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Original article

Correlation between MRI appearances and serum alkaline phosphatase levels in Osteogenic sarcoma

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ABSTRACT

Introduction: Magnetic resonance imaging is a pictorial depiction of the patho-anatomy of a bony lesion. As different parts of the tumor in Osteogenic sarcoma concurrently undergo various biological processes i.e. osteoblastic new bone formation, cell death, necrosis, bony destruction and revascularization etc., we hypothesized that the image seen in MRI could be used to assess the tumor behavior at that time. This study was done as a preliminary study with the aim to find whether the MRI pictures can have identifiable patterns and if present whether they can be linked to biological behavior. We could identify 2 distinct patterns in T2 weighted images which correlated well with serum alkaline phosphatase a serum marker and the duration of symptoms and so we are reporting our observations. **Material and method:** T2 weighted MRI pictures of 15 cases of Osteogenic sarcoma were studied for identifiable patterns in matrix. These patterns if found were to be linked to biological behavior in the form of serum alkaline phosphatase levels and duration of symptoms.

Results: We could identify 2 unique patterns named by us as Group 1 Heterogeneous type (4 cases) which had a raised serum alkaline phosphatase level and had a history at presentation of less than 3 months duration. In Group 2 homogenous type (5 cases) the serum alkaline phosphatase levels were low and the cases presented after 6 months. As we could not identify any logical pattern in rest of the cases we labeled them as miscellaneous. **Discussion:** MRI patterns can be used as markers of disease activity as there are 2 clear poles correlating well with serum alkaline phosphatase levels (high or low). Intermediate patterns may be the natural biological behavior and waxing and waning of the tumor disease activity.

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1. Introduction

Magnetic resonance imaging has emerged as an important diagnostic tool in planning the management of Osteogenic sarcoma. It is described that a T1 weighted MRI image is useful in identifying marrow replacement or edema¹ and is sufficient

for planning level of resection in Osteogenic sarcomas of the long bones.² A T2 weighted image is used to delineate soft tissue extension of bone tumors as the tumor becomes hyper intense in contrast to surrounding fat and muscles.¹ Role of MRI in Osteogenic sarcoma till date is limited to find out involvement of bone, soft tissue infiltration, skip lesions

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within bone and across the joint, involvement of facial compartments, proximity of lesion to the nearby anatomy and involvement of neurovascular bundle in the tumor. MRI is not used to diagnose types of bone tumors as no diagnostic pattern have been described till now for various tumor types nor MRI patterns have been correlated to disease activity. We did this prospective study to find out whether the MRI appearance in Osteogenic sarcoma can be categorized into well defined groups and to study any co-relation with duration of symptoms or other biochemical markers specially serum alkaline phosphatase. We chose Osteogenic sarcoma because it is the most common primary malignant bone tumor and so we will be getting more cases compared to other tumors in the duration of this study of 1 year.

Serum alkaline phosphatase (ALP-2) has been used as a serum marker to define the osteoblastic activity in Osteogenic sarcoma. It has been found to be raised in highly malignant Osteogenic sarcoma and decreases after neo-adjuvant chemotherapy, surgical ablation or radiotherapy.^{3–7}

On a careful examination of MRI pictures of 15 cases of Osteogenic sarcoma confirmed on histopathology we found that although T1 picture resembled an X-ray but on T2 weighted images definite patterns that correlated with serum alkaline phosphatase levels were identified. We have tried to identify and classify these MRI pictures in patients with primary Osteogenic sarcoma of the long bones and correlate them with duration of symptoms and serum alkaline phosphatase levels as a marker of disease activity.

2. Materials and methods

This study was done as a prospective Type 2 study where we reviewed 38 cases of suspected malignant bone tumors in our institute from July 2008 to September 2009. Out of these, 15 cases of histologically confirmed Osteogenic sarcoma of long bones constitute the study material. Patients who had received neo-adjuvant chemotherapy at some other center before reporting to us were excluded from the study. All cases were evaluated for age, sex, duration of symptoms, clinical morphology of tumor and X-ray of representative part in 2 planes perpendicular to each other. X-ray chest posterior-anterior view, blood investigations including serum alkaline phosphatase, MRI of the part and finally core needle biopsy was done for confirmation of diagnosis.

MRI was done by GE (General Electric, USA) 1.5 T MRI scanner and in all cases T1 and T2 weighted images were taken in sagittal, coronal and axial planes. We selected the slice showing the maximum tumor mass in all sagittal, coronal and horizontal plane and studied the destruction pattern. Although the T1 picture in all these 15 cases remained alike, the T2 pictures could be identified in all planes into 2 distinct patterns based on gross similarities on inspection and are described as follows:

Type 1: The heterogeneous group – Fig. 1. It consisted of 4 cases which showed large areas of relative T2 hypointensity with smaller areas of T2 hyperintensity within the tumor. *Large Hypo and Small Hyper intense Type* as depicted in Fig. 3.

Type 2: Homogeneous group – Fig. 2. It consisted of 5 cases which showed homogeneous T2 hypointensity uninterrupted by areas of necrosis, fluid levels or variegated tissue signal.

Fig. 1 – Type 1 – the heterogeneous group where the MRI images show large areas of relative T2 hypointensity with smaller areas of T2 hyperintensity within the tumor.

The bone involved was relatively intact with no major destruction seen on any of the images. *Hypointense Type* as depicted in Fig. 4.

The remaining appearances which did not match to these distinct patterns were labeled as **Type 3: Miscellaneous patterns** Fig. 5.

To further standardize the appearances the MRI sections were shown to 5 radiologists separately without discussing with them patient's clinical features or laboratory findings to remove any bias and they were able to identify the 2 major appearances.

The age and sex distribution of these 15 cases has been depicted in Table 1. There were 11 males and 4 females. Three cases presented in the age group below 10 years, 10 cases between 11 and 20 years, and 1 case each between 21–30 years and 41–50 years. The bones affected were the distal femur in 8 cases, proximal tibia in 4 cases, proximal humerus in 2 cases and distal humerus in 1 case as depicted in Table 2.

Fig. 2 – Type 2 – the homogeneous group where the MRI images show homogenous T2 hypointensity, uninterrupted by areas of necrosis, fluid levels or variegated signal. The bone involved is relatively intact, with no major destruction seen on any of the images.

This table shows that in Type 1 heterogeneous group, the levels of serum alkaline phosphatase were raised and all cases reported early (3 months). In contrast to this, in Type 2 homogenous group the levels of serum alkaline phosphatase were within the normal range and these case presented late (more than 6 months). In Type 3 miscellaneous patterns (6 cases), no classic patterns and no distinguishing features could be identified All of these cases gave a history of complains between 3 and 6 months. Statistical analysis of dispersion was applied which suggested a clear relationship

1. **Are alkaline phosphatase levels significantly different in various MRI types of Osteosarcoma?**: Yes, the values in MRI Type 3, 388 IU units and Type 1, 1496 IU units were maximally different and the difference was significant $p = 0.02$ as depicted in [Table 4](#).
2. The analysis clearly shows relationship between MRI types and serum alkaline phosphatase levels. Type 1 and Type 2 MRI patterns have a clear relationship to serum alkaline phosphatase levels as they are high in Type 1 and normal in Type 2. Similarly all Type 1 tumors presented early and Type 2 presented late. But the miscellaneous MRI types may be actually stages and do not necessarily mean different types of tumor.

Fig. 4 – MRI of 5 cases with Type 2 homogeneous pattern visible.

4. Discussion

Osteogenic sarcoma is the second most common primary malignant bone tumor.⁸ Serum alkaline phosphatase level as a bio-chemical marker is strongly related to the prognosis both in Osteogenic sarcomas and their metastasis.⁹ At present

the role of MRI is limited to measure the extent of tumor within the bone and in the soft tissues so that the relationship of the tumor to the nearby anatomical structures can be determined.¹⁰ We found serum alkaline phosphatase level and duration of symptoms to be correlating with these MRI patterns found in Osteogenic sarcomas.

CASE 10 **CASE 11** **CASE 12** **CASE 13** **CASE 14** **CASE 15**

Fig. 5 – Miscellaneous group consisted of 6 cases, the MRI pictures of which showed variable proportion of T2 hyperintensity as compared to T2 hypointensity areas and no classical pattern of destruction.

Table 1 – Age and sex distribution of Osteogenic sarcoma.

Age groups (Years)	Male	Female	Number of cases
0–10	2	1	3
11–20	7	3	10
21–30	1	0	1
31–40	0	0	0
41–50	1	0	1
Total	11	4	15

Table 2 – Bones affected by Osteogenic sarcoma.

Serial number	Bone affected	Number of cases
1	Distal Femur	8
2	Proximal Tibia	4
3	Proximal humerus	2
4	Distal humerus	1
	Total	15

Magnetic resonance imaging is a pictorial depiction of the patho-anatomy of a bony lesion as different parts of the tumor in Osteogenic sarcoma are concurrently undergoing various processes i.e. osteoblastic new bone formation, cell death and necrosis, bony destruction, revascularization, etc. Thus the image that appears to be haphazard and is considered to be of no significance as far as diagnosis is concerned is actually not so and is a marker of disease activity suggesting the tumor to be of a high grade or low grade. Although the T1 weighted images in all these 15 Osteogenic sarcoma were somewhat similar but the T2 weighted images showed a different background. Comparing the T2 weighted images of these 15 patients revealed 2 patterns in 9 patients while 6 could not be classified and had to be put in a miscellaneous group.

Type 1 – Heterogeneous group: High levels of serum alkaline phosphatase.

Type 2 – Homogeneous group: Low levels of serum alkaline phosphatase.

Type 3 – Miscellaneous patterns with variable levels of serum alkaline phosphatase.

To confirm whether this grouping into patterns was just coincidental, depicted a particular stage in disease activity or denoted a low or high grade of tumor activity, a correlation was done with regards to serum alkaline phosphatase levels as markers of disease activity. We found a raised serum alkaline phosphatase level only in 7 out of 15 Osteogenic sarcoma cases. However, all cases in the Type 1 – heterogeneous pattern showed an increased alkaline phosphatase level as well as increased disease activity/high grade of Osteogenic sarcoma. Similarly, all the cases with Type 2 homogeneous pattern had normal serum alkaline phosphatase levels showing a low grade of Osteogenic sarcoma or low grade of disease activity. The miscellaneous patterns may be intermediate phases in the biological activity of Osteogenic sarcoma and therefore could not be classified. To further confirm our findings, statistical analysis of dispersion was applied which suggested a clear relationship between MRI types and serum alkaline phosphatase levels. Type 1 and Type 2 MRI patterns have a clear relationship to serum alkaline phosphatase levels as they are high in Type 1 and normal in Type 2. But the MRI types in the miscellaneous group may be actually stages and does not necessarily mean different types of tumor.

Discussing our findings further, we logically conclude that:

1. Serum alkaline phosphatase levels are not increased in all cases of Osteogenic sarcoma.
2. The serum alkaline phosphatase level is an indicator of the disease activity in Osteogenic sarcoma and raised levels denote a fast growing, high-grade tumor.
3. Definite patterns can be identified in T2 weighted MRI images of Osteogenic sarcomas which give an indication of the disease process and the tumor grade i.e. high in Type 1 and low in Type 2.

Table 3 – Relationship of MRI type with level of serum alkaline phosphatase and duration of symptoms.

Serial number	MRI pattern	Number of cases	Level of serum alkaline phosphatase (normal <135 IU/liter)	Serum alkaline phosphatase level: raised or normal	Duration of symptoms		
					<3 Months	3–6 Months	>6 Months
1	Type 1 heterogeneous pattern	4	226	Raised	Yes		
2			500	Raised	Yes		
3			480	Raised	Yes		
4			290	Raised	Yes		
5	Type 2 homogenous pattern	5	90	Normal		Yes	
6			118	Normal	Yes		
7			9	Normal		Yes	
8			106	Normal		Yes	
9	Type 3 miscellaneous patterns	6	90	Normal		Yes	
10			240	Raised			Yes
11			100	Normal			Yes
12			48	Normal			Yes
13			120	Normal	Yes		
14			520	Raised			Yes
15			246	Raised			Yes

Table 4 – Alkaline phosphatase levels in various MRI types of Osteosarcoma.

Type	No. of cases	Sum of serum alkaline phosphatase levels	Standard deviation
1 Large hypo small hyper areas	4	1496	18,690
2 Homogeneous	5	413	1831
3 Miscellaneous 1	3	388	9861
4 Miscellaneous 2	3	886	41,825

KW statistics $P = 0.02$.

4. These patterns may not be different types of Osteogenic sarcoma but different stages of natural progression and disease activity of the tumor as they are correlating well with serum alkaline phosphatase levels and duration of presentation.

This original study is the first which is coming out with the concept that MRI in Osteogenic sarcoma can have identifiable appearances on T2 weighted images and these appearances are related to biology. On one hand you have a homogenous pattern similar to T1 and the other pole has heterogeneous picture. These 2 patterns are distinct and can be identified easily. There are other patterns without uniform identifiable patterns and their significance is not known now. Incidentally in this small study all homogenous Type 1 destructions had a normal serum alkaline phosphatase and heterogeneous Type 2 had it raised. As this is a preliminary study we hypothesize this with biological behavior, as serum alkaline phosphatase has prognostic value known to all. It is difficult to say at this stage whether these appearances are different stages in the same tumor at different times or are radiologically distinct variants as this will require the same case having MRI done repeatedly at regular intervals, but this study is the first to bring the concept of having a pattern in MRI appearances and so we are reporting them. Due to limited resources we did this study only on 15 cases. No correlation was found between X-ray and MRI pattern or histopathology and MRI pattern in our cases. Limitations of our study are small number which may not be statistically significant, study of MRI patterns in cases of Osteogenic sarcoma only and no follow-up or prognostic interpretation. A larger series of observations at a center with more cases and facilities may bring more light to this preliminary observation at a later date.

Conflicts of interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

REFERENCES

1. Witte Dexter H. *Magnetic Resonance Imaging in Orthopaedics*. In: *Campbell's Operative Orthopaedics*. 11th ed., vol. 1. Mosby Elsevier Publications; 2008:151–155.
2. Onikul E, Fletcher BD, Parham DM, et al. Accuracy of MR imaging for estimating intraosseous extent of Osteosarcoma. *Am J Roentgenol*. 1996;167:1211–1215.
3. Bacci G, Dallari D, Battistini A, et al. The prognostic value of serum alkaline phosphatase in osteosarcoma of the limbs. *Chir Organi Mov*. 1992 Apr–Jun;77(2):171–180.
4. Levine Alan M, Rosenberg Steven A. Alkaline phosphatase levels in osteosarcoma tissue are related to prognosis. *Cancer*. 1979;44:2291–2293.
5. Brozmanova E, Skrovina B. Biochemical and haematological findings in malignant bone tumors. *Neoplasia*. 1974;21:75–82.
6. Kaplan M. Alkaline phosphatase. *N Engl J Med*. 1972;86:200–202.
7. Ohno T, Mitsutoshi A, Tateishi A, et al. Osteogenic sarcoma: a study of one hundred and thirty cases. *J Bone Jt Surg*. 57A:397–404.
8. Heck Jr Robert K. *Malignant Tumours of Bone*. In: *Campbell's Operative Orthopaedics*. 11th ed., vol. 1. Mosby Elsevier Publications; 2008:901–907.
9. Man TK, Chintagumpala M, Visvanathan J, et al. Expression profiles of osteosarcoma that can predict response to chemotherapy. *Cancer Res*. Sep 15 2005;65(18):8142–8150.
10. O'Flanagan SJ, Stack JP, McGee HM, Dervan P, Hurson B. Imaging of intramedullary tumour spread in osteosarcoma. A comparison of techniques. *J Bone Jt Surg (Br)*. 1991;73:998–1001.