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Case Report of the positive exostosin-1 without B-cell lymphoma-2 gene expression of giant cell tumor lesion in hereditary multiple exostosis

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ABSTRACT

INTRODUCTION: The giant cell tumor, in which BCL-2 gene was expressed only in its malignant transformation, is a benign, primary skeletal neoplasm with variable biologic aggressiveness. The is of the giant cell tumor. A coexistence with hereditary multiple exostosis with expression of EXT-1 is very rare. The correlation between giant cell tumor in hereditary multiple exostosis is still not clearly determined.
PRESENTATION OF CASE: A 31-years-old female presented with pain and lump on her left wrist and a coexistence of non tender multiple lump in the right and left knee. A wide excision of the tumor and reconstruction using non vascularized fibular graft was performed, followed by histopathology and immunohistochemistry of EXT-1 and BCL-2.
DISCUSSION: In this case, the tumor showed negative BCL-2 and positive EXT-1 gene expression. Giant cell tumor and hereditary multiple exostosis also demonstrated associations of chromosomes 11 with a different pathological process.
CONCLUSION: Giant cell tumor in hereditary multiple exostosis revealed positive EXT-1 without BCL-2 expression. It still need more investigation to confirm the relationship between these tumors.

1. Introduction

Giant cell tumor (GCT) is a locally aggressive neoplasm. It often characterized by osteolytic destruction at the end of a long bone and large multinuclear cells in its histologic appearance. It is benign in nature and known to be able to both recur and transform into malignancy [1–3]. The malignant subtype of GCT is usually expressed some genes like the B-Cell Lymphoma 2 (BCL-2) gene [4]. The GCT was rarely found in coexistence with other benign lesion such as hereditary multiple exostosis (HME) [5,6]. The reason behind that coexistence is still unclear, whether caused by either a transformation of HME or only considered as two separated lesions. Hereditary multiple exostosis is an autosomal dominant condition which characterized by the development of multiple exostosis and possess interfamilial and intrafamilial phenotypical variability in severity, size, and number of lesions. This HME lesions are primarily caused by the presence of Exostosin-1 (EXT-1) gene that occur in approximately 90% of cases [7]. The aim of this report is to identify the BCL-2 and EXT-1 gene in GCT with coexistence of HME. It also served as a preliminary research to prove that the GCT with the expression of EXT-1 and BCL-2 in patients with HME tend to be more aggressive with high local recurrence and worse prognosis.

2. Presentation of case

A 31-years-old female presented with pain and lump on her left wrist since 4 months ago. Physical examination revealed a lump located on left wrist. The size of the lump clinically was 5 cm by 6 cm with shiny skin, clear border, firm in consistency, and fixed to the bone (Fig. 1a). Her wrist extension and flexion was limited to 10° of flexion and 5° of extension due to pain and mass. On the right and left knees, we found non-tender multiple lumps (Fig. 1b). The x ray of left wrist revealed osteolytic lesion with some geographic patterns (Fig. 1c).

She had wide surgical excision of the tumor which extended to the wrist joint and 3 cm upper the tumor followed by recon-

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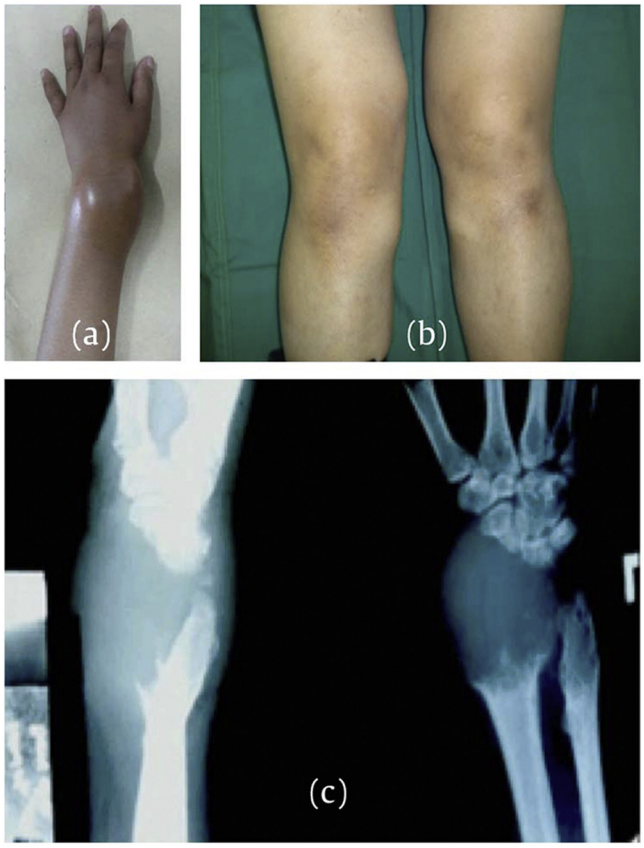

Fig. 1. Clinical and X-ray Findings.

struction using non vascularized fibular graft. Proximal fibular graft has harvested, including the head of left fibula. We found multiple bony masses with clinical characteristics of multiple exostosis on the proximal site of fibular graft (Fig. 2a). The excised part of the radius has replaced with non-vascularized fibular graft, then fixed with plate and screws. The distal part of the graft was transfixed with Kirschner wire (Fig. 2d).

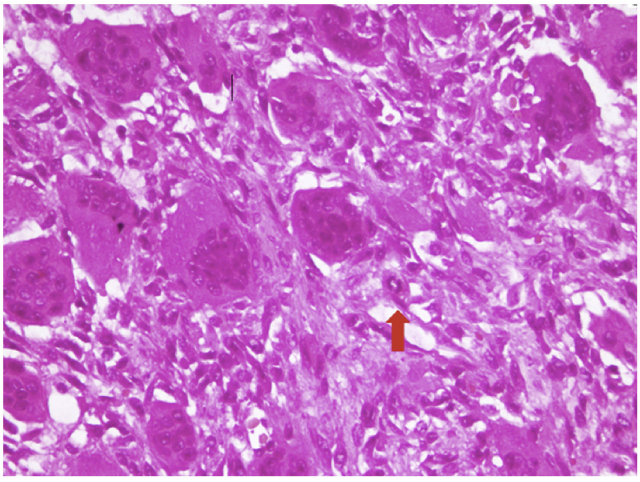

Fig. 3. The histopathological result.

Histopathology and immunochemistry examination of EXT-1 and BCL-2 revealed some important findings. Histopathological finding revealed GCT with an eosinophilic cytoplasm, round ovals nucleus, vesicular chromatin with small nucleus prominent, and a slight mitosis (Fig. 3). Immunochemistry finding revealed existence of EXT-1 but no existence of BCL-2 (Fig. 4).

Mayo Wrist score was used to evaluate her functional outcome two years post operation. The result is good with total score 90. The patient feels no pain, already returned to regular activities, range of motion return to 75–99% and the grip strength is 100% (Fig. 2e).

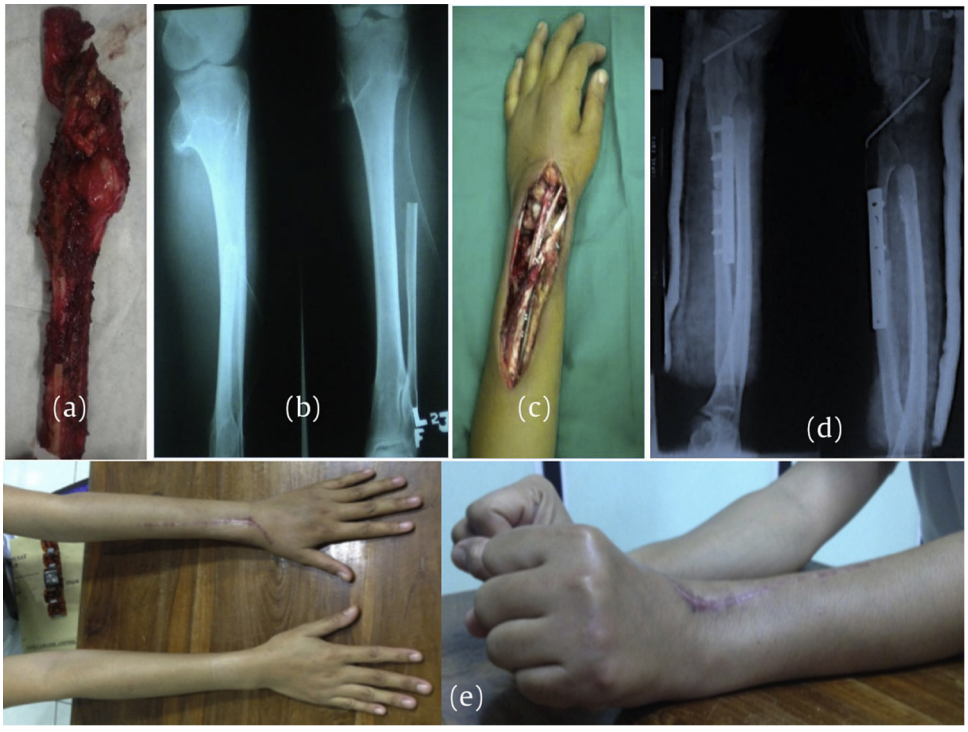

Fig. 2. Post wide excision and reconstruction using fibular graft.

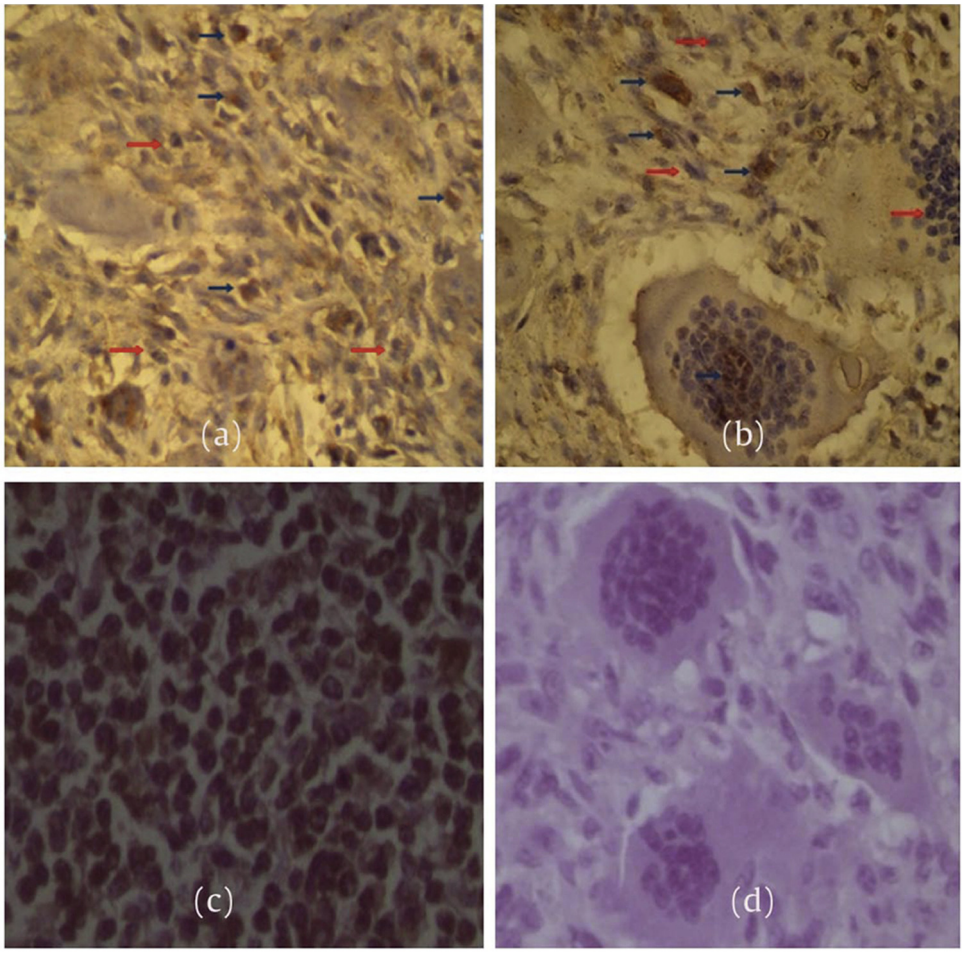

Fig. 4. The immunohistochemistry result (EXT-1 and BCL-2).

3. Discussion

The case presented a GCT of the left wrist with another lesion of HME on the right and left knee. This case was very rare because we were not able to find more cases in the literature matching this coexistence. There were only two cases reported in the last ten years. The first one was reported by Heybeli et al. (2002) mentioning a coexistence of giant cell tumor over the left leg, *para*-articular osteochondroma over the left hip and an idiopathic thrombocytopenic purpura (ITP) [5]. A curettage of GCT lesion was performed, followed by washing out the remainder with hot saline, then filled with autogenous iliac bone graft and cement. Furthermore, proximal femoral resection and prosthetic reconstruction were performed on her hip. The histopathological examination revealed a GCT of bone. Rodriguez-Franco et al. (2015) has reported a case of GCT of proximal tibia in patient with history of multiple osteochondromatosis [6]. The tumor was resected, a skeletal reconstruction with GMRS prosthesis was performed, followed by soft tissue reconstruction with rotation flap. Histopathological examination revealed GCT with area of fibrohistiocytic pattern and component of aneurysmal bone cyst. The report also suggested a positive genetic polymorphism in the EXT-2 gene [6].

In this case, we suspected the existence of two tumors in one patient. The immunohistochemistry examination was performed to assess gene profile in both lesions. There was revealed a positive expression of EXT-1 gene and negative expression of BCL-2 gene from GCT mass of left wrist. The cells giving positive reaction of anti-EXT-1 with B chomogen method (Fig. 4a and b). Positive reaction was pointed by blue arrow, on the other hand, negative reaction was represented by red arrow. There was observed some cells giving negative reaction to BCL-2. Positive control showed coloration on nucleus and cytoplasm, whereas no coloration on nucleus and cytoplasm was found on negative as seen on Fig. 4c and d, respectively.

Currently, EXT-1 gene has considered as an important causative factor in hereditary multiple exostosis [8–10]. Hereditary multiple exostosis is genetically heterogeneous with three loci on chromosomes 8q24.1, 11p13, and 19q. The first EXT-1 locus that located on chromosome 8 (8q24.1) was discovered by Cook in 1993, which also linked with chromosome 11q24. The distal end of 8q locus is responsible for the formation of HME and was identified as the EXT-1. Later on, a new gene on chromosome 11 (11p11-13) was identified as a locus for HME and named EXT-2. A third locus on chromosome 19p, suspected of causing HME was named EXT-3, but it is considered to be a minor contributor to the actual formation of HME [10]. Most of the EXT-1 and EXT-2 genes (80%) prompt to mutation by nonsense, frameshift or splice-site mutations leading to premature termination of the EXT proteins [11].

Giant cell tumor of the bone is a benign, primary skeletal neoplasm with variable biologic aggressiveness that demonstrates telomeric associations of chromosomes 11, 16, 19, 20, and 21, reduction of telomere length, marker chromosomes, double minutes, chromosome fragments, ring chromosomes, and polyploidy [12]. Some gene that expressed in GCT such as iP53, H-ras, C-myc,

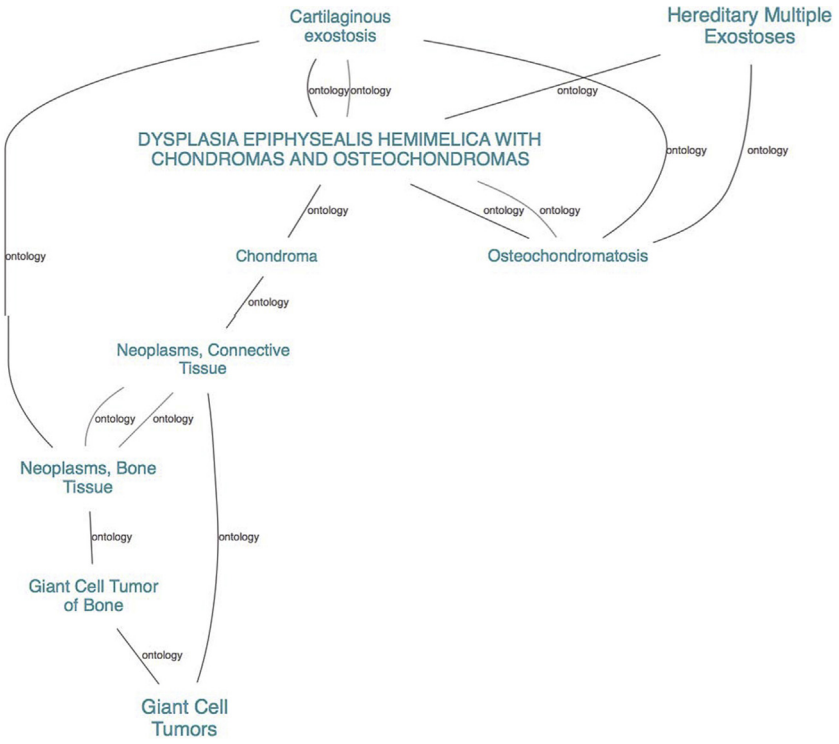

Fig. 5. Diagram of relations between GCT and HME.

MMP-9, MIB-1 and BCL-2 had important rules for malignant transformation [13] . The presence of EXT-1 gene in GCT was rare as seen on this case.

We have also performed immunohistochemistry of BCL-2 for finding the apoptosis process in the tumor lesions. BCL-2 is an anti-apoptosis protein whose overexpression contributes to the uncontrollable proliferation of gliomas and other neoplasm's [14]. BCL-2 is a human proto-oncogene located on chromosome 18q21.3. This gene was discovered as the translocate locus in B-cell lymphomas. It encodes an integral membrane protein (25 kDa protein), mainly localized to inner mitochondrial membrane, endoplasmic reticulum and nuclear envelope. This gene was preventing cells from undergoing apoptosis. The BCL-2 overexpression increases lifespan of B cells, maintains memory B cells, plasma cells and neurons by prolonging life span without cell division. It also may participates in ion channel formation and alteration of membrane permeability that necessary for initiation of apoptosis. A non-phosphorylated BCL-2 inhibits apoptosis [14].

Khooei et al. (2010) in their study reported a higher value of BCL-2 in malignant subtype of GCT [4]. This implies that malignant transformation could trigger GCT cells to express this marker more frequently, thus, it could be regarded as an indicator for malignant transformation and unfavorable clinical course. Pammer et al. (1998) studied expression of regulatory apoptotic proteins in peripheral giant cell lesions containing osteoclast-like giant cells that showing only weak positivity for BCL-2 [15]. In this case the BCL-2 result is negative, revealing that the giant cell tumor was not transformed into malignant.

Based on the results of this study, GCT characterized as benign aggressive with negative BCL-2 gene expression and showed similarity with HME by a positive EXT-1 gene expression. The GCT and HME also demonstrated associations of chromosomes 11 with different pathological process [12].

A data based on ontology between HME and GCT assuming that GCT may arise from a transformation of HME. Further investigation is needed to confirm the relationship between these tumors (Fig. 5)[16].

4. Conclusion

Giant cell tumor in hereditary multiple exostosis revealed positive EXT-1 without BCL-2 expression. In this case, this coexistence revealed a probability of GCT that arised from HME but did not showed malignant transformation. Further advanced researches are needed to confirm the association between HME and GCT lesion.

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