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Warfarin-Associated Multiple Digital Necrosis Complicating Heparin-Induced Thrombocytopenia and Raynaud's Phenomenon After Aortic Valve Replacement for Adenocarcinoma-Associated Thrombotic Endocarditis

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Necrosis of the digits is a rare complication of warfarin therapy of obscure pathogenesis. We report a 61-year-old woman with a 12-month history of Raynaud's phenomenon who developed multiple digital necrosis following aortic valve replacement with mechanical prosthesis for aortic insufficiency caused by nonbacterial thrombotic endocarditis. Exacerbation of Raynaud's phenomenon occurred during the postoperative period, with daily episodes of ischemia of the fingers and toes that improved with local warming. However, coincident with the occurrence of immune heparin-induced thrombocytopenia, and while undergoing routine warfarin anticoagulation because of the mechanical valve prosthesis, the patient abruptly developed progression of digital ischemia to multiple digital necrosis on postoperative day 8, at the time the international normalized ratio reached its peak value of 4.3. All limb pulses were readily palpable, and vascular imaging studies showed thrombosis only in the superficial femoral and popliteal veins of the right leg. Coagulation studies showed greatly elevated levels of thrombin–antithrombin complexes and prothrombin fragment F1.2 levels, consistent with uncontrolled thrombin generation. After vitamin K administration, no abnormalities of the protein C anticoagulant pathway were identified, consistent with previous studies of other patients with warfarin-induced necrosis complicating heparin-induced thrombocytopenia. Subsequently, the patient was shown to have metastatic breast adenocarcinoma, which explained the patient's initial presentation with nonbacterial thrombotic endocarditis. This patient case suggests that multiple digital gangrene can result from the interaction of various localizing and systemic factors, including compromised microvascular blood flow (Raynaud's phenomenon), increased thrombin generation (heparin-induced thrombocytopenia, adenocarcinoma), and warfarin-induced failure of the protein C natural anticoagulant pathway. Am. J. Hematol. 75:56–62, 2004. © 2003 Wiley-Liss, Inc.

Key words: heparin-induced thrombocytopenia; warfarin-induced necrosis; Raynaud's phenomenon; adenocarcinoma; disseminated intravascular coagulation

INTRODUCTION

Necrosis of the distal extremities is a rare complication of warfarin anticoagulation [1–3]. Recently, this syndrome has been linked to acquired hypercoagulability disorders with prominent thrombocytopenia, such as immune heparin-induced thrombocytopenia and cancer-associated disseminated intravascular coagulation (DIC) [3–8]. In contrast, congenital hypercoagulability disorders without prominent thrombocytopenia, such as

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congenital abnormalities of the protein C anticoagulant pathway, tend to be associated with "classic" warfarin-induced skin necrosis that typically affects central tissue sites, such as breast, abdominal wall, or thigh [3,9,10].

In general, necrosis of the distal extremity that occurs during warfarin use in heparin-induced thrombocytopenia or adenocarcinoma is associated with extensive deep-vein thrombosis affecting the same limb [3–8,11,12]. Termed "venous limb gangrene," these patients typically have a "supratherapeutic" international normalized ratio (INR) during warfarin therapy, generally greater than 4.0 (usual therapeutic range, 2.0–3.0) [3–8]. Such an elevated INR has been shown to be a surrogate marker of severe, acquired protein C depletion secondary to warfarin therapy, usually because of concomitant severe reduction in factor VII [4–6]. Despite the elevated INR, thrombin generation persists, which leads to microvascular thrombosis when there is concomitant severe impairment of the protein C natural anticoagulant pathway. Thus, warfarin-induced venous limb gangrene is believed to result from a profound disturbance in the procoagulant–anticoagulant balance [3–8].

Digital necrosis is a very rare complication of warfarin treatment of obscure pathogenesis [10,13]. We observed a patient who developed multiple digital necrosis affecting all four limbs on postoperative day 8 following cardiac surgery. Prior to developing digital necrosis, the patient had several days of postoperative digital ischemia consistent with the patient's history of Raynaud's phenomenon. Unfortunately, when the postoperative course was additionally complicated by immune heparin-induced thrombocytopenia together with routine warfarin anticoagulation for a mechanical aortic valve, the digital ischemia abruptly progressed to multiple digital necrosis. Our purpose in presenting this case is to report that multiple pathogenic factors can interact to explain an unusual prothrombotic complication of anticoagulant therapy, in particular, the interaction of postoperative Raynaud's phenomenon and heparin-induced thrombocytopenia in influencing the clinical expression of warfarin-induced necrosis as that of multiple digital necrosis.

CASE REPORT

A 61-year-old woman with a 12-month history of Raynaud's phenomenon underwent elective aortic valve replacement with mechanical prosthesis (Model R500, 23-mm, Sulzer Carbomedics Canada Ltd., Calgary, Alberta) for severe aortic insufficiency, as well as four-vessel coronary bypass grafting. Eight weeks prior to cardiac surgery she had developed transient visual disturbance, which was shown by CT imaging to represent a right posterior parietal lobe infarct. Preoperative blood work revealed a normal complete blood count (hemoglobin, 125 g/l; white blood count, 7.1×10^9/l with normal differential; platelet count, 268×10^9/l) and normal screening coagulation assays (international normalized ratio, 1.1 [normal, 0.9–1.2]; activated partial thromboplastin time, 29 sec [normal, 26–38 sec]; and thrombin time, 9 sec [normal, 7–11 sec]). Aortic valve replacement surgery and four-vessel coronary bypass surgery were performed after giving the patient 24,000 units of unfractionated heparin prior to cardiopulmonary bypass.

Pathologic evaluation of the aortic valve showed nonbacterial thrombotic endocarditis involving the aortic valve, with mild fibrotic thickening and rolling of the free margin, and the inflow aspect showing several gray–tan friable excrescences occupying about two-thirds of the surface area (1.4×0.4 cm), predominantly along the margin of apposition.

Each day during the first postoperative week, the patient had clinical manifestations of Raynaud's phenomenon, with intermittent cyanosis of all of the fingers and toes that responded favorably to conservative management with warm towels. The patient received unfractionated heparin (5,000 IU twice daily by subcutaneous injection) between postoperative days 1 and 4 (Fig. 1). Anticoagulation with warfarin was commenced on day 2, with a total of 12.5 mg given as 5, 5, and 2.5 mg from postoperative day 2 to day 4, respectively.

On day 8, the patient abruptly developed progressive ischemia leading to necrosis affecting 7 fingers and 10 toes. At this time, the INR had risen to 4.3 (target therapeutic range, 2.0–3.0). All of the pulses of the lower and upper extremities were readily palpable. Duplex ultrasound imaging of all four extremities revealed deep-vein thrombosis involving just the right superficial femoral and right popliteal veins, with no thrombus visualized in the right common femoral vein, left common femoral, left superficial femoral, or left common femoral veins. Additionally, thrombosis was not observed in any of the major veins of either upper limb. Vitamin K, 0.5 mg, was given by mouth, with the INR falling 42 hr later to 1.4. However, progressive necrosis was apparent (Fig. 2A–D), and the patient was referred to a hematologist on postoperative day 11. As the platelet count had fallen by 68% from 221 (day 4) to 71 (day 11), and in a temporal profile consistent with immune heparin-induced thrombocytopenia (onset of thrombocytopenia on day 5 post-cardiac surgery), heparin-induced thrombocytopenia was clinically suspected. Therefore, the heparinoid, danaparoid sodium (Orgaran), was

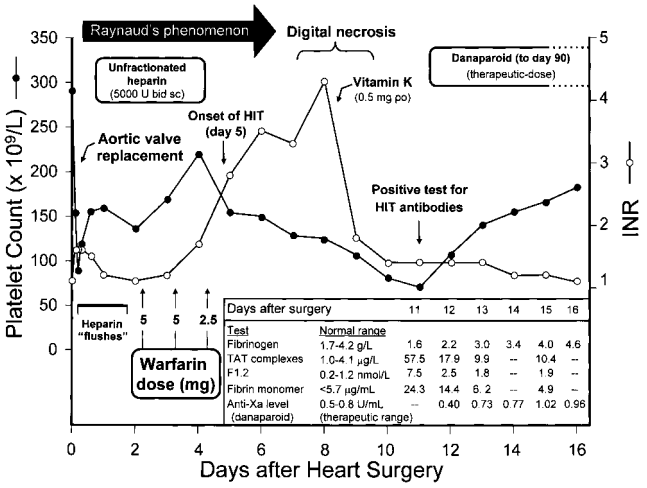

Fig. 1. Clinical course of patient with multiple digital necrosis. Serial platelet counts and international normalized ratio (INR) values are shown following cardiac surgery (day 0). Heparin-induced thrombocytopenia began on day 5, when the platelet count abruptly began to fall. Digital ischemia secondary to postoperative Raynaud's phenomenon abruptly progressed to multiple digital necrosis when the INR rose to a supratherapeutic level of 4.3 (day 8). (Insert) Results of coagulation studies from postoperative days 11–16. This shows evidence for increased thrombin generation (increased thrombin–antithrombin complexes and prothrombin fragment F1.2 levels) that fell during therapy with the anticoagulant, danaparoid. Decompensated DIC (as shown by reduced fibrinogen levels together with increased fibrin monomer levels) improved during danaparoid therapy. Abbreviations: bid sc, twice-daily by subcutaneous route; F1.2, prothrombin fragment 1.2; HIT, heparin-induced thrombocytopenia; TAT, thrombin–antithrombin complexes; U, units.

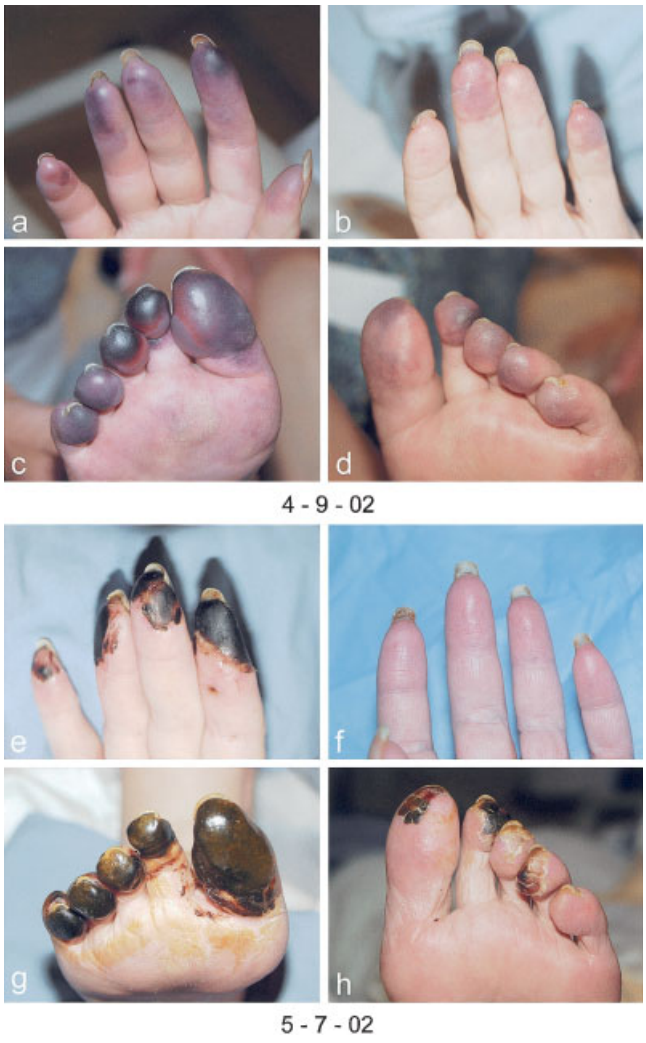

Fig. 2. Multiple digital necrosis. Postoperative day 12 (4-9-02): (a) right hand, (b) left hand, (c) right foot, and (d) left foot. Postoperative day 40 (5-7-02): (e) right hand, (f) left hand, (g) right foot, and (h) left foot. In general, areas of skin showing the greatest ischemic changes on postoperative day 12 corresponded following demarcation to necrosis on day 40.

given (initial bolus, 2,250 U; then 400 U/hr × 4 hr, then 300 U/hr × 4 hr, then 200 U/hr, with subsequent dose adjustments to maintain anti-factor Xa levels between 0.5 and 0.8 U/ml, as described). Over the ensuing weeks, evolving ischemic necrosis led to demarcation of gangrenous and viable tissues that roughly paralleled the extent of tissue injury at the time that anticoagulation with danaparoid was initiated (Fig. 2E–H).

On postoperative day 18, the patient developed left hemiparesis. CT imaging showed a new infarct involving the precentral gyrus of the right frontal lobe. The platelet count was 150×10^9/l, and the anti-factor Xa level on danaparoid was therapeutic (0.79 anti-Xa U/ml; target therapeutic range, 0.50–0.80 anti-Xa U/ml). The platelet count continued to recover, and no further thrombotic events occurred.

A diagnostic workup was performed to investigate possible explanations for nonbacterial thrombotic endocarditis. These revealed a right breast mass; biopsy showed infiltrating duct carcinoma, grade II, with lymphovascular invasion. Subsequently, adenocarcinoma cells were also detected in pleural fluid. The patient died on postoperative day 113 from progressive respiratory failure caused by lymphangitic spread of metastatic breast cancer into the lungs. At the time of death, neither surgical debridement nor amputation of the necrotic digits had been required, nor had autoamputation occurred.

MATERIALS AND METHODS

Blood Sampling and Processing

Blood was collected by clean venipuncture into sodium citrate (3.2%; 9:1) and immediately processed into platelet-poor plasma (10 min at 2,879*g*, then

spun again). Routine tests were performed on the same day, and specialized coagulation assays were performed on samples stored at −70°C prior to testing in batches. For complete blood counts, blood was collected into tubes containing ethylenediaminetetraacetic acid (EDTA). Serum was used to investigate the presence of antibodies that cause heparin-induced thrombocytopenia. Blood for investigational studies was taken with the informed, written consent of the patient.

Testing for Heparin-Induced Thrombocytopenia Antibodies

An enzyme-immunoassay (EIA) that detects IgG antibodies against platelet factor 4/heparin complexes was performed, as described [14,15]. Two commercial EIAs that detect heparin-induced thrombocytopenia antibodies were also used: Asserachrom HPIA (Diagnostica Stago, Asnieres-sur-Seine, France) and GTI-PF4 (GTI Inc., Brookfield, WI) [16]. In addition, a fluid-phase EIA was performed, as described by Newman and colleagues [17]. Additionally, testing for platelet-activating HIT-IgG antibodies was performed using a washed platelet activation assay that quantitates release of radiolabeled serotonin from normal donor platelets that have been washed and resuspended in divalent cation-containing buffer, as described [16,18]. The heparin preparations used for heparin-induced thrombocytopenia antibody testing were unfractionated heparin of porcine intestinal mucosal origin (Heparin Leo, Leo Pharma Inc., Thornhill, Ontario) and enoxaparin (Lovenox, Aventis Pharma-Canada, Laval, Quebec).

Coagulation Assays

Prothrombin time was performed using the AMAX CS-190™ instrument and Thromborel® S thromboplastin (Dade-Behring, Newark, DE), with international sensitivity index (ISI) of 1.1, and reported as the international normalized ratio (INR). Fibrinogen was measured using Clauss clotting method, using STA-Fibrinogen 5 (Diagnostica Stago). Protein C activity was measured using Protein C Reagent (Dade Behring, Marburg, Germany). Antithrombin levels were measured using COAMATIC antithrombin (Chromogenix, Milan, Italy). Both protein C and antithrombin were measured using the STA analyzer. Anti-factor Xa levels during danaparoid therapy were determined by a chromogenic assay using the STA analyzer and Rotachrom HBPM/LMWH test kit (both from Diagnostica Stago), with danaparoid used to generate a standard curve. The following coagulation assays were performed using EIA: free protein S (Asserachrom, Diagnostica Stago); prothrombin fragment F1.2 (Enzygnost F1.2 Micro, Dade-Behring); soluble fibrin monomer, also known as thrombus precursor protein (ABS TpP, American Biogenetic Sciences, Inc., Copiague, NY); and thrombin–antithrombin complexes (Enzygnost TAT, Dade-Behring).

RESULTS

Heparin-Induced Thrombocytopenia Antibodies

Serum obtained on postoperative day 11 tested strongly positive for heparin-induced thrombocytopenia antibodies using each of the assays performed. In the washed platelet activation assay (platelet serotonin release assay), the percent serotonin release ranged between 96% and 100% at three pharmacologic heparin concentrations (UFH, 0.1 and 0.3 IU/ml; low-molecular-weight heparin [LMWH], 0.1 IU/ml; controls $< 5\%$). Reactivity was similarly strong (94–98% release) using a sample from postoperative day 27. The patient's serum tested strongly positive in both commercial EIA's (Stago, 3.444 absorbance units [negative, < 0.471]; GTI, 2.623 absorbance units [normal, < 0.400]); an in-house EIA that only detects PF4/heparin antibodies of the IgG class was also strongly positive (2.409 absorbance units; normal, < 0.450). Finally, the fluid-phase EIA tested positive (3.05 absorbance units when tested at 0.6 IU/ml unfractionated heparin; normal, < 0.37). In vitro cross-reactivity of heparin-induced thrombocytopenia antibodies against danaparoid was assessed by substituting danaparoid in therapeutic concentrations for heparin in the fluid-phase EIA, with negative results (less than 0.10 absorbance units).

Coagulation Studies

There was evidence for greatly increased in vivo thrombin generation on postoperative day 11, using plasma obtained prior to initiation of danaparoid therapy (Fig. 1, insert): the thrombin–antithrombin levels were markedly increased, as were the prothrombin fragment F1.2 levels. From postoperative day 11 to day 15, progressive reduction in thrombin–antithrombin complexes, prothrombin fragment F1.2, and soluble fibrin monomer levels occurred as anti-factor Xa levels rose during danaparoid therapy (Fig. 1, insert). Further evidence that the patient had decompensated DIC includes the relatively low fibrinogen levels pre-danaparoid (1.6 g/l) that increased to high-normal levels (4.6 g/l) by postoperative day 16 during danaparoid treatment.

Blood samples obtained following normalization of the INR post-vitamin K showed normal levels of protein C activity (0.83 and 0.85 U/ml on plasma

from postoperative days 12 and 20, respectively; normal, 0.70–1.80), normal levels of free protein S (median, 0.55 U/ml, and range 0.51–0.70 on nine different plasma samples tested from postoperative days 9–36; normal, 0.50–1.26 U/ml), and antithrombin (0.99 U/ml; normal, 0.77–1.30 U/ml). Unfortunately, a blood sample was not available from postoperative day 8, when the INR was 4.3, to determine whether either or both of the protein C natural anticoagulant factors (protein C, protein S) were significantly reduced when digital necrosis occurred. Normal results were obtained when patient plasma was tested for activated protein C resistance. Testing of the patient's plasma for nonspecific inhibitor (lupus anticoagulant) gave normal results.

Other Laboratory Studies

Testing for homocysteine, cryoglobulins, complement (C3 and C4), anticardiolipin antibodies, antinuclear antibodies, anti-ribonucleoprotein, anti-Sm (Smith), anti-SSb (Latimer), anti-SSa (Rose), and anti-Jo-1 were normal or negative.

DISCUSSION

Raynaud's phenomenon that begins after the age of 50 years is occasionally a marker of malignancy, most often adenocarcinoma [19,20]. Resection of the neoplasm or cytoreduction with chemotherapy can lead to partial or complete remission of the vasospastic phenomena [21–23]. In our patient, Raynaud's phenomenon occurred beginning at age 60 and may have represented a para-neoplastic phenomenon. In addition, the patient developed aortic valve insufficiency because of nonbacterial thrombotic endocarditis (also known as marantic endocarditis). Nonbacterial thrombotic endocarditis is strongly associated with antiphospholipid antibody syndrome (Libman-Sacks endocarditis) [24,25] and adenocarcinoma [26]. In our patient, testing for antiphospholipid antibodies was negative. However, metastatic breast adenocarcinoma was diagnosed during the postoperative period.

During the early postoperative period, the patient had intermittent ischemia to the fingers and toes consistent with Raynaud's phenomenon, which responded to application of warm towels. However, beginning on day 5, the patient developed a fall in the platelet count at a time when progressive increase in platelet count is expected [27,28]. The timing of this platelet count fall is consistent with immune heparin-induced thrombocytopenia [29]. Indeed, the patient tested strongly positive for HIT antibodies by both washed platelet activation assay ($>95\%$ serotonin release) and strong positive EIA (>2.4 absorbance units using multiple solid-phase EIAs, as well as a fluid-phase EIA). Such a high level of test results is strongly associated with clinical heparin-induced thrombocytopenia, with an associated likelihood ratio of approximately 50 [30]. These serological findings are diagnostic of heparin-induced thrombocytopenia in this clinical context. Moreover, the platelet count promptly increased during anticoagulation with danaparoid.

On postoperative days 2, 3, and 4, the patient received routine anticoagulation with warfarin, which was given because of the mechanical aortic valve. Unfortunately, this course of warfarin therapy led to increasing levels of the INR that coincided with the episode of HIT that began on postoperative day 5. Thus, by postoperative day 8, when necrosis of the fingers was observed, the patient had concurrence of three risk factors for limb necrosis: (i) vasospasm attributable to postoperative exacerbation of Raynaud's phenomenon; (ii) immune heparin-induced thrombocytopenia (which increases in vivo thrombin generation); and (iii) warfarin-induced increase in the INR to 4.3 (a risk factor for impaired function of the protein C natural anticoagulant pathway in the setting of heparin-induced thrombocytopenia [3–8]).

The interaction of heparin-induced thrombocytopenia and warfarin (coumarin) therapy that results in a supratherapeutic INR has been linked to the pathogenesis of venous limb gangrene [3–8]. It is believed that the concurrence of heparin-induced thrombocytopenia and warfarin therapy plays key roles in the pathogenesis of this syndrome. Heparin-induced thrombocytopenia leads to in vivo platelet activation [31,32] and, possibly, endothelial cell [33] and monocyte activation [34], which lead to accelerated in vivo thrombin generation. In vivo thrombin generation was shown in our patient by the greatly elevated levels of thrombin–antithrombin complexes and prothrombin fragment F1.2 levels, which only returned to near-normal when danaparoid was given. The supratherapeutic INR in patients with venous limb gangrene has been linked to severe, acquired deficiency in protein C natural anticoagulant. Unfortunately, the diagnosis of warfarin-induced necrosis was not suspected in this patient until after treatment with vitamin K, and near-normalization of the INR, so we had no opportunity to test the possibility that protein C activity was markedly reduced when progression to digital necrosis occurred. Following vitamin K therapy, normal levels of protein C activity and free protein S were documented; furthermore, the patient did not have activated protein C resistance. These findings are consistent with previous reports of warfarin-induced venous limb gangrene complicating heparin-induced thrombocytopenia, in whom con-

genital abnormalities of the protein C anticoagulant pathway are generally not observed [3–6].

Figure 3 summarizes the pathogenesis we propose to explain the occurrence of multiple digital gangrene in our patient. Metastatic breast adenocarcinoma is a plausible explanation for the patient's presentation with recent-onset Raynaud's phenomenon and aortic insufficiency secondary to nonbacterial thrombotic endocarditis. Following cardiac surgery, the patient developed exacerbation of Raynaud's phenomenon. The digital ischemia was managed by warming of the extremities, and it appeared clinically stable until the patient developed concurrence of heparin-induced thrombocytopenia and routine administration of warfarin anticoagulation because of the mechanical aortic valve. We suggest that the interaction of microvascular vasospasm secondary to Raynaud's phenomenon predisposed the patient to develop the unusual complication of multiple digital necrosis, rather than the more "typical" manifestation of venous limb gangrene, which usually additionally affects tissues proximal to the digits. It is noteworthy that the limb that sustained the greatest degree of digital necrosis (right lower limb toes) is the same limb that had deep-vein thrombosis detected by Doppler ultrasonography. This is in keeping with the observation that, in venous limb gangrene, acral necrosis typically occurs in limbs with deep-vein thrombosis than in limbs unaffected by deep-vein thrombosis [3–8,11,12].

Our case adds to recent literature indicating the danger of warfarin anticoagulation in patients who have heparin-induced thrombocytopenia [3–8]. It also underscores the importance of interpreting even moderate falls in the platelet count that occur on postoperative day 5 or later following cardiac surgery as being strongly suggestive of heparin-induced thrombocytopenia [28,29]. In our patient, the heparin had already been stopped on postoperative day 4, which may have contributed to the delay in diagnosis, since the platelet count fall began *after* the heparin had been stopped. This phenomenon of "delayed-onset heparin-induced thrombocytopenia" has been recently noted in the literature [35–37]. Our case adds further support to the view that heparin-induced thrombocytopenia that begins after stopping heparin is a high-risk situation for thrombotic events—including progressive thrombosis during warfarin administration—as ongoing activation of platelets and coagulation occurs for several days or weeks that is unopposed by residual heparin.

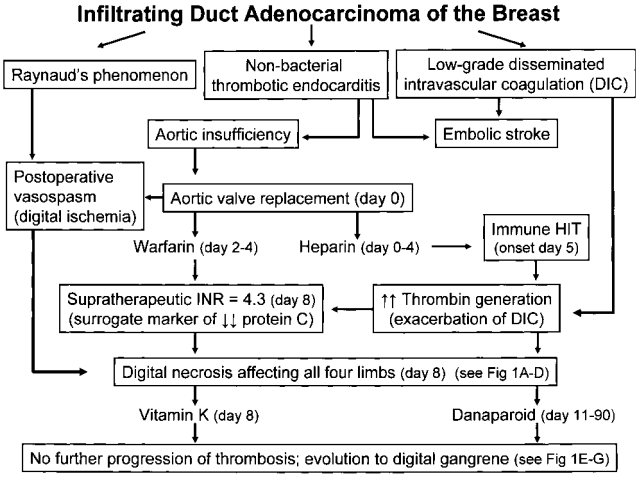

Fig. 3. Proposed pathogenesis of multiple digital gangrene.

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