

Case Report

Multiple bone giant cell angioblastomas in children: a case report and literature review

Ren-Ya Zhang^{1*}, Xiu-Ming Miao^{2*}, Zong Gao^{3*}, Hong-Sheng Tian⁴, Shuai Chen¹

¹Department of Pathology, Affiliated Hospital of Jining Medical University, Jining, Shandong Province, P. R. China; Departments of ²Pathology, ³Neurosurgery, ⁴Radiology, Affiliated Hospital of Shandong University of TCM, Jinan, Shandong Province, P. R. China. *Equal contributors.

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Abstract: Giant cell angioblastoma (GCAB) is a rare locally aggressive vascular tumor that occurs primarily in the soft tissue and bones of infants and children. To date, only twelve cases have been reported in the literature, of which seven cases occurred in infants, two cases in children, and three cases in adults. Most of them were single-site cases. As the 13th case, this study presents the first case report of multiple giant cell angioblastomas occurring in the distal metaphysis of tibia, calcaneus, and astragalus, with detailed radiological and histological features. Histologically, the infiltrating tumor tissue was composed of hemangiomatous nodules arranged in clusters or flakes, with notable mononuclear-multinucleate giant cells and hemosiderin deposition. The nodular stroma showed that collagenization and hyaline degeneration were interphase, in which the ectatic thin-walled blood vessels or distorted thick-walled vessels with mucus degeneration were visible. Main clinical symptoms were intermittent pain and lameness. There was no special treatment in the child after the biopsy and no significant progress was made during the next three months. However, after a year of follow-ups, the child was found with an obvious limp and the right limb was about 2 cm longer than the left one.

Keywords: Vascular tumor, bone tumor, giant cell angioblastoma, immunohistochemistry

Introduction

Giant cell angioblastoma (GCAB) is a very rare congenital soft tissue tumor. There have been a total of twelve cases, first reported by Gonzalez-Crussi et al. in 1991 to a recent report by Yu et al. [1-3]. Although studies have shown that GCAB is an independent disease entity, it still has not been classified as a new category of tumors, according to WHO (2013) classification of soft tissue and bone tumors [1-6]. Due to the limited number of cases and poorly defined clinical and pathological features, it is doubtful whether GCAB is a vascular tumor entity, presenting great problems to pathologists [3, 4]. This study presents another case with multiple patterns, occurring in the distal metaphysis of tibia, calcaneus, and astragalus. An explicit diagnosis combining common pathological results with X-rays, computed tomography (CT), and immunohistochemistry was confirmed. Moreover, relevant studies were reviewed, aiming to raise the diagnostic level of GCAB, seek-

ing its biological behavior as basis for clinical treatment and prognosis.

Case report

Clinical history

The patient, a 5-year-old girl, had a sprained right ankle a year ago. She subsequently developed intermittent pain and claudication. In her local hospital, the doctor initially considered her suffering to be from a low-grade infection. Due to persistent symptoms, she was referred to our hospital for further treatment. The patient was born at full term from a healthy pregnancy. Upon physical examination, the girl showed equal length of both lower extremities, no deformities, and local tenderness of the right foot. She displayed no significant limitation of activity, while displaying slight pain of dorsiflexion and muscle strength decline in dorsiflexion and eversion. Additionally, the feeling and blood transport of her right lower extremities were



Figure 1. X-ray imaging features of giant cell angioblastoma of bone. A. X-ray shows the cortex on the outer side of the right distal tibia with a long strip of bone defect. B. X-ray shows the outer edge of body and the inner edge of forepart of the right calcaneus with cortical defects. C. X-ray shows in the medullary cavity of the right astragalus, there were two sizes and round low-density lesions, with thin marginal bone sclerosis protruding to the center of the lesions.

well, without pathological symptoms. According to X-ray, CT scan, and three-dimensional reconstruction, the cortex on the outer side of the right distal tibia showed a long strip of bone defect, consistent with the long axis of the tibia. The side of the medullary cavity revealed a “scallop-like” or “map-like” thin layer clearly separated from the medullary cavity (**Figure 1A**). At the edge of the lesion, there were some bone protrusions and no periosteal reaction, but mild swelling in surrounding soft tissues. Bone cortical defects in the posterior of right distal fibula, the outer edge of the body, and inner edge of the forepart of the right calcaneus were similar to the above description (**Figure 1B**). The medullary cavity of right astragalus showed two sizes and round low-density lesions, the periphery of which displayed a clearly thin and sclerotic edge with some bone ridges protruding to the center of the lesions (**Figure 1C**). MRI showed local bone cortices in the distal metaphysis of right tibia, distal epiphysis of right fibula, right astragalus,

and calcaneal with multiple long T1 short T2 signals and low SPAIR signal, with clear boundary defects of bone cortices in the inner upper side of the right astragalus with long T1 short T2 signal and high SPAIR signal. Surgical fenestration revealed thin cortices and a small number of gray-red tissues found in the cavity. These were sent for pathological examination.

Materials and methods

Specimens were fixed in 10% buffered formalin, dehydrated routinely, and embedded in paraffin for pathological study. Next, 4 μ m sections were stained with hematoxylin and eosin (H&E) and observed by two pathologists with expertise in bone and soft tissue pathology. Moreover, immunohistochemistry analysis was performed in representative tumor sections using EnVision two-step method and the following antibodies: CD31 (MAB-0031, JC70A), CD34 (MAB-0034, QBEnd/10), vimentin (MAB-0735, MX034), Actin (Smooth Muscle) (SMA,

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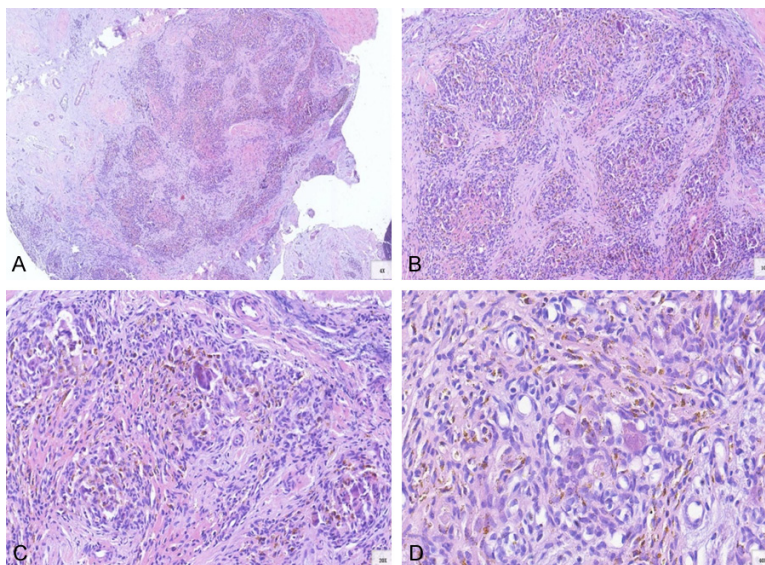


Figure 2. Pathological findings of giant cell angioblastoma. A. At low magnification, the tumor cells were arranged in irregular nest-like hemangiomatous nodules, with stromal collagenization and hyaline degeneration (HE, $\times 40$). B. The scattered mononuclear-multinucleated giant cells with eosinophilic cytoplasm and hemosiderin deposition were noteworthy in the hemangiomatous nodules (HE, $\times 100$). C. At high magnification, cells of nodules were long spindle cells, with indistinct cell boundary and fine chromatin (HE, $\times 200$). D. Peripheries of nodules had visible fissures and single circular microvascular lumens. The abundance of oval-to-spindle tumor cells, mild with occasional nuclear ditches, were densely distributed between microvascular lumens and blood vessels (HE, $\times 400$).

Kit-0006-2, 1A4), CD68 (Kit-0026, KP1), LCA (Kit-0024, PD7/26+2B11), desmin (Kit-0023, D33), Ready-to-use; Maixin Bio, Fujian, China.

Pathological findings

Histologically, the tumor tissue was characterized by irregular nest-like hemangiomatous nodules, with denatured fibrous connective tissues distributed in these nodules (**Figure 2A**). The most prominent histological appearance of hemangiomatous nodules was scattered with mononuclear and multinucleate giant cells (nuclear less than 10), showing the eosinophilic cytoplasm. Additionally, widespread deposition of hemosiderins could be noted (**Figure 2B**). These nodules were like the large glomerular-like structure of Kaposiform hemangioendothelioma. At high magnification, cells in the nodules were long oval or long spindle cells, with unclear cell boundaries, fine chromatin, no abnormalities, no necrosis, and no pathological mitosis (**Figure 2C**). Peripheries of these structures, resembling the large glomeruli, had visible fissures and the single open circular micro-

vascular lumens had one or two endothelial cells and one or more red cells. In addition, the abundance of oval-to-spindle tumor cells, that were mild and of occasional nuclear ditches, were densely distributed between the microvascular lumens and blood vessels (**Figure 2D**). The nodular stroma showed that collagenization and hyaline degeneration were interphase, in which the ectatic thin-walled blood vessels or distorted thick-walled vessels with myxoid degeneration could be seen, scattered in the distribution of star-like cells.

Immunohistochemistry

Immunohistochemical stains exhibited that vimentin was strongly positive throughout the solid tumor (**Figure 3A**). Hemangiomatous nodules and single open circular

microvascular lumens were strong positive for CD31 and CD34 (**Figure 3B, 3C**). CD68 and LCA in mononuclear-multinucleated giant cells were positive (**Figure 3D, 3E**), while desmin and SMA were negative, with ki67 2%-5% (**Figure 3F**).

Clinical follow-up

There was no special treatment for the child after surgery. No significant progress was seen, according to CT examination, during the first three months after discharge. After one year of follow-ups, the child was found with an obvious limp and the right limb was about 2 cm longer than the left limb.

Discussion

Giant cell angioblastoma (GCAB) was first reported by González Crussi et al. [2]. As they described, a baby girl presented with one mass of the right forearm at birth. After three months, the lesion involved flexion of the forearm to the hand and local surgical resection of the tumor was performed. Later, extensive lesions lead to an unfortunate amputation, but with good post-

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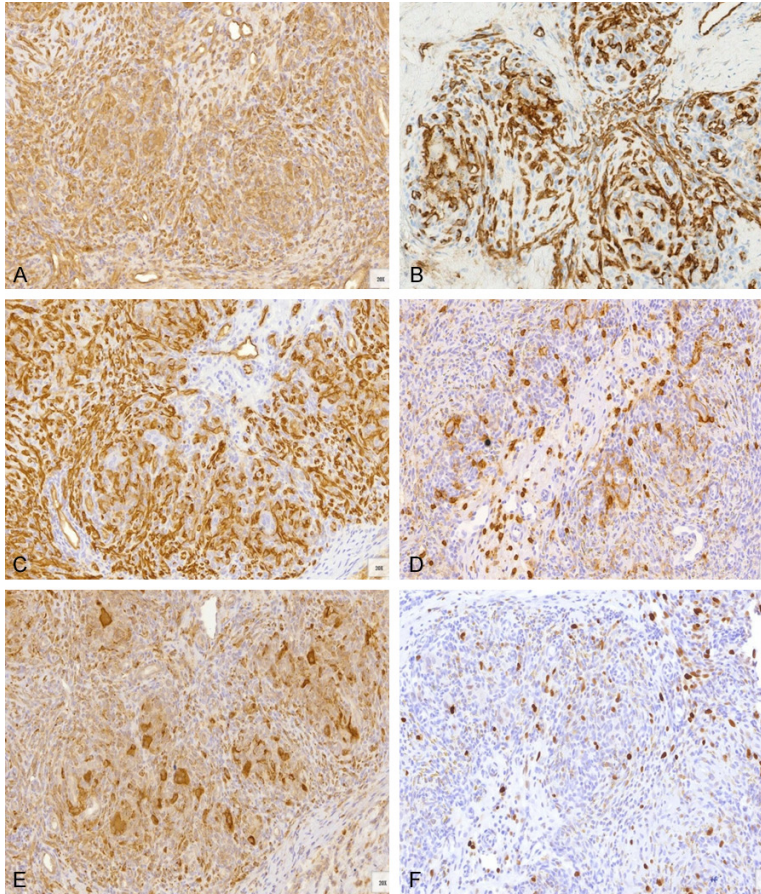


Figure 3. Immunohistochemical stains of giant cell angioblastoma. A. Tumor cells were diffusely positive for vimentin (HE, $\times 200$). B. The fissures of nodular and single round microvascular lumens were positive for CD31 (HE, $\times 200$). C. The fissures of nodular and single round microvascular lumens were positive for CD34, as well as oval-to-spindle hemangiopericytes (HE, $\times 200$). D. LCA was positive in mononuclear-multinucleated giant cells and lymphocytes (HE, $\times 200$). E. CD68 was positive in mononuclear-multinucleated giant cells and lymphocytes (HE, $\times 200$). F. Ki-67 decorated less than 5% lesion cells (HE, $\times 200$).

operative prognosis. According to findings and histopathology, they first proposed this pathological diagnosis of giant cell angioblastoma. Ten years later, Vargas et al. reported another three cases [3]. It was proven that GCAB is a unique and rare vascular disease entity, with slow growth and local infiltration. Two cases treated with interferon alfa 2b (IFN2b), after extended resection, had better effects and even appeared to be cured [7]. There have been twelve cases in the literature up to now [1], including seven cases of foreign reports and five cases in China (Table 1). The present study presented an additional case, increasing the number to thirteen. Of these, seven cases occurred in infants, three in children, and three

in adults, including seven males and six females, with no gender differences. Additionally, five cases occurred in patients with skin erythema or ulcers and pain. Eight cases of primary bone tissue, most of them presenting with joint pain or limited mobility and soft tissue swelling, consistently showed bone destruction. It is noteworthy that, in three cases of patients with GCAB originating from the long bones of the lower extremity, one case developed dysfunction in the lower limbs of the 23-month-old child with decreased muscle strength in the affected side [1]. The other two cases developed into dysplastic limbs with the affected side being 2 cm longer than the contralateral side [4], leading to the typical symptom of a limp. The patient reported in the present study had only decreased dorsal extension and valgus strength of the foot, at first diagnosis, but after one year the affected limb appeared about 2 cm longer than the contralateral side without additional therapy. This further confirmed the biological behavior of GCBA with invasion of surrounding tissues.

Mao et al. [5], according to prognosis, divided GCAB into two subtypes: type I without infiltration of peripheral tissue, prognosis good; type II infiltration of peripheral tissue, prognosis poor. Recalling the clinical data of previously reported cases, GCAB was found in superficial soft tissues with clinical symptoms of the skin, including erythema, ulcers, and palpable mass. It was found in bones with joint or local pain, as the first symptom, even restricting mobility or dysplastic of the lower extremities. The present study suggests that prognosis of GCAB is related to age, location, and duration of the disease. In addition, GCAB mainly occurs in infants and young children, even though there were three cases of adults. Based on these facts, it was

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Table 1. Clinical features of the 12 reported cases of GCAB

No.	Information Literatures	Age	Sex	Size (cm)	Site	Clinical diagnosis	Follow-up (months)
1	Gonzalez-Crussi et al., 1994	3 months	F	8.5	Right forearm	Hemangioma	Uneventful
2	Vargas et al., 2001	7 months	M	1.5	Palate	UA	NP, 56
3	Vargas et al., 2001	49 days	M	3.3	Right hand	Vascular tumor	NP, 27
4	Vargas et al., 2001	25 days	F	UA	Scalp	UA	UA
5	Marler et al., 2002	10 months	M	UA	Palate	UA	72
6	Marler et al., 2002	Neonate	M	3.3	Right hand	Vascular tumor	32
7	Mao et al., 2012	4 years	M	3.0	Right thigh-bone	UA	Recurrent, 17
8	Crivelli-Ochsner et al., 2013	41 years	M	2.4	Popliteal fossa	Chondromatosis	16
9	Lin Yu et al., 2015	23 months	F	2.0	Right femur	Fibrous dysplasia	2
10	Lin Yu et al., 2015	8 years	M	2.0	Left hip, knee joint	Tuberculosis	10
11	Lin Yu et al., 2015	37 years	F	2.0	LumbarVertebra	Tuberculosis	21
12	Lin Yu et al., 2015	56 years	F	3.0	Left metacarpus, phalange	Tuberculosis	9
13	Present case*	5 years	M	2.0	Tibia, calcaneus and astragalus	Low-grade infection	Limp, 12

M: male, F: female, cm: centimeters, UA: unavailable, NP: no progression, *Current case.

speculated that occurrence of GCAB may be related to genetic pathology. This conclusion, however, needs to be confirmed by further study.

For the first time, the present study reported multiple giant cell angioblastoma in the distal metaphysis of the tibia, calcanea, and astragalus. The child was hospitalized with intermittent pain of right foot and slight limp. It was considered as a low toxicity infection in the local hospital before admission. Physical examination showed a slight limp in the right lower limb and muscle strength declining in the right foot dorsiflexion, along with eversion with slight pain. Imaging findings revealed that there were cortical bone colobomas in the interior posterior margin of right distal tibia, the outer edge, and anterior interior margin of the right calcaneus. At the edge of the lesions, there was no periosteal reaction, but rather mild swelling around the soft tissue. In the medullary cavity of the right astragalus, there were two sizes and round low-density lesions, with thin marginal bone sclerosis protruding to the center of the lesions. Surgical fenestration procedure revealed bone destruction with thin cortices and a small amount of gray-red tissues were found in the cavity. These were sent for pathological examination. Pathological findings and immunophenotypes were essentially the same as those described by previous reports. At the same time, this study made pathological sections of this case for expert discussion. However, the opinions of experts varied. Most of them considered the tumor to be vascular-derived, such as tufted hemangiomas and Kaposiform hemangioendothelioma, while oth-

ers suspected granulomatous inflammation or a giant cell tumor of tendon sheath [8].

The histological morphology of GCAB overlaps with those of plexiform fibrohistiocytic tumors (also known as Nakagawa hemangioblastoma), juvenile hemangiomas, and Kaposiform hemangioendothelioma [9]. The most prominent histopathological morphology is that the tumor tissue consists of irregular hemangiomatic nodules that are “shell-like” tumor nests of tufted hemangiomas, in which mononuclear and multinucleate giant cells and hemosiderin deposition were visible. At high magnification, cells in the neoplasm were long oval or long spindle cells with vague cell boundary, eosinophilic cytoplasm, fine chromatin, and without abnormality, necrosis, and pathological mitosis. Epithelioid cells of these long ovoid or long spindle cells were arranged in large clusters along a certain polarity around mononuclear-multinucleated giant cells, resembling large glomerular-like structures in Kaposiform hemangioendothelioma. These structures had peripheral visible fissures and single circular microvascular lumens with one or two endothelial cells and one or more red cells. The oval-to-spindle hemangiopericytes, mild with occasional nuclear ditches, were densely distributed between the periphery of the microvascular lumens and blood vessels (**Figure 2D**). Additionally, nodular stroma showed collagenization and hyaline degeneration. The hardened stroma were displayed as dilated thin-walled blood vessels or tortuous thick-walled vessels with myxoid degeneration, all consistent with pathological changes of juvenile hemangioma. In addition, immunohistochemistry showed

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that the internal fissures in hemangioma nodules and single open circular microvascular lumens were strong positive for CD31 and CD34, which were more supportive of these viewpoints. Therefore, pathological characteristics of GCAB demonstrated the process of tumor progression from the immature vessel nest with disordered growth to degeneration.

It has been proven that, at the molecular level, occurrence and generation of blood vessels include at least two groups of tyrosine kinase receptors (TIE1 and TIE2). One group mainly affects differentiation and proliferation of endothelial cells, while the other group controls the formation of vascular walls and generation of vascular bed. The disordered expression of tyrosine kinase receptors or loss of one receptor could lead to abnormal tumor angiogenesis [10-12]. Whether the pathological mechanisms of GCAB are related to the loss of the tyrosine kinase receptors, further verification is required. GCAB, tufted hemangiomas, Kaposiform hemangioendothelioma, and juvenile hemangiomas have similar morphological points. Thus, there may be some inevitable links between them in occurrence and prognosis of the disease.

Although giant cell angioblastoma shows characteristic tissue morphology and immunophenotype, it also needs to be differentiated from other diseases, including Kaposiform hemangioendothelioma, tufted hemangiomas, plexus fibrous histiocytoma, giant cell tumor of tendon sheath, tuberculosis, giant cell angiofibroma, and so forth. Kaposiform hemangioendothelioma is commonly found in the deep or retroperitoneal soft tissue of infants or young children. It also can display Kamai syndrome [13]. The tumor is composed of nodules with varying sizes, each of which include fissure-like vascular cavities, capillaries, and short bundle-like spindle cells. It lacks significant nucleolus, compared to GCAB. Plexus fibrous histiocytoma is common in the dermis and subcutaneous parts of upper limbs of children and adolescents, composed of the clump-like distribution of nodules or spindle cell bundles. The center of the nodule is composed of mononuclear giant cells or osteoclast-like giant cells, surrounded by spindle-shaped fibroblasts or fibroblasts-like cells. However, compared to GCAB, the boundaries of tumor parenchyma and stroma are not clear and the giant cells lack a significant large nucleolus. Tufted hemangiomas

is more common in the skin or subcutaneous tissue of children's necks and upper limbs. It is mainly composed of hemangiomatous nodules, nodules without multinucleated giant cells. Giant cell tumors of tendon sheath are common in the small joints of young and middle-aged females. It has monocytes or multinucleated osteoclast-like cells similar to GCAB, yet it does not arrange in nodules. Giant cell repair granuloma usually arises in adult female skulls and short bones of hand or foot, accompanied by the proliferation of fibrous tissue and a variety of inflammatory cells infiltration. Osteoclast-like multinucleated giant cells are smaller and more, mainly located in the hemorrhagic region. Compared to GCAB, bone tuberculosis is common in the spine and limb joints of children or adolescents, accompanied by necrosis and inflammatory cell infiltration. Necrosis can be separate from living bone after the formation of dead bone, finally leading to the formation of the cavity. However, the nucleolus of multinucleated giant cell is not conspicuous and acid-fast staining can be positive. Moreover, giant cell angiofibroma occurs frequently in adult men around the eyes, with rich blood vessels and discontinuous multinucleated giant cells expressing CD34. Multinucleated giant cells of GCAB express CD68, not CD34.

In conclusion, giant cell angioblastoma is a rare type of vascular-derived intermediate tumor with localized infiltration and no biological characteristics of distant metastasis. It commonly occurs in infants and young children but can also be found in adults. Due to the tumor's original occurrence in the bone or deep soft tissue, it may not be found in time. Once clinical symptoms arise, the tumor has invaded the surrounding tissue. The present study presented GCAB of children with multiple features, occurring in the distal metaphysis of tibia, calcaneus, and astragalus. Even though local or extended surgical resection is basic clinical treatment, postoperative antiangiogenic therapy can achieve better results, perhaps even the cure. There have been too few cases reported to fully understand the pathological mechanisms of GCAB. More case accumulation is necessary for further study.

Disclosure of conflict of interest

None.

Address correspondence to: Ren-Ya Zhang and Shuai Chen, Department of Pathology, Affiliated

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Hospital of Jining Medical University, 89 Guhuai Road, Jining 272029, Shandong Province, P. R. China. Tel: +86-0537-2903217; Fax: +86-0537-2903281; E-mail: hzzhang_1964@163.com (RYZ); chenshuaiwei@126.com (SC)

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