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Paradoxical Deep Vein Thrombosis in Congenital Hypofibrinogenemia in a Patient with Prior Severe Bleeding and Spontaneous Intracerebral Hemorrhage: A Case Report

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Abstract

Introduction

Congenital hypofibrinogenemia is usually framed as a bleeding disorder, but paradoxical thrombosis is increasingly recognized. The simultaneous occurrence of severe spontaneous intracerebral hemorrhage and unprovoked deep vein thrombosis in a single patient is rarely reported, and much of the published management experience comes from specialized centers with access to fibrinogen concentrate, antigen assays, and genetic testing. We describe such a patient managed in a Middle Eastern center where these resources were not available.

Clinical findings

A 37-year-old nulliparous Jordanian woman with congenital hypofibrinogenemia, diagnosed at age 17 after refractory bleeding following appendectomy and complicated at age 28 by a spontaneous medullary hemorrhage with full neurological recovery, presented with a three-day history of painful left calf swelling without a provoking factor. Examination showed unilateral calf swelling and tenderness without active bleeding.

Diagnoses, interventions, and outcomes

Compression Doppler ultrasonography demonstrated an acute occlusive popliteal deep vein thrombosis. Functional fibrinogen by the Clauss method was 0.45 g/L (reference 2.0–4.0 g/L). Fibrinogen antigen, reptilase time, viscoelastic testing, and FGA/FGB/FGG sequencing were unavailable locally. She was managed with subcutaneous enoxaparin 1 mg/kg every 12 hours and cryoprecipitate targeted to maintain a trough functional fibrinogen of at least 1 g/L. Symptoms resolved by hospital day 2. A subsequent bleeding episode was managed with fresh frozen plasma and enoxaparin dose reduction. At six months she remained free of recurrent thrombosis and major bleeding.

Conclusion

Low fibrinogen does not protect against venous thromboembolism, and concurrent anticoagulation with cryoprecipitate-based replacement is feasible when fibrinogen concentrate is unavailable. Reported per the CARE guideline.

Keywords: congenital hypofibrinogenemia, deep vein thrombosis, intracerebral hemorrhage, cryoprecipitate, enoxaparin

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1. INTRODUCTION

Fibrinogen is a 340 kDa hepatic glycoprotein composed of paired Aα, Bβ, and γ chains encoded by FGA, FGB, and FGG on chromosome 4q31.3. It is the principal substrate of thrombin and the structural backbone of the mature fibrin clot, and it supports platelet aggregation through binding to integrin αIIbβ3. Fibrin itself, sometimes designated antithrombin I, sequesters thrombin within the clot and limits further thrombin generation.[1,2] Reference values for plasma fibrinogen lie between approximately 1.5 and 4.0 g/L, with a circulating half-life of three to five days.[1]

The International Society on Thrombosis and Haemostasis (ISTH) classifies congenital fibrinogen disorders according to the integrated assessment of clinical phenotype, fibrinogen activity, and antigen concentration, distinguishing afibrinogenemia, hypofibrinogenemia, dysfibrinogenemia, and hypodysfibrinogenemia.[3] Afibrinogenemia and severe hypofibrinogenemia are inherited in an autosomal recessive pattern and are most often encountered in populations where consanguinity is common, whereas mild hypofibrinogenemia and dysfibrinogenemia frequently follow an autosomal dominant pattern.[1,4] Afibrinogenemia has an estimated prevalence of approximately 1 per 1,000,000; hypofibrinogenemia is more common but its true frequency is unknown because mildly affected individuals often remain undiagnosed.[2,4]

The clinical phenotype is heterogeneous. Bleeding manifestations range from umbilical-stump hemorrhage in the neonatal period to mucocutaneous bleeding, hemarthroses, gastrointestinal or genitourinary bleeding, and life-threatening intracranial hemorrhage.[1,5] Reproductive complications, including recurrent miscarriage, placental abruption, and postpartum hemorrhage, are well described in affected women.[1,6] Paradoxically, both venous and arterial thrombotic events occur across the spectrum of fibrinogen disorders, sometimes without an identifiable trigger and sometimes after replacement therapy, with frequent thromboembolic events documented in afibrinogenemia, including a registry estimate of approximately 18% in this subtype.[6-10] Recent data from the Prospective Rare Bleeding Disorders Database covering 123 patients with congenital fibrinogen disorders confirmed that thrombotic events span all subtypes, with rates of 11% in afibrinogenemia and 10% in hypofibrinogenemia, alongside a separately reported 5% rate of thrombosis associated with replacement-therapy prophylaxis in that cohort.[10] The dual risk of catastrophic bleeding and thrombosis makes treatment decisions difficult, and high-quality evidence to guide anticoagulation in this population remains scarce.[1,6,7]

We describe a young woman from Jordan with congenital hypofibrinogenemia and a striking personal and family history of bleeding who developed an unprovoked popliteal deep vein thrombosis (DVT) and was managed with concurrent anticoagulation and fibrinogen replacement using cryoprecipitate, in a center without ready access to fibrinogen concentrate, antigen assays, or genetic testing. The case is reported in accordance with the CARE guideline for case reports.[11]

2. CASE PRESENTATION

2.1. PATIENT INFORMATION AND CLINICAL FINDINGS

A 37-year-old nulliparous woman with known congenital hypofibrinogenemia presented to the emergency department with a three-day history of progressive pain and swelling in the left calf. She reported no recent immobilization, long-distance travel, surgery, trauma, hormonal therapy, infection, pregnancy, or malignancy. Vital signs on arrival were within normal limits. Examination of the lower extremity demonstrated unilateral swelling and tenderness over the left calf without erythema, palpable cord, or evidence of active bleeding. The remainder of the physical examination was unremarkable.

2.2. PAST MEDICAL AND FAMILY HISTORY

The diagnosis of hypofibrinogenemia was first established at age 17 following an appendectomy that was complicated by massive postoperative hemorrhage requiring multiple reoperations. Investigation at that time revealed prolonged clotting times and reduced functional fibrinogen on a coagulation panel. She subsequently received intermittent cryoprecipitate transfusions for episodes of large ecchymoses and gingival bleeding. One admission was prompted by sharp left-knee pain attributed to a ruptured Baker's cyst with significant coagulopathy and a markedly prolonged INR, which was managed conservatively with cryoprecipitate and fresh frozen plasma (FFP).

At age 28 she had a spontaneous hemorrhagic stroke that presented with right-sided hemiparesis. Brain magnetic resonance imaging showed a medullary hemorrhage. She was managed with cryoprecipitate and FFP transfusions and made a complete neurological recovery without residual deficit. She had not been maintained on regular prophylactic fibrinogen replacement before the present admission.

Family history was relevant. One sister died of a hemorrhagic stroke; a second sister had recurrent first-trimester miscarriages; and a brother had received fibrinogen concentrate for an upper-extremity venous thrombosis. All three siblings carried a diagnosis of hypofibrinogenemia. Both parents were first cousins and clinically asymptomatic, and several distant relatives reportedly died of unexplained bleeding. The patient had never been pregnant. She had also experienced premature ovarian insufficiency with menopause at age 21, a comorbidity not known to be associated with congenital hypofibrinogenemia and considered incidental to the present case.

2.3. DIAGNOSTIC ASSESSMENT

Compression Doppler ultrasonography of the left lower extremity revealed a non-compressible left popliteal vein with echogenic intraluminal material, consistent with an acute occlusive popliteal DVT without proximal extension.

Initial laboratory studies showed a functional fibrinogen of 0.45 g/L by the Clauss method (reference 2.0–4.0 g/L),

a prothrombin time of 22.2 seconds, an activated partial thromboplastin time of 38 seconds, an INR of 1.68, a markedly prolonged thrombin time, and an elevated D-dimer. Platelet count was within normal limits. Liver and kidney function tests and serum albumin were normal, and FibroScan demonstrated no evidence of liver fibrosis. Mixing studies showed correction of both the prothrombin time and the activated partial thromboplastin time after a 1:1 mixture with normal plasma, a result compatible with a quantitative factor deficit and against a circulating inhibitor. Intrinsic and extrinsic pathway factor activities measured by clot-based assays were within normal limits, indicating an isolated fibrinogen abnormality rather than a broader clotting-factor deficiency. Fibrinogen antigen testing, which would have allowed formal distinction between hypofibrinogenemia and hypodysfibrinogenemia under the ISTH classification, was not available locally; reptilase time and viscoelastic testing were similarly unavailable, and genetic analysis of FGA, FGB, and FGG was not performed because of resource and access constraints.[1,3,4]

Acquired causes of hypofibrinogenemia were systematically excluded. Disseminated intravascular coagulation was considered unlikely given stable serial platelet counts and the absence of a progressive consumptive pattern, and the elevated D-dimer was attributed to the acute thrombus. Liver disease was excluded by normal biochemistry and FibroScan; nephrotic syndrome and protein-losing states were excluded by preserved renal function and a normal serum albumin; and there were no clinical features suggestive of an underlying malignancy or systemic illness. A formal inherited and acquired thrombophilia evaluation, including factor V Leiden, prothrombin G20210A, antithrombin, protein C and protein S levels, and antiphospholipid antibody testing, was not performed during the index admission, which is acknowledged as a limitation. In the context of a lifelong bleeding phenotype, parental consanguinity, and a strong family history of bleeding and thrombosis, the findings were most consistent with congenital hypofibrinogenemia.[1,3,4]

2.4. THERAPEUTIC INTERVENTION

Following multidisciplinary discussion among internal medicine, hematology, and vascular medicine, therapeutic anticoagulation was initiated with subcutaneous enoxaparin at 1 mg/kg every 12 hours. Cryoprecipitate transfusions were administered concurrently with the goal of maintaining a trough functional fibrinogen of at least 1 g/L, in line with expert consensus, with serial monitoring of the coagulation panel and fibrinogen level throughout.[6,12,13]

She was discharged on hospital day 7 on enoxaparin 60 mg twice daily for a planned three-month course, balancing treatment of proximal DVT against the patient's substantial hemorrhagic risk, with weekly cryoprecipitate transfusions arranged through the day-care unit. Extended anticoagulation was deferred at three months in view of the ongoing hemorrhagic risk inherent to her underlying disorder. The day-by-day trend of coagulation parameters during the index admission is shown in Table 1.

2.5. FOLLOW-UP AND OUTCOMES

One month after discharge she was readmitted with diffuse ecchymoses without a single dominant bleeding focus. She received three units of FFP daily for eight days, and the enoxaparin dose was reduced to 40 mg twice daily, after which the bleeding tendency resolved. Anticoagulation was completed at three months from the diagnosis of DVT and then discontinued. At follow-up six months after the initial presentation, she remained asymptomatic, with no recurrent thrombotic or hemorrhagic events on a maintenance regimen of intermittent FFP every three weeks.

2.6. TIMELINE AND COAGULATION TRENDS

Table 1 summarizes the daily coagulation panel during the index admission and reflects the response to combined anticoagulation and cryoprecipitate replacement.

3. DISCUSSION

3.1. COEXISTENCE OF BLEEDING AND THROMBOSIS IN INHERITED FIBRINOGEN DISORDERS

Inherited fibrinogen disorders have historically been framed as bleeding diatheses, yet the cumulative literature describes a meaningful incidence of venous and arterial thrombosis in the same patient population. In a literature review of thrombosis in inherited fibrinogen disorders, Korte and colleagues identified 128 patient reports across 62 case reports and 8 case series, with thromboses occurring without a recognizable trigger in approximately half.[7] Lak and colleagues observed spontaneous thrombotic events in 2 of 55 Iranian patients with afibrinogenemia, an early indication that thrombosis can occur even in the most severely fibrinogen-deficient individuals.[8] More recently, prospective registry data from the Prospective Rare Bleeding Disorders Database describing 123 patients with congenital fibrinogen disorders confirmed that thrombotic events span all subtypes, with rates of 11% in afibrinogenemia and 10% in hypofibrinogenemia, alongside a separately reported 5% rate of thrombosis associated with replacement-therapy prophylaxis in that cohort.[10] Recent case reports have further documented paradoxical ischemic events in patients with hypofibrinogenemia, including ischemic stroke and concurrent cerebellar and spinal cord infarction.[14,15] Our patient experienced a spontaneous popliteal DVT in the absence of conventional risk factors during a phase in which she was not receiving regular replacement, a presentation consistent with this body of evidence and with the framework set out in a recent dedicated review of the thrombotic paradox in congenital fibrinogen deficiencies.[16]

3.2. MECHANISMS OF THE PARADOX

The mechanistic basis of thrombosis in patients with reduced fibrinogen remains incompletely understood. The dominant hypothesis invokes loss of the antithrombin-I activity normally provided by fibrin, with prolonged circulation of free thrombin and a net prothrombotic milieu.[1,6,7,

Table 1. Trend of coagulation parameters during the index admission. PT, prothrombin time; INR, international normalized ratio; aPTT, activated partial thromboplastin time. Fibrinogen measured by the Clauss method (laboratory reference 2.0–4.0 g/L).

Day	PT (s) / INR	aPTT (s)	Fibrinogen (g/L)
Day 1	Specimen clotted	Specimen clotted	Specimen clotted
Day 2	22.2 / 1.68	38.0	0.45
Day 3	21.0 / 1.62	Not available	0.40
Day 4	Not available	Not available	Not available
Day 5	17.7 / 1.36	34.1	Not available
Day 6	18.1 / 1.39	33.3	0.50
Day 7	Specimen clotted	Specimen clotted	Specimen clotted

[17] Abnormal fibrin clot architecture, with thinner fibers and altered porosity, has also been implicated, as has impaired fibrinolysis in selected variants.[7,16,17] Altered platelet-mediated hemostasis has also been proposed as a possible contributor.[7] Fibrinogen replacement, while essential for hemostasis, has been temporally associated with thrombotic events in case series, although the strength of this association remains uncertain.[6,7,12] In our patient, thrombosis arose during a phase in which she was not receiving regular replacement, which argues against a treatment-associated mechanism in this episode.

3.3. DIAGNOSTIC CONSIDERATIONS

Definitive classification of a congenital fibrinogen disorder requires both a functional assay (typically Clauss) and a fibrinogen antigen measurement; the activity-to-antigen ratio distinguishes hypofibrinogenemia from dysfibrinogenemia and hypodysfibrinogenemia under the ISTH framework.[3,4] Genetic analysis of FGA, FGB, and FGG can confirm the diagnosis, identify the inheritance pattern, and in selected kindreds suggest a phenotype-specific risk profile.[1,4] Neither fibrinogen antigen testing nor genetic analysis was available in our setting. The diagnosis was therefore established on clinical grounds, supported by a strongly suggestive personal and family history, persistently low functional fibrinogen, and exclusion of acquired causes. We acknowledge that, without antigen and reptilase testing, a coexisting qualitative defect cannot be formally excluded, although the long-standing isolated low Clauss fibrinogen, the autosomal recessive pattern suggested by parental consanguinity, and the consistent sibling phenotypes argue most strongly for a quantitative deficit.

3.4. THERAPEUTIC TENSION BETWEEN ANTICOAGULATION AND HEMOSTASIS

There is no randomized evidence to guide anticoagulation in patients with congenital fibrinogen disorders. Published experience supports the cautious use of unfractionated heparin, low-molecular-weight heparin, and vitamin K antagonists, and, in selected patients, direct thrombin inhibitors such as lepirudin when heparin cannot be used safely.[6,7,18] Evidence on direct oral anticoagulants in this population remains limited and largely restricted to case reports, although recent expert opinion supports considering them as a first-line option in selected venous thrombosis cases in patients with quantitative fibrinogen disorders, a position not yet supported by randomized data.[6] Low-molecular-weight heparin was selected in this case because of the absence of fibrinogen concentrate and the absence of a locally available specific reversal agent for direct oral anticoagulants, factors that argue for a familiar parenteral anticoagulant with established local monitoring and partial reversibility in a patient with prior catastrophic bleeding.[7] Expert reviews and case-based reports commonly describe concurrent fibrinogen replacement during therapeutic anticoagulation, with the goal of preserving a level adequate for hemostasis without overshooting into a prothrombotic range. Expert reviews and consensus documents propose a target trough fibrinogen of approximately 1 g/L throughout the antithrombotic course, although the supporting evidence base is weak and management remains individualized.[6,12,13]

In our case, fibrinogen concentrate was unavailable, so cryoprecipitate served as the replacement product during anticoagulation, with a target fibrinogen of at least 1 g/L. The interval bleeding episode one month after discharge, which manifested as diffuse ecchymoses rather than as a localized hemorrhage, is in keeping with the expected difficulty of titrating anticoagulation against an unstable underlying coagulopathy. It was managed by switching to FFP and reducing the enoxaparin dose, with symptom resolution and no recurrent thrombosis at six months. The decision to limit anticoagulation to three months reflected the conventional three-month course for a first proximal DVT and the substantial competing hemorrhagic risk in this patient; extended anticoagulation, which is often considered for unprovoked venous thromboembolism in young patients, was judged unsafe in the absence of fibrinogen concentrate availability and dedicated rare-disease support.

3.5. WHAT THIS CASE ADDS

Detailed published experience with thrombosis in congenital fibrinogen disorders has emerged from large referral centers with access to fibrinogen concentrate, antigen and

reptilase testing, viscoelastic assays, and rapid genetic confirmation.[1,3,6,7,10] The present case adds three points that we believe extend the existing literature. First, it documents the simultaneous burden of life-threatening bleeding (an unprovoked medullary intracerebral hemorrhage with full neurological recovery) and unprovoked deep vein thrombosis in a single patient, in a kindred with siblings on opposite ends of the bleeding-thrombosis spectrum, an observation in keeping with the marked clinical heterogeneity that has been emphasized in recent reviews of these disorders, including in hypofibrinogenemia specifically.[1,4,17,19] Second, it illustrates a workable management strategy in a Middle Eastern center serving a consanguineous kindred where fibrinogen concentrate, antigen testing, and genetic analysis are not routinely available, using cryoprecipitate, FFP, and weight-adjusted enoxaparin alone, complementing a recent regional report from the United Arab Emirates in which a patient with congenital hypofibrinogenemia and prior intracranial hemorrhage developed concurrent cerebellar and spinal cord infarction and was managed with fibrinogen replacement without anticoagulation, in contrast to the present case in which the active venous thrombus and less severe coagulation derangement permitted concurrent anticoagulation.[15] Third, it demonstrates that thrombosis can occur in this population during a period without prophylactic replacement, which is consistent with prior reports and argues against a purely treatment-associated mechanism in our patient.[7,8,10]

3.6. LIMITATIONS

The principal limitations of this report are diagnostic. Without a fibrinogen antigen measurement and a reptilase time we cannot formally exclude a coexisting qualitative defect, and without genetic testing the underlying mutation and inheritance pattern remain undefined. A formal inherited and acquired thrombophilia panel was not performed during the index admission, so a coexisting prothrombotic state cannot be excluded on laboratory grounds. Anti-Xa monitoring of enoxaparin and viscoelastic testing were not performed, and no follow-up imaging of the popliteal vein was obtained to document thrombus resolution. The patient perspective reported here reflects the clinical encounter rather than a structured patient-reported outcome instrument.

4. CONCLUSION

Congenital hypofibrinogenemia can produce both life-threatening bleeding and unprovoked thrombosis in the same patient. Clinicians should not assume that a low fibrinogen level confers protection against venous thromboembolism, and they should be prepared to administer therapeutic anticoagulation alongside fibrinogen replacement in carefully selected cases.[6,7,10,14,17] In settings where fibrinogen concentrate is unavailable, cryoprecipitate combined with FFP and weight-adjusted low-molecular-weight heparin provided a workable management strategy in this case, although close clinical and laboratory monitoring is essential.[6,7] Genetic counseling and, where feasible, FGA/FGB/FGG sequencing should be offered to affected individuals and to first-degree relatives in consanguineous kindreds.[1,4] Prospective enrollment of treated cases into existing rare-disease registries would further help refine the management of this rare and clinically dichotomous disorder.[10]

5. PATIENT PERSPECTIVE

The patient reported that the dual fear of bleeding and clotting episodes was the most difficult aspect of living with her condition, particularly in the absence of a clear plan that she could rely on outside the hospital. She valued the close communication between her hematology and primary care teams during this admission and the provision of a written plan of action for new symptoms after discharge.

CONFLICT OF INTEREST / COMPETING INTERESTS

The authors declare no conflicts of interest relevant to this work.

ETHICS APPROVAL AND CONSENT

Written informed consent was obtained from the patient for publication of this case report and any accompanying clinical data. The work was conducted in accordance with the principles of the Declaration of Helsinki. Identifying details have been removed or modified to protect patient confidentiality.

AI TOOL USE DISCLOSURE

The authors declare that no artificial intelligence tools were used in the preparation of this manuscript.

THIRD-PARTY MATERIAL PERMISSIONS

All tables and figures are original, and no third-party material requiring permission has been used.

AUTHOR CONTRIBUTIONS (CREDIT)

Conceptualization: Hisham Bawa'neh (Lead), Daria Ja'arah (Lead). Data curation: Daria Ja'arah (Supporting). Investigation: Daria Ja'arah (Lead). Resources: Hisham Bawa'neh (Lead). Writing – original draft: Hisham Bawa'neh (Lead). Both authors approved the final version submitted for publication and agree to be accountable for all aspects of the work.

DATA AVAILABILITY

Data sharing is not applicable to this case report because no datasets were generated or analyzed beyond the clinical information presented in the manuscript.

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REPORTING GUIDELINES

This case report was prepared in accordance with the CARE guidelines for case reports.

PREPRINT DISCLOSURE

This manuscript has not been posted as a preprint and has not been previously published.

ABBREVIATIONS

aPTT, activated partial thromboplastin time; CARE, CAse REport; DVT, deep vein thrombosis; FFP, fresh frozen plasma; INR, international normalized ratio; ISTH, International Society on Thrombosis and Haemostasis; PRO-RBDD, Prospective Rare Bleeding Disorders Database; PT, prothrombin time.

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