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Morphological classification for prediction of malignant transformation in multiple exostoses

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Abstract. – AIM: To explore the value of morphological classification in predicting malignant transformation in multiple exostoses (ME).

PATIENTS AND METHODS: The imaging data of 116 patients (totally 190 tumors) with ME were retrospectively analyzed. All the tumors were pathology confirmed after surgical resection, including 175 exostoses from 101 patients, and 15 exostotic chondrosarcomas in 15 cases. Based on the ratio of diameter between tumor tip and tumor base (R1), tumors were classified into two types: cauliflower-like tumor (R1 ≥ 1.0) and non-cauliflower-like tumor (R1 < 1.0). In addition, non-cauliflower-like tumors were further classified into two subtypes according to the ratio of tumor height to tumor base diameter: sessile type (R2 < 1.0) and pedunculated type (R2 ≥ 1.0). The relationship between tumor shape and malignant transformation was studied.

RESULTS: Of all the 175 exostoses from 101 patients, 27 were cauliflower-like tumors and 148 were non-cauliflower-like tumors. Of all the 15 exostotic chondrosarcomas in 15 cases, most tumors were cauliflower-like ($\chi^2 = 38.0075$, $p < 0.05$). Cauliflower-like tumor for the prediction of exostotic chondrosarcoma, the sensibility, specificity, positive predictive value, negative predictive value were 86.7%, 84.6%, 32.5%, 98.7%, respectively.

CONCLUSIONS: Tumor malignant transformation was more common in cauliflower-like tumors than in non-cauliflower-like tumors. The morphological classification and preventive resection of cauliflower-like tumors maybe helpful in preventing the malignant transformation of ME.

Key Words:
Homocysteine (Hcy), Atherosclerosis (AS), Oxidative stress, Lutein.

Introduction

Malignant transformation is one of the most serious complications of multiple exostoses (ME), which needs surgical treatment in most cases[1]. The early prediction of malignant transformation is important for making therapeutic plan. The traditional classification method is based on the tumor base diameter, i.e., sessile type and pedunculated type[2]. This only reflects the shape difference between tumors and can not illustrate the relationship between tumor shape and malignant transformation. In this work, through the study of the shape of cartilage cap and bone tissue of 190 tumors in 116 patients with ME, a new classification method was proposed to improve the knowledgement of tumor shape for clinicians as well as for radiologists.

Patients and Methods

Patients

This retrospective study was approved by the Institutional Review Board, and written informed consents from patients were waived.

The image data of 3568 cases with osteochondroma or exostosis were collected and retrospectively studied, all patients admitted to Hangzhou First People's Hospital and the Second Affiliated Hospital of Zhejiang University School of Medicine from January 2003 to June 2013. Among all the cases, 116 of 182 ME cases finally received surgical treatment, including 77 males and 39 females, aged from 4 to 55 years (Median 13.2

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years). Among these cases, 15 exostotic chondrosarcomas were found in 15 patients, including 12 males and 3 females, aged from 13 to 55 years (median 37.6 years), and 13 patients were with age older than 18 years. Thirteen patients visited the Outpatient Clinic due to painful mass, 18 due to trauma, 85 due to painless mass. Among the 116 ME patients, 36 were with family history, and the other 80 cases were uncertain.

Morphological Classification of Tumors

Based on the ratio of diameter between tumor tip and tumor base (R1), tumors were classified into two types: cauliflower-like tumor (R1 ≥ 1.0, Figure 1a and 2a) and non-cauliflower-like tumor (R1 < 1.0, Figure 1b). In addition, non-cauliflower-like tumors were further classified into two subtypes according to the ratio of tumor height to tumor base diameter (R2): sessile type (R2 < 1.0, Figure 1c and 2b) and pedunculated type (R2 ≥ 1.0, Figure 1d and 2c).

The distribution and classification of tumors were confirmed by two radiologists with 10 years working experience in orthopedics department.

Statistics Analysis

Statistical analysis was performed with use of commercially available software SPSS version 12.0 (SPSS Inc, Chicago, IL, USA). Chi Square test was used to compare the rate of malignant transformation in cauliflower-like tumors with that in non-cauliflower-like tumors, a p value < 0.05 was considered significant.

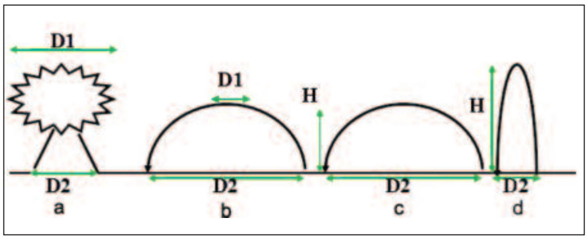

Figure 1. ***a,*** Cauliflower-like tumor (R1 = D1/D2 ≥ 1.0). ***b,*** Non-cauliflower-like tumor (R1 = D1/D2 < 1.0). ***c,*** Sessile type (R2= H/D2 < 1.0). ***d,*** Pedunculated type (R2 = H/D 2 ≥ 1.0).

Results

Imaging Manifestations of 15 Exostotic Chondrosarcoma Cases

The computed radiography (CR) images of 15 exostotic chondrosarcoma cases were all available, with 8 cases have both computed tomography (CT) contrast enhancement images and contrast-enhanced magnetic resonance imaging (MRI) scan images, 4 cases have plan CT scan images, and other three cases only have computed radiography images. From the image data of 12 ME cases with CT or/and MRI images, tumor cartilaginous cap

Figure 2. ***A,*** Cauliflower-like tumor. ***B,*** Sessile type of non-cauliflower-like tumor. ***C,*** Pedunculated type of non-cauliflower-like tumor.

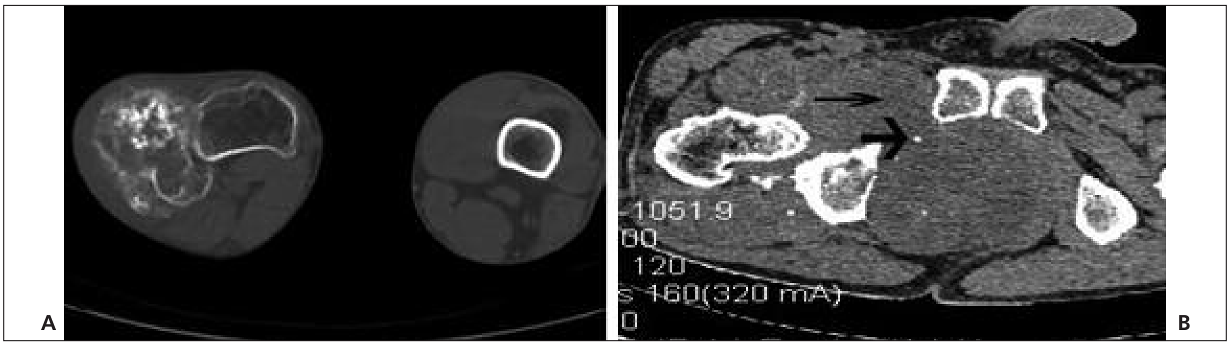

Figure 3. ***A,*** Ccauliflower-like tumor at the proximal end of left tibia. The arrow showed that cartilaginous cap was calcified and thickened. The diagnosis of exostotic chondrosarcoma was confirmed by histopathology. ***B,*** Soft tissue mass on the right pubis (*fine arrow*), punctate calcification was observed in the mass (*coarse arrow*). The diagnosis of exostotic chondrosarcoma was confirmed by histopathology.

were calcified and thicken than 2.5 cm (Figure 3a), 10 cases were with cartilaginous cap destruction (Figure 3a), 8 cases were with bone substance destruction at the tumor base, 9 cases were with soft tissue mass surrounding the tumor (Figure 3b), 2 cases with synovial sac formed. Eight cases were examined by contrast-enhanced MRI scan, tumor cartilaginous caps were presented as septa or arc/ring-like intense enhancement (Figure 4a, 4b). Malignant transformation was not diagnosed before the surgery in three cases with only CR examinations.

Morphological Classification and Malignant Transformation

All the studied 116 patients received surgical partial resection, 190 tumors were resected, 15 chondrosarcomas of 15 patients were pathologically confirmed (Figure 5), the other 175 tumors from 101 cases were diagnosed to be exostosis (Figure 6). Of all the 15 exostotic chondrosarcomas, 13 were cauliflower-like tumors, the other two were non-cauliflower-like tumors in sessile type. Of all the 175 exostoses, 70 were non-cauliflower-like tumors in pedunculated type, 78 were in sessile type, and 27 were cauliflower-like tumors. The relationship between tumor classification and malignant transformation was displayed in Table I.

Through chi square test, the incidence rate of exostotic chondrosarcomas was significantly higher in cauliflower-like tumors than in non-cauliflower-like tumors, $\chi^2 = 38.008$, $p < 0.05$.

The predictive value of cauliflower-like tumor for exostotic chondrosarcoma was presented in Table II.

Discussion

ME is a kind of congenital bone dysplasia, majorly affects endochondral bones. It is a kind

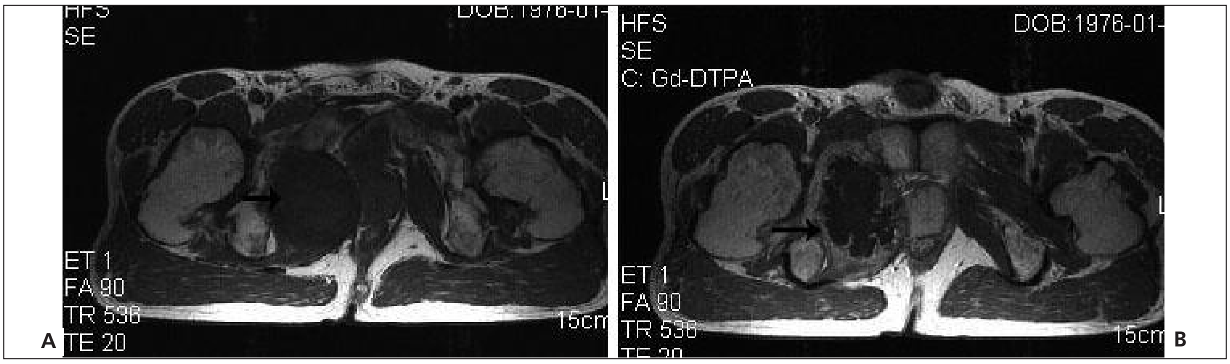

Figure 4. For the same ME patients. T1WI presents long T1 signal. Intense enhancement of the posterior mambrane and interval (*showed by arrow*). The diagnosis of exostotic chondrosarcoma was confirmed by histopathology.

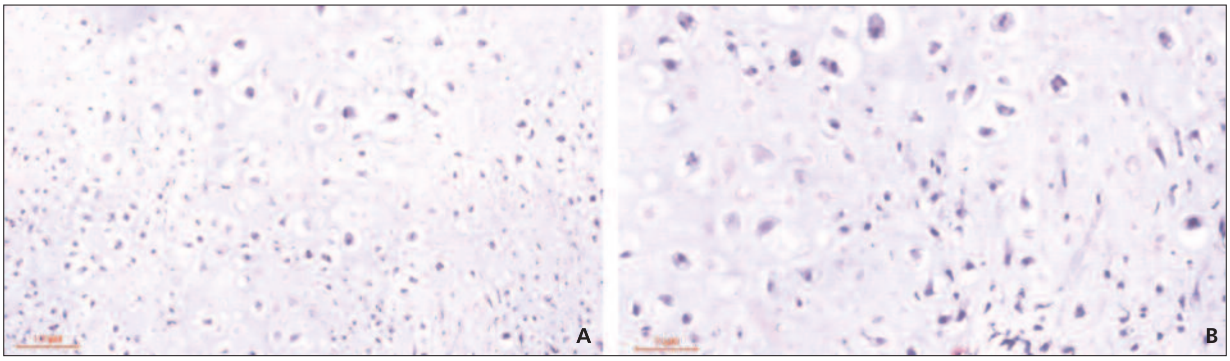

Figure 5. HE staining. ***A,*** High density of chondrocytes, cells with large atypical nucleus, increased amount of binucleus cells (× 100). ***B,*** High density of chondrocytes, cells with large atypical nucleus, increased amount of binucleus cells (× 200).

of benign bone tumor generally arises in the metaphyses of long bones, and some cases are autosomal dominant inheritance. The clinical treatment mostly focuses on its complications, among which malignant transformation is mostly concerned. Exostotic chondrosarcoma is the most common type of malignant transformation of ME (90%). The rate of malignant transformation was differently reported in varies literatures, which was 9.2% in the work of Altay et al[3], 27% in that of Garrison et al[4] and 0.6-2.8% in that of Kivioja et al[5]. However, most scholars believed that that rate should be 1-5%[6,7]. In this work, the rate was 12.9%. Considering all the studied patients were screened in outpatient clinic, surgical resection was applied for those probably with malignant transformation, and this rate should be a little higher than the incidence rate in natural populations. Since there are multiple tumors in patient with ME, it is impossible and not necessary to preventively resect all the tumors. Therefore, it is important to find malignant transformation in the early phase or to predict the malignant transformation and, thus, to preventively resect it.

The development and malignant transformation of exostosis is generally originated from the chondrocyte in cartilage cap[8], only little ME cases reported that the malignant transformation originated in the stalk[9]. Rather than blood supply, the cartilage cap is supplied by synovial fluid, hence, ischemia and calcification occur in part of the cartilage cap due to the limited infiltration distance of synovial fluid[10-12]. In the case, calcification is a mark of tumor activity: for slow-growing tumor, the calcification area is small and with smooth edge, plan scan or CT reveals the non-cauliflower-like tumor, either sessile type or pedunculated type; while for active tumor, the calcification area is of un-

Table I. The relationship between tumor classification and malignant transformation.

	Pathology exostotic chondrosarcoma	Exostosis	χ^2	p
Cauliflower-like tumor	13	27		
Non-cauliflower-like tumor (pedunculated type + sessile type)	2	148	38.008	0.000

Table II. Predictive value of cauliflower-like tumor for exostotic chondrosarcoma.

	Sensibility	Specificity	Positive predictive value	Negative predictive value
Cauliflower-like tumor	86.7 (13/13+2)	84.6 (148/148+27)	32.5 (13/13+27)	98.7 (148/148+2)

even thickness, in the shape of ring like, half-ring like or arc like, and the tumor is cauliflower-like on plan scan or CT image. Once malignant transformation occurs in active tumor, the calcification may be reabsorbed to some degree and destructed. Therefore, occurrence and absorption of calcification reflect the different stage of the disease development in cartilage cap, which could be used in differential diagnosis of benign and malignant tumors.

Giudici et al[2] focused on the relationship between malignant transformation and cartilage cap, and they reported that malignant transformation occurs more in sessile type tumors, with larger cartilage cap area, than in pedunculated type. However, detailed study about the possibility of malignant transformation still lacks. The development and malignant transformation of ME is originated in cartilage cap, and the tumor shape is somewhat related to the bone tissue under cartilage. For differential diagnosis of benign and malignant tumors, the shape of cartilage cap and bone tissue (tumor tip) can more accurately reflect the biological property of the tumor than the tumor base diameter. Contrast-enhanced MRI scan of the cartilage cap is a relatively accurate way for differential diagnosis. De Beuckeleer et al[13] reported that the low signal intensity septa on T2WI and the septa or arc/ring-like intense enhancement on contrast-enhanced T2WI should be the candidate reference for malignant tumors. Geirnaerdt et al[14] reported that fast dynamic technique is helpful for differential diagnosis of benign osteochondroma and low-grade malignant osteochondroma. Contrast-enhanced MRI scan was performed for the studied 8 cases before surgery, tumor cartilaginous caps were presented as septa or arc/ring-like intense enhancement. MRI is of great advantage in differential diagnosis. However, due to its low penetration, high cost and contraindication, MRI can not be applied in routine examination as well as in the long term follow up examinations. Relatively, plan scan and CT can not provide the detail information of uncalcified cartilage cap, but it can be used to trace the disease progression of ME patients with calcified cartilage cap. Primary diagnosis can be drawn based on the morphological change of the calcification area, and then MRI could be applied to further confirm the diagnosis of malignant transformation. This could reduce misdiagnosis with acceptable economic burden. Our study revealed the potential relationship between tumor shape and malignant transformations, i.e., exostotic chondrosarcomas were more common in cauliflower-like tumors (13/40), while benign exostoses were more common in non-cauliflower-like tumors (148/150). cauliflower-like tumor for the prediction of exostotic chondrosarcoma, the sensibility, specificity, positive predictive value, negative predictive value were 86.7%, 84.6%, 32.5%, 98.7%, respectively. In clinical practice, more attention should be paid to cauliflower-like tumors thus to detect the malignant transformation in the early phase and to reduce the operation wound as well as the recurrence rate after surgery.

Conclusions

Based on the X ray and CT image data, the classification method proposed in this work is a supplementary of the traditional classification method. This classification can be easily applied in the clinical practice and, thus, deserves widely applied.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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