Cystic angiomatosis in child: clinical experience and review of literatures

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Case Report

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Abstract

Background: Cystic angiomatosis is a rare disease characterized by the proliferation of vascular and lymphatic channels lined by a single layer of endothelial cells. Here, we reported a child of cystic angiomatosis with multifocal lesion in bone, who was diagnosed by biopsy surgery and evaluated by whole exome sequencing.

Case Description: In this case presentation, we report a case of 11-year-old boy who had the pain in chest. Computed tomography revealed the multiple lytic of bone in ribs, clavicle, vertebra thoracalis, skull, mandibula, shoulder blade and so on. Blood test showed that ALP was 393U/L with the normal of 20–110 U/L and VEGF was 287.26 pg/ml with the normal of 0-142 pg/ml. The patient was performed by the biopsy surgery in ribs and diagnosed of cystic angiomatosis by pathological examination. The whole exome sequencing showed the single nucleotide substitutions in the coding region including BRIP1, CHEK2, GRM4, and MUC16. Besides, the up-regulated genes were involved of CASC15, CENPF, ABCA13, ALK, BLM, FGFR3.

Conclusions: In this article, we report a rare case of cystic angiomatosis in a child with multiple lesions of bone and abnormal VEGF and ALP in peripheral blood examination. Then, the whole exome sequencing could be performed in order to explore the potential molecular mechanism in the development of cystic angiomatosis.

Introduction

Cystic angiomatosis is a rare, benign disease with characterized by disseminated multifocal hemangiomatous and/or lymphangiomatous lesions of the skeleton. It was firstly reported by Jacobs and Kimmelstiel in 1953[1]. The disease is mainly involved of axial or appendicular bone including pelvis, long bones and shoulder gridles[2]. The visceral organ of lungs liver or spleen is also affected[3]. The radiological appearance of systemic cystic angiomatosis is usually confused with secondary malignat neoplasia, langerhans cell histiocytosis, metastatic cancer or skeletal involvement in other malignancies[2, 4, 5]. In most cases, those patients are asymptomatic. When the affected bone is involved of pathological fracture or adjacent soft tissue injury, the clinical symptom including pain, swelling of affected area or function limitation could occur in patients[6]. Neurological symptom could be present in the vertebral localization or skull lesion[7]. It was difficult to diagnose the systemic cystic angiomatosis, and the pathologic result was usually unpredictable in some cases. Although the previous literature showed that cystic angiomatosis was related with the disorder of vascular malformations[3], the exact pathogenetic mechanism disease was still not clear.

Thus, we report a case of 11-year-old boy presenting chest pain with typical multifocal skeletal involvement, which was diagnosed as cystic angiomatosis by repeatedly biopsy surgery. Then, the whole exome sequencing was performed in order to explore the potential molecular mechanism in the development of cystic angiomatosis.

Case Presentation

A 11-year-old boy was referred to the pediatric orthopedics in hospital with the pain in chest. There was no remarkable family history or trauma history. Radiological examination showed the multiple cystic lesions in left ribs, right humerus and the proximal of left radius and the fracture of right lib. The left ribs showed the multiple lytic lesions with the thin of cortical bone (Fig. 1). Computed tomography (CT) revealed that the multiple lytic of bone in ribs, right clavicle, vertebra thoracalis, mandibula and shoulder blade without the swelling of tissue. The biopsy surgery was performed in the lesion bone of left rib and right humerus. It was regrettable that there was no definite pathological result. Unfortunately, the boy had a pathological fracture in the affected area of humerus after surgery and was treated by a brace of upper limb.

In order to diagnosis the disease, the boy was referred to our hospital. Routine blood results showed that alkaline phosphatase (ALP) was 393U/L with the normal of 20–110 U/L and vascular endothelial growth factor (VEGF) was 287.26 pg/ml with the normal of 0-142 pg/ml. Positron Emission Computed Tomography (PET) showed that avid radioisotope uptake in affected areas involving vertebra thoracalis, rumpbone, acetabular bone, pubic bone, skull, mandibula, clavicle and shoulder blade (Fig. 2 and Fig. 3). The additional open biopsy was performed in left ribs. The cortex of ribs was thinned with the cortox surface of kermesinus. The inside space of rib was dilated, filled with the hydatid fluid of erythrine. The pathological examination in the second rib showed the hyperplastic fiber connective tissue with the collagen sclerosis, and lymphocyte infiltration and partial foam-like tissue cells. No obvious eosinophile granulocyte was found in lesion. Besides, the affected area in the third rib showed the fibrous connective tissue and dilated blood vessels with bleeding in the trabecular bone, and the dilated lymphatic vessels with lymphocytes (Fig. 4). There were CD31(+), D2-40(+), SATB2(+), CD20(+), SMA (+), S-100 (-) and BRAF-V600E (-) in immunohistochemical staining. There was no evidence of malignancy in pathological examination. The final diagnosis was generalized as cystic angiomatosis.

According to whole exome sequencing, there were some single nucleotide substitution in the coding region including BRIP1(c.2071A > T (p.I691F) 8.3%), CHEK2 (c.1555C > G (p.R519G) 2.7%; c.1525C > T(p.P509S) 1.8%), GRM4 (c.278G > C(p.R93P) 5.4%), and MUC16 (c.39613C > T(p.P13205S) 3.2%; c.39611A > C(p.K13204T) 1.3%), which may indicate the pathogenesis of the disease. Besides, the up-regulated genes were involved of CASC15, CENPF, ABCA13, ALK, BLM, FGFR3 and so on. Gene Ontology (GO) functional enrichment analysis revealed that Biological Process (BP) of upregulated gene included regulation of ossification, embryonic cranial skeleton morphogenesis, chondrocyte differentiation. Cellular Component (CC) analysis revealed that upregulated DEGs were primarily enriched in ciliary membrane, spectrin-associated cytoskeleton and spectrin. Molecular Function (MF) of upregulated DEGs were demonstrated to include bHLH transcription factor binding, ionotropic glutamate receptor binding and Wnt-protein binding. According to KEGG pathway enrichment analysis, upregulated DEGs were mainly enriched in pathways involved in Pathways in cancer, PI3K-Akt signaling pathway, MicroRNAs in cancer, Transcriptional misregulation in cancer ($P < 0.05$).

Discussion

Cystic angiomatosis is a rare disease characterized by multifocal bony cysts with a honeycombed appearance and thin-walled blood vessel proliferation with bone destruction. Bone trabecula under cortex is gradually replaced by hemangiomatous or lymph angiomatous tissue. The first decades of life, particular puberty, is one of the highest rates of cystic angiomatosis and adult older than 60 years of age may be the second peak of occurrence[3]. The clinical symptom varies from accidentally found by radiograph to pathologic fracture or skeletal abnormalities of slowly progression, or rare severe visceral lymphangiomatosis, especially for lung, liver, or spleen[6]. Radiograph imaging shows multifocal, skeletal intramedullary cysts, with a thinned and relatively well-preserved bony cortex and without peripheral soft tissue involvement and periosteal reaction[7].

The typical characteristics of cystic angiomatosis reveals multifocal intramedullary skeletal cysts with relatively well-preserved cortical bone without periosteal reaction and peripheral involvement of soft tissues in the lesion of bone, while metastasis, multiple myeloma, or other malignant disease are usually involved of peripheral or tissue reaction[3, 4]. Bone cysts are oriented along the long axis of the bone with a sclerotic peripheral ring. Cystic angiomatosis and Gorham-Stout disease (GSD) present the similar features in the destruction and resorption of bone[4, 8]. But, cystic angiomatosis shows the sclerotic appearance in the margin of cysts and sclerosing lesion rather than osteolysis in affected bone, which is the important performance in GSD. Most previous studies showed that GSD could lead to the progressive massive osteolysis resulting in cortical bone loss, and leading to severe deformations and disability, whereas there was medullary cavity without progress of disease in cystic angiomatosis[9]. Thus, cystic angiomatosis usually has a better prognosis than GSD[10].

It is known that bone biopsy is the standard method in the treatment of cystic angiomatosis. However, those previous studies have usually reported that histological diagnosis is significantly difficult in some diseases and repeated bone biopsy was usually needed for final diagnosis[5]. In our study, the first biopsy surgery was performed in other hospital and the lesion of lib and humerus was filled with bone fluid as result of undefined diagnosis regrettably. In the second bone biopsy, we found that fibrous connective tissue and dilated blood vessels with bleeding in the trabecular bone, the dilated lymphatic vessels with lymphocytes and cystic wall of endothelial lining. The cystic wall of endothelial lining was reported in most literatures[6, 11]. We considered that these were consecutive phases in development process of cystic angiomatosis as result of different histological result. Thus, we should evaluate the different radiological performance in the content of bone cystic before the bone biopsy.

There was an increase in ALP and bone marker osteoprotegerin, osteopenia, and interleukin-6 in cystic angiomatosis[7]. In our case, ALP was 393U/L with the normal of 20–110 U/L, and VEGF was 287.26 pg/ml with the normal of 0-142 pg/ml. VEGF represents a growth factor with important pro-angiogenic activity and promote the vascular permeability and cell migration. Besides, VEGF and their endothelial tyrosine kinase receptors are involved of vasculogenesis, angiogenesis and lymphangiogenesis and VEGF signalling through VEGFR-2 could promote the angiogenic pathway. VEGFR1 and VEGFR2 is mainly

focus on vascular endothelial cells, and VEGFR-3 is especially focus on lymphangiogenesis[12]. Histological examination shows that the vessels of vascular or lymphangiomatous is involved of vascular endothelial growth factor (VEGF) and podoplanin. CD31 is other notable markers of cystic angiomatosis, indicating a hematopoietic lineage. In our case, CD31 is also positive in the immunohistochemistry indicating the lymphatic or angiomatous proliferations. The current medical treatment in cystic angiomatosis in mainly involved of bisphosphonates, interferon-a, and calcitonin[7]. Thus, anti-VEGF and anti-VEGFRs therapy may be potential in blocking angiogenesis or pathological processes in cystic angiomatosis.

In the whole exome sequencing, we found some single nucleotide substitution in the coding region including BRIP1, CHEK2, GRM4, and MUC16. Besides, the up-regulated genes in the result were involved of CASC15, CENPF, ABCA13, ALK, BLM, FGFR3 and so on. Those genes may indicate the pathogenesis of cystic angiomatosis. BRIP1 pathogenic germline variants may have a causal role in CRC as moderate cancer susceptibility alleles and be associated with hereditary CRC predisposition. It could increase the risk of developing hereditary ovarian cancer[13]. CASC15 is involved in the regulation of biological processes in many diseases, which could be a new biological therapeutic target[14]. CASC15 has been found to be down-expressed abnormally in ovarian cancer, glioma and neuroblastoma[15]. CENPF plays a key role in the regulation of the cell cycle[16]. CENPF levels contributed to increased cell proliferation by mediating apoptosis and cell cycle in osteosarcoma with the poor prognosis of osteosarcoma[17]. GO functional enrichment analysis revealed that the BPs of upregulated gene included regulation of ossification, embryonic cranial skeleton morphogenesis, chondrocyte differentiation. CC analysis revealed that upregulated DEGs were primarily enriched in ciliary membrane, spectrin-associated cytoskeleton and spectrin. The MFs of upregulated DEGs were demonstrated to include bHLH transcription factor binding, ionotropic glutamate receptor binding and Wnt-protein binding.

Conclusions

multiple lytic bone lesions without periosteal reaction and involvement of soft tissues in children should be evaluated in the diagnosis of cystic angiomatosis. Peripheral blood examination including VEGF or ALP may promote the evaluation of the disease. The different radiological performance related with content of cystic should be considered before bone biopsy. In the future studies, we should focus on molecular mechanism and signaling pathway in the development of disease and promote the biological treatment of cystic angiomatosis.

Abbreviations

CT
Computed tomography
ALP
Alkaline phosphatase
VEGF

Vascular endothelial growth factor
PET
Positron Emission Computed Tomography
CHEK2
checkpoint kinase 2
BRIP1 – BRCA1 interacting helicase 1
GRM4
Glutamate metabotropic receptor 4
MUC16
mucin 16
CASC15
Cancer susceptibility 15
CENPF
Centromere protein F
ABCA13
ATP binding cassette subfamily A member 13
ALK
ALK receptor tyrosine kinase
BLM
BLM RecQ like helicase
FGFR3
Fibroblast growth factor receptor 3
GO
Gene Ontology
BP
Biological Process
CC
Cellular Component
MF
Molecular Function
GSD
Gorham-Stout disease

Declarations

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Authors' contributions

W.C.L and L.L participated directly in the case and diagnosis of the patient, Z.D.W and H.C conducted a review and editing, G.L performed the pathology study, and Z.C.F and W.C.L wrote the paper. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate

Not applicable.

Consent for publication

We have obtained written informed consent from the patient for the publication of this article. The individual person's data contained in the manuscript has been obtained

consent for publication by patients.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

The multiple lesion bone in left ribs in CT (a and b) and MRI (c), The lesion in right humerus and pathological fracture (d), MRI scan (T2) showed multiple lytic areas in the scapula (e) and vertebral bodies (f).

Figure 2

PET showed that avid radioisotope uptake in areas involving vertebra thoracalis (a, b and c), rumpbone (d), acetabular bone (e), pubic bone (f).

Figure 3

PET showed that avid radioisotope uptake in areas involving skull (a, b and c), mandibula (d), clavicle (e) and shoulder blade (f).

Figure 4

Histopathological examination showed the fibrous connective tissue, dilated blood vessels and dilated lymphatic vessels around trabecular bone (a). There were the positive of CD31 (b) and D2-40 (c) in immunohistochemical staining.

Figure 5

GO functional enrichment analysis revealed that BP, CC and MF of upregulated gene.

Figure 6

The bubble diagram of TOP30 DEGs in GO function enrichment (a) and KEGG function enrichment (b).