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CASE REPORT

Coexistence of Congenital Dysfibrinogenemia and Antiphospholipid Syndrome in Pregnancy: A Case Report

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Abstract: Congenital dysfibrinogenemia (CD) and antiphospholipid syndrome (APS) are two distinct thrombotic disorders that can have significant clinical implications, especially in pregnancy. CD is a rare inherited condition caused by mutations in fibrinogen genes, leading to abnormal fibrin polymerization and fibrinolysis, and causes bleeding tendencies, thrombosis and pregnancy complications. APS, an acquired autoimmune disorder, increases the risk of recurrent thrombosis and adverse pregnancy outcomes, such as miscarriages and stillbirths. This report describes a 35-year-old woman with genetically confirmed congenital dysfibrinogenemia (CD) (heterozygous FGG c.1001A>C) who subsequently developed antiphospholipid syndrome (APS). Notably, although lupus anticoagulant and β2GP1-IgM positivity were present since 2017, APS remained undiagnosed until 2023, following her third miscarriage. In retrospect, she fulfilled the Sydney criteria with recurrent early pregnancy loss, persistent antibodies, and livedo reticularis. During her successful pregnancy in 2021, management focused exclusively on CD: fibrinogen levels were monitored (0.47–0.98 g/L), and fibrinogen concentrate was administered during cesarean delivery due to fetal growth restriction. This resulted in a live infant birth, despite the later recognition of placental thrombosis as APS pathology. This case highlights how CD may mask the diagnosis of APS. The aunt's uneventful pregnancy, with the same FGG mutation but no APS, confirms CD's limited obstetric impact. The delayed APS recognition underscores the importance of reevaluating antiphospholipid status in CD patients experiencing new thrombotic or obstetric events. However, the management of combined CD and APS remains theoretical.

Keywords: congenital dysfibrinogenemia, antiphospholipid syndrome, pregnancy, thrombosis, miscarriage, livedo reticularis

Introduction

Congenital dysfibrinogenemia (CD) is an autosomal dominant inherited coagulation disorder characterized by defective fibrin polymerization and/or fibrinolysis, resulting from structural alterations in fibrinogen.[1] This disorder is caused by heterozygous missense mutations in one of the fibrinogen genes—FGA, FGB, or FGG—that encode the three pairs of polypeptide chains of fibrinogen.[2] The clinical manifestations of CD are highly heterogeneous, ranging from asymptomatic cases to those presenting with bleeding and/or thrombotic complications.[1] Pregnancy poses significant risks to women with CD, requiring multidisciplinary counseling.

Antiphospholipid syndrome (APS) is an acquired autoimmune disorder characterized by recurrent arterial or venous thrombosis and/or adverse pregnancy outcomes, such as early miscarriages and stillbirths.[3] The coexistence of CD and

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APS has not been previously reported and presents a further challenge in clinical management, particularly during pregnancy, due to the complex interaction between these inherited and acquired thrombotic disorders.

Here, we present a rare case of a 35-year-old woman diagnosed with both CD and APS during pregnancy. We describe the diagnostic approach that led to the identification of a novel mutation in the FGG gene associated with CD and the use of pathological findings from the placenta and laboratory analysis. Additionally, we discuss the management strategies used to minimize obstetric complications through vigilant monitoring and careful intervention.

Case Report

A 35-year-old female experienced a spontaneous miscarriage at 8 weeks of gestation in 2016 (G1). In 2017, laboratory tests revealed a reduced fibrinogen (Fbg) level of 0.51 g/L, along with prolonged activated partial thromboplastin time of 32.6 s, prothrombin time of 13.0s, and thrombin time of 22.2s. Subsequent Fbg antigen assay showed 1.83 g/L (concurrent Fbg activity 0.37 g/L) with a ratio of $0.37/1.83 < 0.7$, raising suspicion of dysfibrinogenemia. Genetic sequencing performed in 2017 identified a heterozygous mutation in the FGG gene (c.1001A>C, p.N334T). Other missense mutations at the same locus have been previously reported in association with familial dysfibrinogenemia inherited in an autosomal dominant manner.[4] Genetic testing of her family members confirmed that the same mutation was present in her father and paternal aunt, both of whom had significantly reduced Fbg levels. The patient's mother tested FGG gene wild type. None of her paternal relatives had a history of bleeding or thrombotic events. Besides, her aunt experienced a successful and asymptomatic pregnancy at the age of 26 and gave a birth to a girl.

During her second pregnancy from July 2020 to March 2021 (G2), we monitored her Fbg levels regularly, which fluctuated between 0.47 and 0.98 g/L. Fetal growth restriction was observed in the later stages of pregnancy (Figure 1). At 39 weeks of gestation in March 2021, the patient underwent an elective cesarean section under combined spinal-epidural anesthesia, following a collaborative discussion by a multidisciplinary team including obstetricians, hematologists, and anesthetists. Prior to anesthesia, 1 g of Fbg concentrate was administered, raising the post-transfusion Fbg activity to 1.02 g/L. The delivery resulted in a live male infant weighing 2800 g, with intraoperative hemorrhage of 200 mL. Placental pathology revealed thrombosis and infarction in the chorionic plate (Figure 2). In 2023 (G3), at 9 weeks of gestation, the patient underwent dilation and curettage due to a missed miscarriage.

Regarding antiphospholipid syndrome (APS), the patient tested positive for lupus anticoagulant (LA) and β2-glycoprotein I IgM (β2GP1-IgM) since 2017 (Table 1), and she had a history of two early (<10 weeks) spontaneous miscarriages. The pathology of the placenta from the full-term delivery in 2021 showed features suggestive of thrombotic occlusion. In 2023, the patient tested high-titer positive for LA, anticardiolipin antibodies (ACL), and β2GP1 antibodies (Table 1), fulfilling the diagnostic criteria for APS. Physical examination revealed livedo reticularis on the skin of the right upper and lower limbs. According to the Sydney 2006 classification criteria for APS, the patient met one clinical and one laboratory criterion, confirming the diagnosis of APS. Her father tested negative for LA, ACL, and β2GP1 antibodies.

Diagnostic Overshadowing and Management Timeline

This case illustrates how CD initially masked APS recognition:

2017–2021: Management focused solely on CD (fibrinogen monitoring/replacement).

2021 delivery: Placental thrombosis was noted but attributed to CD; APS serology (positive since 2017) was not acted upon.

2023: Recurrent miscarriage triggered APS diagnosis. Critically, no pregnancy received combined CD+APS therapy.

Discussion

CD, though rare, can manifest in a variety of ways, from asymptomatic cases to severe bleeding or thrombosis. Genetic testing identified a heterozygous mutation in the FGG gene, supporting the diagnosis of familial dysfibrinogenemia and emphasizing the importance of genetic testing for personalized management and family counseling. APS, diagnosed through positive LA, ACL, and (β2GP1 antibodies, further complicates the case. This patient's history of recurrent miscarriages and placental thrombotic occlusion highlights the risks of APS, requiring careful anticoagulation therapy and close monitoring during pregnancy.

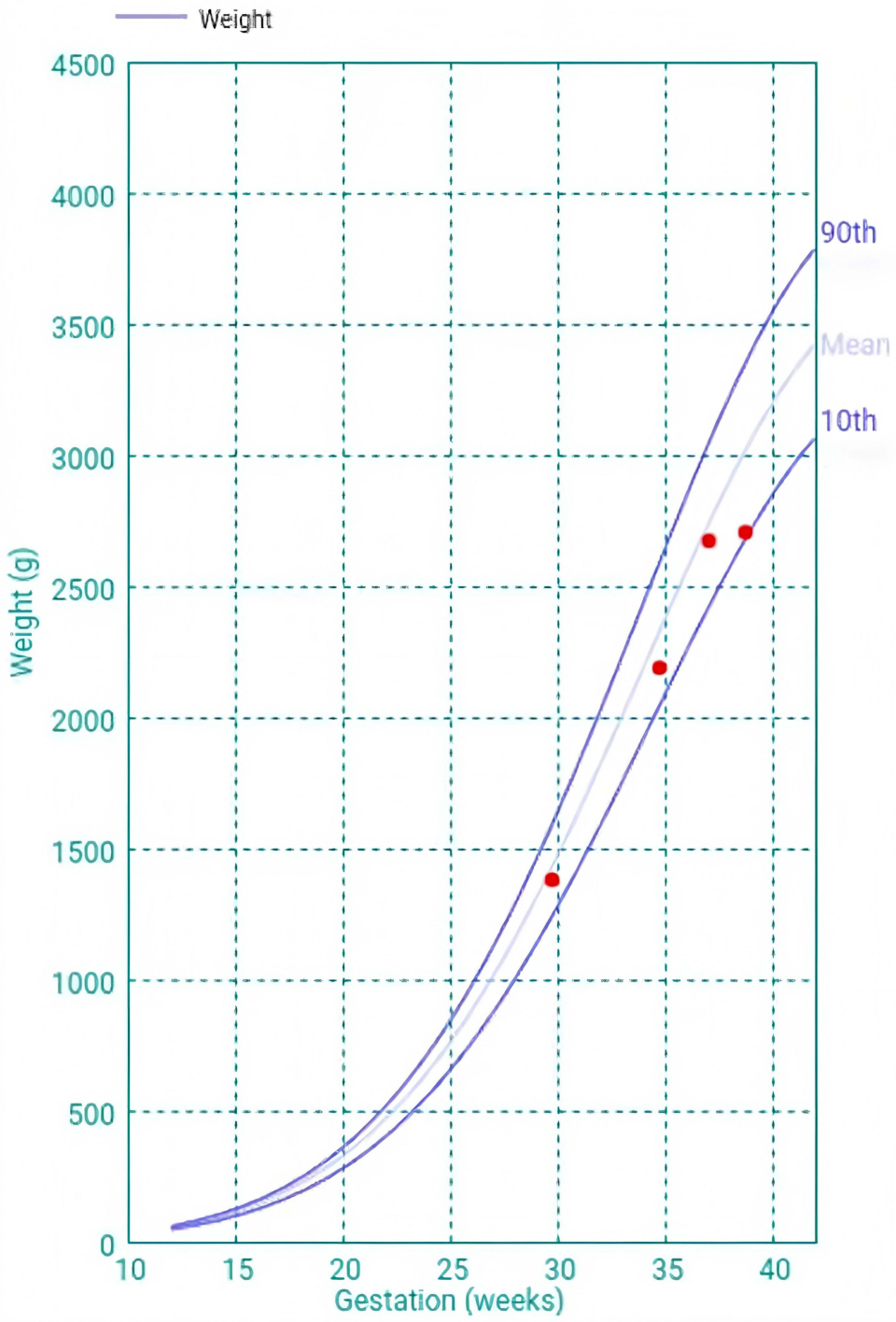

Figure 1 Ultrasonographic estimation of fetal weight change curves in late pregnancy.

A key clinical sign, livedo reticularis, was observed in this patient, which has been associated with APS.[5] This pattern occurs when thrombi form in the small blood vessels of the skin's microcirculation, leading to capillary dilation and blood stasis, creating a lattice-like appearance.[6] The patient reported persistent livedo reticularis for over a decade, suggesting that microthrombi may have been present for an extended period. The positive β2GP1-IgM test in 2017, coupled with a history of two early miscarriages, aligns with the diagnostic criteria for APS, highlighting the heightened thrombotic risk in our patient. Placental pathology from the full-term delivery revealing features of thrombotic occlusion

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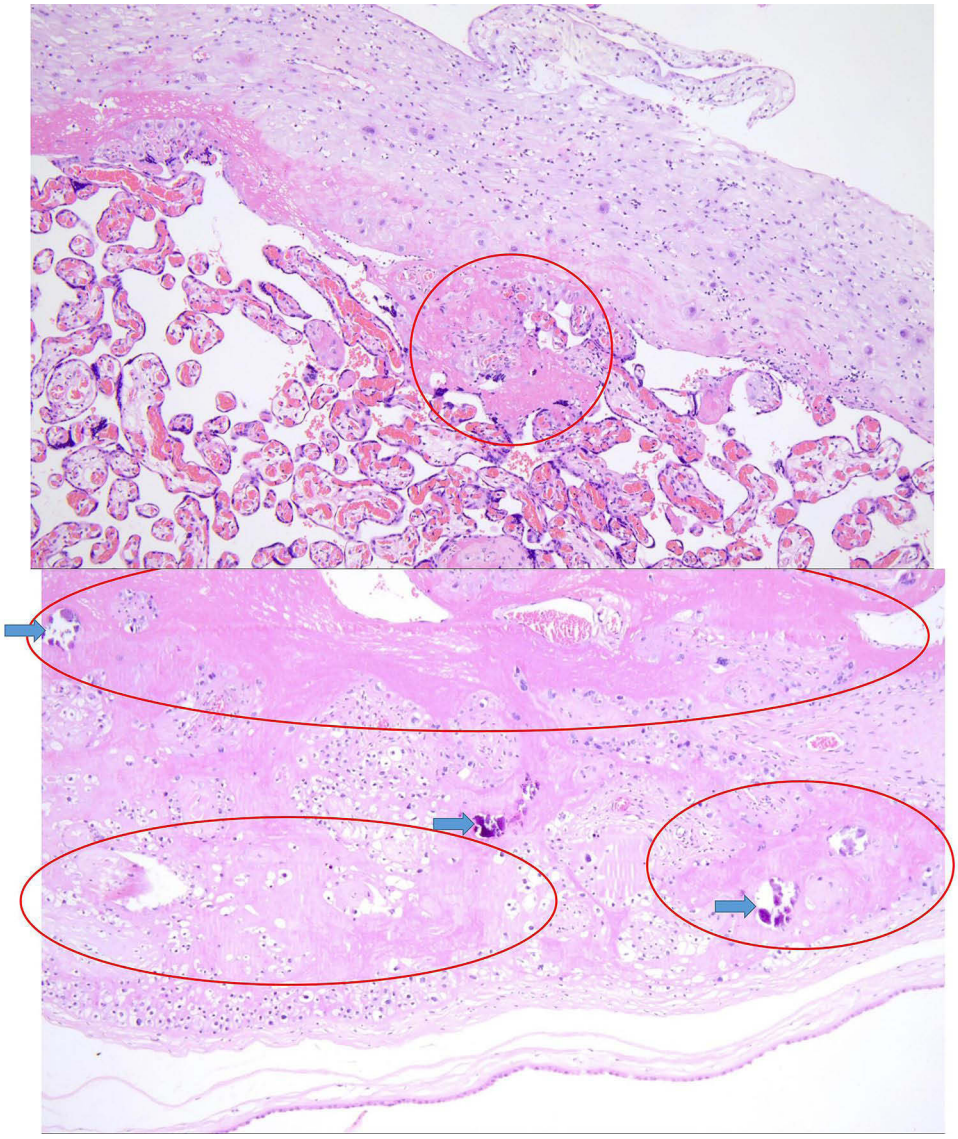

Figure 2 Placental pathology. The thrombosis in the chorionic plate are circled in red lines. The infarction are indicated by the arrows.

further emphasizes the impact of APS on obstetric complications and necessitates aggressive anticoagulation therapy and close obstetric monitoring in subsequent pregnancies.

Pregnancy management in patients with CD and APS presents a unique set of challenges. The fluctuating Fbg levels observed during the patient's pregnancies underscore the necessity of vigilant monitoring and individualized management to optimize maternal and fetal outcomes. The use of Fbg concentrate prior to the elective cesarean section exemplifies the tailored approach to perioperative hemostatic management, aiming to minimize bleeding complications while ensuring adequate hemostasis. Furthermore, the occurrence of fetal growth restriction and placental infarctions highlights the potential obstetric complications associated with these dual thrombotic disorders, warranting multidisciplinary collaboration to balance the risks of bleeding and thrombosis during pregnancy and delivery. While CD alone may not invariably cause pregnancy complications (as evidenced by the aunt's successful pregnancy), in this case, the coexistence of APS was the primary driver of adverse outcomes. Placental thrombosis and infarction are hallmark pathological features of APS, directly linked to recurrent miscarriages and fetal growth restriction observed here. Notably, the patient's paternal aunt with the same FGG mutation had an uneventful pregnancy, underscoring the variable expressivity of CD. This

Table 1 Changes in Coagulation-Related Markers in Patients

Characteristic	2017-3-28	2017-5-22	2020-8-20	2023-11-15
LA	0.89		0.89	2.61
ACL-IgM	(-)	(-)	(-)	8.52MPLU/mL
β2GP1-IgM	25RU/mL	(-)	(-)	28.0AU/mL
ANA	S1:80			
C3, g/L		0.586	0.666	
C4, g/L		0.124	0.512	
Fbg, g/L	0.51		0.56	0.35
APTT, s	32.6		28.9	28.7
PT, s	13.0		12.3	12.4
D-Dimer, mg/L	0.18		0.31	0.15
PLT, 10^9/L	195		191	220

Abbreviations: LA, lupus anticoagulant; ACL, anticardiolipin antibodies; β2GP1, β2-Glycoprotein I Antibody; ANA, Antinuclear Antibody; C3 and C4, Complement 3 and Complement 4; Fbg, Fibrinogen; APTT, Activated Partial Thromboplastin Time; PT, Prothrombin Time; PLT, Platelet Count.

contrast highlights that the severe obstetric complications in our patient (recurrent miscarriages, placental thrombosis) were likely attributable to APS rather than CD alone.

In the context of APS, the presence of high-titer APLs and the associated thrombotic events raise questions about the optimal anticoagulation regimen for pregnant patients with CD and APS. Balancing the risks of thrombosis and bleeding in this population requires a nuanced approach, taking into account the dynamic changes in Fbg levels during pregnancy and the increased thrombotic propensity conferred by APS. Further research is needed to delineate the most effective anticoagulation strategies in this challenging clinical scenario, emphasizing the need for prospective studies to guide therapeutic decision-making.

Genetic counseling and family studies play a crucial role in the management of CD. The identification of the same FGG gene mutation in the patient's father and aunt underscores the hereditary nature of the disorder, necessitating family screening and counseling to assess the thrombotic risk in affected individuals and guide appropriate management strategies. Moreover, the absence of abnormal bleeding or thrombotic events in the patient's mother despite who did not carrying the mutation raises intriguing questions about the variable expressivity and penetrance of CD, warranting further investigation into the genetic and environmental factors influencing the clinical phenotype. This confirms the autosomal dominant inheritance pattern, as the mutation was inherited from the paternal side, while the wild-type status in the mother explains her lack of clinical manifestations.

Overall, this case reveals three critical insights: First, CD alone did not preclude successful pregnancy. Second, APS was the primary driver of recurrent miscarriage, with placental thrombosis, identified even in the "successful" pregnancy confirming its pathological role. Third, we acknowledge that combined management of CD and APS remains theoretical in this case, as our data cannot prove mechanistic interactions beyond APS's well-established thrombogenic pathology. Therefore, this report serves not as evidence of dual-disorder synergy, but as a critical alert to the risk of diagnostic overshadowing in rare coagulopathies and the necessity of rescreening for APS when new thrombotic or obstetric complications arise in CD patients.

Conclusion

This case report contributes to the limited literature on the co-occurrence of CD and APS, highlighting two critical clinical lessons: the focused management of CD may inadvertently delay APS diagnosis—demonstrated by the persistence of antiphospholipid biomarkers during the 2021 pregnancy while placental APS pathology remained unrecognized. Besides, recurrent miscarriage was driven by APS-specific thrombotic mechanisms rather than CD, underscoring that any new obstetric complication in CD patients warrants comprehensive APS re-evaluation. While CD alone may not invariably cause pregnancy complications, the coexistence of both disorders significantly amplifies obstetric risks. The

recurrent miscarriages, fetal growth restriction, and placental thrombotic pathology observed in this patient are primarily attributable to APS-mediated thrombosis, with CD potentially exacerbating the prothrombotic milieu. Future prospective studies remain essential to determine whether inherited fibrinogen disorders functionally amplify APS-related thrombotic risks.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Peking Union Medical College Hospital. Written informed consent from the patient was obtained for this study. Institutional approval is not required to release case details.

Consent for Publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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Disclosure

Zi Wang and Su Mao are co-first authors for this study. The authors declare that they have no competing interests in this work.

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