Original Article

Giant cell angioblastoma in the femur: three additional pediatric cases provide more data of its clinicopathological features

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Abstract: Objective: To study the clinical and pathological features of giant cell angioblastoma in children. Method: The clinical and pathological data of 3 pediatric cases of giant cell angioblastoma were retrieved and reviewed from the medical records in Children’s Hospital of Fudan University. Histological and immunohistochemical analysis was made. Results: There were 2 boys and 1 girls. The age was 6 years, 1 years, and 7 years respectively. The tumors were all located in the femur. The size of lesion was between 1 cm to 2 cm in maximum diameter. The main complaint included joint dysfunction, unsteady gait, and leg length discrepancy. Histologically, all the three cases showed the same morphological features: onion-skin nodules, multinucleated giant cells, and fibrocollagenous stroma. The tumor stroma could vary from the abundant fibroblasts and myxoid area to the totally collagen according to the different age. Immunohistochemically, they had the same immunoprofile. The spindle to oval mononuclear tumor cells expressed variably markers of vascular endothelium such as CD34, CD31, and Factor VIII. The multinucleated giant cells were positive for CD68. All the patients received tumor resection and two of the tumors recurred in the follow-up interval. Conclusion: Giant cell angioblastoma is a rare vascular tumor. It has a typical morphological feature and unique immunophenotype. All the data show it may be an intermediate tumor for its invasive growth pattern and repeatedly recurrence.

Keywords: Giant cell angioblastoma, bone, children, clinical, pathological study

Introduction

Giant cell angioblastoma (GCA) is a very rare vascular neoplasm first designated by Gonzalez-Crussi et al in 1991 [1]. To the best of our knowledge, only eleven cases have been reported including eight in children and three in adults [1-7]. Seven cases developed in bones and four in soft tissues. All these tumors have the same morphological features: onion-skin nodules, scattered multinucleated giant cells and fibrocollagenous stroma. CD34 and CD31 were expressed in the nodules and CD68 was positive in the giant cells on immunohistochemistry. Little atypism, rare mitosis, low ki-67 indexes, local invasive growth pattern, and indolent clinical course suggest that GCA may be an intermediate or low-grade malignant tumor. Only little knowledge of clinicopathological features about GCA was described in the World Health Organization classification of pathology and genetics of tumors of soft tissue and bone published in 2013 for its rarity. Herein we report three pediatric cases of GCA in bone.

Materials and methods

Case selection

Medical records and archival surgical pathology specimens of three cases of giant cell angioblastoma were retrieved from Children’s hospital of Fudan University with the permission of the ethics committee and they were studied using the methods outlined as follows.

Case histories

Case 1: The patient, a six-year-old girl, was admitted to our hospital for the extention dysfunction of the left knee joint for more than one
year in 2009. X-ray and CT scan showed a mass at the distal left femur with the bone destruction (Figure 1A). Lesion biopsy and removal was administered. The histopathological diagnosis was GCA. The tumor recurred in 2011 and 2014 and the girl received the operations again. She was uneventful 23 months after the latest surgery.

Case 2: The patient, an one-year-old boy, was admitted to our hospital for the dysfunction of the right knee joint, unsteady gait and leg.
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Case 3: The patient, a seven-year-old boy, first presented to our hospital for unsteady gait and leg length discrepancy for two months in 2012. X-ray, CT scan and MRI scan showed multiple bone destructions at left distal femur (Figure 1C). The whole blood assay revealed the count of red blood cells, white blood cells, platelets and hemoglobin were normal. Blood sedimentation rate was normal and the T-SPOT-TB test displayed a negative result. The patient was suspected to have tuberculosis and was given anti-tuberculosis therapy for half a year. But he

length discrepancy for two months in 2011. Radiology displayed bone destruction at distal right femur and swelling of the peripheric soft tissue in the knee joint (Figure 1B). The whole blood assay was normal. The patient was suspected to have Langerhans'cell histiocytosis and was given lesion clearance and allograft bone implantation. The histopathological analysis desmontrated the diagnosis was GCA. The tumor recurred in 2013 and the boy was administered surgery for a second time. The patient was uneventful 27 months after surgery.

Figure 2. Microscopic findings of GCA. A. The nodular arrangement and the sclerotic collagenous stroma was highlighted (× 50, case 3). B. Tumor aggregates of onion-skin arrangement with scattered multinucleated giant cells were shown (× 200, case 2). C. Focal glomeruloid structures were detected (× 400, case 3). D. The adjacent cortex of the femur was invaded (× 100, case 2). E. A lot of fibroblasts and focal loose myxoid area together with lymphoplasmacytic infiltration was also observed (× 50, case 2).
did not achieve symptomatic remission. He came to our hospital for a second time. Thorough curettage of the lesion at distal femur on the left side was performed and GCA was defined by pathology. The patient was uneventful 26 months after surgery.

**Histological and immunohistochemical analysis**

The specimens of three cases were fixed in formalin, sampled and then embedded in paraffin. Tissue sections (5 mm thick) were cut for hematoxylin and eosin and immunohistochemical stains. Immunohistochemical stains for CD34, CD31, Glut1, CD68, Factor VIII, D2-40, CD45, SMA, Vimentin, pan-cytokeratin and Ki-67 were carried out via a Multimer HRP conjugate method with an Roche Ventana BenchMark XT automated stainer and a commercial peroxidase-conjugated DAB detection kit (Ultraview Universal DAB detection kit). All the primary antibodies were ready-to-use without dilution. All immunohistochemical stains were carried out with appropriate positive and negative controls.

**Results**

**Macroscopic findings**

Grossly, the specimens were all grey and fragmented. They measured about $2 \times 2 \times 1$ cm, $1 \times 0.8 \times 0.6$ cm, and $2 \times 1.5 \times 1$ cm respectively.

**Histopathological findings**

Microscopically, the tumors were composed of spindle to oval mononuclear cells and scattered multinucleated giant cells. They formed a nodular structure and were separated by the fibrocollagenous stroma (Figure 2A). The majority of the tumor cells had large oval nuclei and unclear cell borders and some of them formed numerous small vascular lumens in which red...
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## Table 1. Clinicopathologic features of GCA

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex/Age</th>
<th>Location</th>
<th>Chief complaint</th>
<th>Maximum tumor diameter (cm)</th>
<th>Management</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Gonzalez-Crussi et al [1]</td>
<td>F/3 months</td>
<td>Right forearm</td>
<td>Mass</td>
<td>8.5</td>
<td>Amputation</td>
<td>Uneventful</td>
</tr>
<tr>
<td>2 Vargas et al and Marler et al [2, 3]</td>
<td>M/7 months</td>
<td>Central palate</td>
<td>Pain</td>
<td>1.5</td>
<td>Partial excision and IFN α for 4 years</td>
<td>NTP for nearly 5 years</td>
</tr>
<tr>
<td>3 Vargas et al and Marler et al [2, 3]</td>
<td>M/7 weeks</td>
<td>Right hypothenar eminence</td>
<td>Mass and pain</td>
<td>3.3</td>
<td>Subtotal resection and IFN α for 1 year</td>
<td>NTP for 29 months</td>
</tr>
<tr>
<td>4 Vargas et al [2]</td>
<td>F/25 days</td>
<td>Scalp</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Mao et al [4]</td>
<td>M/15 months</td>
<td>Left tibia</td>
<td>Leg length discrepancy and pain</td>
<td>0.8*</td>
<td>Resection</td>
<td>UA</td>
</tr>
<tr>
<td>6 Mao et al [5]</td>
<td>M/4 years</td>
<td>Right thighbone</td>
<td>Unsteady standing</td>
<td>3</td>
<td>Thorough curettage</td>
<td>Recurrent 17 months after surgery</td>
</tr>
<tr>
<td>7 Crivelli-Ochsner et al [6]</td>
<td>M/41 years</td>
<td>Popliteal fossa</td>
<td></td>
<td>2.4</td>
<td>Radical resection</td>
<td>AWRM for 16 months</td>
</tr>
<tr>
<td>8 Yu et al [7]</td>
<td>M/23 months</td>
<td>Right proximal femur</td>
<td>Claudication</td>
<td>2.0</td>
<td>Thorough curettage</td>
<td>AWRM for 2 months</td>
</tr>
<tr>
<td>9 Yu et al [7]</td>
<td>M/8 years</td>
<td>Left distal femur</td>
<td>Pain and limitation of mobility</td>
<td>2.0*</td>
<td>Focal cleaning</td>
<td>AWRM for 10 months</td>
</tr>
<tr>
<td>10 Yu et al [7]</td>
<td>F/37 years</td>
<td>Lumbar vertebra</td>
<td>Backache</td>
<td>2.0*</td>
<td>Focal cleaning</td>
<td>AWRM for 21 months</td>
</tr>
<tr>
<td>11 Yu et al [7]</td>
<td>F/56 years</td>
<td>Left metacarpus and phalange</td>
<td>Swelling, pain and numbness</td>
<td>3.0*</td>
<td>Focal clearance</td>
<td>Alive with disease for 9 months</td>
</tr>
<tr>
<td>12 our case 1</td>
<td>F/6 years</td>
<td>Left distal femur</td>
<td>Joint dysfunction</td>
<td>2.0</td>
<td>Lesion clearance</td>
<td>Recurrent in 2011 and 2014 and uneventful for 23 months after the latest surgery</td>
</tr>
<tr>
<td>13 our case 2</td>
<td>M/1 years</td>
<td>Right distal femur</td>
<td>Joint dysfunction, unsteady gait and leg length discrepancy</td>
<td>1.0</td>
<td>Lesion clearance and allograft bone implantation</td>
<td>Recurrent in 2013 and uneventful for 27 months after the latest surgery</td>
</tr>
<tr>
<td>14 our case 3</td>
<td>M/7 years</td>
<td>Left distal femur</td>
<td>Unsteady gait and leg length discrepancy</td>
<td>2.0</td>
<td>Thorough curettage</td>
<td>AWRM for 26 months</td>
</tr>
</tbody>
</table>

f, female; M, male; Cm, centimeters; AWRM, alive without recurrences and metastases; IFN α, interferon α; UA, unavailable; #, The maximum diameter of the partial resection specimen or biopsy specimen; NTP, no tumor progression.
blood cells could be seen. They aggregated in onion-skin nodules which were demarcated from each other by the spindle tumor cells (Figure 2B). Multinucleated giant cells were dispersed in the nodules (Figure 2B). Some of the nodules looked like the glomeruloid structures (Figure 2C). Hemosiderin deposition was displayed in the peripheral area of the nodules and the mesenchymal stroma. Nuclear atypia, mitotic figures, necrosis and calcification were not seen in the tumors. The tumors invaded the adjacent cortex of the femurs (Figure 2D). Several thick-wall arteries were founded in the stroma (Figure 2A). The volume of the collagen and fibroblasts in the stroma of the 3 cases was variable. Compared with the left two cases, case 2 had more fibroblasts and less collagen (Figure 2E). Focal loose myxoid area together with lymphoplasmacytic infiltration was also seen in the stroma of case 2 which was hardly seen in case 1 and case 3 (Figure 2E).

Immunohistochemical findings

Immunohistochemically, the spindle to oval mononuclear tumor cells were positive for CD34, CD31, Factor VIII and Vimentin variably, but negative for Glut1 (Figure 3A and 3B). The multinucleated giant cells were positive for CD68 (Figure 3C). All the tumor cells were negative for cytokeratin and SMA (Figure 3D). The proliferation index Ki-67 of the three tumors was estimated at 6%-7%. The tumor cells were negative for PAS stain and had absent reticular fibers for reticulin stain to some extent.

Discussion

Vascular tumors are very common in children with a predominance of hemangioma and kaposiform hemangioendothelioma. Most of them are located in the soft tissue or internal organs. Vascular tumors in the bones are rare. Giant cell angiofibroma is a distinct vascular entity and Gonzalez-Crussi et al described the first case in 1991 [1]. The cases reported between 1991 and 2012 were all children so some experts supposed that it was a unique tumor just in children until Crivelli-Ochsner et al presented the first adult case in 2013. Only 14 cases including our three cases (10 cases in the bones vs 4 cases in the soft tissue) have been reported in the literature. The clinicopathologic features of all the cases were summarized in Table 1. Male had the predominance (M:F=9:5). The age interval was between 25 days and 56 years. There were 11 children and 3 adults. 7 of the 11 pediatric cases were infants suggesting that giant cell angiofibroma may be a congenital disease. The location of the tumors included femur (6 cases), tibia (1 case), vertebra (1 case), metacarpus and phalange (1 case), forearm (1 case), palate (1 case), hypothenar eminence (1 case), scalp (1 case) and popliteal fossa (1 case). The most common complaint included a swelling mass, pain and dysfunction. The tumors were 1.0-8.5 cm in maximum diameter excluding 5 unavailable cases. Grossly, the tumors were grey and solid. Histologically, all the cases showed the common morphological features: onion-skin nodules, multinucleated giant cells, and fibrocollagenous stroma. The nodules were composed of oval mononuclear tumor cells. A lot of attenuated cavities could be found around them. The spindle tumor cells demarcated the nodules and there was a transition between the oval tumor cells and the spindle tumor cells. Multinucleated giant cells were interspersed in the nodules. Progressive study of all the tumor stroma including the recurrent specimens in our patients showed that myxoid area and abundant fibroblasts was predominant in patients younger than 2 years old especially in infants, however, sclerotic collagen was more common in older patients. This might suggest the different stages of evolution of the tumor stroma according to the different age. Nuclear atypia, mitotic figures, necrosis and calcification were not seen in the tumors. All the tumors showed an infiltrative growth pattern. Immunohistochemically, all the tumors had the same immuno-profile. The spindle to oval mononuclear tumor cells variably expressed markers of vascular endothelium such as CD34, CD31, and Factor VIII. The multinucleated giant cells were positive for CD68. Ultrastructural study was conducted in 2 cases and revealed the mononuclear tumor cells showed the features of endothelium [1, 2].

The differential diagnosis for GCA includes non-specific inflammatory granuloma, tuberculosis, capillary hemangioma, kaposiform hemangioendothelioma, Langerhans’cell histiocytosis (LCH), pseudomyogenic hemangioendothelioma, giant cell tumor of bone. Non-specific inflammatory granuloma is a non-neoplastic lesion and it has a background of many inflam-
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inflammatory cells and typical wreath like multinucleated giant cells which is uncommon in giant cell angioblastoma. Tuberculosis should be emphasized in the differential diagnosis for GCA because several cases of GCA had been given anti-tuberculosis therapy for the unawareness of this rare tumor leading to the misdiagnosis. Tuberculosis usually has an evident caseous necrosis in the centre and Langhans giant cells in the peripheral area of the lesion. Acid-fast stain can help to find tubercle bacillus. Capillary hemangioma does not have the onion-skin nodules and the multinucleated giant cells are absent. Kaposiform hemangioendothelioma is hard to be distinguished from GCA for they both can have glomeruloid structures but the platelet count is usually low clinically in kaposiform hemangioendothelioma and the multinucleated giant cells are uncommon morphologically. We suppose there is an overlapping between GCA and kaposiform hemangioendothelioma because they have nodular arrangement, glomeruloid structures, infiltrative growth pattern, and Glu1 negativity. Whether they have some relationship with each other is still unclear. LCH does not have so many vascular cavities and the tumor has a strong membranous expression for CD1a and Langerin. The tumor cells of pseudomyogenic hemangioendothelioma typically have abundant cytoplasm mimicking rhabdomyoblasts or epithelioid cells and express keratin AE1/AE3 and CD31 but do not have the CD34 positivity. Giant cell tumor of bone has a typical X-ray manifestations of soap-bubble sign and does not have so many vessels and also lacks the expression of vascular markers.

The biological behavior of GCA is uncertain for its rarity and only limited data have been acquired. According to the reported cases GCA has an infiltrative growth pattern and tumor recurrence is very common but metastasis is never seen. These suggest GCA may be an intermediate vascular tumor which has been adopted in the latest edition of WHO classification of tumors of soft tissue and bone. No standard therapy has been established for this tumor. Surgery may be the mainstay of the therapy strategy. But we should realize that surgery is invasive and for some intractable cases radical resection is hard to achieve. And surgery itself could lead to the joint malformation and dysfunction in some GCA cases in bone. Marler et al reported two tough cases of GCA were successfully cured with interferon-α which suggests interferon-α could be a supplement to surgery and may replace surgery in the therapy to some extent [3]. We advise our oncologists to use it and try our best to improve the quality of life in GCA cases. Chemotherapy or radiotherapy has not been reported in GCA. The prognosis of the reported GCA cases was good though some patients should tolerate the distress of relapse. The follow-up periods were 2 months to nearly 5 years. Most of the patients were event-free in the reported follow-up time though in the left patients the tumor recurred.

In conclusion, GCA has a typical morphological feature and unique immunophenotype. It may be an intermediate vascular tumor because of its invasive growth pattern and repeatedly recurrence. The tumor stroma can variably transform from the abundant fibroblasts and myxoid area to the totally collagen according to the different age. Our pediatric series provide more insights to GCA.

More data are needed to understand the biological and clinical behavior of this tumor.

Disclosure of conflict of interest

None.

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