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Placenta Accreta Spectrum Disorder Associated With Late Onset Pre-Eclampsia: A Case Report

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ABSTRACT

Placenta Accreta Spectrum (PAS) disorder is a condition characterized by abnormal adherence and various levels of invasive placentation, whereas the physiopathology of pre-eclampsia (PE) involves insufficient trophoblast invasion of maternal blood vessels in early pregnancy and subsequent placental insufficiency. In this case report, we elaborate on these two pathologies and describe the case of a patient with PAS disorder, who developed term PE.

1 | Introduction

Placenta accreta spectrum (PAS) disorder is defined as an abnormal location of the placenta in the myometrium caused by the implantation of the gestational sac within a uterine scar area [1, 2]. In the most severe forms of PAS, the placental bed invades all layers of the uterus to reach the peritoneal cavity or the bladder [1]. In the majority of cases, PAS is related to a defect in the endometrial-myometrial interface leading to this abnormal placental development. The most frequent cause for this defect is a previous cesarean delivery; however, there are other risk factors such as other prior uterine surgeries, Asherman syndrome, multiparity, maternal age, and placenta previa (PP) [2]. After 16 weeks of gestation, the low implantation of the placenta can be described as PP or low-lying placenta, depending on the distance from the cervical os regardless of the presence of PAS; in PP, the placenta covers the internal os, whereas in low-lying placenta, the distance from the placental edge to the internal os is less than 20 mm [3]. When combining PP and a previous cesarean delivery, the risk of PAS increases significantly [2]. The diagnosis of PAS relies firmly on the histopathologic examination of the specimen after delivery [1]. However, PAS can be suspected antenatally by means of ultrasound and/or MRI. There are several ultrasound signs that indicate the possible existence of a PAS, such as the presence of multiple vascular lacunae within the placenta, diminished retroplacental myometrial thickness, disruption of the normal hypoechoic zone between the placenta and the myometrium, disruption of the interface between the uterine serosa and the bladder, ... but the most important association that can be found is the presence of a PP [2].

Pre-eclampsia (PE) is defined as new onset hypertension arising after 20 weeks of gestation, accompanied most often by proteinuria (defined as 300 mg or more per 24-h urine collection, or 2+ in a dipstick reading, or a ratio of protein/creatinine greater than or equal to 0.3). However, in the absence of proteinuria, other signs and symptoms can be associated with hypertension to define PE, such as thrombocytopenia (platelet count less than 100×10^9/L), and/or renal insufficiency (serum creatinine greater than 1.1 mg/dL or a doubling of the serum creatinine in the absence of other renal disease), and/or impaired liver function (elevated blood levels of liver transaminases to twice normal concentration), and/or pulmonary edema, and/or new-onset headache unresponsive to medication and unexplained by other diagnosis, and/or visual disturbances [4–6]. New onset hypertension is defined as a systolic blood pressure of 140 mmHg

or higher, or a diastolic blood pressure of 90 mmHg or higher occurring on two occasions at least 4 h apart, or a systolic blood pressure of 160 mmHg or higher or a diastolic blood pressure of 110 mmHg or higher [4]. The risk factors for developing PE include nulliparity, increased BMI, maternal age, multiple pregnancies, assisted reproduction, diabetes,... [4, 6]. In the literature, PE is subdivided into two major entities: early-onset PE before 34 weeks related to abnormal uteroplacental perfusion secondary to defective remodeling and invasion of the uterine spiral arteries in early pregnancy, and late-onset PE at ≥ 34 weeks caused by a mismatch between placental perfusion and metabolic demands of the growing fetus [6].

The relationship between PAS and PE is currently not well-defined; a recent study by Liu et al. concluded that there is a decreased incidence of PE in the case of PAS; however, PAS was not an independent predictive factor of PE in their study [7]. There are more publications investigating the relationship between PP and PE, and the authors report a decreased incidence of PE in patients with PP, sometimes referring to PP as a protective mechanism against PE [8–10].

2 | Case History/Examination

We report the case of a 30-year-old woman, with a spontaneous singleton pregnancy, no underlying medical conditions, and a booking BMI of 26.3 kg/m^2. She was a G3P1 with a history of one uncomplicated pregnancy delivered by elective cesarean section for breech presentation at term (9 years earlier) and an early miscarriage treated by dilation and curettage.

At the second trimester anomaly scan, a diagnosis of anterior PP was made with a strong suspicion of PAS (Figures 1–3) that grew stronger after performing an MRI (Figure 4). The ultrasound revealed an anterior PP lateralized to the left with almost absent retroplacental myometrial thickness, which was correlated with the MRI results of non-visualization of the retroplacental myometrium. A management plan was then established consisting of an elective cesarean delivery at 37 weeks of gestation with bilateral double-J stent and femoral catheter placement prior to surgery. The patient was also counseled about the risk of severe hemorrhage and the need for a cesarean-hysterectomy based on surgical findings. During the cesarean section, the patient suffered from a severe hemorrhage necessitating hysterectomy. A small breach of the urinary bladder was diagnosed during surgery and sutured directly. Therefore, the patient kept the Foley catheter 10 days postoperatively. The patient did not suffer from any postoperative urinary complications.

Her monthly antenatal care visits were uncomplicated and her blood pressure was normal until term with values varying between 110/60, 120/80, and 130/70 mmHg. At 28 weeks of gestation, fetal growth was normal and the uterine arteries Doppler pulsatility indexes were measured and were within the normal range, with values of 1.15 for right-sided UtA PI (91th percentile) and 0.81 for left-sided UtA PI (50th percentile) according to the Fetal Medicine Foundation (FMF) calculator [11]. The systolic and diastolic waveforms were also normal and no notch was found. Fetal growth was normal at 33 weeks of gestation with an estimated fetal weight (EFW) of 1825 g, which corresponded to the 30th percentile, according to Intergrowth charts [12]. The umbilical Doppler PI (UA

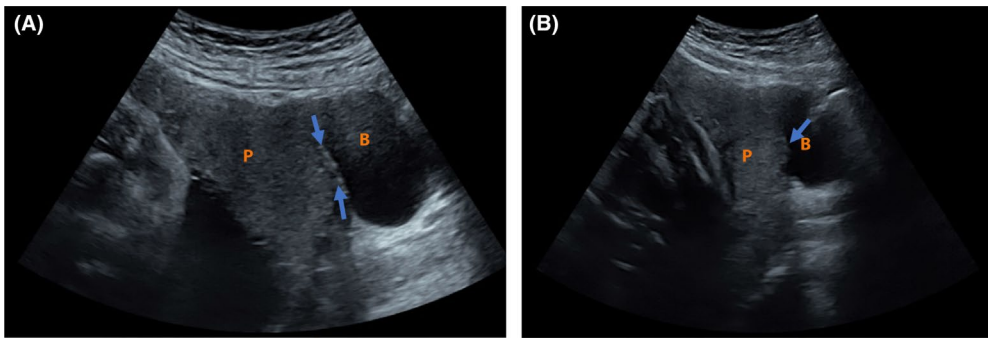

FIGURE 1 | Ultrasound image at 28 weeks of pregnancy showing a sagittal view of the lower uterine segment. B, bladder; P, placenta. (A) Myometrial thinning and (B) mild placental bulging.

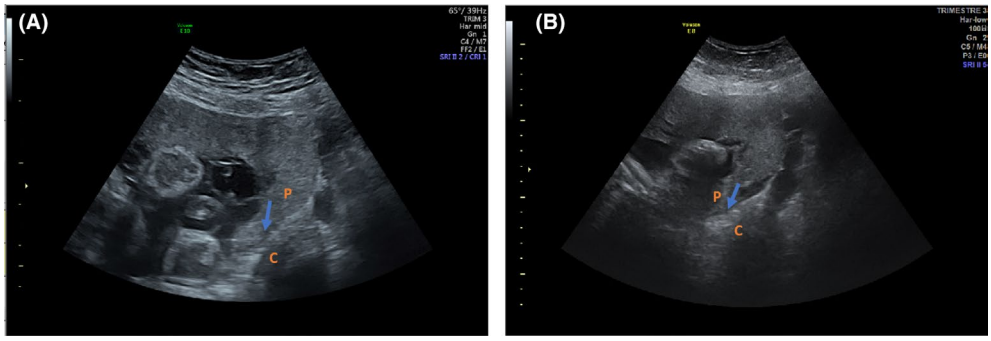

FIGURE 2 | Abdominal ultrasound images showing a placenta previa covering the internal cervical os. C, cervix; P, placenta. (A) At 28 weeks of pregnancy and (B) at 33 weeks of pregnancy.

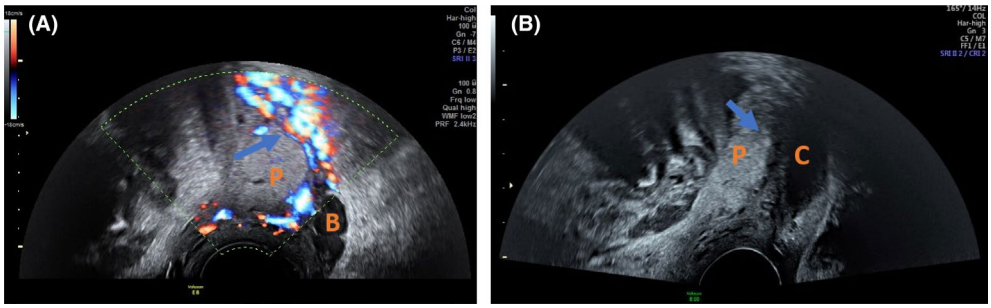

FIGURE 3 | Vaginal ultrasound images showing: (A) Important retroplacental vascularization and (B) placenta previa covering the internal cervical os. B, bladder; C, cervix; P, placenta.

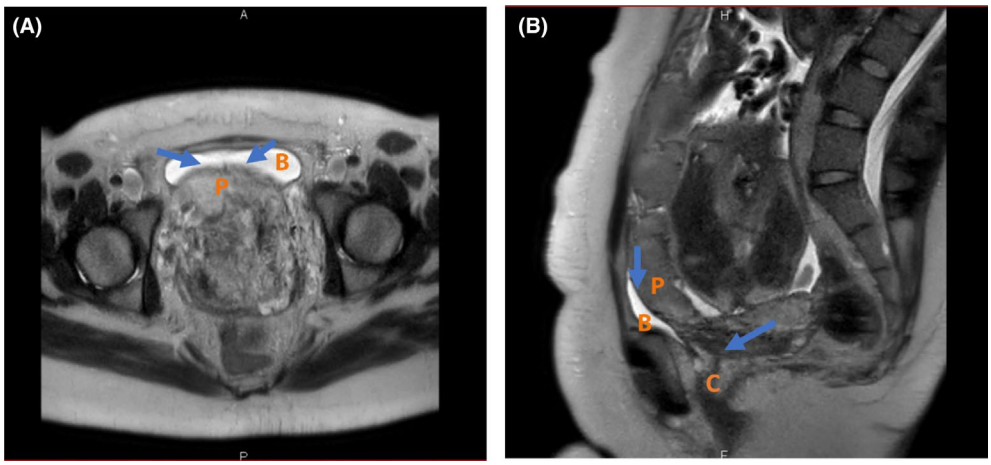

FIGURE 4 | T2 weighted MRI at 28 weeks of pregnancy showing a placenta anterior and previa. No myometrium can be identified under the placenta in the lower segment of the uterus. (A) Coronal view and (B) sagittal view (showing a placenta previa covering the internal cervical os).

PI) was also within the normal range, with a value of 1.00 for UA PI (68th percentile), according to Intergrowth charts [13]. During her antenatal care visits, the patient also benefited from several ultrasounds to assess fetal viability and the placental status, all of which showed normal fetal growth and normal UA PI, without any signs of distress or intrauterine growth restriction.

3 | Differential Diagnosis, Conclusion and Results

She attended the delivery suite at 37 weeks of gestation for her organized admission the day before the planned cesarean delivery with elevated blood pressure (measurements taken every 5 min: 204/113, 197/107, 202/113, 203/110, 202/107, 198/98, and 203/105 mmHg) associated with proteinuria and lower limb edema. She was admitted to the Maternal Intensive Care unit with a diagnosis of late-onset PE in addition to PAS. No evidence of neurological signs and symptoms was found during her admission. Her BMI at the time of admission was 32.9 kg/m^2 with a total weight gain of 20 kg during her pregnancy. The fetal monitoring (CTG) showed normal reactivity and variability with a baseline fetal heart rate of 130 beats/min.

At the time of admission, the patient's laboratory results were as follows: WBC 13,300/mm^3, hemoglobin 12.4 g/dL, hematocrit 35.8%, platelets 222,000/mm^3, haptoglobin 0.71 g/L, normal coagulation test results, fibrinogen 5.3 g/L, CRP 18.1 mg/L, proteins 48 g/L, albumin 27 g/L, creatinine 0.53 mg/dL, uric acid 6.7 mg/dL, sodium 135 mmol/L, potassium 4.3 mmol/L, calcium 2.02 mmol/L, total bilirubin 0.2 mg/dL, ASAT 18 U/L, ALAT 9 U/L, LDH 247 U/L, proteinuria 8101 mg/L, protein/creatinine ratio 7580 mg/g. The soluble fms-like tyrosine kinase-1/placental growth factor ratio (sFlt-1/PlGF) was elevated at 179.

Upon hospitalization, the patient was treated with 2 IV antihypertensive agents (nicardipine and labetalol) and magnesium sulfate in order to stabilize her blood pressure at values of 140/90 mmHg or below and to reduce the risk of eclampsia. On the second day of admission, she underwent double J-stent placement, as per the management protocol at our center for patients with PAS, and a cesarean-hysterectomy with a midline incision (Figure 5). A diagnosis of PAS with bladder wall invasion was confirmed by histopathological examination of the specimen (Figure 6) with the presence of a residue of the bladder wall with parietal muscular layers, and with evidence of direct contact of placental tissue to external muscular fibers of the bladder, making it a grade 3E according to the current histopathological classification for PAS [14]. Histopathological examination also revealed signs of chronic ischemia and recent multiple thrombosis at the site of placental implantation. During the surgery, the patient was transfused with 5 units of packed RBCs. Her post-op labs were as follows: WBC 9240/mm^3, hemoglobin 9.3 g/dL, hematocrit 35.8%, platelets 83,000/mm^3, normal coagulation test results, fibrinogen 1.9 g/L, CRP 5.5 mg/L, proteins: 30 g/L, albumin 16 g/L, creatinine 0.97 mg/dL, sodium

138 mmol/L, potassium 4.7 mmol/L, calcium 1.65 mmol/L, total bilirubin 0.4 mg/dL, ASAT 13 U/L, ALAT 5 U/L, LDH 163 U/L.

She delivered a girl with a birthweight of 2230 g and an Apgar score of 5 and 8 at 1 and 5 min of life, respectively.

In the postpartum period, the blood pressure was controlled at levels below 140/90 mmHg with oral medications (propranolol and nifedipine). The patient was discharged 11 days after her admission with a blood pressure of 140/80 mmHg. Later on, the patient continued to have increased blood pressure, and she was eventually diagnosed with chronic hypertension. Two months after the cesarean section, the patient suffered from an acute subarachnoid hemorrhage due to a ruptured aneurysm of the anterior cerebral artery, which was treated successfully by embolization. It was controlled 6 months later by MRI angiography, and the patient is followed up with a yearly MRI. Her last MRI 7 years after delivery revealed a stable condition. During this time, she was treated with Aspirin 80 mg, which was stopped 5 years after her delivery. Her latest blood pressure medications were a beta-blocker and a drug combining an ACE-inhibitor, a calcium channel blocker, and a thiazide diuretic.

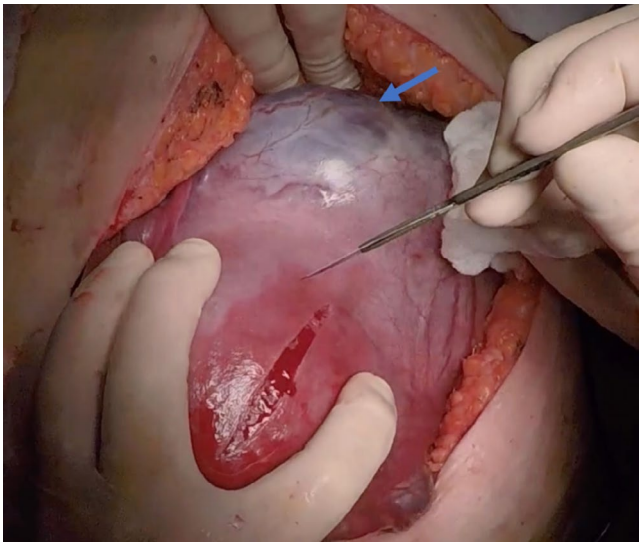

FIGURE 5 | Intraoperative picture showing placental bulging at the level of the inferior segment.

4 | Discussion

PAS/PP and PE are entities that are usually not described together in a single patient. We reviewed the literature to search for cases of PAS associated with PE, and we only found 4 articles between 1994 and 2022.

A study by Liu et al. on the effects of abnormal placental location and PAS on the risk of hypertensive disorders of pregnancy (HDP) concluded that PP and PAS are associated with a decreased incidence of HDP, and that PP (but not PAS) was even a protective mechanism. However, the authors acknowledge that earlier gestational age at delivery in the case of PP and/or PAS might be a confounding factor influencing the development of HDP in these women [7]. A meta-analysis performed by Lingli et al. showed that HDP was significantly correlated with a lower prevalence of PAS and that the presence of PAS was significantly correlated with a lower prevalence of HDP, but the authors could not assess confounding factors such as gestational age at delivery, ethnicity, ... [15]. Another study by Ying et al. concluded that PP is associated with a significant reduction in both early and late-onset PE; however, concurrent PAS was not associated with a further reduction of the risk of developing PE [9]. Cobo et al. reported a case of PP associated with PAS that presented with severe early-onset PE requiring a cesarean-hysterectomy. The patient also developed eclampsia in the postpartum period [16]. Another case was reported by Hung, discussing a patient with PAS, PP, and pulmonary hypertension that developed early-onset PE requiring delivery [17]. These two case reports describe patients who developed early-onset PE in the presence of PAS and PP and challenge the theory of the protective effect of PAS/PP on PE.

PAS and PE are often considered to have opposing physiopathologies that could prevent them from co-existing in one patient; PE is related to defective remodeling of the uterine spiral arteries, hence a defective trophoblast invasion, whereas PAS is characterized by an increased trophoblast invasion. The antiangiogenic factor sFLT-1 is increased 2 to 5-fold in patients with PE as compared to normal pregnancies, whereas the presence of lower levels of sFLT-1 has been shown in patients with abnormal invasive placentation [6, 18]. In this case report, the sFLT-1/PlGF ratio was elevated in a patient that was diagnosed with both PAS and late-onset PE.

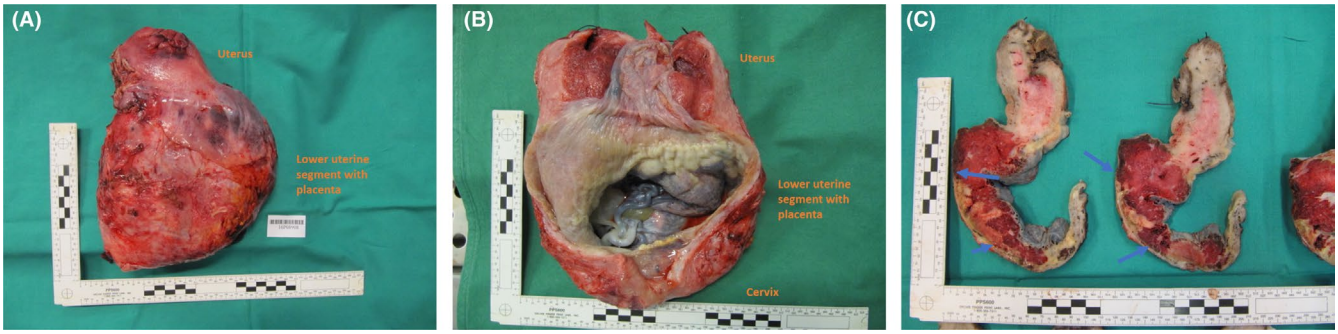

FIGURE 6 | Post cesarean hysterectomy specimen pictures during histopathological studies showing: (A) Entire specimen showing the uterus and the bulging lower uterine segment. (B) Sagittal cut opened specimen showing the uterus, the lower uterine segment with placenta in situ, and the cervix. (C) Two sagittal cut specimens showing the placental invasion.

However, the physio-pathologies of early-onset and late-onset PE are different; early-onset PE is caused by uteroplacental malperfusion due to inadequate invasion of the trophoblast, whereas late-onset PE is associated with a mismatch between uteroplacental perfusion and the metabolic demands of the growing fetus later in pregnancy [19]. Moreover, recent studies suggest that uteroplacental malperfusion in PE could also be related to the presence of suboptimal cardiovascular performance even before pregnancy [5]. In this case report, the woman was diagnosed with chronic hypertension in the postpartum period, which could unmask a poor cardiovascular function that was not known before the pregnancy. Indeed, her blood pressure values were within the normal range until 37 weeks of gestation. Therefore, late-onset PE may arise in a woman diagnosed with PAS characterized by excessive trophoblast invasion in the setting of a mismatch between fetal demands and uteroplacental perfusion due to underlying suboptimal cardiovascular function.

In the literature, most studies have found a decreased incidence of PE in patients with PP and/or PAS and even a protective mechanism against PE for PP. The authors suggested that the abundance of blood supply in cases of PP could explain the lower incidence of PE in these women, as compared to women with PE and inadequate trophoblast invasion with diminished blood supply and oxygenation of the placenta [9, 10, 18].

However, scientific guidelines recommend early delivery before 37 weeks for PAS, ideally between 34 and 36 weeks of gestation [2]. Gestational age at delivery has an impact on the incidence of PE that is more frequent after 37 weeks [7]. Therefore, for most women with PP and/or PAS, delivery is planned during the late pre-term or early-term period potentially before the development of late-onset PE. As late-onset PE is seven times more frequent than early-onset PE, this intervention bias could partially explain the lower incidence of PE that has been described in pregnancies complicated by PP and/or PAS.

In this case report, the diagnosis of PAS and PP was suspected antenatally at the second trimester anomaly scan. The patient developed severe late-onset PE at 37 weeks of gestation, and she required a delivery by cesarean-hysterectomy for PAS. The diagnosis of PAS was confirmed by histopathological examination of the hysterectomy specimen. PAS/PP and PE are often considered as two entities that cannot co-exist due to their different pathophysiologies involving respectively excessive and defective trophoblast invasion. However, one should not forget the difference between the pathophysiology of early-onset and late-onset PE that may arise from a mismatch between fetal demands and uteroplacental supply. Moreover, patients with PAS usually undergo planned delivery before 37 weeks of gestation, possibly before the development of PE, making it a valid reason for the previously described decreased incidence of PE with PAS.

Author Contributions

Sophie Lorquet: investigation, writing – review and editing. **Frédéric Chantraine:** conceptualization, formal analysis, methodology, project administration, supervision, validation, writing – review and editing. **Laure Noel:** conceptualization, formal analysis, investigation, methodology, resources, validation, visualization, writing – review and editing. **Sandy El Sayed:** conceptualization, data curation, formal analysis, methodology, resources, visualization, writing – original draft.

Consent

The patient in this case report has given written informed consent to the publication of her case details.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support this case report are available from the corresponding author upon request.

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