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CASE REPORT

Highly thrombogenic phenotype and impaired wound healing in a patient with congenital dysfibrinogenemia: case report

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Abstract

Background: Congenital fibrinogen disorders are classified based on both fibrinogen levels and the clinical phenotype. For dysfibrinogenemia, normal fibrinogen levels are typical.

Key Clinical Question: We highlight the importance of comprehensive thrombotic risk assessment, including lipoprotein a (Lp[a]) and hypertriglyceridemia in association with severe thrombosis and poor wound healing in dysfibrinogenemia.

Clinical Approach: We report the case of a 42-year-old male patient with a rare congenital thrombotic-related dysfibrinogenemia (fibrinogen Naples) and multiple thrombotic episodes throughout his life and an unhealing ankle wound. Despite all thrombotic episodes and surgery, the patient had undetectable D-dimer, suggestive of fibrinolytic defect, further supported by over 4-fold elevated Lp(a) levels. The last arterial thrombosis was preoperatively managed by plasma exchange, antithrombotics, and thereafter continued fibrinogen replacement therapy, under which the chronic wound has healed.

Conclusion: The combination of thrombogenesis, abnormal fibrinogen, and high Lp(a) levels is a clinical and research topic deserving more attention.

KEYWORDS
congenital fibrinogen disorders, fibrinogen, fibrinolysis, lipoprotein a, thrombogenesis, thrombosis, wound healing

Essentials

- Congenital fibrinogen disorders are associated with both bleeding and thrombotic phenotypes.
- Lipoprotein a is a thrombogenic and atherogenic molecule, inhibiting the fibrinolytic pathway.
- Dysfibrinogenemia can affect wound healing.
- Continuous fibrinogen replacement therapy showed healing capacity, despite high lipoprotein a levels.

1 | INTRODUCTION

Fibrinogen is a 340-KDa glycoprotein, synthesized by the liver, and present in platelets and plasma in concentrations ranging from 2 to 4 g/L. Fibrinogen's primary structure consists of 3 polypeptide chains, Aα, Bβ, and γ, encoded by 3 genes, *FGA*, *FGB*, and *FGG*, respectively [1]. Fibrinogen, an acute phase reactant, has preeminent roles, not only in coagulation and hemostasis but also in inflammation, neoplasia, and wound healing [2]. In the clotting process, fibrinogen first undergoes an enzymatic cleavage by thrombin, followed by formation of fibrin monomers that assemble in a polymerized structure, which is further covalently crosslinked by factor (F)XIII [3]. An important driving step is the interaction between thrombin and its binding site on fibrinogen γ, exosite I, via electrostatic complementarity, leading to removal of free thrombin from circulation and to fibrinolysis.

Complete fibrinogen deficiency was first described in 1920 by Fritz Rabe and Eugene Salomon [4]. Fibrinogen disorders can be rare congenital or highly prevalent acquired ones (eg, liver cirrhosis, trauma, cancer, and autoimmune disease) [5]. Historically, congenital fibrinogen disorders (CFDs) were divided into type I, affecting the quantity of circulating fibrinogen (afibrinogenemia and hypofibrinogenemia), and type II, affecting the quality of circulating fibrinogen (dysfibrinogenemia and hypodysfibrinogenemia) [6]. Since CFDs are complex, with both bleeding and thrombotic phenotypes, the International Society on Thrombosis and Haemostasis (ISTH) scientific and standardization committee on FXIII and fibrinogen reclassified CFD into several subgroups mainly according to the fibrinogen levels and the clinical phenotype. A strong thrombotic phenotype, defined as dysfibrinogenemia type 3B (ie, thrombosis-related dysfibrinogenemia), was associated with few mutations [7], of which group our patient case represents. To our knowledge, defective healing is not well investigated earlier in association with dysfibrinogenemia and lipid abnormalities. We highlight the importance of comprehensive thrombotic risk assessment, including lipoprotein a (Lp[a]) and hypertriglyceridemia in association with severe thrombosis and poor wound healing in dysfibrinogenemia.

2 | CASE PRESENTATION

A 42-year-old patient was referred to our institution for an open ulcerated wound in the ankle area (Figure A). Upon further investigation, it was realized that the patient had a diagnosis of hypodysfibrinogenemia already, 10 years ago, when the first thrombotic event (arterial cerebral infarction) occurred at the age of 29 years. Unfortunately, this diagnosis was overlooked by his treating physicians for a long time. Throughout his life, the patient had several both arterial and venous thrombotic events despite antithrombotic therapy: transient ischemic attack, cerebral infarction, pulmonary embolism, and symptomatic peripheral arterial occlusive disease in both upper and lower extremities necessitating thrombectomies and several arterial bypasses that were further complicated by delayed chronic wound healing and graft loss (Table). Echocardiography excluded a patent foramen ovale. During most of the remote clinical incidents, fibrinogen supplementation was not properly organized before operations. Informed, written consent was obtained and is available upon request.

Finally, a thorough investigation was undertaken in 2018 upon remission, at our hospital, with a comprehensive laboratory analysis, including a genetic investigation. Our focus in this report is on the interphase between thrombophilia and vascular surgery, and the management of this complicated case of dysfibrinogenemia, with a highlight on his latest acute arterial thrombosis in his upper extremity.

The laboratory profile of the patient consisted of very low functional fibrinogen levels (Clauss method) between 0.5 and 0.8 g/L (2-4 g/L), but a fibrinogen antigen level of 1.6 g/L (1.8-3.4 g/L) by latex immunoassay, continuously prolonged thrombin time of >140 seconds (17-25 seconds), and even activated partial thromboplastin time of >60 seconds (28-37 seconds). On the other hand, the patient had normal prothrombin time, antithrombin, and von Willebrand factor levels on all occasions. Antiphospholipid antibodies, lupus anticoagulant, protein C and S deficiency, FV Leiden, and prothrombin gene mutation were all excluded. Despite the multiple documented thrombotic events, his D-dimer levels were constantly unmeasurable at <0.3 mg/L (<0.5 mg/L).

All coagulation factor levels were checked several times and were normal, including FXIII level, except for an elevated FVIII level fluctuating between 91 and 271 IU/dL (60-160 IU/dL) during baseline and the acute thrombotic episodes. Platelet counts were within normal ranges and platelet function analysis (PFA-200) did not show abnormalities, excluding primary hemostatic defects, aligning with an absent bleeding history.

Rotational thromboelastometry (ROTEM Sigma) revealed abnormal clotting time and clot firmness in fibrin-based thromboelastometry and absence of fibrinolysis in aprotinin-based thromboelastometry. Genetic testing was compatible with homozygosity for a missense mutation in the gene encoding the Bβ chain: *FGB* exon 2: c.292 G>A Ala98Thr (Ala68Thr in the mature chain), first described as fibrinogen Naples [8], providing the diagnosis of dysfibrinogenemia 3B.

2.1 | Emergency care during a new arterial thrombosis

Suddenly, the patient needed urgent vascular surgery due to an arterial thrombosis in upper extremity, despite uninterrupted antithrombotic therapy (aspirin 50 mg twice daily; low-molecular-weight heparin [LMWH]; dalteparin 10,000 IU twice daily [115 IU/kg; weight, 87 kg]; body mass index, 27.5 kg/m^2) with an anti-FXa activity ranging between 0.36 and 0.84 U/mL. Preoperatively, the patient was diagnosed with an extreme dyslipidemia and levels of triglycerides (TGs) at 8.5 mmol/L (<1.7 mmol/L) and Lp(a) at 1090 mg/L (<250 mg/L). A therapeutic plasma exchange was performed using LG-Octaplas and 5% albumin with the aim to provide normal fibrinogen and lower the TG and Lp(a) concentrations before surgery and beyond, to alleviate the thrombogenic plasma profile. Postoperatively, fibrinogen

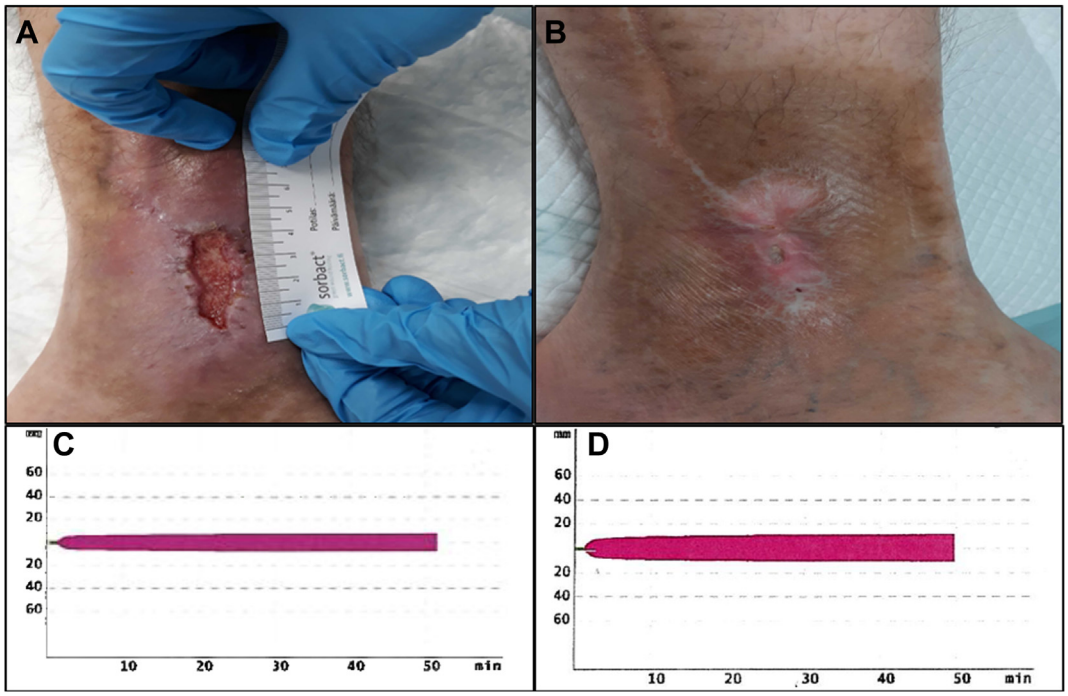

FIGURE Wound development in the ankle area (A, B) and FIBTEM analysis before (C) and after the biweekly fibrinogen replacement therapy. (A) Before and (B) after treatment. (C, D) FIBTEM analysis before and after biweekly fibrinogen supplementation, respectively. FIBTEM, fibrin-based thromboelastometry.

substitution was managed by RiaSTAP 2 to 4 g daily doses according to the fibrinogen (Clauss) profile for 2 weeks.

In addition to supplementing fibrinogen, the patient was managed by antithrombotic medication with combined dalteparin 10,000 IU twice daily, aspirin, and lipid lowering agents. After discharge, we continued fibrinogen concentrate substitution 2 g intravenous biweekly, which resulted in a modest fibrinogen level (Clauss assay) increase up to 1.3 g/L (Figure C, D), but blood circulation clearly improved. Gradually, under the fibrinogen substitution therapy, his ankle wound remarkably healed after 6 years (Figure B).

3 | DISCUSSION AND CONCLUSIONS

This multifaceted case and pathophysiology behind dysfibrinogenemia despite persistently low both functional and antigenic levels was confirmed by genetic and thromboelastographic studies [6]. Collectively, in association with several documented thromboses, elevated TG and Lp(a) levels exacerbated thrombogenesis and shutdown of fibrinolysis, while precluding bleeding despite extensive antithrombotic therapy. Overall, our patient was stabilized with preoperative plasma exchange, statins, efficient and combined antithrombotics, and continued fibrinogen supplementation.

From a genetic perspective, a wide spectrum of mutations accounting for CFD have been identified. A few molecular defects strongly correlate with the clinical presentation and predict the individual thrombotic vs bleeding tendency [3]. The *FGB* exon 2: c.292 G>A Ala98Thr missense mutation was previously associated with thrombotic events, first in 2 siblings in Naples, Italy, who were both homozygous and alike our patient suffered from arterial stroke at an early age. A third homozygous relative experienced a postoperative deep vein thrombosis, whereas other heterozygous family members were asymptomatic [8]. The same mutation was identified in 5 Chinese patients, 2 of whom had thrombosis [3], and in a young Japanese boy with a sinus thrombosis [9]. The young cousin of our patient had a sudden death without available details. Functionally, this mutation causes both defective fibrinopeptide FpA and FpB release, and thrombin binding at the fibrinogen substrate site in the E domain on fibrin, increasing thrombin in circulation [8].

From a metabolic and atherogenic perspective, the patient had elevated TG and Lp(a) levels. Interestingly, TGs relate with poor fibrinolysis, and Lp(a) structure shows a striking homology with plasminogen [10], with competing binding between Lp(a) and plasminogen to fibrin. Lp(a) reduces endogenous fibrinolysis, promotes smooth muscle proliferation, and formation of foam cells [11]. Jointly, these factors and resistance to common lipid lowering drugs render Lp(a) a thrombogenic and atherogenic molecule [11]. The elevated levels of Lp(a) in our dysfibrinogenemic patient impaired the fibrinolytic pathway, compatible with the unmeasurable D-dimer levels, despite during his recurrent thrombotic events [12] and the abnormal wound healing.

From an inflammatory perspective, impaired wound healing is a well-known complication in FXIII deficiency [12]. Despite normal antigenic levels of FXIII in afibrinogenemia patients, the FXIII activity is reduced since fibrinogen activates FXIII via thrombin. Physiologically, fibrin polymerization, angiogenesis, and cell migration will ultimately heal the wound [13], but not in our patient. Such a long history

TABLE Summary of patient's clinical events/treatment.

Year	Clinical event	Antithrombotic treatment
Before referral to our institution		
Early 2010	Cerebral infarction—first thrombotic episode at the age of 29 y	Dipyridamole 200 mg + aspirin 25 mg twice daily
Late 2010	Diagnosis of hypodysfibrinogenemia (low levels of antigenic and functional fibrinogen)	
Early 2014	Delayed wound healing in the right leg posttrauma	
Late 2014	Diagnosis of peripheral arterial disease, PAD	
2015	Pulmonary embolism	Dipyridamole and aspirin stopped Dalteparin 7500 IU twice daily
Early 2016	Transient ischemic attack	Dalteparin dose increased to 10,000 IU twice daily
Late 2016	Symptomatic PAD due to leg thrombosis	
2017	Arterial bypass surgery of the right lower limb due to an unhealed wound at ankle area	Dalteparin 5000 IU twice daily + aspirin 50 mg once daily for a short period followed by dalteparin 10,000 twice daily
After referral to our institution		
Early 2018	Severe hypertriglyceridemia and elevated lipoprotein (a)	
Late 2018	Arterial bypass surgery for unhealed upper extremity wound	Dalteparin 10,000 IU twice daily + aspirin 50 mg twice daily. RiaSTAP 2 g every second week Ezetimibe 10 mg once daily Rosuvastatin 40 mg once daily
2021	Multiple ulcers and unhealed ankle wound	Dalteparin 7500 twice daily + aspirin 50 mg twice daily. RiaSTAP 2 g every second week Rosuvastatin 40 mg once daily

PAD, peripheral arterial disease.

of skin ulcers is worth reporting with this *FGB* missense mutation, which remarkably improved by continued fibrinogen substitution [14].

In conclusion, a rare homozygous CFD case, which in association with elevated TG and Lp(a) levels, ensued recurrent thrombosis and poor wound healing, but was successfully managed with fibrinogen replacement therapy. We highlighted the comprehensive analysis of the thrombogenicity, and how fibrinolysis was impaired according to low D-dimer levels and ROTEM analysis. The combination of high Lp(a) levels, abnormal fibrinogen, and thrombogenesis deserves clinical and research attention. A continuous compilation of cases for registries (The Rare Bleeding Disorders Database) is fundamental to capture relevant data.

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ETHICS STATEMENT

As a case report, no formal ethical approval was necessary. However, informed, written consent was obtained and is available upon request.

AUTHOR CONTRIBUTIONS

N.E.B. wrote the manuscript. R.L. and T.S. treated the patient and supervised the work. A.C. and M.N.A. performed the genetic studies and contributed to the reporting and discussing of the data.

RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

DATA AVAILABILITY

All data and materials are available from the corresponding author upon reasonable request.

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