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Research paper

Retrospective investigation of "paint brush borders" sign in association with local recurrence of giant cell tumor of bone after intralesional curettage

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1. Introduction

Giant cell tumor of bone (GCTB) is characterized by a large number of osteoclastic giant cells uniformly distributed amongst a background of mononuclear pindle-like stromal cells and rounded monocytes [1–3]. It is one of the most prevalent musculoskeletal tumors in East and South-East Asia as opposed to Western countries (20% vs 5%)[4,5]. The end of long bone is involved in more than 80% of cases and 75% of them occur in proximal tibia and distal femur [6], and is mainly treated with intralesional curettage [7,8]. As an intermediate tumor with a tendency of local invasion, clinical treatment of GCTB is challenged by a high rate of local recurrence (13–65%) [8,9].

Prognostic factors for local recurrence of GCTB need to be identified in terms of surgical treatments, clinical features, imaging findings, and genetic and molecular aspects [10]. The residual tumor after surgery was considered responsible for local recurrence [9]. Features on tumor border are worthy of clinical investigation. Thankfully, GCTB can be probed in many ways depending on the non-invasive imaging device used or the mode by which it operates [11,12]. Magnetic resonance (MR) imaging is especially valuable for the diagnosis of bone tumors due to its heightened sensitivity to soft tissue disease and multiplanar image acquisition [13]. "Paint brush borders" sign (Figs. 1 and 2) is one of common MR features on the border of GCTB, and can likely be found on conventional MR images [10]. However its clinical value was unclear and had never been correlated with local recurrence yet. We firstly describe this MR sign as penetrating irregular margins with “paint brush" appearance protruding toward the bone from edge of GCTB. Morphology information of tumor edge might associate with tumor residues.

High activities of matrix metalloproteinase (MMP) and vascular endothelial growth factor (VEGF) have been linked to biological aggressiveness of GCTB [14,15]. Kumta et al. demonstrated that elevated levels of VEGF and MMP-9 in GCTB correlated well with local recurrence [16]. In bone tumors, co-overexpression of receptor activator of nuclear factor-κ B (RANK) and RANK ligand (RANKL) was identified as a potential discriminating factor for poor prognosis [17], and the expression of RANKL affected the proliferation of neoplastic GCTB cells in another study [18]. Based on these studies, GCTBs with elevated levels of these proteins might be more prone to recur.

The purpose of this study was to investigate the role of preoperative MR features of "paint brush borders" sign in predicting local recurrence. The pathological basis and the immunohistochemistry (IHC) findings in terms of VEGF, MMP-9, RANKL, and RANK were involved. Also we retrospectively analysed the characteristics of this sign based on a prospectively collected database. At least two years followed up was required.

2. Materials and methods

2.1. Patients

This study was approved by our institutional review board and was carried out in accordance with the relevant guidelines and regulations. Written informed consent was obtained from all patients prior to enrolment in the study. All patients had histopathologically confirmed GCTB located in the proximal tibia or distal femur. MRI scans of all patients were obtained and analysed prior to surgery. Fifty-five patients that underwent intralesional curettage, which is the preferred treatment for GCTB and which was performed consistently by a sub-group of orthopedic specialists in our hospital, were registered and followed up

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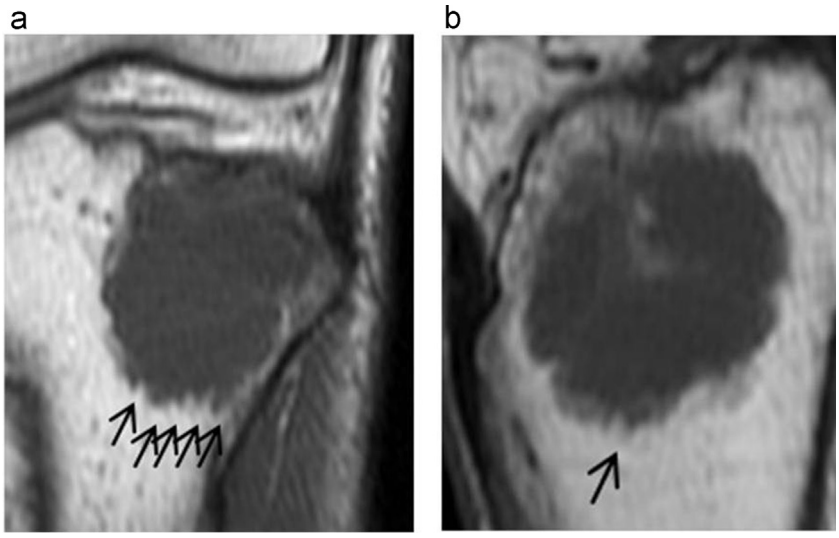

Fig. 1. A 59-year-old man with GCTB in proximal tibia treated with curettage. (A) Coronal and (B) sagittal T1WI show "paint brush borders" sign that a number of protrusions (black arrows) protruding toward the bone from edge of GCTB.

in this study from January 2005 to July 2015. Moreover, from March 2013 to July 2016, 36 patients with GCTB around the knee were enrolled for investigation of IHC features, including the protein expressions of VEGF, MMP-9, RANKL, and RANK. Twenty-two of these patients overlapped with the former group; en bloc resection was performed in the other 14 patients, two of whom were enrolled for investigation of the pathologic basis of specific preoperative MRI features. Over 2 years of followed-up results were obtained.

2.2. Imaging procedures

MR examinations were performed on a 1.5-T superconducting whole-body imager (Signa, General Electric Medical System) with dedicated extremity coils.

A combination of axial, sagittal and coronal images was obtained using the following sequences: spin-echo T1-weighted (TR range/TE range, 450–600/15–20), fast spin-echo T2-weighted (TR range/TE range, 3500–4000/80–120). Fat-suppressed fast spin-echo T2-weighted (TR range/TE range 3500–4000/80–120) was performed on sagittal or coronal plane. Field of view, slice thickness and interslice gap varied depending on diseased region and tumor size. Slice thickness was 5 mm and interslice gap was 0.5 mm. The imaging matrix ranged from 192×256 to 256×256.

2.3. Imaging analysis and classification

"Paint brush borders" sign were observed in axial, sagittal and coronal by three senior musculoskeletal radiologists (X. D. [28 years of experience], L.D. [19 years of experience], and H. W. [15 years of experience]). Patients with "paint brush borders" sign were classified into the positive group. However, if a mutual consensus could not be reached, the verdict of the majority was accepted.

2.4. Intralesional procedure

For each case, the intralesional procedure was recorded explicitly. All 56 patients were treated with intralesional curettage conducted by a senior orthopedic surgeon (J. X. [20 years of experience]). The tumor tissue was first removed with a curette after a wide cortical window was created. The remainder of the tumor cavity was eliminated with a high-speed burr. Phenol was applied in the borders of the cavity with cotton-tipped applicators and then neutralized with alcohol in 31 cases; the remaining 25 cases were treated without additional adjuvant. Finally, the tumor cavity was carefully packed with polymethylmethacrylate (PMMA) filling.

2.5. Follow up and recurrence

All patients were reexamined by X-ray or MR annually, regardless of whether or not they were symptomatic. Patients were followed up for at least two years. The extension of the radiolucent zone on radiographs after bone cement filling was a reliable indicator for possible local recurrence. The recurrent tumor represented high signal intensity around PMMA on T2WI. The patients should be reexamined immediately if any relative symptoms (abnormal pain and swelling) occur after surgery.

2.6. Correlation with pathology

Surgical specimens were obtained from two patients treated with en block resection. According to the acquired images, formalin-fixed and paraffin-embedded specimens were sectioned and hematoxylin-eosin stained.

2.7. Immunohistochemistry

IHC was performed on formalin-fixed, paraffin-embedded tumor tissue samples, cut into 3-μm-thick sections representative of the tumor. The sections were deparaffinised, rehydrated, and treated using the automated immunostainer BenchMark XT (Ventana Medical Systems SA, Strasbourg, France), following antigen retrieval with citrate buffer (pH 6.0) for 25 min. Subsequently, the sections were incubated with the relevant antibodies for 1 h at 37 °C, followed by addition of the polymeric detection system ultraView Universal DAB Detection Kit reagents (Ventana Medical Systems). Finally, the sections were automatically counter-stained with Gill's modified haematoxylin and cover-slipped with EUKITT® (ORSAtec GmbH, Bobingen, Germany). The tissues were immunostained according to the manufacturer's instructions with the following four antibodies: MMP9 (ab38898, polyclonal, 1:1000; Abcam, Cambridge, UK), VEGF (Anti-VEGF Receptor 1 Antibody, Y103, 1:250; Abcam), RANK (Receptor Activator for Nuclear Factor-κ B, 64C1385; Abcam), and RANKL (Receptor Activator for Nuclear Factor-κ B Ligand, 12A668; Abcam). Mouse brain tissue was used as a positive tissue control for the anti-VEGF antibody, and RAW 264.7 cells were used as the positive tissue control for the other antibodies. IHC on adjacent sections in the absence of the primary antibody was performed as a negative control. The sections were analysed with an Olympus light