dis*. 2002 Apr;61(4):362-364.
14. Hernández-Rodríguez J, Tan CD, Rodríguez ER, Hoffman GS. Gynecologic vasculitis: an analysis of 163 patients. *Medicine (Baltimore)*. 2009 May;88(3):169-181. doi: 10.1097/MD. 0b013e3181a577f3.
15. Abu-Farsakh H, Mody D, Brown RW, Truong LD. Isolated vasculitis involving the female genital tract: clinicopathologic spectrum and phenotyping of inflammatory cells. *Mod Pathol*. 1994 Jun;7(5):610-615.

16. Hoppé E, de Ybarlucéa LR, Collet J, Dupont J, Fabiani B, Puéchal X. Isolated vasculitis of the female genital tract: a case series and review of literature. *Virchows Arch*. 2007 Dec;451(6): 1083-1089. doi: 10.1007/s00428-007-0514-4.

17. Doria A, Bajocchi G, Tonon M, Salvarani C. Pre-pregnancy counselling of patients with vasculitis. *Rheumatology (Oxford)*. 2008 Jun;47 Suppl 3:iii13-iii15. doi: 10.1093/rheumatology/ken152.

This article meets the Accreditation Council for Graduate Medical Education and the American Board of Medical Specialties Maintenance of Certification competencies for Patient Care and Medical Knowledge.