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Expression of insulin-like growth factor II mRNA binding protein 3 (IMP3) in enchondroma and chondrosarcoma

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ABSTRACT

Atypical cartilaginous tumor and enchondroma are similar in histopathologic aspects. Although the clinical course, radiologic and pathologic examinations enable distinction in most cases, difficulties are still encountered by the pathologists. There is no known biomarker to help make a distinction between benign and malignant cartilaginous tumors. Insulin-like growth factor II mRNA binding protein (IMP3) is a member of an oncofetal family of proteins that is expressed in different human malignancies and rapidly emerging as a prognostic and diagnostic marker in surgical pathology. In this study, IMP3 expression was examined by immunohistochemistry in 36 enchondromas and 42 chondrosarcomas of different histologic grades. The results showed that all 36 cases of enchondroma were negative for IMP3, while it was overexpressed in 15 of 42 chondrosarcomas (36%) ($P<0.01$). Significant higher levels of IMP3 were detected in grade III chondrosarcomas (6 of 7; 85.7%) when compared to low-grade tumors (6 of 19; 31.5% in grade II and 3 of 16; 18.7% in Atypical Cartilaginous Tumor). We proved statistically significant difference in IMP3 expression between enchondromas and ACTs ($P=0.025$). Our study clearly demonstrated differentiation-dependent expression of IMP3 in chondrosarcoma, and suggests IMP3 as a novel marker for differentiating problematic cases of enchondroma from well-differentiated chondrosarcomas. To our knowledge, this study is the first study to clarify expression of IMP-3 in chondromas and chondrosarcomas.

1. Introduction

Chondrosarcoma is a malignant cartilage-forming tumor and is the third most common primary malignant bone tumor exceeding in frequency by multiple myeloma and osteosarcoma. More than 90% of these neoplasms are referred to as conventional chondrosarcomas, which are subdivided into three grades based on histologic features. In the 2013 WHO classification of tumors of bone, the synonym "atypical cartilaginous tumor (ACT)" was introduced for "grade I chondrosarcoma [1]. Atypical cartilaginous tumor is the most frequent grade, compromising 61% of chondrosarcomas. Enchondroma is a very common and benign cartilaginous tumor most frequently arising in the small bones of the hands and feet, particularly in the phalanges, in the first and second decades of life ACT and enchondroma are similar in histopathologic aspects. Biopsy interpretation of ACT versus enchondroma is problematic and largely depends on clinical and radiological findings [2]. Although a combination of clinical, radiologic and pathologic examinations enables distinction in some cases, difficulties are still encountered by the pathologists to identify benign enchondroma from ACT or low-grade chondrosarcoma from high-grade chondrosarcoma in many cases. There is no reliable diagnostic marker to help make a distinction between benign and malignant cartilaginous tumors.

On the other hand, it is important to assess the histologic grade and biologic behavior of chondrosarcomas to determine the surgical management of these tumors. Therefore, some biologic markers

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(such as A disintegrin, metalloproteinase 28 and GADD45β) [3,4] have been studied to aid in the diagnosis of chondrosarcoma and to determine their biologic aggressiveness. However, usefulness of these markers in clinical practice should be confirmed.

IMP3, insulin-like growth factor II mRNA binding protein, is a member of oncofetal family of proteins, which plays an important role in RNA trafficking and stabilization, cell growth and migration during early embryogenesis. It belongs to a family of IMPs including two other proteins, IMP1 and IMP2, which is expressed in fetal tissues, but has low or undetectable expression in adult tissues [5].

Recent studies indicated that IMP3 is expressed in different human malignancies. In some studies it is identified as a prognostic marker and IMP3 expression correlates with aggressive biologic behavior as in pancreatic carcinoma [6], renal cell carcinoma [7], lung adenocarcinoma [8], oral squamous cell carcinoma [9], superficial urothelial carcinoma [10] colon cancer [11] and ovarian serous tumors [12]. In several other studies it is suggested as a diagnostic biomarker to differentiate malignant and benign conditions including differentiation of cervical adenocarcinoma in situ [13], malignant pancreatic lesions [14], malignant follicular patterned thyroid tumors [15], uterine and extrauterine leiomyosarcomas [16], esophageal adenocarcinoma [17] and malignant mesothelioma from the benign counterparts [18].

The prevalence and significance of IMP3 in chondroma and chondrosarcoma is unknown and this study was designed to investigate the expression of IMP3 in chondroma and conventional chondrosarcoma and to test whether its level correlates with chondrosarcoma grade.

2. Procedure

2.1. Patients and tissue sample

Seventy-eight cases of enchondroma and chondrosarcoma biopsy and resection specimens were identified from the archive of Department of Pathology at Shafa yahyaeian Orthopedics Hospital in Tehran, from 2001 to 2013. The samples consisted of 36 enchondromas and 42 chondrosarcomas, including 16 cases of ACT, 19 cases of grade II and 7 cases of grade III chondrosarcoma.

Diagnosis of each case was confirmed by two pathologists based upon reviewing of clinical and imaging findings as well as re-examination of H&E-stained slides. Chondrosarcoma cases were graded based on World Health Organization classification [2]. Chondromas are hypocellular, non-vascular tumors with abundant hyaline cartilage matrix. The nuclei are small and round with condensed chromatin. There is no mitotic activity. ACT is moderately cellular and contains hyperchromatic plump nuclei of uniform sizes. It is cytologically similar to enchondroma but has an infiltrative pattern of growth. It nearly always requires supportive evidence from clinical and radiological data for diagnosis. Grade II tumors are more cellular and showing nuclear atypia and grade III tumors are more cellular and pleomorphic than grade II tumors [2].

Representative formalin-fixed paraffin-embedded blocks with adequate amount of tissue were selected for immunohistochemistry study.

2.2. Immunohistochemical staining and statistical analysis

IMP3 immunohistochemical staining was performed on 5 μm-thick sections processed from formalin-fixed paraffin-embedded tissue. All staining processes were performed in room temperature. The provided sections were mounted on silanized slides and briefly were deparaffinized in xylol and rehydrated in serial alcohol. Antigen retrieval was made by autoclave treatment with 10 mM citrate buffer pH = 6 for 15 min. To suppress endogen peroxidase activity, tissues were exposed to hydrogen peroxide 3%, then incubated with monoclonal mouse antibody against IMP3, clone 69.1 (1/100 dilution, Dako, Glostrup, Denmark) for 1 h at room temperature. Following incubation with second antibody, anti-Rabbit/mouse immunoglobulin, the slides were treated with 3,3′diaminobenzidine (all reagents Dako, Glostrup, Denmark) for an hour. The sections were counterstained with hematoxylin. All patient samples along with positive control sample of placenta and negative control sample of normal hyaline cartilage were stained for IMP3.

Cytoplasmic and/or membranous expression of IMP3 protein and its intensity was determined by a pathologist using bright-field microscopy and confirmed by another pathologist expert in bone and soft tissue pathology. The results were assumed positive when at least 10% of tumoral cells expressed IMP3. Immunohistochemistry results was scored on a 0–3+ scale regarding the intensity of staining, in which score of 0 assigned to cases with no specific staining, 1+ to weak, 2+ to moderate and 3+ to strong staining. Furthermore, we assessed the extent of staining based on the percentage of stained cells in each tissue sample.

Statistical analysis was performed using SPSS 17 software and chi-square or Fisher exact tests. $P < 0.05$ was considered statistically significant.

3. Results

Of 36 patients in enchondroma group 12 cases (33.3%) were male and 24 cases (66.7%) females with average age of 33.1 years (±10.8). Of 42 chondrosarcomas 23 cases (54.7%) were male and 19 cases (45.3%) were female with average age of 45.4 years (± 17.5).

IMP3 was overexpressed in chondrosarcoma but not in benign neoplastic tissue. Immunohistochemical analysis of chondrosarcomas (Fig. 1) showed positive cytoplasmic and membranous staining in 15 cases (35.7%). In contrast, no marker staining was seen in any of 36 enchondromas. IMP3 expression was not similar in different grades of chondrosarcoma. Positive staining was seen in 3 of 16 cases of ACT (18.7%), 6 of 19 cases of grade II chondrosarcoma (31.5%) and 6 of 7 chondrosarcomas of grade III (85.7%) (Table 1). The highest level of expression was detected in grade III tumors, followed by grade II and the lowest level of expression was in ACTs. By Fisher's exact test, there was significant statistical difference in marker expression between enchondroma and ACT ($P = 0.025$). Positive predictive value (PPV) of IMP3 for well-differentiated chondrosarcoma (ACT) versus enchondroma was 100%.

IMP3 expression intensity was predominantly weak in ACT and grade II chondrosarcomas (6 of 9, 66.6%). High grade neoplasms predominantly showed moderate to severe staining (5 of 6, 83.3%) (Fig. 2). Analysis by Pearson chi-square test indicated that IMP3 expression intensity is significantly higher in grade III chondrosarcomas than grades I and II ($P < 0.01$).

Assessing the extent of reaction, positive staining was seen in 10–50% of tumor cells in ACT, 30–60% in grade II and 5–70% in grade III chondrosarcoma. Chondrosarcomas of different grades showed no statistically significant difference in the percentage of positive cells on ANOVA test. However, pairwise comparisons using independent sample *t*-test revealed significant difference in extent of reaction between grade III chondrosarcomas and grade II ($P = 0.006$) and I ($P < 0.01$), but not between ACT and grade II chondrosarcomas ($P = 0.776$).

4. Discussion

Because of the lack of reliable diagnostic markers or molecular methods as well as the histological and radiographical similarity,

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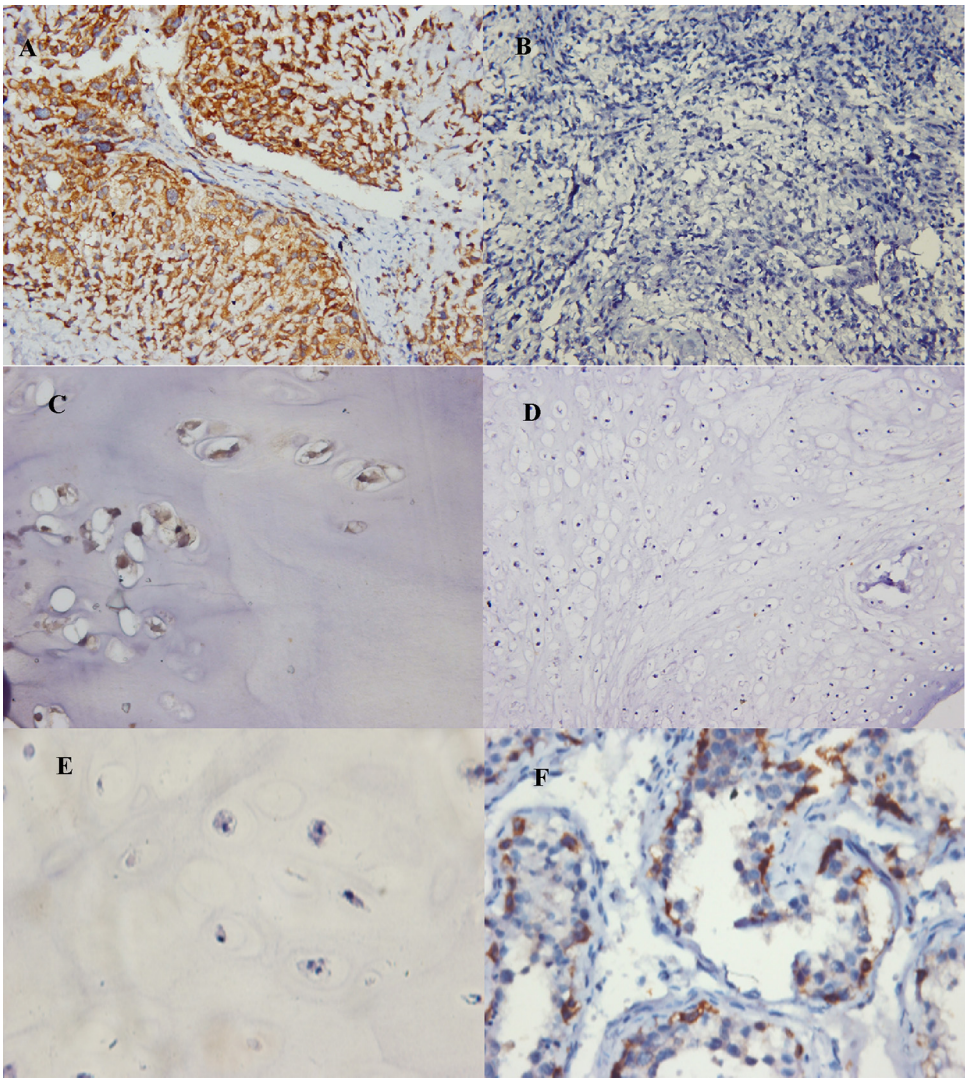

Fig. 1. IMP3 expression in (A)— high-grade chondrosarcoma (positive). A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM02449; (B)—High grade chondrosarcoma (Negative). A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM02450; (C)—ACT (positive). A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM02451; (D)—ACT (Negative). A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM02452; (E)—enchondroma (negative). A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM02453; (F)—placenta (positive control) A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM02454.

Table 1
IMP3 expression in enchondroma and different grades of chondrosarcoma.

Neoplasm	IMP3 expression status		
	Negative no. (%)	Positive no. (%)	Total no. (%)
Enchondroma	36 (100%)	0 (0%)	36 (100%)
ACT	13 (81.3%)	3 (18.7%)	16 (100%)
Chondrosarcoma grade II	13 (68.5%)	6 (31.5%)	19 (100%)
Chondrosarcoma grade III	1 (14.3%)	6 (85.7%)	13 (100%)

it is very difficult to distinguish between enchondroma and ACT or to identify ACT from a high-grade one. Differentiation is important because the therapeutic consequences range from radiologic follow-up to radical operation. In this study, we examined IMP3 expression in chondrosarcomas of different histologic grades and in comparison with chondroma. We found that IMP3 is overexpressed in chondrosarcoma but not in its benign counterpart enchondroma. Importantly, our results showed that high-grade chondrosarcomas demonstrate stronger degrees and extent of IMP3 expression compared to low-grade ones, indicating that IMP3 could become a novel marker to identify different grades of chondrosarcoma as well as a poor prognostic factor for chondrosarcoma. However, additional investigation and survival studies will be needed to clarify if up-regulation of IMP3 contributes to unfavorable outcome or not. Furthermore, overexpression of IMP3 in high-grade chondrosarcomas raises the possibility that IMP3 may play a role in tumor progression. Other markers have also been introduced in chondrosarcoma that have positive association with tumor grade such

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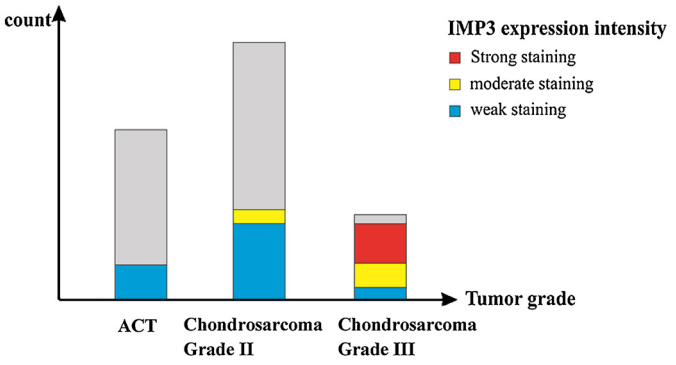

Fig. 2. IMP3 expression intensity in different grades of chondrosarcoma.

as ezrin, a membrane cytoskeleton linker and regulator of cellular signaling [19], and steroid receptor coactivators [20]. In the study by Bai et al., CXCR4 (CXC chemokine receptor 4) expression levels were higher in high-grade chondrosarcoma cells than in low-grade specimens, but enchodroma cases were not included in their research [21].

IMP3 is a fetal protein that is expressed in embryonic tissues but is undetectable in adult tissues. IMP3 was first defined in pancreatic carcinoma by Schaeffer et al. as KOC (KH-domain containing protein, over expressed in cancer) [6]. Thereafter, it has been shown as an oncofetal protein that is overexpressed in many malignancies [6–18] including sarcomas. IMPs play roles in RNA trafficking and stabilization, cell growth and migration during early embryogenesis [5]. It has also marked effects on cellular adhesion and invasion during development and cancer formation [22] by formation of invadopodia and regulation of cellular proliferation in cancerous cells [23]. Invadopodia is defined as a structure of metastatic tumoral cells similar to podosome. These structures are located in the subsurface of cell membrane with a core full of actin containing varied values of different proteins such as integrin B, multisignal molecules and metalloproteinase of cell matrix. Invadopodia is generally related to extension to extracellular matrix and destruction of its surrounding matrix, increasing invasive capacity of malignant cells [24].

IMP3 may be a potential target for immunotherapy as it is reported immunogenic in lung carcinoma [25]. This would be a helpful tool in improving treatment options, because chondrosarcoma is resistant to current chemotherapy regimens and radiotherapy.

We also tried to obtain a diagnostic marker to differentiate ACT from chondroma by using antibody to IMP3, which yielded a statistically significant difference in expression of this marker between these two groups. IMP3 could serve as a biomarker to distinguish chondroma from low-grade chondrosarcoma. Other immunohistochemical markers have been studied in this regard. Expression of estrogen receptors alpha and beta [26] and steroid receptor coactivators [20] has been shown to be correlated with chondrosarcoma grade and dedifferentiation, but it was not helpful in differentiating chondroma from low-grade chondrosarcoma. Proliferative markers are shown to be more frequent in high-grade than in low-grade chondrosarcomas or in enchondromas [27,28]. Ki-67 shows little or no nuclear staining in ACT except for Ki-MCM6, which is claimed to discriminate between chondroma and low-grade chondrosarcoma in many cases [27]. A disintegrin and metalloproteinase 28 are correlated with high histologic grade and are suggested as helpful tools in distinguishing between low-grade chondrosarcoma and chondroma [3].

Studies assessing IMP3 expression in various mesenchymal tumors are limited in comparison to epithelial ones. Cornejo et al. recently reported the use of IMP3 biomarker to establish definitive diagnosis of malignant smooth muscle tumors in uterine and soft tissue. They concluded that the expression of IMP3 in both uterine and soft tissue leiomyosarcomas can be used as a positive biomarker to increase the level of confidence in establishing a definitive diagnosis of a malignant smooth muscle tumor [16].

Chen et al. found different expression patterns of IGF2 and IMP3 in conventional, parosteal, and periosteal osteosarcomas. The microvessel density in osteosarcoma with IGF2 and IMP3 cytoplasmic staining was more than that with nuclear staining. They thought that IGF2 and IMP3 inhibition could be promising in tumor vascular targeting therapy [29].

In another study by Yamamoto et al., it is shown that among gastrointestinal inflammatory myofibroblastic tumors and leiomyosarcomas, IMP3-positive cases were histologically and/or clinically aggressive subtypes. Other kinds of tumors, including GIST, desmoid fibromatosis, leiomyoma and schwannoma, were essentially negative for IMP3. They suggest that IMP3 may be an ancillary tool in identifying aggressive abdominal mesenchymal tumors other than GIST [30].

To our knowledge, this is the first study to clarify expression of IMP3 in chondromas and chondrosarcomas. We concluded that IMP3 overexpression correlates with high histologic grade in chondrosarcoma and probably may facilitate tumor progression. It may serve as a prognostic marker and possible therapeutic target, which should be investigated by further studies. The authors suggest IMP3 as a novel diagnostic marker for use in routine clinical practice to differentiate enchondroma from ACT in suspected or ambiguous lesions.

5. Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.prp.2016.02.006.

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