Digital Skin Necrosis in Congenital Afibrinogenaemia Associated with Hepatitis C Virus Infection, Mixed Cryoglobulinaemia and Anticardiolipin Antibodies

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Congenital afibrinogenaemia is a rare genetic disorder transmitted as an autosomal recessive trait and characterized by the complete absence of fibrinogen in the plasma. We report a 41-year-old woman who suffered from congenital afibrinogenaemia and hepatitis C viral infection and presented with ischaemic necrosis and livedo of the toes. Laboratory investigations showed the presence of mixed cryoglobulinaemia and anticardiolipin antibodies. Resolution occurred with plasmapheresis. We discuss the pathophysiology of this unusual condition and review the literature for skin manifestations associated with this rare haemostasis disorder. Key words: digital necrosis; congenital afibrinogenaemia; hepatitis C virus infection; cryoglobulinaemia; anticardiolipin antibodies syndrome.

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CASE REPORT

A 41-year-old woman had been diagnosed with congenital afibrinogenaemia at the age of 5 years since she experienced spontaneous recurrent intraperitoneal bleeding and haematomas. Details of the molecular analysis of the mutation of the fibrinogen gene have been reported previously (3). She received multiple administrations of fresh plasma and fibrinogen concentrate. At the age of 37, post-transfusion active HCV infection was diagnosed. Treatment with recombinant interferon alpha (Intron A, Schering Plough, Nutley, NJ, USA), $3 \times 10^6$ U injected subcutaneously three times a week for 1 year, resulted in the absence of detection of the HCV-RNA in serum by polymerase chain reaction, but a relapse of circulating HCV-RNA was noted 2 months after cessation of the treatment. During the same period, the patient complained of a permanent blue discoloration of the lateral sides of the feet. Oral nifedipine treatment for a 1-month period was ineffective. One year later, 20 days after a perfusion of $3$ g of fibrinogen concentrate (human fibrinogen, Clottagen®, LFB, Les Ulis, France) for a haematoma of the right breast, the patient complained of a marked dark-blue discoloration of the fifth toes. She had taken no other medication before the onset of symptoms and had not been exposed to cold temperatures at the time. On admission, a livedo reticularis over the dorsal aspect of the feet was noticed. The fifth toes were blue, painful to the touch, and a central necrotic zone was present on the right pad (Fig. 1). The clinical examination was otherwise unremarkable.

Investigations including full blood count, calcium, phosphate, renal and liver function tests were all normal. Circulating HCV-RNA was positive. The prothrombin time, the partial thromboplastin time and the fibrinogen level (<0.3 g l$^{-1}$), normal 1.9–4 g l$^{-1}$) were not measurable. Enzyme immunoassay revealed positive ACL of the IgG subclass at 25 UGPL l$^{-1}$ (normal <15 UGPL l$^{-1}$), whereas ACL of IgM isotype and lupus anticoagulant (LA), anti-beta2-glycoprotein I antibodies (antiβ2-GP I) were absent. LAs were assessed according to the ISTH recommendations (4). ACL and

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antiβ2-GP I were determined by quantitative ELISA (QuantaLite Inova diagnostics, San Diego, CA, USA). The standards and controls were obtained from the Antiphospholipid Standardization Laboratory (Louisville, USA). The normal values were levels below: 13.5 GPL/ml or 11 MPL/ml for IgG or IgM ACL respectively, and 20 SGU/ml for both IgG or IgM anti-β2-GP I.

A type III mixed polyclonal cryoglobulinaemia was present. Quantitation of protein C, protein S, antithrombin and homocysteine, and search for Factor V Leiden and prothrombin gene G20210A polymorphism revealed no abnormality. A cutaneous biopsy (3-mm punch) was performed on the distal pad of the left fifth toe, immediately after administration of fibrinogen concentrate. Histological examination demonstrated a non-inflammatory hyaline thrombosis of the blood vessel of the reticular dermis and a mild cell infiltration of lymphocytes, with no evidence of vasculitis or leucocytoclasia (Fig. 2).

Plasmapheresis was instituted consisting of exchange of 1.0–1.6 plasma volumes followed by the administration of 4.5–6 g of human fibrinogen during each session. A series of six cycles of plasma exchanges in a 6-week period was carried out, resulting in a fading of the blue discoloration of the toes and a partial regression of the livedo after the third session. Thirty-six additional cycles were done during the next 7 months, leading to a complete clearing of the cutaneous lesions. At the same time, repeated cryoglobulin analyses were negative.

**DISCUSSION**

Cutaneous manifestations of afibrinogenaemia are so far paradoxically limited to skin arterial thrombosis (5–11), leading to leg ulcers and digital necrosis. The main clinical features and haemostasis investigations are summarized in Table I. The ischaemic necrosis always involves the toes and is most commonly associated with a blue discoloration or a livedo reticularis of the feet.

![Fig. 2. Hyalinizing thrombosis with no evidence of vasculitis or leucocytoclasia (haematoxylin-eosin; original magnification × 40).](image)

**Table 1. Cutaneous manifestations of thrombosis-associated afibrinogenaemia: review of the literature**

<table>
<thead>
<tr>
<th>Ref. no.</th>
<th>Age, sex</th>
<th>Clinical manifestation</th>
<th>Associated manifestation</th>
<th>Treatment, outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>36, F</td>
<td>Necrosis of the toes</td>
<td>Cerebral haemorrhage, carotid and aortic thrombosis</td>
<td>Died 7 months later</td>
</tr>
<tr>
<td>6</td>
<td>37, F</td>
<td>Necrosis of a toe</td>
<td></td>
<td>Prostaglandin: improvement</td>
</tr>
<tr>
<td>7</td>
<td>13, F</td>
<td>Necrosis of the toes</td>
<td></td>
<td>Fresh frozen plasma, heparin, vaso dilative drugs: improvement</td>
</tr>
<tr>
<td>8</td>
<td>37, M</td>
<td>Necrosis of the toes and fingers</td>
<td>Deep venous thrombosis</td>
<td>Amputation of toes</td>
</tr>
<tr>
<td>9</td>
<td>32, F</td>
<td>Necrosis and blue toes, leg ulcers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>14, F</td>
<td>Gangrene of a foot</td>
<td>Occlusion of iliac and hypogastric arteries</td>
<td>Amputation of toes</td>
</tr>
<tr>
<td>10</td>
<td>30, M</td>
<td>Necrosis of a toe, livedo of the foot</td>
<td></td>
<td>Ilomedin: no improvement. Surgical arterial bypass, heparin, aspirin</td>
</tr>
<tr>
<td>11</td>
<td>30, M</td>
<td>Leg ulcer</td>
<td>Venous insufficiency in the left lower extremity</td>
<td>Fresh frozen plasma, excision of ulcer, skin transplantation Plasmapheresis: improvement</td>
</tr>
<tr>
<td>This study</td>
<td>41, F</td>
<td>Necrosis of a toe, livedo of the feet</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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The severity of the lesions is variable, leading to amputation in three of eight cases due to thrombosis of large arterial vessels.

Hypothetically, two thrombotic mechanisms could explain our observations. First, fibrinogen perfusion could have led to a temporary local hyperfibrinogenaemia and a local disturbance of the balance between coagulation and fibrinolysis. However, this mechanism has so far not been clearly documented. In addition, arterial thrombotic events during afibrinogenaemia have been described in the absence of any substitutive therapy (8). In our case, the pathogenic role of the fibrinogen administration seems unlikely since the first cutaneous symptoms appeared about 3 weeks after the perfusion, while the half-life of human fibrinogen is about 96–144 h. In addition, the subsequent repeated perfusions of fibrinogen associated with plasmapheresis were not deleterious for the skin symptoms. The second hypothesis is based on the presence of a congenital or acquired thrombophilic associated disorder that could predispose to or trigger a coagulation activation, even in the absence of plasma fibrinogen. Previous laboratory studies have clearly demonstrated that platelet aggregation could occur without fibrinogen by the contribution of other adhesive proteins, like von Willebrand factor, fibronectin and vitronectin (12–14). Two previous clinical observations of necrosis-associated afibrinogenaemia mentioned the possible role of congenital protein C deficiency (6, 7). In our case, the laboratory investigations exhibited the presence of ACL and mixed cryoglobulinaemia. However, even if antiphospholipid antibodies and particularly IgG ACL are frequently found in patients with HCV infection, they are mostly of low titre (as in our case) and not significantly associated with the survey of thrombotic events in absence of antiβ2-GP I antibodies (15). Cryoglobulins are composed of cold-sensitive immunoglobulins that precipitate at and below normal body temperature. The association of chronic active hepatitis C, mixed cryoglobulinaemia (type II or III), and skin lesions including palpable purpura, livedo reticularis, distal ischaemia or cutaneous ulcers are well documented (16–18). The cutaneous lesions are mainly supposed to be due to deposition of circulating immune complexes in the blood vessels, thus leading to vasculitis (18). However, vascular obstruction by deposition of cryoglobulin in the form of tubular micro-crystallites or platelet aggregation by anti-platelet antibodies are other possible mechanisms (19, 20). In our observation the pathogenic role of the cryoglobulinaemia is suggested by the efficacy of the plasmapheresis resulting in the complete clearing of the cutaneous lesions concurrently with the removal of the cryoglobulin.

In conclusion, the development of cutaneous necroses in afibrinogenaemia patients requires a complete haemostasis evaluation, including laboratory tests for congenital or acquired thrombophilia.

REFERENCES


