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Peripheral Digit Ischemic Syndrome Can Be a Manifestation of Postoperative Thrombotic Thrombocytopenic Purpura

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Abstract: In addition to common dysfunction of the brain and kidney, thrombotic thrombocytopenic purpura (TTP) may present with atypical clinical features due to the involvement of other organs such as the lung, pancreas, heart, eye, and skin. We have also observed the unusual presentation of peripheral digit ischemic syndrome (PDIS) in some patients with postoperative TTP. To clarify this relationship between TTP and PDIS, the hematologic data from the medical records of patients with known diagnoses of thrombotic microangiopathy (TM) were examined in a single institution. A total of 94 patients were diagnosed with TM. Among these patients, PDIS developed in six patients and in all these patients PDIS occurred with postoperative TTP. Four patients also had acute respiratory distress syndrome (ARDS). Because of delayed diagnosis of TTP, only two patients survived and four died. One patient responded to plasma exchange and survived, and another patient recovered from postoperative TTP without plasma exchange. However, both patients required the amputation of multiple digits. In conclusion, PDIS is another atypical manifestation of TTP and has occurred exclusively in patients with postoperative TTP in this series. Once PDIS developed, the prognosis was poor and amputation of digits was needed in surviving patients. Early recognition of this atypical manifestation of TTP is essential for a favorable outcome. Key Words: Acute respiratory distress syndrome, Peripheral digit ischemic syndrome, Postoperative thrombotic thrombocytopenic purpura, Thrombotic thrombocytopenic purpura, Thrombotic microangiopathy, Thrombocytopenia.

Peripheral digit ischemic syndrome (PDIS) is a serious clinical condition characterized by progressive ischemic changes of the fingers and toes due to either a local pathological condition or manifestation of a systemic disease. Eventually, without an effective treatment, this condition may lead to gangrene of the involved digits. When this syndrome is the clinical presentation of a systemic disease, it poses a serious threat to the patient that ultimately could lead to death. Several different causes of PDIS have been recognized. Decreased tissue perfusion of the blood due to altered blood circulation (1,2), vasculitis (3–5), peripheral vascular spasm (6,7), peripheral vascular thrombotic diseases (8–10), and systemic thromboembolic diseases (11–13) are the known causes of PDIS.

Recently, we have also encountered PDIS in some patients with thrombotic thrombocytopenic purpura (TTP). This manifestation was noticed in TTP of the postoperative setting. Because of this unusual observation, we reviewed the medical records of patients who were previously diagnosed with TTP and other thrombotic microangiopathy (TM), and also recorded the clinical data of patients with newly diagnosed TTP and TM. PDIS was found to be exclusively associated with postoperative TTP. In this article, the importance of PDIS in the understanding and management of postoperative TTP is discussed.

PATIENTS AND METHODS

All identifiable cases of TTP and other TM, which includes hemolytic uremic syndrome and the syndrome in which hemolysis, elevated liver enzymes, and low platelet count (HELLP) are associated with pregnancy, which were diagnosed at the Good Samaritan Hospital in Dayton, OH, USA, were documented and recorded from 1981 to 1994. The data...
on these syndromes on newly diagnosed patients were tabulated at the time of diagnosis from 1995 to 2002. The essential diagnostic criteria for TTP and other TM were unexplained thrombocytopenia (platelet count <100,000/μL) and microangiopathic hemolytic anemia (MAHA). Thrombocytopenia attributable to conditions such as blood transfusions, immune drug reactions, chemotherapy, infections, heparin-induced thrombocytopenia, consumption coagulopathy, antiphospholipid antibody syndrome and others, was excluded after pertinent clinical and laboratory evaluations, as previously described (14,15).

The laboratory studies performed included prothrombin time, activated partial thromboplastin time, assay of coagulation factors, D-dimers, soluble fibrin monomers, and fibrinogen levels in most patients. The heparin-induced platelet aggregation test (16), 14C serotonin release assay (17), and heparin and platelet factor 4-associated antibody assay were also performed for patients treated with heparin when available. Special attention was paid to differentiating between TTP and heparin-induced thrombocytopenia according to a previously published description (18) because, in a postoperative setting, both conditions can cause PDIS in association with thrombocytopenia. Thrombocytopenia due to such infections as sepsis and pneumonia was excluded by an appropriate clinical examination and laboratory studies, including blood cultures, radiologic, and other imaging studies. The diagnosis of microangiopathic hemolytic anemia (MAHA) was established on the basis of the evidence of brisk hemolysis with the demonstration of schistocytes in the peripheral blood. Hemolysis was confirmed by reticulocytosis, hypohaptoglobinemia, and elevated lactic dehydrogenase levels. Negative antiglobulin tests and other hematologic features excluded autoimmune hemolytic anemia.

The diagnosis of PDIS was established by physical examination. Peripheral digit ischemic syndrome usually began with the mottling of the fingers and toes. Gradually, the digits showed bluish discoloration as gangrene set in, ultimately progressing to dry gangrene and atrophy of the distal digits. The pulse of the arteries proximal to the digit, such as that of the dorsal pedis area, was preserved since the ischemic changes were caused by arteriolar capillary microthrombi in the periphery of the digits.

Since PDIS occurred exclusively in postoperative TTP, the patient’s characteristics, including the underlying pathology, pre-TTP surgical procedure, and affected digits, were recorded. In addition to typical manifestation of TTP, including the dysfunction of the brain and kidney, dysfunction of other organs was evaluated. Hematologic data reviewed included the hemoglobin, hematocrit, platelet count, reticulocyte count, and lactic acid dehydrogenase and haptoglobin level. The reports of the peripheral blood film were reviewed and the series of the blood films of all patients with PDIS were examined (JCC). The degree of schistocytosis was estimated as follows (19): the score of 0 for less than 1% of schistocytes among red blood cells, 1+ for 1–2%, 2+ for 2–5%, 3+ for 5–10%, and 4+ for more than 10%. The treatment of patients who developed PDIS was reviewed. Typically, the daily plasma exchange was performed with fresh frozen plasma 3.5–4.0 L through a double lumen dialysis catheter inserted in either the jugular or femoral vein. The total number of therapeutic plasma exchanges, if utilized, was identified for each patient. The response of TTP to therapeutic plasma exchange, the patient outcome, and the digit outcome were also recorded.

**RESULTS**

Ninety-four patients (35 patients in retrospective review and 59 patients at diagnosis) fulfilled the diagnostic criteria for TTP and other TM. The primary diagnosis of TTP was present in 78 patients, hemolytic uremic syndrome in 7, and HELLP syndrome in 9. Among these patients PDIS developed in 6 patients, all in postoperative TTP (Table 1). No patient with hemolytic uremic syndrome and HELLP syndrome developed PDIS.

As shown in Table 2, the differential diagnosis from heparin-induced thrombocytopenia was based on the lack of heparin usage in three patients (Patients 1, 4 and 6). Three other patients had received the therapeutic doses of heparin until 2 days (Patient 2), 3 days (Patient 3), and 8 days (Patient 5) prior to establishing the diagnosis of TTP. In addition, these three patients had negative heparin-induced platelet aggregation tests and 14C serotonin release assays. Also, as shown in the same table, prothrombin times, activated partial thromboplastin times and fibrinogen levels as well as clinical presentations were inconsistent with consumption coagulopathy (DIC). Elevated D-dimers presumably were the result of thrombin generation related to surgery and were considered insignificant.

Two patients were retrospective cases (Patients 1 and 2) and four patients were prospective ones for a total of three men and three women. All were older than 65 years. Two patients had severe coronary artery disease and developed PDIS following multi-vessel bypass grafting. Two developed PDIS after
intestine surgery: one bowel resection for adhesions
associated with diverticulitis and the other postchole-
cystectomy. The remaining two patients developed
PDIS after vascular surgery: one repair of injured
neck vessels and the other postarteriovenous fistula
for renal hemodialysis. All six patients had neurolog-
cal manifestations in addition to thrombocytopenia
and MAHA. Significant renal failure was present in
four patients and the evidence of hepatitis was
present in one patient. However, it was difficult to
determine whether renal failure and hepatic insuffi-
ciency were the manifestations of TTP or were the
result of advanced cardiopulmonary dysfunction. An
unusual finding was acute respiratory distress syn-
drome (ARDS), which was seen in four patients and
required a prolonged care. Involved toes or fingers
are noted in Table 1. PDIS was symmetrical and mul-
tiple digits were involved simultaneously in similar
stages of the ischemia. The presentation was isolated
thrombotic phenomenon without evidence of macro-
thrombosis in either arterial or venous systems.

Hematologic data are presented in Table 3. No
patients had evidence of MAHA and thrombocy-
topenia prior to the surgery, but postoperative hema-
tologic data confirmed that all patients developed
TTP postoperatively. This was supported by signifi-
cant anemia, reticulocytosis, elevated lactic dehydro-
genase level, decreased haptoglobin, negative
antiglobulin tests and presence of schistocytes after
surgery. However, the degree of schistocytosis was
less prominent than that expected in classical cases
of TTP. This fact might have contributed to the over-
looked diagnosis of TTP because of a low index of
suspicion, particularly postoperatively. In retrospect,
without a careful hematologic evaluation by a hema-
tologist, especially review of the blood films as well
as appropriate hemolytic studies, the diagnosis of
postoperative TTP could have been easily over-
looked in all of these patients with PDIS.

Initially the management of PDIS was conserva-
tive. In three patients who had been on heparin, the
drug was discontinued when thrombocytopenia was
noted. None of these patients received dipyridamole,
steroid, intravenous immunoglobulins or immuno-
suppressive therapy. However, Patient 1 received a
fresh frozen plasma infusion once without any bene-

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### TABLE 1. Patient characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Race/Sex</th>
<th>Underlying Pathology</th>
<th>Surgery</th>
<th>Features of TTP</th>
<th>Involved Digits</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>68/black/male</td>
<td>Bleeding from neck injury</td>
<td>Repair of damaged neck vessels</td>
<td>A, T, N, K</td>
<td>Bilateral toes</td>
</tr>
<tr>
<td>2</td>
<td>65/white/female</td>
<td>Chronic renal failure</td>
<td>Arteriovenous fistula formation</td>
<td>A, T, N, K, L</td>
<td>Left toes, right fingers</td>
</tr>
<tr>
<td>3</td>
<td>68/white/female</td>
<td>Coronary artery disease</td>
<td>3 vessel CABG, mitral valve replacement and tricuspid valve annuloplasty</td>
<td>A, T, N, L</td>
<td>Bilateral toes</td>
</tr>
<tr>
<td>4</td>
<td>72/white/female</td>
<td>Intestinal adhesions, diverticulitis</td>
<td>Bowel resection</td>
<td>A, T, N, L</td>
<td>Bilateral toes</td>
</tr>
<tr>
<td>5</td>
<td>66/white/male</td>
<td>Coronary artery disease</td>
<td>3 vessel CABG</td>
<td>A, T, N, K, L, H</td>
<td>Bilateral toes, bilateral fingers</td>
</tr>
<tr>
<td>6</td>
<td>70/white/male</td>
<td>Cholecystitis</td>
<td>Cholecystectomy</td>
<td>A, T, N, K</td>
<td>Bilateral toes, bilateral fingers</td>
</tr>
</tbody>
</table>

A, MAHA (microangiopathic hemolytic anemia); CABG, coronary artery bypass graft; H, hepatitis; K, renal failure; L, ARDS (acute respiratory distress syndrome); N, neurologic manifestation; T, thrombocytopenia.

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### TABLE 2. Results of heparin usage and coagulation tests

<table>
<thead>
<tr>
<th>Patient</th>
<th>Heparin Usage</th>
<th>HIT Test Results</th>
<th>PT (s)</th>
<th>PTT (s)</th>
<th>Fibrinogen (mg %)</th>
<th>Factor VIII (%)</th>
<th>D-dimers</th>
<th>Soluble fibrin monomers</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No</td>
<td>Not done</td>
<td>14.3</td>
<td>38.6</td>
<td>215</td>
<td>ND</td>
<td>ND</td>
<td>Positive</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>HIPAT(–)</td>
<td>15.1</td>
<td>36.0</td>
<td>175</td>
<td>68</td>
<td>ND</td>
<td>Negative</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>HIPAT(–)</td>
<td>18.5</td>
<td>32.7</td>
<td>297</td>
<td>66</td>
<td>&gt;1</td>
<td>ND</td>
</tr>
<tr>
<td>4</td>
<td>No</td>
<td>Not done</td>
<td>15.0</td>
<td>29.0</td>
<td>291</td>
<td>61</td>
<td>&gt;1</td>
<td>ND</td>
</tr>
<tr>
<td>5</td>
<td>Yes</td>
<td>HIPAT(–)</td>
<td>14.7</td>
<td>32.5</td>
<td>305</td>
<td>ND</td>
<td>ND</td>
<td>Negative</td>
</tr>
<tr>
<td>6</td>
<td>No</td>
<td>Not done</td>
<td>18.7</td>
<td>32.5</td>
<td>165</td>
<td>80</td>
<td>&gt;1</td>
<td>ND</td>
</tr>
</tbody>
</table>

°Fibrinogen (normal value: 200–400 mg percentage); †D-dimers (normal value: < 0.25 μg/mL); HIPAT, Heparin-induced platelet aggregation test; HIT, Heparin-induced thrombocytopenia; ND, Not done; PT, Prothrombin time (normal value: 11–13.6 s); PTT, Activated partial thromboplastin time (normal value: 25.5–38.6 s); SR Assay, ¹⁴C serotonin release assay.
fit. As shown in Table 4, no plasma exchange was given in three patients due to supportive care. Three patients underwent plasma exchanges. Among six patients with PDIS, one patient treated with plasma exchange and another who had received supportive care without the exchange survived. But both patients required surgical interventions. Patient 3 required an amputation of the entire right forefoot and Patient 5 the amputation of multiple digits. Four patients died due to advanced TTP leading to multi-organ failure, including cardiac, respiratory, central nervous system and renal failure without improvement of PDIS.

**DISCUSSION**

Peripheral digit ischemic syndrome has rarely been reported in hematologic diseases and no cases of TTP have been described with this syndrome in the literature except by this author (JCC). Sometimes acute PDIS has been observed in intensive care settings, especially postoperatively, due to various causes. Chronic diseases such as essential thrombocythemia (20), collagen vascular diseases (3–5), Raynaud’s disease (6), Buerger’s disease (7), peripheral arteriosclerosis (8) and many others (1,2,21–26) have caused PDIS. Acute PDIS may also occur in patients with cholesterol emboli (27), peripheral thrombi arising from detached atherosclerotic plaques from atherosclerotic sites (28), heparin-induced thrombocytopenia with thrombosis syndrome (14), and consumption coagulopathy (29). Now, as a result of our experience, TTP should be included as another cause of acute PDIS.

Perhaps the pathogenesis of acute PDIS in TTP patients can be explained by the hypothesis that diffuse arteriolar capillary microthrombi occur in the peripheral digits since, other than peripheral ischemic changes of the digits, there were neither arterial nor venous macrothrombi observed in any of these patients. Indeed, this finding is the characteristic of the pathology of TTP in other organs such as the brain and kidney. Diffuse arteriolar capillary microthrombi would result in diffuse hyaline thrombi seen in pathologic examination and subsequent organ ischemia. In PDIS patients, this explanation is also consistent with the speculation that ARDS is caused by diffuse microthrombi in the alveolar capillaries of the lung (30). Suspected pathogenesis of TTP is the microaggregation of platelets in the arteriolar capillaries following platelet activation. Evidence indicates that the platelet aggregating agonist in classical TTP is probably the unusually large von Willebrand factor multimers that are derived from

### TABLE 3. Patient hematologic data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Hemoglobin (g/dL)</th>
<th>Hematocrit</th>
<th>Platelets (×10^3/µL)</th>
<th>Reticulocytes (%)</th>
<th>Blood Smear (schistocytes)</th>
<th>LDH (U/L)</th>
<th>Haptoglobin (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11.3</td>
<td>0.324</td>
<td>47 000</td>
<td>5.4</td>
<td>2+</td>
<td>451</td>
<td>&lt;5</td>
</tr>
<tr>
<td>2</td>
<td>7.6</td>
<td>0.242</td>
<td>19 000</td>
<td>7.0</td>
<td>1+</td>
<td>1244</td>
<td>&lt;5</td>
</tr>
<tr>
<td>3</td>
<td>8.4</td>
<td>0.242</td>
<td>55 000</td>
<td>9.1</td>
<td>1+</td>
<td>857</td>
<td>&lt;5</td>
</tr>
<tr>
<td>4</td>
<td>8.6</td>
<td>0.255</td>
<td>62 000</td>
<td>8.6</td>
<td>2+</td>
<td>697</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>9.9</td>
<td>0.288</td>
<td>27 000</td>
<td>4.5</td>
<td>1+</td>
<td>6000</td>
<td>&lt;5</td>
</tr>
<tr>
<td>6</td>
<td>9.7</td>
<td>0.301</td>
<td>35 000</td>
<td>5.0</td>
<td>2+</td>
<td>ND</td>
<td>40</td>
</tr>
</tbody>
</table>

LDH, lactic dehydrogenase; ND, Not done; Control values: hemoglobin, 14–18 g/dL (male), 12–16 g/dL (female); hematocrit, 0.40–0.50 (male), 0.38–0.50 (female); platelets, 140–440×10^3/µL; reticulocyte, 0.5–1.5%; schistocytes, 0, less than 1%; 1+, 1–2%; 2+, 2–5%; 3+, 5–10%; 4+, more than 10%; LDH, 90–180 U/L; haptoglobin, 20–150 mg/dL.

### TABLE 4. Plasma exchange and outcome

<table>
<thead>
<tr>
<th>Patient</th>
<th>Exchange plasmapheresis (no.)</th>
<th>Response</th>
<th>Patient outcome</th>
<th>Digit outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>No response due to delayed diagnosis</td>
<td>Died</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>None</td>
<td>No treatment due to delayed diagnosis</td>
<td>Died</td>
<td>NA</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>Complete remission</td>
<td>Survived</td>
<td>Amputation of the right forefoot</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>No response due to delayed diagnosis</td>
<td>Died</td>
<td>NA</td>
</tr>
<tr>
<td>5</td>
<td>None</td>
<td>No treatment with PE, but improved after 8 weeks’ intensive care support</td>
<td>Survived</td>
<td>Amputation of 2nd through 5th distal phalanges of the fingers of left hand and all toes</td>
</tr>
<tr>
<td>6</td>
<td>None</td>
<td>No treatment due to delayed diagnosis</td>
<td>Died</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA, Not applicable.
the endothelial cell. In classical TTP, the von Willebrand factor-cleaving protease that cleaves the unusually large von Willebrand factor multimers is removed by an autoantibody (31). Arteriolar capillary microthrombi in the peripheral digits, which are made of platelet aggregates induced by large von Willebrand factor multimers after release from injured endothelial cells during the surgery, may be responsible for PDIS.

The observations that all patients with PDIS developed acute TTP following surgical procedures, and four patients were associated with ARDS suggest acute TTP in postoperative patients may represent a different spectrum of the syndrome from classical TTP. The presentation of postoperative TTP is atypical since schistocytosis is less prominent and it tends to involve organs such as the lungs and digits. Perhaps endothelial injury during surgery when underlying arteriosclerotic disease is severe may play an important role in the pathogenesis of PDIS since this presentation has occurred in elderly patients with advanced arteriosclerotic disease. Therapeutic plasma exchange is an effective treatment for postoperative TTP if the treatment is initiated early (19,32). Further clinical observation and laboratory investigation, such as the pattern of unusually large von Willebrand factor multimers and assay of von Willebrand factor-cleaving protease, may clarify the pathogenesis of postoperative TTP.

Unlike other acute PDIS, these TTP-associated ones have occurred bilaterally, often in all the digits simultaneously. Peripheral digit ischemic syndrome caused by detached thrombi from atherosclerotic plaques is usually unilateral. It is also unlikely to occur simultaneously in the digits of both fingers and toes. Peripheral digit ischemic syndrome in heparin-induced thrombocytopenia and thrombosis syndrome (HITTS) can be similar to that of TTP, but this condition is often associated with both venous and arterial thromboli and involves large vessels. Peripheral digit ischemic syndrome due to DIC can be identical to that of TTP, and additionally, this condition may be associated with MAHA and thrombocytopenia. The diagnosis of DIC can usually be differentiated from TTP if hypofibrinogenemia and fibrin degradation products as well as prolonged prothrombin and activated partial thromboplastin times are present. However, the differential diagnosis can be complicated if the patient with TTP develops hepatic failure due to progression to multiorgan dysfunction, in which case hypofibrinogenemia, prolonged prothrombin time, and activated partial thromboplastin time may occur. The assay of appropriate coagulation factors, especially factor VIII and liver-dependent factors, may help in differentiating between coagulopathy due to hepatic failure caused by TTP and that of DIC.

With our experience, it should be noted that acute PDIS can rarely be one of the manifestations of TTP. Once it occurs, a serious consequence may follow since PDIS may portend the development of multiorgan dysfunction and TTP in this setting tends to be more life-threatening than in classical TTP. The demise of the patient may occur due to delayed diagnosis, and even if the patient survives postoperative TTP, the loss of multiple digits is likely to occur as a result of irreversible ischemic changes. It is prudent to evaluate all the patients with postoperative thrombocytopenia for its etiology (14). Also, the early sign of PDIS and coexisting thrombocytopenia should alert the clinician the possibility of TTP.

In a patient with PDIS, a high index of suspicion for TTP is critical in recognizing the diagnosis early. As soon as the diagnosis of TTP is established or is strongly suspected on the basis of thrombocytopenia and MAHA, plasma exchange should be initiated since this is the most efficacious therapy (33). Amputation of the digits cannot be avoided once advanced ischemic changes have already taken place.

REFERENCES


