A Spontaneous Prothrombotic Disorder Resembling Heparin-induced Thrombocytopenia

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ABSTRACT

BACKGROUND: Antibodies against the “self” protein, platelet factor 4 (PF4), bound to heparin—the cause of immune heparin-induced thrombocytopenia—are believed invariably to be triggered by preceding heparin therapy. We describe a novel syndrome, spontaneous heparin-induced thrombocytopenia, in which clinical and serologic features characteristic of this adverse drug reaction develop in patients despite the absence of preceding heparin therapy.

METHODS: Three patients met the study criteria (clinical and serologic features of heparin-induced thrombocytopenia without preceding heparin exposure), of whom 2 patients were identified among 225 patients (0.89%, 95% confidence interval, 0.11%-3.17%) with serologically confirmed heparin-induced thrombocytopenia recognized during an 18-year period at 1 hospital. The platelet serotonin-release assay was used to detect heparin-dependent immunoglobulin G-induced platelet activation, and 2 enzyme immunoassays were used to detect antibodies against PF4/heparin.

RESULTS: Two patients presented with thrombocytopenia and multiple arterial thrombosis, and 1 patient presented with anaphylactoid reactions after 2 subcutaneous injections of low-molecular-weight heparin. All 3 patients had high levels of platelet-activating anti-PF4/heparin antibodies of immunoglobulin G class at presentation despite the absence of previous heparin exposure. However, each patient did have a preceding infectious or inflammatory event; 1 patient had concomitant antiphospholipid antibodies.

CONCLUSION: Circumstances other than heparin use can trigger a spontaneous disorder that closely mimics heparin-induced thrombocytopenia, further supporting the autoimmune nature of this adverse drug reaction.

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Heparin-induced thrombocytopenia is an acquired prothrombotic disorder.1,2 The immune response targets platelet factor 4 (PF4), which forms neoepitopes when it binds to heparin.3 The resulting immunoglobulin (Ig)G/PF4/heparin immune complexes activate platelets via their Fcγ receptors,4 resulting in high thrombotic risk.5,6 A central concept is that the antibodies are invariably triggered by preceding treatment with heparin, more often unfractionated compared with low-molecular-weight heparin.1,2,6 On occasion, heparin-induced thrombocytopenia has autoimmune features. For example, thrombocytopenia and thrombosis can begin several days after all heparin has been stopped, so-called delayed-onset heparin-induced thrombocytopenia,1,2 perhaps because unusually high levels of antibodies react with platelet-associated PF4 bound to non-heparin glycosaminoglycans (chondroitin sulfate).7 In theory, such a disorder might even arise spontaneously, presenting as de novo thrombocytopenia and thrombosis or rapid-onset thrombocytopenia with anaphylactoid reactions on first heparin use. We report 3 patients whose clinical profiles support these concepts.

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There was no previous hospitalization or history of heparin and lower limb arteries, pulmonary embolism, and hepatic amputations. Autopsy revealed multiple thrombi (coronary agent), lower limb necrosis undergoing thrombectomies and earlier after local injury. Despite prednisolone into his wrist 8 days after articular injection of metronidazole for periodontitis and an intra-articular injection of methylprednisolone into his wrist 8 days earlier after local injury. Despite undergoing thrombectomies and receiving ancré (defibrinogenating agent), lower limb necrosis developed. Fatal cardiac arrest occurred 2 hours after the amputations. Autopsy revealed multiple thrombi (coronary and lower limb arteries, pulmonary embolism, and hepatic vein thromboses). No neoplasm was found.

Patient 1
A 69-year-old man without previous hospitalization presented with bilateral lower limb ischemia caused by iliac/femoral artery thromboses and thrombocytopenia (platelet count, 17 × 10⁹/L). The only remarkable preceding events were a 5-day course of ampicillin for periodontitis and an intra-articular injection of methylprednisolone into his wrist 8 days earlier after local injury. Despite undergoing thrombectomies and receiving ancré (defibrinogenating agent), lower limb necrosis developed. Fatal cardiac arrest occurred 2 hours after the amputations. Autopsy revealed multiple thrombi (coronary and lower limb arteries, pulmonary embolism, and hepatic vein thromboses). No neoplasm was found.

Patient 2
A 40-year-old woman without previous hospitalization developed sudden left-sided hemiparesis as the result of cerebral infarction (right middle cerebral artery thrombosis) (Figure 1A). The only remarkable recent events were several outpatient incision-and-drainage procedures for groin cysts (without heparin use). The platelet count was 297 × 10⁹/L at the time of her stroke but decreased during the next few hours to 175 × 10⁹/L, at which time symptomatic acute femoral artery thrombosis occurred. Embolectomy was performed, and heparin was intravenously administered intraoperatively and postoperatively, with further platelet count decreases (nadir, 59 × 10⁹/L). Heparin was stopped, and neurosurgery was performed for cerebral edema. The alternative anticoagulant, danaparoid, was given postoperatively, with platelet count recovery.

Patient 3
A 24-year-old woman was admitted with a 2-week history of an upper respiratory tract infection and a 1-week history of productive cough and pleuritic chest pain; pneumonia was diagnosed (rales, chest x-ray findings) (Figure 1B). There was no previous investigation or history of heparin exposure. The baseline platelet count was 301 × 10⁹/L. However, pending investigation for pulmonary embolism, she received enoxaparin (1 mg/kg) by subcutaneous injection. Within 30 minutes, she developed shaking chills, tachycardia, cyanosis, hypoxemia, and flushing, which subsided by 2 hours. (No repeat platelet count was measured at this time). The patient received a second subcutaneous dose of enoxaparin 43 hours later, with recurrence of these symptoms and signs. After this second reaction, the platelet count measured 62 × 10⁹/L. Although computed tomography pulmonary angiography ruled out pulmonary embolism, danaparoid was administered pending platelet count recovery.

RESULTS
The 3 patients showed positive test results for heparin-induced thrombocytopenia antibodies by both the serotonin-release assay and the 2 enzyme immunoassays (Table 1). Testing using blood obtained 36 months (patient 2) and 7 months (patient 3) later showed negative results. Only 1
patient showed positive test results for antiphospholipid antibodies, with negative test results at the 36-month follow-up. “Spontaneous heparin-induced thrombocytopenia” represented 0.89% (95% confidence interval, 0.11%-3.17%) of patients diagnosed with heparin-induced thrombocytopenia at 1 hospital site.

**DISCUSSION**

We describe 3 patients with clinical and serologic features of heparin-induced thrombocytopenia despite the absence of preceding heparin exposure. Two patients presented with thrombocytopenia and thrombosis, with events typical of heparin-induced thrombocytopenia (limb artery thrombosis, stroke, and venous thromboembolism). One patient died; the other had a debilitating stroke and limb amputation.

The third patient, who did not present with thrombocytopenia or thrombosis, developed anaphylactoid reactions on 2 occasions shortly after receiving 2 injections of low-molecular-weight heparin, with an associated platelet count decrease. Similar reactions with abrupt platelet count decrease after intravenous bolus heparin or subcutaneous
Table 1  Serologic Features of 3 Patients with Platelet-activating Anti-PF4/Heparin Antibodies in the Absence of Preceding Heparin Therapy

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, Sex</th>
<th>0 IU/ml UFH (Normal &lt; 10%)</th>
<th>0.1 IU/ml UFH (Normal &lt; 10%)</th>
<th>0.3 IU/ml UFH (Normal &lt; 10%)</th>
</tr>
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<tbody>
<tr>
<td>1 (69, M)</td>
<td>47</td>
<td>99</td>
<td>96</td>
<td>2.03</td>
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<tr>
<td>2 (40, F)</td>
<td>76</td>
<td>91</td>
<td>95</td>
<td>2.72</td>
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<tr>
<td>3 (24, F)</td>
<td>0</td>
<td>37</td>
<td>80</td>
<td>1.87</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Enzyme Immunoassays to Detect Anti-PF4/Heparin Antibodies† (Absorbance, Optical Density Units)</th>
<th>Tests for Antiphospholipid Antibodies</th>
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</thead>
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<tr>
<td>In-house Assay that Detects IgG Anti-PF4/Heparin (Normal &lt; 0.4 U)</td>
<td>Commercial Assay that Detects IgG/IgA/IgM Anti-PF4/Polyvinyl Sulfonate Antibodies (Normal &lt; 0.4 U)</td>
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<tr>
<td>2.91</td>
<td>2.38</td>
</tr>
<tr>
<td>95</td>
<td>92</td>
</tr>
<tr>
<td>1.87</td>
<td>2.62</td>
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<table>
<thead>
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<th>Interpretation</th>
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</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Normal</td>
<td>Negative</td>
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<tr>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Normal</td>
<td>Positive</td>
</tr>
</tbody>
</table>

PF4 = platelet factor 4; PTT-LA = partial thromboplastin time-lupus anticoagulant; RVVT = Russell viper venom time; UFH = unfractionated heparin. For all assays, testing of negative and positive controls reacted as expected. Testing for antibodies was performed for patient 3 using a blood sample obtained 20 minutes after the first injection of enoxaparin (earlier blood samples were not available); for patient 2, the blood tested was obtained before any administration of heparin (patient 1 never received heparin).

*For all patients, reactivity was inhibited to less than 2% in the presence of either Fc receptor blocking monoclonal antibody or high concentrations (100 IU/mL) of UFH.

†For all patients, reactivity in both enzyme immunoassays was inhibited by more than 80% in the presence of UFH, 100 IU/mL, which is a characteristic feature of antibodies causing heparin-induced thrombocytopenia.

‡Low-titer positive reactions in both IgM and IgG anticardiolipin enzyme immunoassays, but negative tests in both IgM and IgG anti-beta2-glycoprotein-1 enzyme immunoassays.

CONCLUSIONS

We report 3 patients who developed an acute illness resembling heparin-induced thrombocytopenia in the absence of preceding heparin exposure. This suggests that on rare occasions a transient prothrombotic disorder resembling heparin-induced thrombocytopenia can occur that on rare occasions a transient prothrombotic disorder can occur in the absence of heparin-induced thrombocytopenia.

Each patient had a serologic profile characteristic of heparin-induced thrombocytopenia with strong positive test results for heparin-dependent antibodies. The results are consistent with an autoimmune pathogenesis. First, the antiphospholipid syndrome, neither of which has been observed in previous heparin-induced thrombocytopenia. Second, high-titer positive reactions in both IgM and IgG anticardiolipin enzyme immunoassays, but negative tests in both IgM and IgG anti-beta2-glycoprotein-1 enzyme immunoassays, and positive reactions in both IgM and IgG anticardiolipin enzyme immunoassays, but negative tests in both IgM and IgG anti-beta2-glycoprotein-1 enzyme immunoassays.

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ACKNOWLEDGMENTS
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References