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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Tumor-mimicking musculoskeletal infectious lesions – experience of a single referral center

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SUMMARY
Introduction/Objectives Bone and soft tissue infections might mimic bone and soft tissue tumors. Therefore, differential diagnosis is important to prevent errors in treatment. This report aims to present the data of patients with indistinct clinical and radiological findings mimicking benign and malignant bone and soft tissue tumors, which were later diagnosed as inflammatory infections.
Methods A retrospective chart review of the clinical, microbiological, radiologic, and pathologic findings of patients presented with a presumed diagnosis of a possible malignant lesion was performed.
Results The study included 21 patients with a median age (IQR) of 37 (1 month – 72 years) years, and 13 (61%) patients were men. In total, 16 (76%) patients were admitted to the hospital with complaints of pain. The diagnoses were hydatid cyst, tuberculous osteomyelitis, cat-scratch disease, chronic osteomyelitis, subacute osteomyelitis, and soft tissue abscess. All patients were treated depending on the diagnosis of the lesion.
Conclusion There are chances of misdiagnosis due to shared common characteristics of tumoral and infectious lesions which might be mildly increased inflammatory markers with deeply seated non-mobile soft tissue masses and aggressive periosteal reactions and/or bone destruction patterns. So, each pseudotumoral lesion due to possible infectious causes should be histopathologically examined and correlated with other clinical and laboratory data in order to achieve a final diagnosis
Keywords: biopsy; imaging; hydatid cyst; tuberculosis; soft tissue abscess; osteomyelitis

INTRODUCTION

Bone and soft tissue sarcomas are extremely rare malignant tumors, which are mesenchymal in origin. Nearly 21% of all pediatric solid malignant tumors and less than 1% of all adult solid malignant tumors are sarcomas [1]. Despite their rarity, sarcomas represent the third leading tumor type in young populations [2].

Benign tumors are classified according to the matrix protein produced by the tumor cells, such as bone, fibrous tissue, cartilage, fat, or blood vessels [3]. Skin and soft tissue infections are characterized by microbial invasion of the layers of the skin and/or underlying soft tissues [4]. Although they are usually caused by bacterial infections, fungal, viruses, parasitic, or mycobacterial aetiologias might be detected [5].

Osteomyelitis is an inflammation of the bone and bone marrow, most caused by bacterial and rarely fungal, parasitic, or *mycobacterium* species [6].

Although data are scarce, infections of the bone and soft tissue might mimic tumoral lesions. However, the treatment approach for the two conditions is very different; hence, differential diagnosis is important to prevent errors in treatment [7, 8].

In this paper, we aimed to present the data of patients with indistinct clinical and radiological findings, mimicking benign and malignant bone and soft tissue tumors, which were later proven to be infectious lesions on biopsy.

METHODS

The study was conducted at the Istanbul Medeniyet University Medical School, Goztepe Training and Research Hospital. The patients signed voluntary consent forms, and the study complied with the ethical standards of the Helsinki Declaration. This is a retrospective study from a prospectively collected database of a tertiary referral center for musculoskeletal tumors. The data of patients with suspected bone and soft tissue tumors or bone sarcomas that were later diagnosed as bone and soft tissue infections by clinical, microbiological, radiological, and pathological methods between 2015

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and 2021 were analyzed parameters analyzed included age, sex, comorbid conditions, main symptoms on admission, history of previous infections, tuberculin skin test (TST), white blood cell (WBC) count, C-reactive protein (CRP) level, sedimentation, direct chest radiographs, computerized tomography (CT), magnetic resonance imaging (MRI) findings, preoperative diagnosis, surgical techniques, microbiological analyses, and pathological diagnoses.

RESULTS

This study included 21 patients. Table 1 presents the overall characteristics of the study population. The median age of the patients was 37 years (1 month – 72 years), and 13 (61%) were male. The most common symptom was pain; 16 patients in the study cohort were admitted to the hospital with complaints of pain.

According to the results of the investigations, four patients had tuberculous (TB) osteomyelitis, two had hydatid cyst, three had cat-scratch disease (CSD), five had subacute osteomyelitis, and one had chronic osteomyelitis. Six patients were diagnosed with soft tissue abscesses mimicking soft tissue sarcoma or soft tissue lymphoma (patient numbers 3, 7, 8, 14, 19, and 20). Two of these patients had been previously diagnosed with chondroma and leiomyosarcoma, respectively, and had undergone resection (patients 7 and 3). The patients were followed up for possible recurrences and metastases.

One patient had a soft tissue mass lesion abutting the sciatic nerve (patient number 14). A preoperative biopsy was consistent with lipoma; however, pathological examination of the excised lesion revealed accompanying chronic fungal infection. One patient with a soft tissue abscess had

Figure 1. Penumbra sign at the proximal humerus of the patient with tuberculous osteomyelitis

Table 1. Characteristics of the patients

Case	Age/ Sex	Comorbidities /Main symptom	Location	Previous history of Infectious disease /Pulmonary involvement / TST	WBC (10^3/uL) / CRP (mg/dl) / Sedimentation (mm/hour)	Pathology	Microbiological analysis	Surgery	Radiology	Treatment
1	15/ M	-/Pain	Cruris	- / - / -	11.1/ 5.82 / 44	Chronic suppurative osteomyelitis	CN	Biopsy and curettage	Medullary oedema	TEIC/DA
2	34/ F	-/Pain	Sacrum	- / - / 17mm at 72 hours	5.2 / 0.7 / 117	Granulomatous infection	CN	Open biopsy	Lytic expansile lesion	RMP/EMB/ INH/PYR
3	47/ F	-/Pain	Shoulder	- / - / -	6.79 / 0.1 / 18	Lipogranulomatous inflammation	CN	Tumoral bed excision	Soft tissue lesion	TEIC/DA/ CIP
4	1 m/ M	-/Pseudoparalysis of right extremity	Thigh	Nosocomial sepsis / - / -	15.8 / 9.22 / 98	Osteomyelitis and septic arthritis	CN	Biopsy and debridement	Lamellar type periosteal. reaction in femur	VA/AK
5	67/ M	-/Pain	Shoulder	- / + / 17 mm at 72 hours	6.8 / 10.3 / 74	Chronic granulomatous inflammation	*S. hominis M tuberculosis complex*	Biopsy and resection arthroplasty of right proximal humerus	Penumbra sign	RMP/EMB/ INH/PYR
6	35/ M	-/Sciatalgia	Gluteal area	- / - / -	6.63 / 3.94 / 25	Consistent with cyst hydatic	CN	Excisional biopsy	Irregular cystic lesion	ALB
7	49/ F	Chordoma/Pain and mass lesion	Sacrum	- / Chordoma metastases / -	8.3 / 21.3 / 20	Dense abscess	CN	Trucut biopsy	Mass lesion posterior to sacrum	CIP/SAM/ AMC
8	39/ F	-/Pain	Groin	- / - / -	6.18 / 0.1 / 25	Consistent with abscess	CN	Fine needle aspiration biopsy	Cystic lesion	TPZ/DA/CIP
9	10/ F	-/Pain	Cruris	- / - / -	10.5 / 0.1 / 40	Inflammatory granulation tissue	CN	Biopsy and curettage	Penumbra sign.	CFZ/AMC

10	9/ M	-/Pain	Symphysis pubis	- / - / -	14.3 / 6 / 117	Inflammatory granulation tissue	*S. aureus*	Curettage	Lytic lesions	TEIC
11	18/ M	-/Pain	Gluteal area	- / +/ -	10.8 / 9 / 47	Inflammatory granulation tissue	CN	Biopsy	Cortical erosive lesion.	CFZ/DA
12	10/ F	-/Pain	Ancle	- / - / -	10.4 / 1.34 / 13	Subacute osteomyelitis	CN	Biopsy and curettage	Bone lesion at distal tibia	CXM
13	28/ M	-/Pain and mass lesion	Supracondylar area	- / - / -	8.4 / 0.1 / 18	Granulomatous inflammation, abscess	CN	Excision	Soft tissue lesion	AZM
14	51/ F	Breast carcinoma / Sciatalgia	Gluteal area	- / - / -	6.89 / 6.7 / 21	Fatty necrotic areas and fungal hyphae	CN	Biopsy and excision	Space-occupying mass lesion	None
15	39/ M	-/Pain and mass lesion	Supracondylar area	- / - / -	7.1/ 6.4 / 17	Granulomatous inflammation consistent with *Bartonella henselae*	CN	Biopsy	Nodular lesion	AZM
16	65/ M	-/Pain	Lumbar region	- / - / -	16.3 / 6.54 / 87	Chronic granulomatous inflammation	*M. tuberculosis complex*	Open transpedicular vertebral biopsy	L3 vertebral lesion	RMP/EMB/ INH/PYR
17	33/ M	-/Mass lesion	Elbow	- / - / -	12.1 / 3.5 / 14	Focal dense plasma cells and lymphoid tissue	CN	Biopsy	Soft tissue lesion	AZM
18	72/ M	-/Pain	Tibia	- / - / -	11.2 / 0.1 / 12	Consistent with cyst hydatic	CN	Biopsy and curettage	Cystic mass lesion	ALB
19	63/ M	-/Mass lesion	Inguinal area	- / - / -	11.1 / 4.8 / 29	Wide suppurative inflammation with microorganisms consistent actinomyces	CN	Biopsy	Soft tissue lesion	AX
20	23/ F	-/Pain and mass lesion	Thigh	- / - / -	16.1 / 2.7 / 4	Hyperkeratosis, acanthosis and epithelial spongious changes	CN	Biopsy	Soft tissue lesion	TPZ/DA/ CIP/ DAP
21	44/ M	HCV-HBV / Pain and mass lesion	Thigh	- / - / -	6.3 / 19.23 / 83	Granulomatous infection	CN	Biopsy and curettage	Mass soft tissue lesion	RMP/EMB/ INH/PYR

WBC – white blood cells; CRP – C-reactive protein; ALB – albendazole; AK – amikacin; AMC – amoksicilin-clavulonate; AZM – azithromycin; AX – amoksicilin; CFZ – cefazole; CN – culture negative; CIP – ciproflaksosin; CXM – cefuroxime; DA – clindamycin; DAP – daptomycin; EMB – ethambutole; INH – izoniazid; PYR – pyrasinamid; RMP – rifampin; SAM – ampicilin-sulbactam; TEIC – teicoplanin; TPZ – piperacilin-tazobactam; VA – vankomicin

an infection with *Actinomyces* species, which was detected on histopathological examination.

Three patients with CSD had mass lesions on the medial side of the epitrochlear region of the elbow. All of them had a one-week-long history of a cat-scratch, and their diagnoses were confirmed on preoperative biopsy. Their symptoms completely resolved after one week of antibiotic therapy (patient numbers 13, 15, 17).

Only one patient with subacute osteomyelitis at the symphysis pubis had a positive culture which revealed Staphylococcus aureus (patient number 10). Two patients had a lesion at the proximal tibiae mimicking Ewing sarcoma and eosinophilic granuloma (patients 1 and 9), and one patient each had a lesion at the distal tibia and the ischium, mimicking eosinophilic granuloma (patients 12 and 11).

One patient with a tuberculosis lesion had a monofocal, extremely painful involvement of the right proximal humerus, mimicking a metastatic bone lesion. Resection arthroplasty was performed after preoperative biopsy and culture, which revealed *Mycobacterium tuberculosis (M. tuberculosis)* infection (patient number 5) (Figure 1). Another patient with TB had multiple lesions of the musculoskeletal system, mimicking metastatic primary bone tumor or metastatic carcinoma. The diagnoses were confirmed with a bone biopsy, which revealed granulomatous inflammation (patient number 2) (Figure 2). One patient had gradually progressive hip pain with decreased range of motion of the hip joint. His roentgenograms revealed lytic bone lesions in the femoral head and neck. MRI revealed destruction of the femoral neck and head with a soft tissue mass mimicking an abscess and a tumoral lesion with contrast enhancement. Biopsy revealed granulomatous abscesses consistent with TB. His erythrocyte sedimentation rate decreased dramatically after the initiation of anti-tuberculosis drug regimen (patient number 21). One patient had low back pain and lesions at L3 and L5, mimicking metastatic bone lesions. However, a biopsy revealed granulomatous inflammation (patient number 16). Although his TST and interferon-γ (IFN-γ) release assay tests

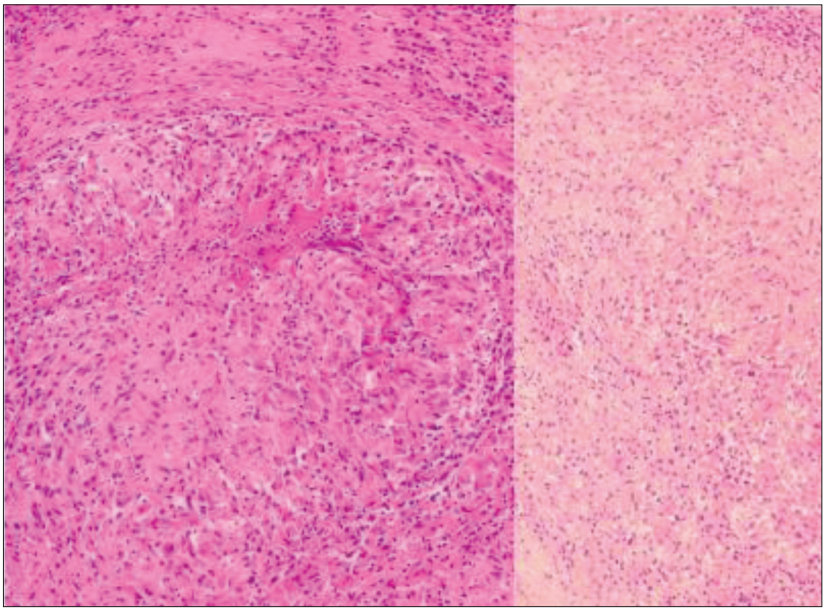


Figure 2. "Langhans" type multinuclear giant cells and lymphocytes (Hematoxylin eosin 400 ×) in granulomas consisting of epithelioid (Histological examination of serial sections revealed granuloma formation accompanied by small focal necrosis in the central area with surrounding lymphocytes; "Langhans" type giant cells were seen embedded in the fibrous stroma (in the center of the granuloma) (black arrow); in the immunohistochemical examination, CD68 was positive in histiocytes

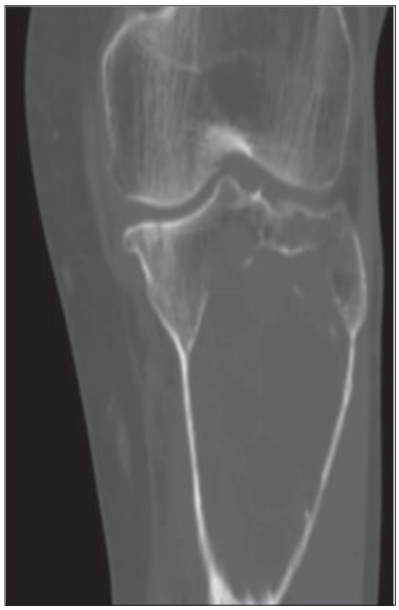


Figure 3. Cystic bone lesion at the proximal tibia due to cyst hydatid mimicking primary bone tumor or metastases

were negative, *Mycobacterium tuberculosis* was detected on the culture. Two patients with TB had completed their anti-TB medications, and two others were still under treatment.

One patient had a bone lesion on the proximal tibia, mimicking a primary bone tumor or metastases. Preoperative biopsy revealed a hydatid cyst which was removed by intralesional curettage and irrigation with hypertonic saline solution, and cement fixation was performed (patient number 18) (Figure 3). One patient had a hydatid cyst in the pelvic soft tissue anterior to the sacrum. Removal of the cysts and irrigation with hypertonic saline solution were performed (patient number 6).

DISCUSSION

In this report, we aimed to present the data of patients who had been referred to our clinic for a suspected bone or soft tissue tumor but were diagnosed with musculoskeletal infections based on their past medical history, physical examination, radiological work-up, and biopsy.

It is essential to differentiate bone and soft tissue infections from benign and malignant bone and soft tissue tumors to proceed with appropriate treatment [9]. A previous history of trauma (open fracture); previous surgeries, immune status of the patient; or presence of any associated disease affecting the immunity, such as diabetes mellitus, renal or hepatic failure, malignancy, malnutrition, alcoholism, intravenous drug use, and tuberculosis infection should be investigated [6, 10]. Any symptoms, such as, poor appetite, malaise, fever, and characteristics of the pain should be investigated. Scars of previous incisions, redness, swelling, or presence of a fistula should be noted [9, 10]. Contact with domestic animals is also important to rule out certain infections such as CSD [11].

Laboratory tests should include blood hemograms, erythrocyte sedimentation rate and CRP levels [9, 10]. Specific serological tests should be performed for the diagnosis of CSD [11], and hydatid cysts [12]. For suspected TB infections, interferon-γ (IFN-γ) release assay or TSTs should be performed [13].

Roentgenography is important for detecting periosteal reactions and bone destruction patterns [14, 15]. CT is important for visualizing details of the bone cortex, and MRI is important for the evaluation of medullary and soft tissue. A periosteal reaction occurs when tumoral lesions, infection, or trauma separate the periosteum from the bone cortex. Benign periosteal reactions usually have a uniform appearance with a single solid layer. The multi-layered (onion- skin) type is an intermediate type between solid periosteal reaction and aggressive periosteal reactions such as spiculated-sunburst or Codman's triangle [15]. Although multi-layered and other more aggressive periosteal reactions usually occur in malignant bone tumors, especially in Ewing sarcoma and osteosarcoma [15, 16], they might also be detected in benign bone lesions such as Langerhans cell histiocytosis, which is characterized by the proliferation of dendritic cells and macrophages, and even in osteomyelitis [17], as in our case with chronic osteomyelitis and septic arthritis in a premature child.

There are three major bone destruction patterns according to the Lodwick classification. Geographic bone destruction is characterized by a narrow zone of transition of the lesion, which is easily separated from the surrounding normal bone. A sclerotic margin of variable thickness encompasses the lesion in type A [18, 19]. Geographic

bone destruction usually occurs in benign or benign aggressive bone tumors and osteomyelitis, as in our patient with subacute osteomyelitis.

Moth-eaten and permeative-type bone lesions are usually accompanied by primary malignant and metastatic bone lesions [16]. Osteomyelitis might occasionally cause these two types of aggressive bone destruction patterns [16], as in our case with TB osteomyelitis. Opportunistic pathogens, especially fungal musculoskeletal infections, might be detected in patients with immunocompromised status [6], as in our case with a history of breast carcinoma and chemotherapy.

TB osteomyelitis of the bone is a rare condition caused by *Mycobacterium tuberculosis*. The bacillus usually prefers the spine and large joints due to the rich vascular supply of the vertebrae and the growth plates of the long bones [20]. Although rare, TB of the bone is an important cause of lytic bone lesions. Pain is the main symptom of bone TB. Fever and systemic symptoms might not occur until the late stages of musculoskeletal TB [20, 21].

Due to the low bacterial load in musculoskeletal tuberculosis, the possibility of detecting the *Mycobacterium* is very low, and for an accurate diagnosis of *M. tuberculosis*, multiple biopsies should be performed, and more time and attention should be paid during microscopy [21]. Biopsy revealed granulomatous osteomyelitis in all our patients with musculoskeletal tuberculosis.

Granulomatous inflammation mimicking bone and soft tissue tumors may be caused by various etiologic factors including infection, autoimmune, toxic allergic, drug and neoplastic conditions.

In cases of negative microbiological findings, differential diagnosis depends on meticulous assignment of clinical findings including laboratory test results, and examination of the histopathological specimens by an expert musculoskeletal pathologist [22, 23].

The penumbra sign is an area of a relatively hyperintense signal between the intermediate to low-signal intensity abscess cavity and the adjacent edematous or sclerotic bone marrow on unenhanced T1-weighted imaging. On histology, the cases exhibiting the penumbra sign showed a rim of active, highly vascular, inflamed granulation tissue around the abscess cavity. The penumbra sign on T1-weighted MRI in subacute and chronic osteomyelitis is very important, with high sensitivity and specificity for differentiating these lesions from musculoskeletal tumors [24, 25]. Other cases of subacute osteomyelitis with lytic bone lesions suspected to have benign or benign aggressive bone tumors were confirmed by histopathological examination because the radiographic findings of soft tissue swelling, cortical tunnelling, focal cancellous lysis, focal cortical resorption, and a periosteal reaction were a diagnostic challenge in these cases [7]. Two of our cases, one with TB osteomyelitis and the other with subacute osteomyelitis due to Staphylococcus infection, displayed the penumbra sign.

Cystic Echinococcosis (CE) occurs in humans as a result of infection by the cestodes of the genus *Echinococcus*. Characteristically, CE lesions are found in the liver and lungs; however, any part of the body might be affected [26, 27]. Skeletal lesions usually involve the vertebrae and rarely the long bones. The cestodes first settle in the epiphyseal and metaphyseal areas because of their relatively high blood supply. Here the cysts proliferate and enlarge, which then lead to a multicystic appearance. They might resemble musculoskeletal tumors with medullary and cortical destruction, and surgery is usually the first therapeutic approach [27]. Curettage and cementation with fixation were performed in our patient with a proximal tibial hydatid cyst. Primary hydatidosis of the skeletal muscle is extremely rare [28]. Excision was performed in our patient with a soft tissue hydatid cyst localized to the pelvis. We also used hypertonic solution locally during surgery in both our cases with bone and soft tissue hydatid cyst, and oral albendazole (15 mg/kg/day) was administered after surgery.

Multiorgan involvement was not observed with positron emission tomography (PET-CT) imaging performed after biopsy findings of four patients with TB osteomyelitis, two patients with hydatic cysts and five patients with subacute osteomyelitis. In cases of nonspecific histopathological findings and culture negative results, differential diagnosis was made because tumoral cells were not detected in the histopathogical specimens of our patients, but two patients (number 2 and 16) had multifocal bone involvement detected with PET-CT imaging.

Microorganisms such as *Mycobacterium tuberculosis* and *Brucella* species should not be overlooked into the etiology of pseudo tumoral infectious lesions in countries with high endemicity. Brucellosis was excluded in our patients with serological test results in addition to culture with increased sensitivity and specificity.

Musculoskeletal tuberculosis, on the other hand, is unfortunately still posing a serious problem and often causes diagnostic challenge especially in developing countries with low incomes and limited health resources. It should be noted that the TST and interferon gamma release assay tests are not highly sensitive and specific for the diagnosis of bone tuberculosis [29, 30].

In our patients with clinically suspected tuberculosis infection but negative culture and serological tests with positive granulomatous inflammation and negative tumoral cells in histopathological specimens, we started empirical antituberculosis treatment. In this process, we evaluated the clinical symptoms and laboratory findings including especially sedimentation rate with close follow- ups. In bone lesions due to TB infection, regression of SUV max values was also taken into consideration for assessment of response to the anti-TB treatment.

Ewing sarcoma is the second most common malignant bone tumor in children and young adults after osteosarcoma. The features of Ewing sarcoma and osteomyelitis might be similar on imaging, and there are numerous reports of Ewing sarcoma being misdiagnosed as osteomyelitis on radiological studies. A sharp and defined margin, optimally visualized on T1-weighted MRI, is the most significant feature differentiating the Ewing sarcoma from osteomyelitis [31]. Our patient with osteomyelitis of the

tibia had overlapping radiographic findings and MRI images with osteomyelitis and Ewing sarcoma; therefore, a biopsy was performed before the final diagnosis.

CSD is an infection that develops from the bites or scratches of flea-bearing cats and is caused by *Bartonella henselae* [11, 32]. The disease, which is one of the causes of chronic granulomatous lymphadenitis, usually resolves with a short course of antibiotics. The medial epitrochlear region is the most common location. It should be suspected, especially in young patients presenting with lymphadenopathy [32]. History of exposure to cats, serology, and biopsy are crucial for the diagnosis [11]. Three of our patients displayed signs and symptoms of CSD, and all had a history of cat scratches.

Pyomyositis might rarely be confused with soft tissue sarcoma due to the absence of signs of inflammation such as warmth and redness and might present only with mass lesions as seen in three of our cases. Clinical and laboratory panels may sometimes be not adequate for diagnosis of bone and joint infections with diverse presentations and the diagnosis may solely be obtained by histopathological analysis [33].

Pseudotumor lesions share imaging characteristics with neoplastic lesions such as periosteal reactions, bone destruction patterns, contrast enhancement patterns on MRI etc.

Meticulous attention should be paid to history of contact with animals or animal products and immune status of the patients [34].

Study limitation

The small sample size, retrospective design and heterogeneity of pathologic diagnosis are limitations of this study.

CONCLUSION

Histopathological examination of lesions due to soft tissue and bone infections should be performed to rule out tumors in cases of doubt. The cause of uncertainty is the shared common characteristics of tumoral and infectious lesions. There may be mildly increased inflammatory markers in cases with deep-seated non-mobile soft tissue masses and aggressive periosteal reactions and/or bone destruction patterns. When the biopsy results are indeterminate, a repeat biopsy is recommended.

Conflict of interest: None declared.

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Мускулоскелетне инфективне лезије које имитирају туморе – искуство једног референтног центра

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САЖЕТАК

Увод/Циљ Инфекције костију и меких ткива могу имитирати туморе костију и меких ткива. Због тога је диференцијална дијагноза важна да би се спречиле грешке у лечењу.
Циљ овог рада је да прикаже податке болесника са нејасним клиничким и радиолошким налазима који имитирају бенигне и малигне туморе костију и меких ткива, који су касније дијагностиковани као инфламаторне инфекције.

Методе Урађен је ретроспективни преглед клиничких, микробиолошких, радиолошких и патолошких налаза болесника са претпостављеном дијагнозом могуће малигне лезије.

Резултати Студија је обухватила 21 болесника средње старости од 37 (1 месец – 72 године) година, а 13 (61%) болесника су били мушкарци. Укупно 16 (76%) болесника који су се жалили на бол примљено је у болницу. Дијагнозе су биле хидатидна циста, туберкулозни остеомијелитис, болест мачјих огреботина, хронични остеомијелитис, субакутни остеомијелитис и апсцес меког ткива. Сви болесници су лечени у зависности од дијагнозе лезије.

Закључак Инфективне лезије костију и меког ткива треба подвргнути хистопатолошком прегледу да би се искључили тумори у случајевима сумње. Постоје шансе за погрешну дијагнозу због заједничких карактеристика туморских и инфективних лезија које могу бити благо повећани инфламаторни маркери са дубоко смештеним немобилним масама меког ткива и агресивним периосталним реакцијама и/или обрасцима деструкције кости.

Кључне речи: биопсија; снимање; хидатидна циста; туберкулоза; апсцес меког ткива; остеомијелитис