



Research Paper

Bone tumours of the clavicle: Histopathological, anatomical and epidemiological analysis of 113 cases

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ARTICLE INFO

Keywords:

Bone tumour
Clavicle
Biopsy
Histology

ABSTRACT

Background: This retrospective study aimed to determine the frequency of bone tumours of the clavicle and their histopathological, anatomical and epidemiological characteristics in a large case series.

Methods: The records of 327 lesions of the clavicle collected from 1976 to 2018 in our bone tumour registry and institute of pathology were reviewed. Following data were evaluated: age, gender, side, radiological assessment, tumour location within the clavicle, and histopathological findings.

Results: Bone tumours were detected in 113 patients with a mean age of 40 years. The lateral third of the clavicle was most frequently involved. Analysis revealed 22 benign, 31 intermediate, and 60 malignant tumours. Eosinophilic granuloma was the most commonly found neoplasm (18.6%), followed by bone metastases (15.0%), Plasma cell myeloma (8.8%), Ewing sarcoma (8.8%), and Osteosarcoma (8.0%). 53% of the tumours were malignant. Mean age was 51 years in the malignant tumour group and 28 years in patients with a benign/intermediate lesion ($p < 0.001$).

Conclusions: The high incidence of malignant bone tumours of the clavicle found in this study highlight the importance of biopsy to prevent delay in diagnosis and treatment of these lesions, especially in patients with increased age. We believe that the results of this study are of clinical importance and may aid the physician in the management of these rare lesions.

1. Introduction

Bone tumours of the clavicle are exceedingly rare with a reported frequency of less than 1% of all bone tumours [1,2]. There is a paucity of literature focusing on these lesions with most of the published articles being case reports or small case series [1–14]. Hence, the majority of physicians have limited experience in the diagnosis and treatment of these lesions. Clinical symptoms like pain and swelling around the clavicle are usually caused by other conditions, like fractures, osteomyelitis, osteoarthritis, e.g., rather than by bone tumours making the diagnosis of these specific lesions more challenging [7].

The clavicle has several characteristics that distinguish it from other long bones and from flat bones. It is the only long bone in the body placed in the horizontal axis; it is the first bone to ossify in the embryo

with two primary ossification centers appearing by 6 weeks and a secondary center at the sternal end, which appears in adolescence and fuses around the age of 25 years; it has no significant medullary cavity; it contains minimal amounts of red marrow; and it has a poor vascular supply [1,7,13,15]. It is assumed that the exceedingly low incidence of bone tumours of the clavicle may be in part attributed to the latter two described characteristics [7].

This study aimed to determine the frequency of bone tumours of the clavicle and their histopathological, anatomical and epidemiological characteristics in a large case series to aid the physician in the management of these lesions. Only patients which were operated in case of suspected bone tumour of the clavicle with a clear histological diagnosis according to the World Health Organization (WHO) classification of bone tumours were included in this analysis.

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<https://doi.org/10.1016/j.jbo.2019.100229>

Received 16 January 2019; Received in revised form 2 March 2019; Accepted 4 March 2019

Available online 06 March 2019

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Table 1
Histopathological findings of all 327 clavicular lesions.

Pathology	Cases	Percent
Osteomyelitis	86	26.3%
Osteoarthritis	60	18.3%
Malignant bone tumours	60	18.3%
Intermediate bone tumours	31	9.5%
Benign bone tumours	22	6.7%
Callus formation	17	5.2%
Osteonecrosis	13	4.0%
Hyperostosis	7	2.1%
Nonunion	6	1.8%
Chondroosteopathia costalis	3	0.9%
Paget disease	1	0.3%
Schwannoma	1	0.3%

2. Methods

2.1. Patient characteristics and study design

The records of all lesions of the clavicle collected from 1976 to 2018 in our bone tumour registry and institute of pathology were reviewed. A total of 327 cases were identified during this 42 years period (Table 1). The bone lesions had been either collected by our institution or from consultation cases sent to our Bone Tumour Registry in case of suspected bone tumour of the clavicle. For histopathological analysis, undecalcified specimens were embedded in methyl-methacrylate and/or embedded in paraffin wax after EDTA-decalcification. The following data were evaluated for this study: age, gender, left or right clavicle, radiological assessment, tumour location within the clavicle, and histopathological findings including type and dignity of the tumour. Following lesions of the clavicle were excluded after evaluation of all 327 cases: osteomyelitis of the clavicle (86 cases), osteoarthritis (60 cases), callus formation after fracture of the clavicle (17 cases), osteonecrosis (13 cases), hyperostosis (7 cases), non-union (6 cases), Chondroosteopathia costalis (Tietze-Syndrome) (3 cases), Paget disease (1 case), Schwannoma (1 case), and non-allocatable lesions of the clavicle (20 cases). Only bone tumours of the clavicle according to the World Health Organization (WHO) classification of bone tumours were included in this analysis [16–18].

2.2. Statistical analysis

Descriptive statistics were given as mean (range) or percentage. Student *t*-tests were applied to compare patient characteristics between

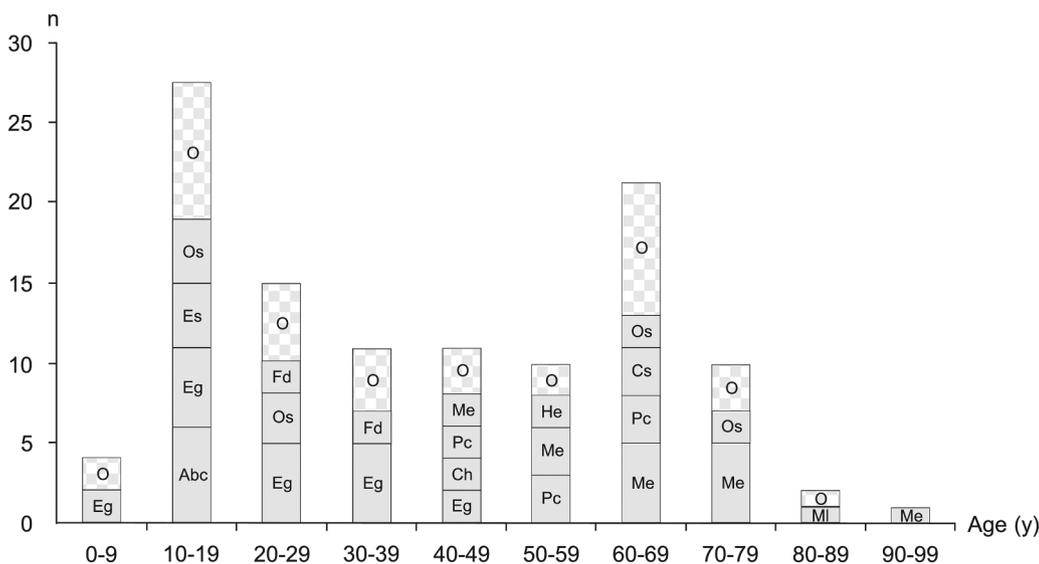


Fig. 1. Age distribution. Age distribution of all bone tumours of the clavicle including data of the most common entities per age group. n, number of patients; O, Others; Eg, Eosinophilic granuloma; Abc, Aneurysmal bone cyst; Es, Ewing sarcoma; Os, Osteosarcoma; Fd, Fibrous dysplasia; Ch, Chondroma; Pc, Plasma cell myeloma; Me, Metastases involving bone; He, Hemangioma; Cs, Chondrosarcoma; Ml, Malignant lymphoma.

Table 2
Benign bone tumours of the clavicle.

Pathology	Cases	Percent	Mean age (y)	Minimum age (y)	Maximum age (y)	Male/Female ratio
Osteochondroma	6	5.3%	33	15	61	2.0:1.0
Fibrous dysplasia	5	4.4%	25	5	33	1.0:1.5
Simple bone Cyst	3	2.7%	18	17	19	All male
Haemangioma	3	2.7%	57	53	65	2.0:1.0
Chondroma	3	2.7%	35	13	49	2.0:1.0
Osteoid osteoma	1	0.9%	13	13	13	Female
Lipoma of bone	1	0.9%	67	67	67	Male

the benign/intermediate and malignant tumour group. *p*-values < 0.05 denote statistical significance.

3. Results

A total of 113 patients with a bone tumour of the clavicle were included in this retrospective study. Patient age averaged 40 years (1 to 91). Analysis of age distribution revealed the presence of two age peaks, one in the second decade and the other in the seventh decade of life (Fig. 1). The study cohort consisted of 55% male and 45% female patients, with a male to female ratio of 1.2:1. Side information was recorded in 92% of patients. The left clavicle was involved in 58% and the right clavicle in 42% of cases, respectively, yielding a left to right side ratio of 1.4:1. The location of the tumour within the clavicle was recorded in 50% of cases, with the lateral third being the most frequent site. The distribution was as follows: 51% lateral third (21% benign or intermediate and 30% malignant lesions), 5% middle third (3% benign or intermediate and 2% malignant lesions) and 44% medial third (28% benign or intermediate and 16% malignant lesions) of the clavicle. 20% of all bone tumours were benign, 27% were intermediate (locally aggressive and/or rarely metastasizing), and 53% were malignant (Tables 2–4). Eosinophilic granuloma was the most commonly found bone tumour in the clavicle (Fig. 2a-d), followed by bone metastases, Plasma cell myeloma (Fig. 3a-b), Ewing sarcoma, Osteosarcoma (Fig. 4a-c), Aneurysmal bone cyst, Osteochondroma, Chondrosarcoma, Malignant lymphoma, and Fibrous dysplasia. Less than five cases each were found in the other nine bone tumor types. The overall benign/intermediate to malignant ratio was 1:1.1. Excluding bone metastases from this analysis, 55% of the clavicle tumours were benign or intermediate, and 45% were malignant, yielding a benign/intermediate to malignant ratio of 1.2:1.

Table 3
Intermediate bone tumours of the clavicle.

Pathology	Cases	Percent	Mean age (y)	Minimum age (y)	Maximum age (y)	Male/Female ratio
Eosinophilic granuloma	21	18.6%	26	1	61	1.1:1.0
Aneurysmal bone cyst	9	8.0%	20	4	62	1.0:1.3
Osteoblastoma	1	0.9%	14	14	14	Male

Table 4
Malignant bone tumours of the clavicle.

Pathology	Cases	Percent	Mean age ± SD (y)	Minimum age (y)	Maximum age (y)	Male/Female ratio
Bone metastases	17	15.0%	66	42	91	1.1:1.0
Plasma cell myeloma	10	8.8%	60	42	78	4.0:1.0
Ewing sarcoma	10	8.8%	27	11	64	1.0:1.5
Osteosarcoma	9	8.0%	39	11	75	2.0:1.0
Chondrosarcoma	5	4.4%	52	27	68	1.0:4.0
Malignant Lymphoma	5	4.4%	50	19	83	1.0:1.5
Undifferentiated high-grade pleomorphic sarcoma	3	2.7%	55	43	62	2.0:1.0
Leiomyosarcoma	1	0.9%	25	25	25	Female

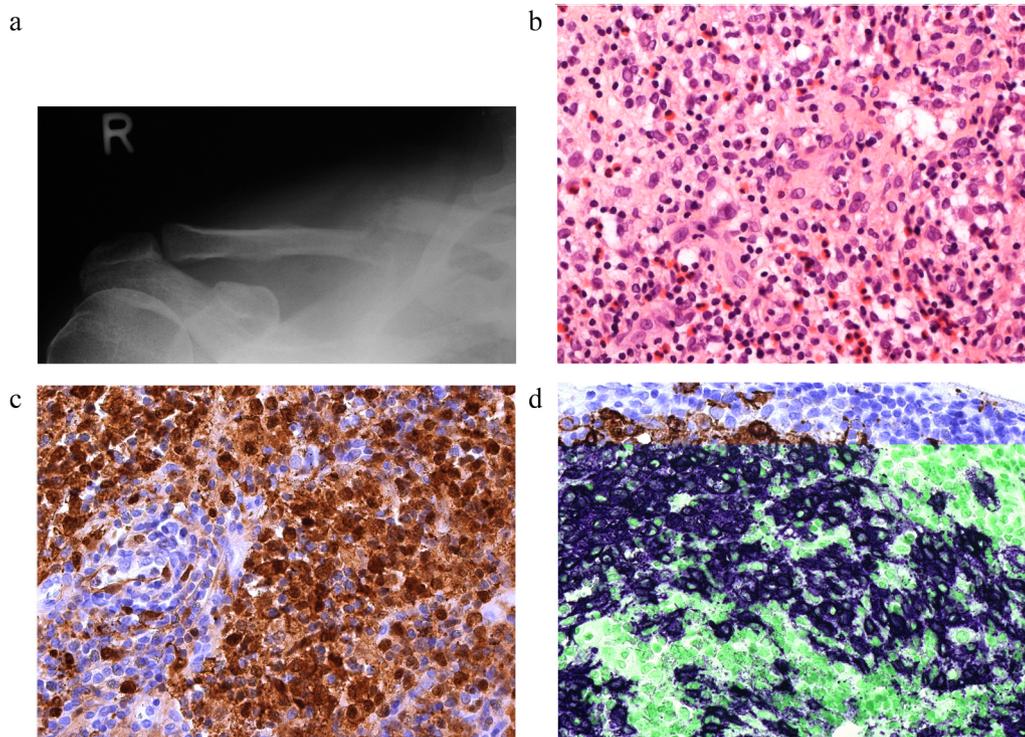


Fig. 2. Eosinophilic granuloma. Anteroposterior radiograph of the right clavicle demonstrates a lytic bone lesion in the middle third with a dislocated pathological fracture in a 55 years old woman (a). Histopathological analysis revealed Eosinophilic granuloma of bone. Mononuclear histiocytic cells with cleaved nuclei, accompanied by eosinophils display the typical histological appearance of Eosinophilic granuloma (stained with hematoxylin and eosin, 400x magnification) (b). On immunohistochemistry the mononuclear cells are positive for S100 (c) and CD1a (d) (400x magnification).

The mean patient age was 28 years (1 to 67) in the benign/intermediate tumour group, with a male to female ratio of 1.3:1. Patient age averaged 51 years (11 to 91) respecting all cases with a malignant bone tumour with a male to female ratio of 1.1:1. Excluding cases with metastases involving the clavicle, the mean patient age was 45 years (11 to 83) in the malignant tumour group, with a male to female ratio of 1.2:1. Statistical analysis revealed that patient age was significantly higher in the malignant tumour group as compared to patients with a benign/intermediate bone tumour of the clavicle ($p < 0.001$).

Further, we have analyzed which type of bone tumour were most common in young compared to old patients. In young patients (0–29 years; 47 cases) Eosinophilic granuloma was the most commonly found bone tumour (12 cases; 25.5%), followed by Aneurysmal bone cyst (8 cases; 17.0%), Ewing sarcoma (7 cases; 14.9%), and Osteosarcoma (5 cases; 10.6%). In old patients (50–79 years; 41 cases) we have found that Bone metastases were most common (13 cases; 31.7%), followed by Plasma cell myeloma (8 cases; 19.5%), Osteosarcoma (4 cases;

9.8%), and Chondrosarcoma (3 cases; 7.3%). Histopathological analysis of all included cases revealed 18 different bone tumours with 7 benign, 3 intermediate, and 8 malignant types, respectively. They were assigned to 8 different tumour type categories according to the World Health Organization (WHO) classification system of bone tumours. The distribution of the 113 clavicle tumours according to WHO classification was as follows: 33.6% tumours of undefined neoplastic nature (Aneurysmal bone cyst; Simple bone cyst; Fibrous dysplasia; Eosinophilic granuloma); 16.8% Myogenic, lipogenic, and epithelial tumours (Leiomyosarcoma of bone; Lipoma of bone; Metastases involving bone); 13.3% Haematopoietic tumours (Plasma cell myeloma; Malignant lymphoma); 12.4% Cartilage tumours (Osteochondroma; Chondroma; Chondrosarcoma); 9.7% Osteogenic tumours (Osteoid osteoma; Osteoblastoma; Osteosarcoma); 8.8% Ewing sarcoma; 2.7% Vascular tumours (Haemangioma); and 2.7% Undifferentiated high-grade pleomorphic sarcoma. Bone metastases were detected in 15.0% of cases. They originated from breast cancer (4 cases), lung cancer (3

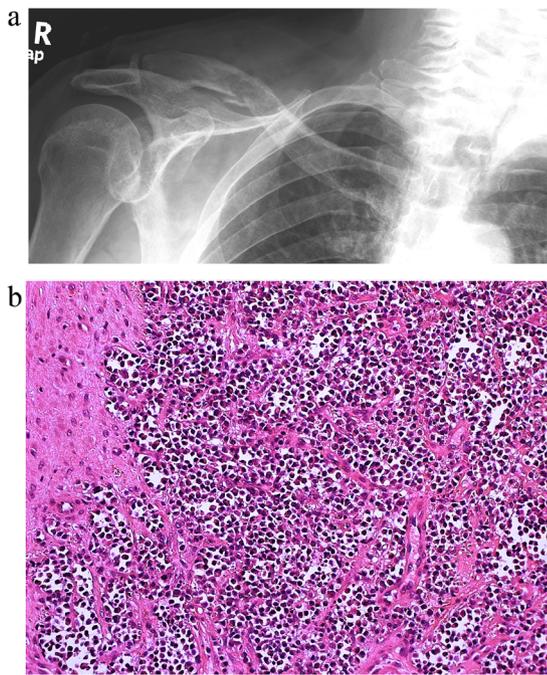


Fig. 3. Plasma cell myeloma of bone. Anteroposterior radiograph of the right clavicle shows a lytic bone lesion in the lateral third with a pathological fracture in a 78 years old man (a). Plasma cell myeloma of bone was diagnosed. Monotonous populations of plasma cells display the characteristic histological picture of plasma cell myeloma (stained with hematoxylin and eosin, 200x magnification) (b).

cases), prostate cancer (2 cases), renal cell carcinoma (2 cases), leiomyosarcoma (1 case), squamous cell carcinoma (1 case), hepatocellular carcinoma (1 case), and cancer of unknown primary origin (3 cases).

4. Discussion

In the most extensive case series to date, we have reviewed 327 clavicular lesions collected in our bone tumour registry and in our institute of pathology over a 42 years period. We have found that osteomyelitis is the most common diagnosis (26.3% of cases), followed by malignant bone tumours (18.3% of cases) as well as osteoarthritis of the sternoclavicular and acromioclavicular joints (18.3% of cases), intermediate bone tumours (9.5% of cases), and benign bone tumours (6.7% of cases). Bone tumours of the clavicle were detected in 113 cases respectively 34.6% of all patients which were operated in case of suspected bone tumour of the clavicle indicating a relatively high incidence of these lesions.

Analysis of the distribution of bone tumours within the clavicle revealed that the lateral third was the most frequent site of involvement in our study (51%), followed by the medial third (44%). Bone tumours of the middle third were rare in this series (5%). These data indicate that the distributional pattern of bone tumours within the clavicle appears similar to that found in long bones, given that the distal end is most frequently involved, and the diaphysis (mid-section) is rarely affected [13]. Comparable results were published by other authors [2,13]. In their review of 80 different articles from East Asian countries with 206 included cases of primary clavicle tumours and tumorous lesions, Ren et al. [2] reported that 34% of the lesions occurred in the lateral third, 29% in the medial third, and 19% in the middle third of the clavicle. Smith et al. [13] reviewed 58 clavicular lesions (48 bone tumours) and found that the lateral third was involved in 41% of cases, the medial third in 14%, and the middle third in 7%. Another finding of our study was, that more malignant than benign/intermediate lesions were detected in the lateral third of the clavicle. In contrast, more

benign/intermediate than malignant lesions were found in the middle third and the medial third. Although the number of cases is relatively low, our results may indicate that the lateral third of the clavicle is more prone to malignant lesions as compared to the middle and medial third.

Histopathological analysis revealed 18 different bone tumours in our case series with 7 benign, 3 intermediate, and 8 malignant types, respectively. We found a high incidence of malignant bone tumours in the clavicle in our series of patients which were operated in case of suspected bone tumour (53% malignant versus 47% benign/intermediate lesions; ratio 1.1:1). This is an important finding, considering that the incidence of malignant bone tumours in the human skeleton is much lower than that of benign/intermediate bone tumours, as reported by several authors [19]. In an epidemiological study of bone tumours with 566 included patients, benign bone tumours accounted for 71.6% of cases and malignant bone tumours for 28.4%, yielding a benign to malignant ratio of 2.5:1 [19]. The femur was the most common location of bone tumours (39.9%), followed by the tibia (17.7%) and the humerus (11.8%) [19]. Our findings are in line with the results of other studies [2,7,13]. In their review of clavicle tumours from East Asia, Ren et al. [2] reported that 57% of cases were benign and 43% were malignant. The main limitation of the review of Ren et al. [2] is, that their analysis is based on clinical data extracted from 80 different articles from East Asian countries with 206 reported cases. Bone metastases were not included in their study [2]. Excluding cases with bone metastases, the percentage of malignant bone tumours was only slightly lower than that of benign/intermediate bone tumours in our series (45% malignant versus 55% benign/intermediate lesions). In another study from the United Kingdom, Presney and Saifuddin [7] reported that 65% (30 out of 46 cases) of the clavicular lesions referred to their unit for image-guided biopsy were malignant (including bone metastases). In one of the first relevant case series including 58 clavicular lesions from the Memorial Sloan-Kettering Cancer Center in New York in 1988, Smith et al. [13] found 63% malignant bone tumours (30 out of 48 cases).

Age distribution analysis of bone tumours of the clavicle revealed two age peaks in our series, one in the second decade (25% of all cases) and the other in the seventh decade of life (19% of all cases). Ren et al. [2] reported one age peak in the second decade of life with a similar percentage (27% of all cases) in their series of bone tumours of the clavicle from East Asia. Further analysis of our data revealed that patient age was significantly higher in the malignant tumour group (mean, 51 years) as compared to patients with a benign/intermediate bone tumour of the clavicle (mean, 28 years). In patients > 50 years of age, 79% had a malignant lesion of the clavicle (33 out of 42 tumours), while only 21% (9 out of 42 tumours) had a benign/intermediate lesion, yielding a malignant to benign/intermediate ratio of 3.7:1. The correlation between patient age and the nature (benign or malignant) of the bone tumour was found to be significant in the review of Ren et al. [2] as well. In their analysis, the mean age of patients with a malignant lesion of the clavicle was higher (36 years) than in patients with a benign bone tumour (24 years) [2]. Basarir et al. [12] reported that patient age was a mean of 54 years in the malignant tumour group and 19 years in the benign tumour group in their analysis of 20 patients with a bone tumour of the clavicle. The results of these studies and our findings indicate that increased patient age may be a risk factor for the development of a malignant bone tumour of the clavicle.

Eosinophilic granuloma was the most commonly found bone tumour in the clavicle (18.6%) in our study, as well as in the review of Ren et al. (18.5%) [2]. This is an exceptional finding, considering that Eosinophilic granuloma is a rare disorder characterized by clonal proliferation of antigen-presenting mononuclear cells of dendritic origin known as Langerhans cells, accounting for less than 1% of all bone tumours [20]. In 80% of cases it affects children and adolescents, but in our series more adults were affected with a mean age of 26 years; 67% of the patients (14 out of 21) were older than 20 years of age, and only 33% of

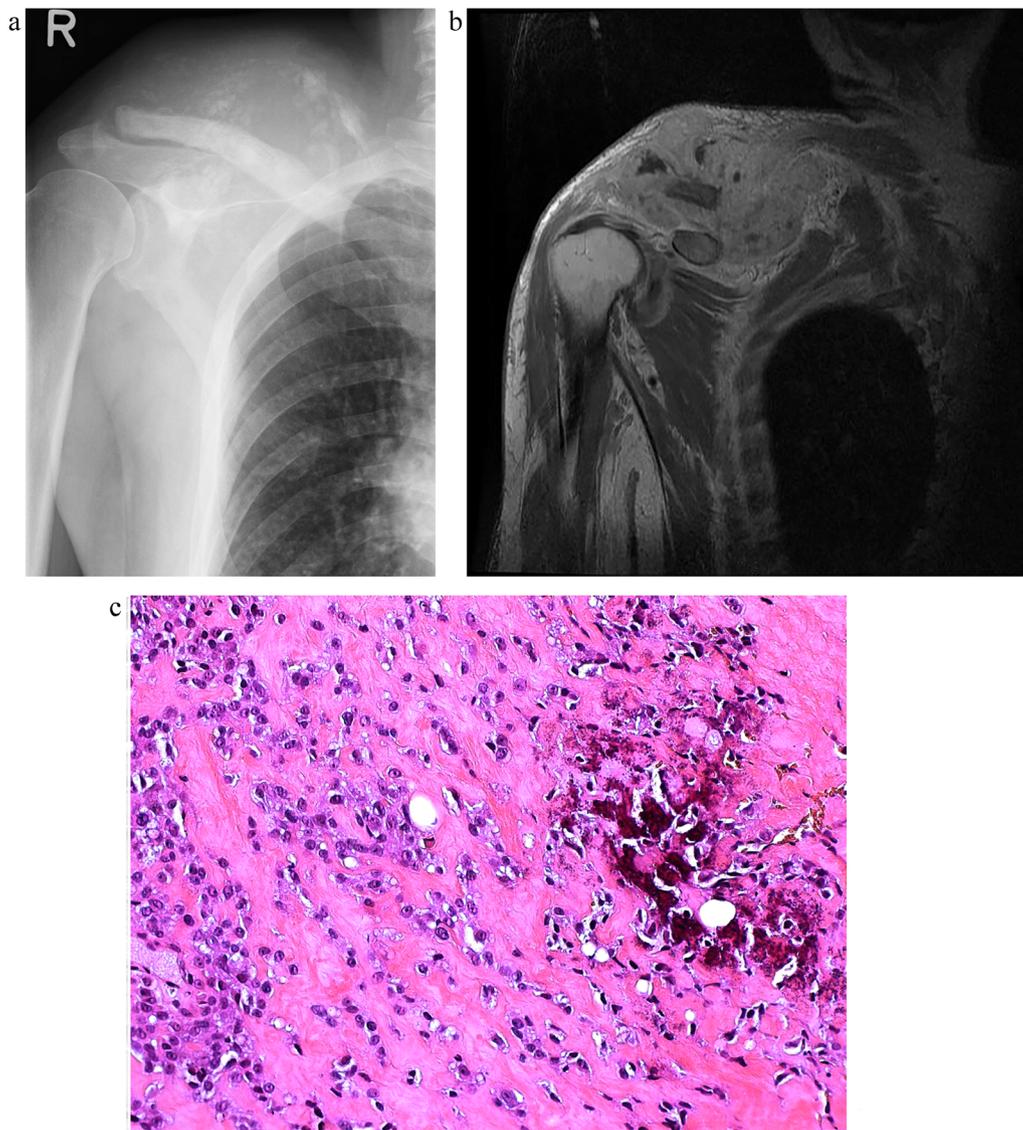


Fig. 4. Osteosarcoma. Anteroposterior radiograph of the right clavicle shows an osteoblastic bone lesion with a partially calcified soft-tissue mass in a 73 years old man (a). T1-weighted MR image demonstrates a huge soft tissue mass around the involved clavicle with locally aggressive features (b). Histopathological analysis revealed high-grade osteosarcoma with epithelioid tumor cells embedded in dense collagenous stroma with formation of neoplastic woven bone, as could be seen in the left part of the picture (stained with hematoxylin and eosin, 200x magnification) (c).

patients (7 out of 21) were children and adolescents [20]. It can affect every bone in the skeleton; however bone lesions are more common in the skull, spine (it is the most common cause of vertebra plana), ribs, and long bones [20]. Radiographs of Eosinophilic granuloma of the long bones usually show a punched-out lytic bone lesion without reactive sclerosis [20].

Bone metastases were the second most commonly found bone tumours in our series (15%), followed by Plasma cell myeloma (8.8%) and Ewing sarcoma (8.8%) as well as Osteosarcoma (8.0%) and Aneurysmal bone cyst (8.0%). Plasma cell myeloma was the third most common bone tumour of the clavicle in our study, although these tumours are less common in other long bones or flat bones [2,19]. In the review of Ren et al. [2], Plasma cell myeloma was the second most common pathologic type found in the clavicle (10.2%). Presney and Saifuddin [7] reported that metastatic disease including plasma cell myeloma was the most common cause of malignant clavicular lesions in their series of 46 cases. Ewing sarcoma was the third most commonly found bone tumour in our series as well, and the most common primary malignant neoplasm of the clavicle, followed by osteosarcoma (8.0%). This is an interesting finding, because Osteosarcoma is known to be the

most common primary malignant bone tumour in humans [19].

The limitations of this study include its retrospective design, and unavoidable preselection bias due to the fact that selected pathologists and surgeons sent their selected cases to the bone tumour registry for second opinion examination as well. All cases which were not operated on are missing. Hence, benign bone tumours of the clavicle may be underrepresented in this study which may have affected the malignant to benign/intermediate ratio. Analysis of the largest case series of clavicular lesions to date, including 327 cases, is the strength of this study.

5. Conclusions

The high incidence of malignancy found in this series of patients which were operated in case of suspected bone tumour of the clavicle, highlight the importance of biopsy to prevent delay in diagnosis and treatment of these lesions, especially in patients with increased age. Open biopsy or core needle biopsy can be used to obtain sufficient material for histological diagnosis, at the discretion of the surgeon [1,7,11]. The authors prefer the open biopsy technique at the clavicular site especially in order to avoid injuries of the neurovascular structures

and the pleura. Surgical options for the treatment of malignancies include total or subtotal claviclectomy with or without reconstruction (fibular autograft or allograft) as supported by the literature [1,2,21,22]. The clavicle often can be resected with no need for reconstruction and good functional outcome, especially in young children. We believe that the results of this study are of clinical importance and may aid the physician in the diagnosis and management of these rare lesions.

Conflicts of interest statement

The authors declare that there are no conflicts of interest.

Funding

The authors did not receive any outside funding, honorarium, grants or other form of payment in support of their research for or preparation of this work.

Authors' contributions

M.P., Conception and design of the study, acquisition of data, revising the article critically for important intellectual content, final approval of the version to be submitted.

N.S., Acquisition of data, analysis and interpretation of data, revising the article critically for important intellectual content, final approval of the version to be submitted.

J.Z., Conception and design of the study, acquisition of data, revising the article critically for important intellectual content, final approval of the version to be submitted.

A.M.L., Acquisition of data, revising the article critically for important intellectual content, final approval of the version to be submitted.

C.S., Acquisition of data, revising the article critically for important intellectual content, final approval of the version to be submitted.

A.S.S., Conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, final approval of the version to be submitted.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jbo.2019.100229.

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