OSTEOSARCOMA OF THE JAWS: A RETROSPECTIVE STUDY

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Abstract- Osteosarcoma is a primary malignant tumor of bone which can involve jaws. This article reviews osteosarcoma of the jaws referred to the Department of oral pathology, dental faculty of Tehran University of Medical Sciences and Pathology Department of Cancer Institute in Imam Khomeini Hospital during 30 years from 1349 to 1378 and also reviews jaw Osteosarcoma in English literature. The purpose of this review is comparing the clinical behaviour of jaw tumors with Osteosarcoma from elsewhere in the body and reporting the observations of clinical, histological and diagnostic findings. For this retrospective review the clinical, radiographic and histopathologic records of 42 patients were obtained, furthermore follow up results were also obtained from patients records. The mean age of patients was 35 years (range 9 to 61 years) with slight male predilection. The most common presenting features were swelling, pain and ulcer. Histologically, the lesions ranged from well differentiated tumors with prominent osteoid formation to poorly differentiated tumors which had bizarre cells and numerous mitosis especially atypical ones. Most of the lesions had areas of chondroid formation, but all of tumors showed neoplastic osteoid, of course in different degrees. The most important problem after treatment was local recurrence. Primary osteosarcomas of the jaws are a group of lesions which are biologically distinct from long bones osteosarcoma and have better behaviour than them. More accurate determination of their clinical behaviour and their management will depend on complete follow up of patients and actual records of patients data.

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Key Words: Osteosarcoma, jaw, malignant bone tumor.

INTRODUCTION

Osteosarcoma is a primary malignant tumor of bone or mesenchymal tissues that histopathologically shows osteoid formation (1,2).

Osteosarcoma of the jaws is uncommon and despite its histopathologic similarities with long bones osteosarcoma is biologically different (3) and represent about 4 to 13% of the total (4-11). The estimated incidence of new cases of jaw osteosarcoma per year is 1 in 1.5 million in the United States (4) and 0.002 in 100.000 in Japan (12). The median age of patients is one or two decades higher than patients with long bones osteosarcoma (range 27 to 39.6 year) (13) and most of the patients are in third or fourth decades of life (11-20). Lesions are slightly more common in men (2,3,13,15) and seems to be equal in both jaws (5,12,17) although some reports show the lesion to be more common in females (19,20,24) or in one jaw (18,21-26). The most common places of occurrence of this lesion are alveolar ridge and body in maxilla and mandible (5,12,13,17,18,22,24,27). Median age of maxillary osteosarcoma has been reported to be higher than the mandibular one (28). The main symptoms of this lesion in jaw are swelling and pain (5,29,30) and the average time between presenting of symptoms and diagnosis range from 3 to 5 months (13,27,31). It seems that predisposing factors such as radiation and Paget's disease has some role in tumor formation (13,32-34).

Histopathologically jaw osteosarcoma has often better differentiation than osteosarcoma of long bones (15,16,35) (except those cases which occur in radiation field (13) and chondroblastic variant seems to be more common than others (18,22,36). Also this lesion is radiographically similar to the lesions of other bones (18.23,.37,38) although sun-ray appearance and codman triangle are less common in jaws (5,18). It seems that combination of sun-ray appearance, PDL, widening and widening of mandibular canal are pathognomonic for jaw osteosarcoma (39,40). CT scanning and MRI can also be effective in tumor diagnosis and determination of its invasion to surrounding tissues (41-43). Treatment of this lesion is radical surgery consisting of complete resection with a margin of normal surrounding tissue (14-16,27,44) which usually accompanies radio or chemotherapy (45,46). Anatomical limitations in face cause some difficulties in achivement of uninvolved margins (46)

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and for this reason local recurrence of the lesion is high (between 33 to 69 percent) (18,27,47).

The rate of metastasis in this lesion is less than long bone osteosarcomas (22,36,48) (except those that occur due to radiation) (20). Diagnosis of tumor in its early stages and complete resection are the most important factors in increasing prognosis of jaw osteosarcoma (27,49,50). In addition it seems that tumor free margins in surgery (8), chemotherapy with multidrugs (8) and radiotherapy after-surgery (50,51,8) have some effects on prognosis. In contrast to long bone osteosarcomas, it seems that chemotherapy before surgery has no effect on the prognosis of jaw osteosarcoma (21,31). Also, other factors such as age, sex, site and histological type seems to have no effect on prognosis (8). Rare cases of low-grade intramedullary osteosarcoma and parosteal osteosarcoma occasionally occur in jaws and have better prognosis than classic type (51-58).

The aim of this article is to review the cases of osteosarcoma of the jaws that were recorded in the Department of Oral Pathology of Tehran University of Medical Sciences and Department of Pathology of Cancer Institute at Imam Khomeini Hospital during the 30-year period to report the observations of clinical and diagnostic significance of this lesion in these centers and compare the results with other reports.

MATERIALS AND METHODS

The clinical and histopathologic records of patients referred to the Department of Oral Pathology (OP) Tehran University of Medical Sciences and Department of Pathology, (OC) Cancer Institute at Imam Khomeini Hospital over the 30-year period from 1970 to 2000 were obtained for retrospective descriptive study. Management and follow-up results were also obtained whenever possible.

RESULTS

In the 30 years period between 1970 to 2000 a total of 32 cases of jaw osteosarcoma were recorded in O.C and 16 in O.P of these 4 were inadequately documented and therefore excluded from the study and 2 cases were recorded in both departments and therefore analyzed just one time. Finally 28 cases from O.C and 14 cases from OP were entered in this study. Unfortunately, in some of the cases the information was not recorded completely and it has been reflected in all of the following results.

Age and sex

The mean age of patients of O.C was 31.7 years (range 9 to 61) and patients of O.P was 31.9 (range 16 to 55). In O.C the mean age of males was 35 years (range 18 to 57) and females was 25.8 (range 9 to 61). In O.P. males mean age was 34 (range 28 to 50) and female was 30 (range 16 to 55). There was no statistically significant difference between the age of males and females in both departments. In O.C there were as 18 males (64.3%) and 10 females (35.7%) which also had no significant difference. In O.C 32.1% of patients were in fourth decade of life and 21.4% were in third decade which were the highest peaks in age distribution. In O.P occurence of lesion in 3rd and 4th decades was equal and were highest peaks either.

Site and presenting features

In O.C 16 (57.1%)tumors were presented in maxilla and 12 (42.9%) in mandible. In males maxillary tumors were more common than mandible (11 to 7) but in females its distribution was equal. In O.P 5 (38.5%) tumors presented in maxilla and 8 (61.5%) in mandible. Six were presented on the right side and 3 on the left side (the side of others had not been determined). In O.C from maxillary tumors, 9 were presented on right side, 4 in left and 2 on midline and from mandibular tumors 5 were presented on right side, 5 in left and 2 in anterior region. In the mandible the most common site was the body or the ascending ramus followed by angle and symphysis, where as in the maxilla it was alveolar ridge, palate and sinus.

In O.C tumor size was recorded in 22 cases with 6.6 cm as median (range 2.5 to 13 cm). Mean size for maxillary tumors was 5.2 cm (range 2.5 to 10 cm) and mandibular tumors 8.3 cm (range 5 to 13 cm). In O.P cases were entered as incisional biopsy and therefore tumor size had not been recorded.

In O.C the most common presenting feature was swelling (19 cases) followed by pain (which affected 5 cases). The mean duration from onset of features to starting the treatment was 5.5 months (ranging from 1 to 12 months). Between 18 patients one had a history of trauma and one had radiotherapy in his medical history, and the others had no history of any predisposing factors. For others details of the medical history were not available.

Histology

Cases of this study showed different histological features. These tumors showed varying degrees of cellularity associated with different proportions of extracellular matrix. In all tumors there was evidence of neoplastic osteoid formation, although in several,

the newly formed bone was well differentiated and not readily distinguishable from reactive bone. The majority of tumors showed some evidence of chondroid formation. In O.C histologic type was determined just for 18 patients, and in 15 (53.6%) it was chondroblastic, 2 (7.1%) pleomorphic and one (3.6%) fibroblastic. In O.P histologic type was determined just for 3 patients (all being chondroblastic).

In some patients a history of histologic misdiagnosis with lesions such as osteoma. chondromyxoid fibroma, chondrosarcoma and fibrous dysplasia have been recorded.

Management

In O.C 9 (39%) patients were treated just by surgery, 6 (26%) surgery and chemotherapy, and 8 (35%) surgery, chemo and radiotherapy. Eightteen patients had been followed-up, which 8 were symptom free for 1 to 60 months, seven recurred for 1 time, 2 for 2 times, 1 for 3 times and 1 for 5 times.

DISCUSSION

For study of rare lesions, such as osteosarcoma of the jaws, small retrospective studies is the best way and represent the sole opportunity for collection and comparison of cases. Results of this report and others like this (4,5,13,22) highlighted several important points about this neoplasm. In spite of this, retrospective studies have some limitations. For these studies accurate observation of patients at first visit and recording of information is very important. In addition, founding of a cancer-registry center for recording the clinical and topographical information of patients has a great value and these centers provide the opportunity for collection of rare cases.

The incidence of osteosarcoma of the jaw has been reported as different from various countries (59,60). Its incidence in Iran can not determined by studies such as this and reaching, the true incidence needs the information of a national cancer registry center. In this study osteosarcoma of the jaws consists 6.2% of all the osteosarcomas which is similar to some other international reports (15,17,28). There are reports from Japan with 1.6% (12) and Nigeria with 19.6% (21) and it shows that there may be a real geographical difference in relation to osteosarcoma of the jaws to total osteosarcoma of body, although it may also be related to sampling technique (12,21). Sex, age and site distribution of this study were similar to some other reports (15-19,27-31,61). It seems that sex has no effect in tumor occurrence because there is no significant difference between male and female and median age of two sex is similar in this tumor, but geographic differences may have some effect in sex distribution (12,62).

In common with some studies it seems that there Is no difference in lesion distribution in maxilla and mandible and in right side or left side (21-23).

The most common site of occurrence in this study was body in the mandible and alveolar ridge in maxilla, which is similar to other reports (12,17,18,22,60). Also the most common presenting feature was swelling followed by pain which shows similarity to previous studies too. Although diagnosis was based on the recognition of osteoid production by malignant cells, these cells are able to produce chondroblastic or fibroblastic extracellular matrix. Of the lesions reported in this study a high percentage designated chondroblastic osteosarcoma (similar to some other reports (10,18,22) but some studies have reported a much lower percentage (13). This may reflect the lack of a clear consensus when defining the osteoblastic and chondroblastic variants and shows that some pathologists did not believe in determining histologic subtype. Designation as osteoblastic or chondroblastic may however be of clinical significance because it has been reported that the latter has a marginally better prognosis (63) and for this purpose some criteria must be appointed for differentiation of these histologic subtypes.

From a biologic perspective the cells of origin of osteosarcoma are by no means well defined, and it is likely that they are not osteoblasts, but undifferentiated mesenchymal precursors with osteogenic potential. Some cellular heterogenicity within tumor clones therefore would not be surprising because fibroblasts chondroblasts and osteoblasts are believed to share a common lineage (64). Furthermore both genetic and locally active epigenetic factors may influence whether a particular cell progresses down as an osteogenic or chondrogenic pathway. When fibrolastic cells derived from marrow stroma were implanted in vivo in diffusion chamber, a bone like tissue formed peripherally, with chondroid or fibroblastic areas centrally (65,66). These observations have suggested that oxygen or nutrient gradient may have a role on cell differentiation to osteoblastic or chondroblastic pathway. Furthermore factors such as angiogenesis or local biological mediators may have effects on localized area differentiation.

Although histologic grading was not determined in this study, in common with the earlier studies, several of the lesions reported here formed a group that showed little cytologic atypia and unlike long bones lesions, a lower rate of metastasis.

The present series of jaw osteosarcoma supports the view that jaw osteosarcomas behave differently from long bones osteosarcomas. There are several ways in which this difference becomes apparent:

1. Jaw osteosarcomas exhibit a mean age of occurrence one decade higher than long bones osteosarcomas.

2. The metastatic rate of jaw osteosarcoma varies from 6 to 51% (4,5) but this rate for the long bones has been reported to range from 78 to 90% (22,68).

3. There is a pronounced difference in evolution time from treatment of the primary lesion to the onset of metastatic disease. In jaw osteosarcomas the meantime of this varies from 20 to 29 months (4,22) but for long bones osteosarcomas this time is only near 6 months (68,69).

The prognosis of jaw osteosarcomas is better than that of long bones osteosarcomas. (22,69). According, to clarek, the reason for this different behaviour is histologically better differentiation of jaw osteosarcoma than long bones lesions (4,5). However Bras demonstrated that there is no major difference in mitotic activity between jaws and long bones osteosarcoma (22,68).

Also Bras suggests an increase in host resistance to the tumor with advancing age, resulting in a lower rate of metastasis, thus the prognosis of long bones osteosarcoma is worse in patients less than 25 years old than patients more than it (68-70). As jaw osteosarcoma occurs at a higher mean age than osteosarcoma at other sites these patients are less prone to develop metastasis and have better prognosis (22). In addition jaw osteosarcoma usually is diagnosed sooner than long bones osteosarcomas and it may have an effect on improvement of prognosis (22,45).

In this study one case had a history of radiotherapy and several authors have commented on the role of radiation in the etiology of osteosarcoma (71) but our observations are not enough to comment on this aspect.

Because many osteosarcomas of the jaws appears cytologically unremarkable, care must be taken to separate them from benign or reactive lesions such as fibrous dysplasia (72,73), osteoblastoma (74,75) and either malignant lesions. In our study some cases were diagnosed as benign lesions before the true nature of the condition became apparent and this delay in diagnosis can influence prognosis. For this reason it appears important to completely investigate the lesion and determine appropriate diagnosis in first biopsy. To date, there are few special investigation that can be used on histopathologic material to assist in the identification of malignancy. It has been suggested that bone matrix proteins may assist in the recognition.of malignant osteoid in the differential dignosis of osteosarcoma. Osteocalcin for example is a bone specific protein that may be useful in distinguishing osteosarcoma form malignant fibrous histiocytoma (76). Howerer it is a late marker of osteoblastic differentiation (77) and expressed with difficulty in some osteosarcoma derived cell lines (78,79). Therefore it might be of limited use to detect poorly differentiated cells of the osteoblast lineage. Both collagen type 1 and osteonectin have been recognized in tumor osteoid (80,81) but it has been difficult to use these data because these proteins are not specific to malignant tissue. Recently cbfa-1 a gene encoding an intracellular osteocalcin promoter has been identified that appears to be specific to cells of the osteoblastic lineage and might have a role in the differential diagnosis of osteosarcoma (82-84).

In addition the detection of alkaline phosphatase activity in imprint preparation obtained from the cut surface of osteosarcomas before fixation is regarded as a diagnostic tool for osteosarcoma if used in combination with radiographs (85).

Molecular and cytogenetic changes in neoplastic cells have been proved but specific data about these changes in jaw osteosarcoma are not available. Cytogenetic abnormalities, such as ring chromosomes have been reported in long bones osteosarcoma (86) but the search for specific deletions or gene rearrangements has not so far been fruitful and only showing changes that are indicative for the malignant process in general rather than specific to osteosarcoma. Chromosomal alterations in the P53 and Rb genes localized to 17p 13 and 13q 14 respectively are common and patients with li-fraumeni syndrome have an increased risk of developing osteosarcoma (87,88).Furthermore, over expression of C-fos (89), C-myc and N-myc has been reported in osteosarcoma (88,90), but changes in Ras have not been seen in this lesion (90). There is some differences in expression pattern of cadherin-1 between normal bone and long bone osteosarcoma (91). Disturbances in cadherin family has some effect on metastasis (92) and differences in metastatic rate of jaw and long bone osteosarcoma may have some relation with cadherin

expression pattern. There also may be differences in C-erb-ß2 expression in osteosarcoma with different grades (88,89).

Between protein markers S 100 was known to he indicative of chondroblastic differentiation (93) but now shows that it also express in some of osteoblastic regions. In addition it is positive in dendritic cells which are antigen presenting cells and can be found in many benign or malignant tumors (94,97). So S 100 is not a definite indicative of tumor differentiation. Finding of a specific Antigenic marker or a specific cytogenic change remain so important and can be very helpful in future (98).

In summary, osteosarcomas of the jaws are less aggressive than those of the long bones and have different behaviour from them. This study showed that accurate recording of patients data (including clinics and follow-up) was extremely important in understanding the nature of this lesion.

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