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Case Report

Primary non-hyperlipidemia xanthoma of bone: a case report with review of the literature

Zhuo Wang[1*], Zhong-Wei Lin[2*], Lei-Lei Huang[1*], Zun-Fu Ke[1], Can-Jiao Luo[1], Wen-Lin Xie[1], Lian-Tang Wang[1]

[1]Department of Pathology, The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China; [2]Department of Cardiology, The First Affiliated Hospital of Guangdong Pharmaceutical University, Guangzhou, China. [*]Equal contributors.

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Abstract: Primary xanthoma of bone is very rare. And its clinical, pathological and radiological presentation is different from other position. It is generally known that xanthoma of bone are usually are associated with lipid disorders. Non-hyperlipidemia xanthoma of bone are exceedingly unusual. In this report, we describe a rare case of primary bone xanthoma without hyperlipidemia and reviews the literature on primary bone xanthomas, focusing on those without hyperlipidemia. The difference of age between non-hyperlipidemia xanthoma of bone and other xanthoma of bone did not existed. But male patients outnumber female in non-hyperlipidemia xanthoma of bone. It often involve the irregular flat bones than the long bones. Inflammatory cells, cholesterol clefts and hemosiderin are rare compared with xanthoma with lipid disorders. At the same time, imaging manifestations is not steady, except for osteolytic sign. So the diagnosis usually depend on a pathological biopsy. Therefore we suggested that non-hyperlipidemia xanthoma of bone was a kind of independent disease. It should be belong to bone tumors of undefined neoplastic nature. Its etiology need more data collection and further analysis.

Keywords: Xanthomas, non-hyperlipidemia, bone, histology

Introduction

Xanthomas of soft tissue are common, occurring as nodules on the skin, subcutis, or tendon sheath in hyperlipidemic patients. Primary xanthoma of bone is very rare. And its clinical, pathological and radiological presentation is different from other position. Bony xanthoma appears at around 20 years of age in a 2:1 proportion of mento-women [1]. It most frequently occur in the appendicular or axial skeleton including the bony pelvis, spine and skull base [2].

Intraosseous xanthomas are lytic, expansile lesions, histologically characterized by lipid-laden histiocytes [3]. The radiological features are protean, involved aggressive or nonaggressive sign. So the diagnosis usually depend on a pathological biopsy.

It is generally known that xanthoma of bone are usually are associated with endocrine or metabolic diseases, mainly lipid disorders [4]. But rarer cases of bone xanthoma can occur in patients with normal lipid profiles. These are exceedingly unusual.

Here the case of male adolescents with an isolated xanthoma of femur is founded. This report introduces the rare case of primary bone xanthoma without hyperlipidemia and reviews the literature on primary bone xanthomas, focusing on those without hyperlipidemia.

Case report

The patient, a 11-year-old juvenile, male, initially experienced a swelling pain in the right thigh section and the right knee after a intense physical activity. The patient was referred to our hospital, resulting from radiographs, computed tomography (CT) and magnetic resonance imaging (MRI) scanning suggested a femur tumor. He had unremarkable personal and family medical histories.

On admission, Physical examination revealed mild swelling at the right thigh section, but no local warmth or redness was apparent. There

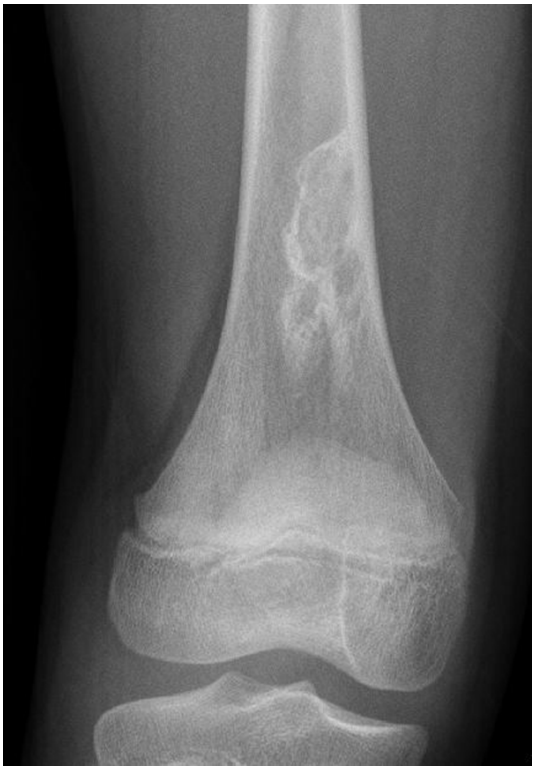

Figure 1. Radiographs imaging: A clearly demarcated expansile osteolytic lesion within femur, partially surrounded by bone sclerosis.

was no palpable soft tissue mass around the right thigh section or the right knee. The range of motion of the ankle was not restricted. No neurological abnormalities were noted. The results from biochemical and hematological tests were all normal. The levels of glycaemia, lipidemia and cholesterolemia of the patient were requested but did not present any alteration. There were no signs of hyperlipidemia or lipid disorders.

Radiographs showed a clearly demarcated expansile osteolytic lesion within femur, measuring approximately 4.5 cm ×2.0 cm ×1.5 cm, partially surrounded by bone sclerosis (**Figure 1**). There was no internal matrix, visible soft tissue mass or periosteal reaction. CT scan at the bone-window level also indicated an osteolytic lesion at the femur. The lateral cortex was thinned, but no cortical breakthrough was observed. T1-weighted MRI exhibited a lesion with central low signal intensity, surrounded by a peripheral ring with high signal intensity. And T2-weighted MRI showed low intensity and a heterogeneously faint contrast effect.

The collected specimens were submitted for pathologic examination. Histologically, the lesion consisted of numerous histocytarian cells with a foamy, granular cytoplasm and central small, round nuclei (**Figure 2**). These cells were surrounded by scarce fibrous connective tissue. No cytological similarities to Langerhans' cells were present. Necrosis, nuclear pleomorphism, and mitosis did not existed. At the same time, lymphocytes, granulation tissues, hemosiderin and cholesterin clefts were not observed. Moreover, there was no evidence of pre-existing lesions.

Immunohistochemically, histocytarian cells were strongly positive for CD68 (RTU, Dako) and vimentin (RTU, Dako) (**Figure 3**). At the same time, CK (RTU, Dako), CD10 (RTU, Dako), CD1a (RTU, Dako) and Langerin (RTU, Dako) were negative. Thus, we confirmed the diagnosis of primary bone xanthoma without hyperlipidemia.

The patient subsequently underwent curettage. Then the patient was under clinical and radiographic follow-up for 3 years and no signs or symptoms of recurrence were observed.

Discussion

Osseous xanthoma typically occurs in the setting of endocrine or metabolic diseases, especially hyperlipidemia, hyperlipoproteinemia and diabetes mellitus [4]. Some researchers thought that lipid leakage from the blood vessels in the site of the lesion devoured by the macrophages, leading to the presence of foamy macrophages [4]. Maybe it is the most likely pathogenesis of the xanthomas with lipid disorders. So the management of the patient's lipids through diet, lifestyle modification, and drug therapy may cause regression of the osseous xanthoma with lipid disorders [5].

However, among the reported primary bone xanthoma, the cases without hyperlipidemia, characteristically indicating that it is independent of this metabolic deviation. The etiology of non-hyperlipidemia xanthoma cases remains unclear [6]. Some non-hyperlipidemia xanthoma cases lacked possible injury history and potential causes, although a mild traumatic episode was suggested by some researchers [6, 7]. Then we analyzed the available literatures about primary non-hyperlipidemia xan-

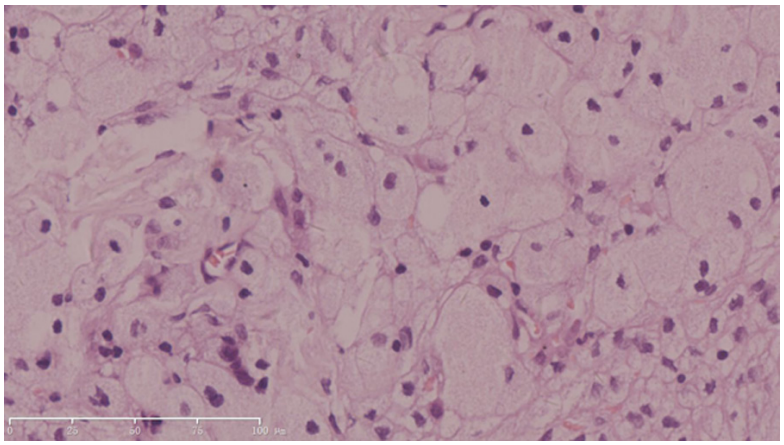

Figure 2. Histological findings (H&E stain, ×400): Numerous histocytarian cells with a foamy and granular cytoplasm and central small and round nuclei.

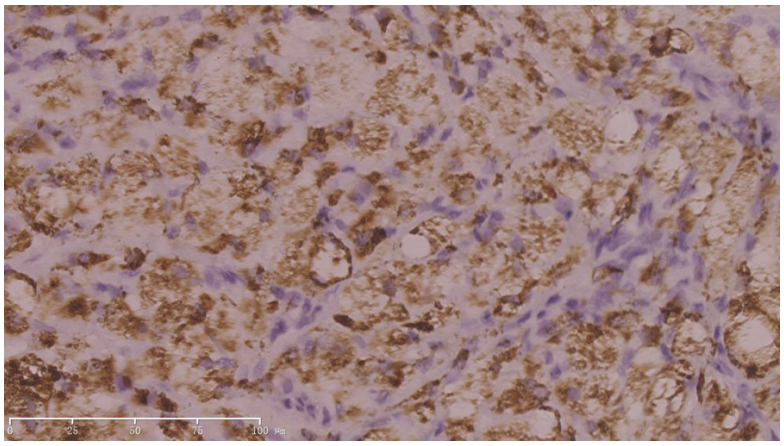

Figure 3. Immunohistochemical findings (streptavidin-biotin-peroxidase method, ×400): Histocytarian cells presenting strong positivity for CD68.

thoma of bone, discussing the clinical features, pathogenesis, imaging manifestations and histopathological features.

These 14 cases of primary non-hyperlipidemia xanthoma of bone, including our case, are shown in **Tables 1** and **2**. Patients ranged in age from 8 to 62 years (mean 27.8 years). These data are consistent with past observations about primary osseous xanthoma [15]. But male patients outnumber female in non-hyperlipidemia xanthoma of bone. It often involves the irregular flat bones than the long bones. It is different from past observations about primary osseous xanthoma [2]. Although some details of were unavailable for partial cases, the important characteristic of non-hyperlipidemia xanthoma of bone is abundant foamy cells. Scattered polymorphonuclear giant cells and fibrous connective tissue often could be observed. Inflammatory cells and cholesterol clefts are extreme circumstances. It is possible relation with the lack of lipid disorders. No reports have found hemosiderin, granuloma, necrosis and nuclear pleomorphism. At the same time, imaging manifestations is not steady, except for osteolytic sign. It is similar with bone cyst. Treatment is typically with curettage and bone grafting and is usually curative.

Taken together, non-hyperlipidemia xanthoma of bone is obvious different from xanthoma in other site. Therefore we suggested that non-hyperlipidemia xanthoma of bone was a kind of independent disease. It should be belong to bone tumors of undefined neoplastic nature. Its etiology need.

Differentiation is possible through a process of elimination by clinical findings, histological examinations and immunohistochemistry. The differential diagnoses of the present case include simple bone cyst, Langerhans cell histiocytosis, Erdheim-Chester disease, Rosai-Dorfman disease and metastasis by clear cell carcinoma, et al.

Simple bone cyst is an intramedullary cystic bone cavity lined by a fibrous membrane. The lesion consist of connective tissue, reactive new bone, haemosiderin and scattered giant cell, et al. Foamy histiocytes may be present, which absolutely is not the main component. So the existence of many different tissue element is easy to different from xanthoma.

Langerhans cell histiocytosis is a disorder of a clonal and likely neoplastic proliferation of pathological Langerhans cells, which have 'cof-

Table 1. The clinical features of previous cases of primary non-hyperlipidemia xanthoma of bone

Series	Age (year)	Sex	Initial symptom	Location	Size	Single/ Multiple	Treatments	Recurrence	Special medicine history	Imaging manifestations
1 [8]	NA	NA	NA	Skull	NA	NA	NA	NA	NA	Well-marginated radiolucent lesion with marginal sclerosis
2 [9]	62	Female	Headaches	Temporal bone	NA	Single	Excision	-	NA	Bone destruction with osteosclerosis in the surrounding area
3 [10]	8	Male	NA	Parietal bone	NA	NA	NA	NA	NA	NA
4 [11]	NA	NA	Pain	NA	NA	NA	Surgical excision	NA	NA	A lytic lesion with a rim of sclerosis
5 [12]	51	Female	Heel pain	Calcaneus	NR	Single	Total excision	-	-	A small, irregularly shaped osteolytic lesion
6 [1]	11	Male	Painless, progressively deforming mandibular asymmetry	Mandibular bone	NR	Single	Curettage	-	NR	A poorly defined image without peripheral reinforcement
7 [5]	21	Female	-	Frontal Bone	1.8×1×0.9 cm	Single	Curettage	-	Non-Hodgkin's lymphoma	medullary cavity with ill-defined margins
8 [3]	44	Male	Pathologic fracture	Distal tibia	NR	Single	Curettage	-	An extensive cigarette-smoking history and a remote history of intravenous drug abuse; A longstanding malunion of the calcaneus secondary to a fall with substantial subtalar and midfoot arthritis	Lytic lesion
9 [3]	23	Male	Hip pain	Iliac crest	N	Single	Curettage	-	-	A lytic lesion with a well-defined border
10 [3]	9	Male	-	Occipital bone	1.7×1.0 cm	Single	Curettage	-	Widespread Hodgkin's lymphoma	
11 [13]	44	Male	Chest wall pain	Rib	4.0 cm	Single	Thoracoscopic surgery	NR	NR	NR
12 [4]	25	Male	-	Mandible	2.0 cm	Single	Curettage	-	-	Diffuse, unilocular and radiolucent lesion with irregular margins
13 [14]	25	Male	Sensation of discomfort in the region	Inferior Orbital Rim	NR	Single	Surgical intervention	NR	-	Lytic, unilocular, and radiolucent lesion with irregular margins
14 (our case)	11	Male	Swelling pain	Femur	4.5×2.0×1.5 cm	Single	Curettage	-	-	A clearly demarcated expansile osteolytic lesion

NA: no acquire; NR: no report.

Table 2. The histopathological features of previous cases of primary non-hyperlipidemia xanthoma of bone

Series	Foamy cells	Polymorphonuclear giant cells	Fibrous connective tissue	Inflammatory cells	Cholesterol clefts	Hemosiderin	Necrosis	Nuclear pleomorphism	Mitosis
1 [8]	NA	NA	NA	NA	NA	NA	NA	NA	NA
2 [9]	+	NA	+	NA	+	NA	NA	NA	NA
3 [10]	NA	NA	NA	NA	NA	NA	NA	NA	NA
4 [11]	+	+	+	NA	NA	NA	NA	NA	NA
5 [12]	+	+	NR	+	NR	NR	NR	NR	NR
6 [1]	+	NR	+	+	+	NR	NR	NR	NR
7 [5]	+	-	NR	NR	NR	NR	-	NR	NR
8 [3]	+	+	NR	NR	NR	NR	NR	NR	NR
9 [3]	+	+	NR	NR	NR	NR	NR	NR	NR
10 [3]	+	+	NR	NR	NR	NR	NR	NR	NR
11 [13]	+	NR	+	NR	NR	NR	NR	NR	NR
12 [4]	+	NR	+	NR	NR	NR	-	-	-
13 [14]	+	NR	+	NR	+	NR	-	-	-
14 (our case)	+	+	+	-	-	-	-	-	-

NA: no acquire; NR: no report.

fee bean nuclei' and a characteristic immunophenotype: CD1a and Langerin positivity. It is not found in xanthoma.

Erdheim-Chester disease is a xanthogranulomatous histiocytosis, belong to a rare, systemic histiocytic disease of obscure etiology [16]. The lesion is composed of non-Langerhans cell histiocytes, scattered Touton-type giant cells and reactive fibrous tissue in multiple organs. Inflammatory cells, such as lymphocytes and plasma cells, often contained in the lesion [16]. So the multifocal disease process lacking an inflammatory cells infiltrate distinguishes this condition from xanthoma.

Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy) is a polyclonal histiocytic disorder of uncertain etiology. Bone involvement is extremely uncommon. The appearance and immunophenotype of abnormal cells in this lesion most closely approximate an activated macrophage with some degree of atypia. The histiocytes of Rosai-Dorfman disease consistently and strongly express CD68, S-100 protein and occasionally other histiocytic antigens including CD1a. Xanthoma do not express S-100 and lack emperipolesis, which could help to differentiation.

Metastatic clear-cell carcinoma, such as metastatic renal clear cell carcinoma, can also be excluded by more histological pleomorphism. Moreover, immunohistochemical staining can help to further identify the tissue of origin.

In conclusion, we have described a case of primary non-hyperlipidemia xanthoma of bone, characteristically indicating that it is independent of this metabolic deviation. It is different from xanthoma with lipid disorders. We suggested that non-hyperlipidemia xanthoma of bone was a kind of independent disease through the available literatures and our case. It should be belong to bone tumors of undefined neoplastic nature. Its etiology need.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Zhuo Wang, Department of Pathology, The First Affiliated Hospital of Sun Yat-Sen University, 58 Zhongshan Road II, Guangzhou 510080, China. Tel: +86 20 87331780; Fax: +86 20-87331780; E-mail: wangzh25@mail.sysu.edu.cn

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