Pulmonary Thromboembolism Associated With Klippel-Trenaunay Syndrome

Erin E. Huiras, MD*; Cheryl J. Barnes, MD‡; Lawrence F. Eichenfield, MD§; Andrew N. Pelech, MD§; and Beth A. Drolet, MD*

ABSTRACT. Klippel-Trenaunay syndrome (KTS) is a rare congenital anomaly characterized by unilateral limb overgrowth, venous varicocities, and capillary malformations (port wine stains) of the affected limb or limbs. Large venous malformations such as those observed in KTS are rare, and many physicians are unfamiliar with the potential complications, which include hypercoagulability, thrombosis, and pulmonary embolism (PE). As a result, patients may suffer from delayed diagnosis of a potentially life-threatening thromboembolic event. We present 2 cases of children with KTS complicated by PE, and we review the English-language literature regarding pathophysiologic features, interventions, and outcomes of PE in the setting of KTS among both pediatric and adult patients, with emphasis on issues relevant to pediatricians. Pediatrics 2005;116:e596-e600. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-1607; Klippel-Trenaunay syndrome, Proteus syndrome, venous malformation, hypercoagulable state, deep venous thrombosis, pulmonary embolism, Kasabach-Merritt syndrome.

I

n 1900, French physicians Klippel and Trenaunay described a patient with massive hemihypertrophy of the lower extremity associated with a large, confluent, red-blue plaque and venous varicosities.1 The term Klippel-Trenaunay syndrome (KTS) has since been used to describe rare, congenital, vascular malformations identified by the classic clinical triad of venous varicosities, ipsilateral cutaneous capillary malformations, and bony/soft-tissue overgrowth of the affected limb or limbs. As our understanding of vascular lesions evolves, it is clear that the constellation of findings reported by Klippel and Trenaunay represents complex, mixed, vascular malformations, often with venous, capillary, and lymphatic components, with various clinical consequences, including hypercoagulability and the complications that ensue. We describe 2 children with KTS of the lower extremity who suffered from pulmonary embolism (PE).

CASE REPORTS

Patient 1

A 14-year-old boy with a combined capillary-venous-lymphatic malformation of the right lower extremity who had been diagnosed as having KTS at birth presented to an outside institution after 2 episodes of syncope. During these episodes, he was unresponsive for several minutes and was observed to have circulatory cyanosis and tonic posturing. Two weeks earlier, the child had been treated for cellulitis, with fever, pain, and warmth of his affected extremity; blood cultures were positive for Staphylococcus aureus, and the patient was treated with a course of orally administered cephalaxin. After the second episode of syncope, the patient was transferred to Children’s Hospital of Wisconsin (Milwaukee, WI) for evaluation.

In the physical examination, the child was pale and lethargic, with a heart rate of 119 beats per minute, a respiratory rate of 28 breaths per minute, and oxygen saturation ranging from 93% to 97% with room air. A cardiac examination revealed a new grade II/VI systolic murmur. The lungs were clear. The right lower extremity was enlarged, with 2+ edema at the ankle to mid-shin level, which was its usual size, according to the boy’s family. There was an extensive red-purple patch extending from the right buttock to the lateral ankle (Fig 1). There were hundreds of red-black, 2- to 10-mm papules and vesicles throughout this patch, many of which were crusted. There was mild tenderness in the right popliteal region, but no cord was palpated. There was no warmth or erythema suggesting active infection. The rest of the physical examination results were unremarkable.

A full neurologic evaluation was performed and did not reveal any neurologic deficits. Electroencephalography showed no evidence of seizure activity. The following day, the patient’s clinical condition worsened and the patient was transferred to the PICU. At that time, he was noted to have a prominent right ventricular tap and a palpable single S2 segment. Two-dimensional echocardiography demonstrated a severely dilated right ventricle, left ventricular hypertrophy, and mild tricuspid and pulmonary insufficiency, predicting increased pulmonary artery pressures. Peak pulmonary systolic pressures were estimated to be 65 to 70 mm Hg. With these findings, the “seizures” were suspected to be actually convulsive syncope resulting from low cardiac output attributable to pulmonary hypertension. Doppler ultrasonography revealed acute deep venous thrombosis (DVT) of the right popliteal vein and chronic recanalized thrombosis of the right superficial femoral vein. Computed tomographic scans of the chest yielded negative results, but ventilation-perfusion scanning showed patchy perfusion defects bilaterally, suggesting multiple microemboli. The patient was treated with enoxaparin. Repeat

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echocardiography performed 1 week later showed normalization of pulmonary artery pressures, and the patient was discharged. A hypercoagulability evaluation was performed on an outpatient basis, during warfarin and enoxaparin therapy. The prothrombin time was 15.6 seconds (normal: 11.0–13.3 seconds), the D-dimer level was 0.8 to 1.6 mg/L (normal: <0.20 mg/L), the fibrinogen level was 322 mg/dL (normal: 200–400 mg/dL), and the platelet count was 376 platelets per mm³ (normal: 150–350 platelets per mm³). Anti-thrombin III, protein C and S, factor V Leiden, and anti-cardiolipin antibody levels were all within normal ranges.

Since the original hospitalization, the child has been admitted twice because of recurrent DVT of the affected leg, despite anticoagulation therapy with warfarin, enoxaparin, and clopidogrel, with the international normalized ratio and partial thromboplastin time being consistently within the therapeutic ranges for DVT. The patient continues to wear compression hose. There has been no evidence of recurrent pulmonary hypertension or PE.

Patient 2

An 11-year-old boy presented at birth with port wine stains involving the left lower abdomen and buttock and the left upper anterior thigh and knee. He had left hemihypertrophy and was noted to have associated cutaneous vascular blebs of the left leg (Figs 2 and 3). MRI scans of the left leg revealed a complex capillary-venous-lymphatic malformation, and the patient had the diagnosis of KTS. Other medical problems included high-functioning autism and obesity.

The patient underwent 5 treatments of his port wine stains with a pulsed-dye laser, which did produce considerable lightening. There was no history of cellulitis, pain, or thrombosis of the left leg. The patient wore compression hose on his affected leg routinely.

The child was in his usual state of health until he was found unresponsive on the floor near his bed one morning. Paramedics were summoned to the scene and, despite resuscitation efforts, the patient was pronounced dead. An autopsy revealed the cause of death to be massive, acute, pulmonary thromboembolism resulting from acute left leg thrombosis. The family stated that the child had been asymptomatic, without recent complaints, pain, or clinical changes in his vascular malformation.

DISCUSSION

The association between extensive venous malformations and hypercoagulability is well established.²⁻⁸ Hematologic evidence of low-grade consumptive coagulopathy has been documented repeatedly for patients with large venous malformations.⁴⁻⁶ Mason et al,⁴ Mazoyer et al,⁵ and Enjolras et al⁶ studied coagulation parameters among patients with large venous malformations and recognized that many patients had hematologic evidence of coagulopathy, defined by elevated D-dimer and soluble fibrin complex levels, decreased fibrinogen levels, and elevated prothrombin times, with normal to moderately low platelet counts. The magnitude of the coagulopathy correlated with the severity of the malformation.⁵ There are no case reports in the liter-
### TABLE 1. Patient Profiles, Interventions, and Outcomes

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Authors</th>
<th>Syndrome</th>
<th>Age</th>
<th>Affected Limb</th>
<th>Presenting Symptoms</th>
<th>Doppler Scan Results</th>
<th>VQ Scan Results</th>
<th>Other Diagnostic Studies</th>
<th>Laboratory Results</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CHW (patient 1)</td>
<td>KTS</td>
<td>14 y</td>
<td>R leg</td>
<td>Syncope</td>
<td>Positive</td>
<td>Positive</td>
<td>Echo: RV hypertrophy; cath: PHTN; chest CT: negative</td>
<td>Hypercoagulability panel normal</td>
<td>LMWH, Coumadin</td>
<td>Survival, recurrent DVT</td>
</tr>
<tr>
<td>2</td>
<td>UCSD (patient 2)</td>
<td>KTS</td>
<td>11 y</td>
<td>L leg</td>
<td>Acute cardiopulmonary arrest</td>
<td>Negative</td>
<td>Low probability</td>
<td>PA: positive PE; cath: PHTN; contrast venography-MR venography: positive</td>
<td>Coumadin, IVC filter</td>
<td>Survival</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Mulik et al</td>
<td>KTS</td>
<td>32 y</td>
<td>L leg and arm</td>
<td>Progressive dyspnea</td>
<td>Negative</td>
<td>Positive</td>
<td>Chest CT: pulmonary artery enlargement; autopsy: multiple PE</td>
<td>Coumadin/heparin, pulmonary endarterectomy</td>
<td>Death after recurrent PE</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Mikula et al</td>
<td>KTS</td>
<td>53 y</td>
<td>R arm</td>
<td>Progressive dyspnea</td>
<td>Negative</td>
<td>Positive</td>
<td>Echo: RV hypertrophy</td>
<td>Coumadin</td>
<td>Survival</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Gianlupi et al</td>
<td>KTS</td>
<td>48 y</td>
<td>Bilateral legs, R &gt; L</td>
<td>Progressive dyspnea, leg edema, jugular venous distension</td>
<td>Negative</td>
<td>Positive</td>
<td>Chest CT: pulmonary artery enlargement; autopsy: multiple PE</td>
<td>Coumadin</td>
<td>Survival</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Macleod et al</td>
<td>KTS</td>
<td>63 y</td>
<td>L arm</td>
<td>Dyspnea, pain/swelling of arm</td>
<td>Positive</td>
<td>Positive</td>
<td>Echo: RV hypertrophy</td>
<td>Coumadin</td>
<td>Survival</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Slavotinek et al</td>
<td>PS</td>
<td>25 y</td>
<td>Bilateral lower extremities</td>
<td>Acute cardiopulmonary arrest</td>
<td>Positive</td>
<td></td>
<td></td>
<td>Normal protein C/S and anticardiolipin Ab levels</td>
<td>Coumadin</td>
<td>Death after recurrent PE</td>
</tr>
<tr>
<td>8</td>
<td>Slavotinek et al</td>
<td>PS</td>
<td>9 y</td>
<td>Multiple venous malformations</td>
<td>Acute cardiopulmonary arrest</td>
<td>Positive</td>
<td></td>
<td></td>
<td>Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Slavotinek et al</td>
<td>PS</td>
<td>18 y</td>
<td>L leg</td>
<td>Acute cardiopulmonary arrest</td>
<td>Positive</td>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Macin and Kent</td>
<td>Isolated congenital capillary/venous malformation</td>
<td>4 wk</td>
<td>L knee</td>
<td>Acute cardiopulmonary arrest</td>
<td>Positive</td>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Walker et al</td>
<td>KTS/PWS</td>
<td>24 y</td>
<td>L leg, R foot</td>
<td>Dyspnea, syncope</td>
<td>Negative</td>
<td>Positive</td>
<td>Echo: RV hypertrophy; cath: PHTN</td>
<td>Coumadin/heparin, pulmonary thrombectomy</td>
<td>Survival, recurrent PE</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Awad et al</td>
<td>KTS</td>
<td>21 y</td>
<td>Chest pain, dyspnea</td>
<td>Positive</td>
<td></td>
<td></td>
<td>Venography, PA/pulmonary angiography, RTBA</td>
<td>Infrarenal and suprarenal IVC filters</td>
<td>Survival, recurrent PE</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Skovbye et al</td>
<td>PS</td>
<td>10 y</td>
<td>Postoperative cardiopulmonary arrest</td>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
<td>Survival, recurrent PE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Eberhard</td>
<td>PS</td>
<td>2 y</td>
<td>Bilateral lower extremities</td>
<td>Postoperative cardiopulmonary arrest</td>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
<td>Death</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Aggarwal et al</td>
<td>KTS</td>
<td>45 y</td>
<td>L leg</td>
<td>Chest pain, diaphoresis, palpitations</td>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
<td>Heparin/Coumadin</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Stone et al</td>
<td>KTS</td>
<td>27 y</td>
<td>L leg</td>
<td>Not described</td>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
<td>Death after recurrent PE</td>
<td></td>
</tr>
</tbody>
</table>

CHW indicates Children’s Hospital of Wisconsin; UCSD, University of California, San Diego; PS, Proteus syndrome; PWS, Parkes-Weber syndrome; R, right; L, left; echo, echocardiography; VQ, ventilation-perfusion; RV, right ventricle; RA, right atrium; PHTN, pulmonary hypertension; PA, pulmonary angiography; cath, cardiac catheterization; CT, computed tomography; MR, magnetic resonance; RTBA, radionucleotide total-body angiography; ECG, electrocardiography; Ab, antibody; AT, angiotensin; LMWH, low-molecular weight heparin.
nature of PE occurring for a patient with an isolated venous malformation. Patients with KTS, however, are known to be at significantly increased risk for PE. The implication is that patients with larger, more complex, mixed, vascular malformations, such as those seen in KTS, are at higher risk for thromboembolic events than are those with less extensive, isolated, venous malformations.

Proteus syndrome, another congenital syndrome associated with large vascular anomalies, also demonstrates hypercoagulability and its complications. A disorder of asymmetric and progressive overgrowth associated with hamartomas and malformations of multiple soft tissues, Proteus syndrome was first described by Wiedemann in 1983. Large complex vascular malformations are a common feature, and several reports have described PE as a complication of this syndrome.

PE has been described in case reports of 8 adult patients with KTS, ranging in age from 21 to 63 years (Table 1). Although no case reports of PE among children with KTS exist in the English-language literature, there are 5 prior reports documenting children (age range: 4 weeks to 18 years) with Proteus syndrome and/or undiagnosed complex vascular malformations complicated by PE; 4 conditions were fatal (Table 1). All 5 patients experienced cardiopulmonary arrests, 2 of which occurred postoperatively. PE is a rare occurrence among healthy children. Therefore, it is imperative to recognize that this phenomenon occurs more frequently among pediatric patients with KTS and Proteus syndrome. It is particularly critical to anticipate this potential complication in situations when even healthy children are at risk for hypercoagulability, such as surgery, trauma, neoplasm, prolonged immobility, or pregnancy.

Mazoyer et al proposed that the coagulopathy among patients with venous malformations is a result of "localized intravascular coagulation" occurring within the malformations. This theory is supported by the observation that blood extracted directly from a venous malformation has greater depletion of coagulation factors, compared with blood drawn from a peripheral site of the same patient. Although the mechanism leading to hypercoagulability has yet to be proven, stagnation of blood in abnormal vascular channels, followed by activation of the coagulation cascade, is presumed to be responsible and was suggested by low-flow Doppler signals and spontaneous contrast echocardiographic results ("rouleaux" formation) for patient 1 of this report. Rarely, localized intravascular coagulation may progress to disseminated intravascular coagulation, especially under acute conditions (eg, sclerotherapy of the venous malformation, surgery, bone fracture, or menstruation). By definition, patients with disseminated intravascular coagulation exhibit both thrombosis and hemorrhage.

It should be emphasized that primarily coagulation factors, not platelets, are depleted among patients with thrombosis and bleeding attributable to large venous malformations. This is in contrast to the Kasabach-Merritt phenomenon, in which bleeding is secondary to profound thrombocytopenia attributable to platelet trapping in an aggressive vascular neoplasm of neonates, usually a tufted angioma or kaposiform hemangioendothelioma. These tumors are mitotically active and highly proliferative, whereas the vascular malformations of KTS and Proteus syndrome do not exhibit rapid cell division. The term Kasabach-Merritt syndrome is often incorrectly used to describe the phenomenon of localized or disseminated intravascular coagulation among patients with venous malformations such as KTS. Kasabach-Merritt syndrome is an entirely separate entity from KTS and other venous malformation syndromes. The young age of the patients (usually <1 year), alarming proliferation of the tumors, and severe thrombocytopenia differentiate Kasabach-Merritt syndrome from coagulopathies associated with vascular malformations. This distinction is of clinical importance, because treatment of the coagulopathy and thrombocytopenia observed in Kasabach-Merritt syndrome is different from treatment of localized intravascular coagulation in KTS and other vascular malformations. The first-line therapy for Kasabach-Merritt syndrome is antiproliferative agents, such as corticosteroids, cytotoxic agents, and immunomodulators (such as interferon-α). These treatments are theoretically ineffective against local or disseminated intravascular coagulation observed among patients with KTS.

There is an apparent trend of failure of conventional anticoagulation therapy (unfractionated heparin and vitamin K antagonists) for thromboembolic complications of KTS and Proteus syndrome. Coumadin and heparin were used to treat most of the patients reported in the literature who survived their initial events (Table 1); however, 8 of 10 patients experienced recurrent episodes of DVT and/or PE, 4 of which were fatal. As reported by Mazoyer et al, thrombosis, bleeding, and pain resulting from localized or disseminated intravascular coagulation in an isolated venous malformation should be treated with low-molecular weight heparin therapy (rather than conventional unfractionated heparin and vitamin K antagonists) and elastic compression. Those authors also reported that, in their experience, vitamin K antagonists and antiplatelet therapy were not successful and lower-molecular weight heparins were more effective than unfractionated heparin.

In several reports, inferior vena cava (IVC) filter placement was also attempted. This treatment also seems to have a high failure rate for patients with KTS. Two of 3 patients with infrarenal IVC filters experienced recurrent PEs with filters in place (Table 1); a fourth developed IVC thrombosis proximal to the site of the filter. Awad et al were able to show with radionucleotide total-body angiography that failure in that case was attributable to an anomalous venous connection between the lower extremities and the IVC, effectively bypassing the filter. The venous malformations of KTS frequently extend proximal to the leg veins and may include the iliac veins and the IVC, often bypassing the site where an IVC filter is placed. Therefore, it seems reasonable...
to propose evaluation of anomalous veins for these patients before deciding on placement of an IVC filter when it is clinically indicated (ie, in cases of recurrent emboli with therapeutic anticoagulation, contraindications to anticoagulation, or complications of anticoagulation). Currently magnetic resonance venography is the preferred method for imaging these abnormalities.

CONCLUSIONS

PE is rare in the pediatric population.24 Pediatricians caring for patients with KTS, patients with Proteus syndrome, and other patients with extensive venous or mixed vascular malformations should maintain a high index of suspicion for this potentially life-threatening complication, especially when patients are undergoing surgery, are pregnant, or have suffered trauma or neoplasm. If DVT or PE is diagnosed, then these patients should receive therapy with elastic compression and low-molecular weight heparin and, when it is clinically indicated, should undergo evaluation for anomalous venous connections with magnetic resonance venography, for IVC filter placement.

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