Clinical Spectrum of Tufted Angiomas in Childhood

A Report of 13 Cases and a Review of the Literature

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Background: Tufted angiomia (TA) is a rare benign vascular tumor that mostly appears during infancy or early childhood. Histologic tufts of capillaries infiltrating the whole dermis in a “cannonball” distribution pattern associated with dilated lymphatic vessels are characteristic of the disease and confirm the diagnosis. Few case series of TA have been published, and the morphologic structure and evolution of TA seem to vary.

Observations: We describe the largest series to date of childhood TA, comprising 13 cases. All children developed lesions within the first year of life; 7 cases were congenital. We found a clear male predominance (9 of 13 children). Presentation was a nascent or florid tumor, usually a dusky red to violaceous plaque, that was indurated, firm, and sometimes associated with hyperhidrosis or hypertrichosis. Locations of the lesions included limbs, abdomen, and genitalia. Five children had spontaneous regression, 5 children had Kasabach-Merritt syndrome, and 1 child had a lesion that stabilized. Two children with painful TA had chronic coagulopathy without thrombocytopenia that was controlled by ticlopidine hydrochloride and aspirin.

Conclusions: The following 3 clinical patterns could be distinguished: TA without complications, TA complicated by Kasabach-Merritt syndrome, and TA without thrombocytopenia but with chronic coagulopathy. To our knowledge, this study is the first to describe the third pattern. Because of the aggressive nature of Kasabach-Merritt syndrome, it is essential to obtain a complete blood cell count when evaluating a child with TA.

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UFITED ANGIOIMA (TA) IS A rare vascular tumor characterized histologically by small tufts of capillaries associated with dilated lymphatic vessels in the dermis. First reported in 1949 by Nakagawa1 as angio-blomastoma and then described in 1971 by MacMillan and Champion2 as progressive capillary hemangiomia, these vascular tumors were finally called TA by Jones3 in 1976 after 10 cases of similar lesions with characteristic histologic findings were reported. Tufted angiomia may be congenital or acquired and most often manifests during infancy or early childhood, but a few cases have been described in adults. Most frequently, lesions are initially seen as solitary tumors or infiltrating plaques that are dusky red or violaceous, sometimes associated with hyperhidrosis or hypertrichosis.4,5 Evolution of the disease seems to vary considerably, including complete or partial spontaneous regression, persistence over the years, or Kasabach-Merritt syndrome (KMS).5,9,10 Because the morphologic structure and evolution vary and because TA case series are lacking in the literature, we describe herein 13 children followed up for TA at our hospital for a mean of 7.5 years.

METHODS

We reviewed all cases of histologically diagnosed TA at Hôpital Necker–Enfants Malades, Paris, France, from January 1, 1988, to December 31, 2007. Tufted angiomia was histologically defined as multiple small hypercellular nodules of capillaries with small lumina distributed in a “cannonball” pattern infiltrating the reticular dermis and sometimes the superficial subcutis. These lobules were lined by a crescent-shaped vessel, and there were some dilated lymphatic vessels scattered in a dense background. The lobules contained globular, epithelioid, or spindle-shaped cells. They were often separated by slitlike spaces containing red blood cells. There were no inflammatory cells. The large scattered vessels and some (but not all) crescent-shaped vessels stained positive for podoplanin (D240 antibody), a lymphatic marker. Some spindle-shaped or epithelioid lobular cells also stained positive, providing evidence of partial lymphatic differentiation.

We excluded children who were unavailable for follow-up. Data collected included sex, age at biopsy, age at onset of TA, initial location and morphologic structure of lesions, presence or absence of KMS, results of biologic and imaging studies (when available), treatment and outcome, associated diseases, and early and late photographs. We defined spontaneous regression as the clinical absence of superficial or deep infiltration. Nevertheless, minimal skin changes...
such as pigmentation could persist. Kasabach-Merritt syndrome is characterized by a vascular tumor and thrombocytopenic coagulopathy (platelet count of <150 × 10^9/L), often associated with other coagulation abnormalities (low fibrinogen level of <200 mg/dL, high D-dimer level of >4 µg/mL, and increased fibrin degradation products) (to convert platelet count to ×10^9/L, multiply by 1.0; fibrinogen to micromoles per liter, multiply by 103/µL), often as-

#### RESULTS

Thirteen children with TA were identified during the study period (Table 1). There were 4 girls (31%) and 9 boys (69%). The mean follow-up was 7.5 years (range, 2-19 years). No family histories of a similar illness were found.

#### PRESENTATION

At birth, nascent or florid tumors were present that were typically poorly defined infiltrating, firm, dusky red to violaceous plaques. Other characteristic features included nodularity, hyperhidrosis, or hypertrichosis. No congenital tumors had been diagnosed in utero by ultrasonography. For noncongenital TA, the clinical presentation was similar. All TAs were painless initially. Because of infiltration, the initial size was difficult to measure but varied from 4 × 1 to 11 × 10 cm in our series.

#### EVOLUTION

We were able to distinguish the following 3 clinical patterns: TA without complications, TA complicated by KMS, and TA without thrombocytopenia but with chronic coagulopathy.

The first clinical pattern of TA was represented by 6 children (46%), among whom no complications occurred. The outcome of these 6 TAs was favorable, with spontaneous regression in 5 children and stabilization in 1 child. The mean follow-up period after regression was 3 years (range, 1-6 years). In patient 1, TA appeared at the age of 5 months on her abdomen. No complications were observed, and the tumor remained the same size, 19 cm. Patient 3 had congenital TA as a 4 × 2-cm violaceous firm tumor over her abdomen. No complications were observed, and the size of the lesion decreased. At age 2 years, complete resolution of TA occurred spontaneously. Physical examination of patient 6 revealed a 6 × 6-cm congenital indurated blue-purple
plaque on the right cheek. The mass was neither warm nor painful. Results of biologic studies were normal except for an elevated D-dimer level (1.9 µg/mL). The lesion spontaneously became less tender after 6 months, with changes in discoloration, and then decreased in size. Findings on physical examination have been normal since age 3 years.

Patient 7 was seen at birth with a prominent erythematous indurated plaque on the abdomen, genitalia, and right thigh. The lesion was tender on palpation, and the range of movement in the right leg was affected. The platelet count was normal. Magnetic resonance imaging showed a large infiltrating vascular mass, and a biopsy specimen confirmed the diagnosis of TA. The tumor spontaneously and rapidly became less tender and decreased in size. At age 5 years, findings on physical examination were normal except for slightly pink-stained skin with minimal cutaneous atrophy. In patient 13, a 3.5 × 1.5-cm blue nodular plaque appeared on the back at age 1 month. It gradually became less infiltrating, with residual skin changes at age 2 years.

The second most frequent clinical pattern was TA complicated by KMS, which was diagnosed in 5 children (38%). Coagulopathy developed before age 8 months in all of them. The youngest age at which KMS was diagnosed was 1 month. No KMS was diagnosed at birth. Three of 5 children with KMS had congenital TA. Clinically, all children with KMS had an expanding, indurated, tender, and painful inflammatory mass (Figure 1). Results of biologic studies revealed profound thrombocytopenia, low fibrinogen level, and high D-dimer level. Histologic examination was performed before the onset of coagulopathy in patient 9 and during the coagulopathy phase in 3 children. A biopsy specimen was obtained from patient 12 several years after the diagnosis of KMS because of pain and venous dilatation on an area of residual hyperpigmented and infiltrated skin. Kasabach-Merritt syndrome was treated by combination therapy in all children except 1, who was cured by corticosteroid therapy alone. All others received 2 to 7 types of therapy that are reported to be effective in KMS. The treatments led to favorable outcomes. A residual lesion was observed in all 5 children, including minimal skin color changes in 2, associated subcutaneous atrophy in 1, and sequelae in muscles and joints in 2. The mean follow-up period after resolution of KMS was 7 years.

Two children (15%) demonstrated the third clinical pattern (TA without thrombocytopenia but with chronic coagulopathy). Both had a vascular tumor that became inflammatory (with warmth, erythema, and edema), painful, and indurated and was associated with fluctuating coagulopathy (fibrinogen level of < 100 mg/dL, D-dimer level of > 4 µg/mL, and increased fibrin degradation products) and a normal platelet count. Patient 4 had a congenital abdominal infiltrating mass that was diagnosed as TA at age 1½ years. This quiescent tumor became inflammatory and painful at age 2 years, with biologic coagulopathy (D-dimer level of 4 µg/mL and fibrinogen level of 100 mg/dL) but without thrombocytopenia (Figure 2). He was treated with a combined daily regimen of ticlopidine hydrochloride and aspirin (each 10 mg/kg of body weight); induration and pain regressed, but coagulopathy persisted. After aspirin was stopped, the tumor again became inflammatory and painful, and coagulopathy worsened. Aspirin therapy was started again, in combination with ticlopidine. Between ages 2 to 8 years, combined treatment with aspirin and ticlopidine stabilized the clinical aspects of TA, but biologic coagulopathy remained. Each time treatment was withdrawn, pain and inflammation recurred. Pa-
tient 8 was seen at age 2 months with a vascular tumor on the thigh. Histologic examination was performed at age 3 months because of local inflammation, pain, and hyperhidrosis. Results of biologic studies were normal. He was treated with corticosteroids because of functional compromise, and clinical signs improved. When corticosteroids were reduced, inflammation reappeared and was associated with coagulopathy but a normal platelet count. Magnetic resonance imaging showed a large infiltrating mass encompassing the right thigh circumferentially, not extending to the bone or muscle. A combined regimen of ticlopidine and aspirin led to clinical improvement, but coagulopathy remained for 6 years with bouts of pain, especially when treatment was suspended. Sequelae in the leg muscles and joints caused impaired mobility.

**COMMENT**

Since the initial 1989 study by Jones and Orkin, few case series of TA have been reported, and the largest of these included 5 children. Our series of 13 children illustrates several clinical patterns of presentation and evolutions of this rare vascular tumor. Because of the clinical variability in TA, histologic examination is required for diagnosis. Histologic findings were well described in the series by Jones and Orkin as tightly packed vessels scattered at various levels in the dermis and in the superficial subcutis, generally occurring in small tufts with a cannonball distribution pattern. Typically, the tufts are encircled by an empty crescent-shaped vessel and are surrounded by a fibrous dermis. Besides these small lobules, most lesions contain scattered larger vessels within the wall and empty lumen resembling lymphatic vessels. The vascular tufts seem to be composed of epithelioid and spindle-shaped endothelial cells closely packed together and separated by clefts containing red blood cells in a kaposisform manner. Some hyalin globules can be seen as well (Figure 3). Histopathologic examination with immunohistochemistry is necessary to exclude other lesions such as hemangioma of infancy, vascular malformations, infantile myofibromatosis, and congenital dermatofibrosarcoma protuberans.12 Immunohistochemistry is positive for
GLUT1 and is specific in 100% of infantile hemangiomas; it never stains infantile vascular tumors such as TA.13 Distinguishing TA from kaposiform hemangioendothelioma (KHE) is challenging because of morphologic and histopathologic similarities (Table 2). The histopathologic overlap is especially dramatic between TA and superficial KHE. Some authors consider these tumors to be on the same spectrum, while others believe they are the same entity and describe superficial KHE as TA.11,13-17

Previous studies4,5,8 of TA described various clinical morphologic structures, including brown, blue, purple, or red poorly delineated macules, as well as indurated nodules or plaques varying in size, sometimes with a mottled appearance or with focal hypertrichosis or hyperhidrosis (Table 3). In our series, male sex clearly predominated (9 of 13 patients), as in the series by Jones and Orkin.8 In that series, the upper trunk and neck were the most commonly reported sites for TA. In others series, TA was commonly found on the limbs.5,18,19 In our series, the upper trunk was affected in only 2 children, whereas the limbs were involved in 7, the abdomen or genitalia in 2, and the cheek in 1.

Although acquired TA has been reported in adults,18-22 TA most commonly appears in infancy and early childhood4,5,8,19. This was corroborated by a 2000 review of 41 cases, more than 50% of which manifested during the first year of life.18 In our pediatric series, all TAs were observed before age 5 months. Cases of congenital TA have been described,4,5,8,19,21-26 but their frequency is uncertain. It was estimated at 10% in 1 study19 and at 22% in a review by Igarashi et al.20 In our series, TAs were congenital in 54% (7 of 13 patients), which is higher than previously reported.

Variations in the evolution of TA have been described. Most often, TA has a slow rate of growth, typically developing and extending over several months and eventually becoming stable in size.7,8 Only 1 TA in our series stabilized in size (patient 2). Spontaneous clinical regression has also been reported.4,7,23-26 The time to regression was less than 2 years in 95% of TAs in a review of 27 spontaneous regressions.21 In our 5 cases of spontaneous regression, 3 occurred in congenital TA and 2 in newborn TA.

Tufted angioma and KHE can be complicated by KMS.9 Since the first description by Kasabach and Merritt27 in 1940, the association of a large vascular tumor and thrombocytopenia in an infant has been considered a rare complication of vascular lesions in infancy. This thrombocytopenic coagulopathy is not observed in the more common hemangioma of infancy but occurs in uncommon vascular tumors such as TA and KHE.10 The frequency of KMS in TA is uncertain. In a study11 of 41 patients with KMS, 8 skin biopsy specimens from 26 patients revealed TA. Kasabach-Merritt syndrome was diagnosed at birth or before age 5 months in 32 of 41 cases (78%) in this study. In our 13 children, 5 (38%) were initially seen with KMS. This frequency seems higher than that in the literature, which contains a few isolated case reports but no case series.11,24,28,29 Therefore, in patients with TA, it may be advisable to obtain at least a complete blood cell count, and a platelet count of less than 150 ×10^9/L should prompt a more extensive evaluation for coagulopathy.

Table 2. Key Differences Between Tufted Angioma and Superficial Kaposiform Hemangioendothelioma

<table>
<thead>
<tr>
<th>Location</th>
<th>Tufted Angioma</th>
<th>Superficial Kaposiform Hemangioendothelioma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Dermis, superficial subcutis</td>
<td>Deep dermis, deep tissues, subcutis, muscle</td>
</tr>
<tr>
<td>Pattern</td>
<td>Small scattered vessels in a fibrotic background, cannonball pattern</td>
<td>Well-delineated lobules in a less fibrotic background</td>
</tr>
<tr>
<td>Creased-shaped vessels</td>
<td>Numerous</td>
<td>Rare</td>
</tr>
<tr>
<td>Lymphatic spaces</td>
<td>Few</td>
<td>Numerous</td>
</tr>
<tr>
<td>Hemorrhage, hemosiderin deposition</td>
<td>Rare</td>
<td>Frequent</td>
</tr>
<tr>
<td>Spindle-shaped cells</td>
<td>Few, associated with round or epithelioid cells</td>
<td>Lobules mainly composed of spindle-shaped cells, with slitlike spaces containing red blood cells</td>
</tr>
</tbody>
</table>

Table 3. Comparison of the Present Series With Previously Published Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>Ratio of Girls to Boys</th>
<th>Age at Onset of TA, Mean</th>
<th>Congenital</th>
<th>Hypertrichosis</th>
<th>Hyperhidrosis</th>
<th>Location</th>
<th>Evolution</th>
<th>KMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jones and Orkin,8 1989</td>
<td>16</td>
<td>7.9</td>
<td>2 y</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>6 Neck</td>
<td>Stabilization or recurrence after treatment</td>
<td>0</td>
</tr>
<tr>
<td>Herron et al,4 2002</td>
<td>5</td>
<td>1.4</td>
<td>2 mo</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>3 Limbs</td>
<td>1 Regression</td>
<td>0</td>
</tr>
<tr>
<td>Wong and Tay,1 2002</td>
<td>5</td>
<td>2.3</td>
<td>3 mo</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>5 Limbs</td>
<td>2 Stabilization</td>
<td>0</td>
</tr>
<tr>
<td>Browning et al,6 2006</td>
<td>5</td>
<td>2.3</td>
<td>At birth</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>2 Face, 3 Limbs</td>
<td>5 Regression</td>
<td>0</td>
</tr>
<tr>
<td>Present series</td>
<td>13</td>
<td>4.9</td>
<td>1 mo</td>
<td>7</td>
<td>1</td>
<td>3</td>
<td>7 Limbs, 4 genitalia, 2 trunk, 1 face</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: KMS, Kasabach-Merritt syndrome; NA, not available; TA, tufted angioma.

Totals 14 because the limb and genitalia areas were affected in patient 11.
ies,1,4,7,21,23-26 of congenital TA have described various courses of evolution (spontaneous regression, stabilization, or KMS). In our series, evolution was similar in congenital and noncongenital TA, including 3 cases of spontaneous regression in each group, 3 cases of KMS in the congenital group and 2 in the noncongenital group, and 1 case of coagulopathy in each group. Our study describes another clinical pattern of TA evolution, chronic coagulopathy, which we observed in 2 children. This pattern is characterized by clinical flares of TA (infiltrating, inflammatory, and painful mass) associated with coagulopathy (defined by low fibrinogen level, high D-dimer level, and increased fibrin degradation products) and a normal platelet count. Despite clinical improvement in the tumor, low-grade chronic consumptive coagulation persisted. Aspirin and ticlopidine (the treatment for KMS) were used for pain coagulopathy.10,30

This regimen led to clinical improvement in these 2 children, despite fluctuating coagulopathy for several years. Bouts of pain with inflammatory signs reoccurred each time treatment was withdrawn.

The management of TA is difficult, and treatment guidelines have yet to be established. Treatment may be categorized as that administered for aesthetic reasons or as that instituted because of complications or anticipated complications such as KMS or functional compromise. Several treatment regimens for TA with or without KMS have been reported, including compression therapy, surgery, laser, topical or systemic corticosteroids, interferon, and chemotherapy.4,6,15,26 A wait-and-see policy seems appropriate because of the benign nature of this tumor and the possibility of spontaneous regression. However, careful follow-up should be implemented, especially in early childhood, to detect complications such as KMS. No malignant changes have been described to our knowledge.

In conclusion, we describe the largest series to date of TA in childhood, with a long follow-up period. Although TA is histologically a benign vascular tumor, its outcomes range from spontaneous regression to KMS with vital or functional compromise. In our series, spontaneous regression was observed more frequently than stabilization of size, which contrasts with previous findings. Moreover, procoagulant was observed more frequently than stabilization of function. In our series, spontaneous regression occurred in 2 children. This pattern is characterized by clinical flares of TA (infiltrating, inflammatory, and painful mass) associated with coagulopathy (defined by low fibrinogen level, high D-dimer level, and increased fibrin degradation products) and a normal platelet count. Despite clinical improvement in the tumor, low-grade chronic consumptive coagulation persisted. Aspirin and ticlopidine (the treatment for KMS) were used for pain coagulopathy.10,30

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