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The Impact of Initial Symptom on the Timing of Diagnosis and Clinical Course of Osteosarcoma

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Abstract

Objective: This study aimed to analyze the attitude of patients and health care providers regarding the initial symptoms of osteosarcoma and the effect of their attitude on the timing of diagnosis and clinical course.

Methods: The osteosarcoma patients who were referred to our clinic between 1995 and 2015 were reviewed retrospectively. The patients were grouped according to their initial symptoms as "pain without swelling," "swelling without pain," or "pain with swelling." The delayed referral and delayed diagnosis durations were noted. The relationship between the type of initial symptom and delays in referral or diagnosis was analyzed. The effect of delays on the prognosis of osteosarcoma was investigated.

Results: One hundred eighty-five patients were available for the final analysis. The median age was 21 (12-69). The pain without swelling group had significantly higher delayed referral (2.10 months) and delayed diagnosis (1.53 months) values compared to both swelling without pain (P = .031, .042) and pain with swelling groups (P = <.001, <.001). The swelling without pain group also showed higher delayed referral (1.30 months) and delayed diagnosis (1.01 months) compared to the pain with swelling group (P = .049, P = .004). No significant difference was found between the groups regarding the rates of metastasis at presentation, recurrence, and 5-year survival.

Conclusion: The symptom of pain without swelling is more likely to be overlooked by patients, their parents, and doctors, compared to swelling with or without pain, and can cause a delay in the diagnosis of osteosarcoma.

Keywords: Osteosarcoma, symptom, prognosis, pain, swelling, misdiagnosis, cancer, referral

Introduction

Osteosarcoma is the most common malignant bone tumor. Its impact on the patient is devastating both physically and psychologically since the tumor makes its peak between the age of 10 and 20 years. The treatment modalities have evolved, and the combination of neoadjuvant chemotherapy and surgery provided limb salvage and increased survival rates; thus, early and proper diagnosis is essential.[1] Several prognostic factors were reported for osteosarcoma, including the presence of metastasis, age < 10 years, high alkaline phosphatase, p-glycoprotein expression, and necrosis ratio after chemotherapy.[2,3]

The most common initial symptoms of osteosarcoma are reported as pain and swelling.[4,5] Before referring to a musculoskeletal oncologist, the patients might go through different phases, including the ignorance of the symptom, mistreatment by bonesetters, and misdiagnosis by the emergency doctor or family physician. The patients might be prescribed treatments like topical or oral analgesics and physical therapy. These can lead to late diagnosis and possibly to loss of the limb or even death.[6,7] We aimed to conduct a retrospective study in the patients with osteosarcoma of the extremity to identify the attitude of patients and doctors toward different initial symptoms and evaluate the possible effect of initial symptom on the clinical outcomes. We hypothesized that the initial symptom of pain without swelling can be overlooked both by the patients and by the doctors, and the delay in diagnosis can have an important impact on the clinical course of the patients.

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Material and Method

Study Design

A retrospective review of osteosarcoma patients treated between 1995 and 2015 was conducted. The study protocol was approved by the institutional review board (no.: 91242). The inclusion criteria were osteosarcoma of the extremity and at least 5 years of follow-up. The exclusion criteria were axial skeleton involvement, pathological fracture as initial symptom, and missing information in the patient file. The axial skeleton involvement was excluded since it is difficult for the patients to feel any swelling in the axial skeleton. The patients with pathological fracture as initial diagnosis were also excluded since it is not likely to overlook a pathological fracture. The management of patients included neoadjuvant therapy and surgery. The limb salvage or amputation decision was made by a musculoskeletal tumor council, including an orthopedic surgeon, medical oncologist, pathologist, and radiologist.

Data Extraction and Analysis

The patient files were reviewed. The type of initial symptom, the date of the appearance of the initial symptom, the date of first medical consultation, the date of diagnosis, localization of the

tumors, metastasis at presentation, and recurrences were recorded. The histological diagnosis of osteosarcoma was accepted as the date of diagnosis. The time passed from the onset of symptoms to the first medical consultation [delayed referral (DR)] and time passed from the first medical consultation to the establishment of diagnosis [delayed diagnosis (DD)] were calculated. The patients were grouped according to their initial symptoms as pain without swelling (P), swelling without pain (S), and pain with swelling (PS). The symptoms like limited range of motion and limping were included in the P group since the main cause of those symptoms was pain. The relationship between the type of initial symptom and the delays in referral or diagnosis was investigated. The effect of delays on treatment outcomes (metastasis at presentation, recurrence, 5-year survival, limb survival, and disease-free survival rates) was also analyzed.

Statistical Analysis

Statistical analyses were performed using IBM Statistical Package for Social Sciences Statistics (IBM SPSS Corp., Armonk, NY, USA) 22.0 program, and *P*-value less than .05 was considered significant. Quantitative variables were given as mean and SD. Levene's test was used to determine whether the values were normally distributed or not. One-way analysis of variance test was used to compare the means, and post-hoc Bonferroni correction was applied to detect significant differences between groups. Kaplan–Meier test was used to assess survivals.

Results

One hundred eighty-five osteosarcoma patients (117 male and 68 female) were included in the final analysis. The median presentation age was 21 years (12-69 years). The patients' first referral symptoms were pain without swelling in 92 patients (50%) and swelling without pain in 53 (29%) patients, while 40 patients (22%) had pain and swelling together. The age and gender distributions were similar between the groups (Table 1). After the first symptom appeared, the average time passed before referring to a hospital (DR) was significantly higher in the P group compared to the S and PS groups ($P = .031$ and $P < .001$, respectively). Delayed referral was significantly higher in the S group compared to the PS group ($P = .049$). The average DD value was also significantly higher in the P group compared to the S and PS groups ($P = .042$ and $P < .001$, respectively). The S group had significantly higher DD compared to the PS group ($P = .004$) (Table 2).

Table 1. Demographic Properties of the Groups

	Pain (P)	Swelling (S)	Pain and Swelling (PS)	*P*
Age	23.8 ± 16.4	19.9 ± 13.5	21.3 ± 14.1	P vs. S = .14 P vs. PS = .41 S vs. PS = .62
Gender	61 male, 31 female	30 male, 23 female	26 male, 14 female	P vs. S = .24 P vs. PS = .88 S vs. PS = .41
Localization	57 Femur 20 Tibia 8 Humerus 5 Fibula 1 Calcaneus 1 Radius	29 Femur 8 Tibia 9 Humerus 6 Fibula 1 Radius	25 Femur 7 Tibia 4 Humerus 3 Fibula 1 Calcaneus	

Table 2. Statistical Comparison of Delays According to the Initial Symptom

	Pain (P)	Swelling (S)	Pain and Swelling (PS)	*P*
Delayed referral (month ± SD)	2.10 ± 2.33	1.30 ± 1.72	0.71 ± 0.85	P vs. S = .031* P vs. PS = <.001** S vs. PS = .049*
Delayed diagnosis (month ± SD)	1.53 ± 1.62	1.01 ± 1.14	0.42 ± 0.63	P vs. S = .042* P vs. PS = <.001** S vs. PS = .004*
Total delay (month ± SD)	3.63 ± 3.27	2.31 ± 2.18	1.26 ± 1.55	P vs. S = .01* P vs. PS = <.001** S vs. PS = .011*
Metastasis at presentation	29.3%	15.1%	15.0%	P vs. S = .12 P vs. PS = .99 S vs. PS = .16
Local recurrence	10.8%	13.2%	7.5%	P vs. S = .67 P vs. PS = .55 S vs. PS = .38
Overall survival (5 years)	70.6%	69.8%	70.0%	P vs. S = .91 P vs. PS = .95 S vs. PS = .94
Disease-free survival (5 years)	64.1%	66.0%	65.0%	P vs. S = .81 P vs. PS = .92 S vs. PS = .91
Limb survival (5 years)	63.0%	62.3%	62.5%	P vs. S = .91 P vs. PS = .94 S vs. PS = .96

*$P < .05$, **$P < .001$.

Among 185 patients, 56 patients (27 patients in the P group, 16 patients in the S group, and 12 patients in the PS group) had died in total, during 5 years of follow-up. The 5-year survival rates were 70.6%, 69.8%, and 70.0% for P, S, and PS groups, respectively (Table 2). The 5-year survival rates including overall survival, limb survival, and disease-free survival were similar between the groups (Table 2). Although the rate of distant metastasis (e.g., lung and skip) at presentation in the P group (29.3%) was almost twice of S (15.1%) and PS (15.0%) groups, it was not statistically significant and did not transform into clinical relevance in terms of survival rates and local recurrence, which were similar between the groups (Table 2).

The reasons for referral to a healthcare center after a period of ignorance were whether no remission of the initial symptom or addition of a new symptom like pain, swelling, limping, or limited range of motion. The misdiagnoses included soft tissue trauma, arthrosis, arthritis, ligament injury, meniscopathy, simple bone cyst, aneurysmal bone cyst, intramedullary edema, abscess, osteomyelitis, myositis ossificans, muscle/tendon rupture, synovitis, non-ossifying fibroma, and sciatic nerve pain. Some of the treatments prescribed during initial evaluation included coldpacks, non-steroid anti-inflammatory drugs, pain killers, rest, bandage, antibiotics, topical analgesics, intramuscular analgesics, and physical rehabilitation. Some patients underwent surgeries including drainage (1 patient), curettage and bone grafting (3 patients), curettage and cementation (2 patients), and embolization (1 patient) at different health centers as a result of misdiagnosis before being referred to our clinic.

Discussion

This study concluded that when swelling is present as an initial symptom, osteosarcoma patients tend to seek help earlier compared to the patients who have only pain as initial symptom. The pain without swelling can be overlooked both by patients and doctors, thus leading to delayed referral or diagnosis. However, these delays did not transform into clinical significance in terms of survival, metastasis, or recurrence.

Kim et al[8] investigated the effect of doctor-associated diagnostic delays on the prognosis of osteosarcoma. They concluded that the surgeons who applied inappropriate procedures and failed to send a tissue sample to pathology, and also the pathologists who made incorrect diagnoses, had a negative effect on the prognosis of osteosarcoma patients.[8] This study pointed out the importance of first medical evaluation both by the surgeon and by the pathologist. Our study also pointed out that the doctors can lead to delays in diagnosis due to inappropriate or incomplete first evaluation of the patient. However, we were unable to show any difference between the prognosis of the patients with and without a delay in diagnosis.

Goedhart et al[9] analyzed the effect of delayed diagnosis on clinical outcome of high-grade bone sarcomas in a 92-patient series. They did not find any association between prolonged delay and survival similar to our study. However, they revealed that metastatic disease was associated with lower survival rates.[9] Although it was not statistically significant, the twice higher rate of metastasis in the P group of our study shows that the initial symptom of pain might have a negative prognostic effect on the clinical course of osteosarcoma.

In a recent study, Vasquez et al[10] retrospectively reviewed 113 osteosarcoma cases and investigated the relationship of diagnosis delay and the time to completion of chemotherapy with clinical outcomes. They were not able to show any relationship between diagnosis delay and clinical outcomes similar to our study; however, a delay in the completion of chemotherapy was associated with poor outcomes.[10] Widhe et al[11] reported that when a palpable mass or swelling is present, the delay in diagnosis significantly decreases in Ewing sarcoma patients, but osteosarcoma patients did not show a similar trend. However, our study showed that the same situation can also exist for osteosarcoma patients, and when swelling is present, the delay in diagnosis can shorten.

In another recent study, Diessner et al[12] evaluated the effect of socioeconomic status, insurance status, or race/ethnicity on the presence of metastases and found that Medicaid insurance or no insurance was associated with metastasis at presentation in soft-tissue sarcomas, suggesting a diagnostic delay. However, no such difference was detected in bone sarcomas.[12] Also, they did not make any analysis for the effect of metastasis rates on the prognosis of the patients. Their study revealed that when a patient has no or limited insurance, they tend to bear the symptoms, thus delaying the diagnosis. All of the patients in our study had insurance provided by the government, and we did not make any socioeconomic analysis of the patients.

Two studies are available in the literature, investigating similar parameters with our study. Pan et al[13] interviewed 30 osteosarcoma patients and questioned their initial symptoms and delays in the diagnosis. All of their patients had pain as initial symptom, while some of them also had accompanying symptoms. The mean DR was 10 weeks and the mean DD was 5 weeks, similar to our study group of P. However, they did not make any statistical analysis on the available data and did not report any survival or prognosis characteristics of the patients.[13] The other study similar to ours is by Yang et al who analyzed 51 osteosarcoma patients comprising of children only. They encountered pain and swelling as the most common symptoms. The mean DR was 30 days, while the mean DD was 21 days. The delay in diagnosis did not correlate significantly with metastasis, response to chemotherapy, limb survival, recurrence, or overall survival, similar to our study. However, they did not make any comparison according to the initial symptom.[4] Our study differs from these 2 studies since we statistically analyzed the effect of initial symptom on delays in referral or diagnosis and on clinical outcome.

This study is not without limitations. The retrospective design of the study diminished the reliability of the information available in the patient files. Besides, the information in the patient files might not be completely correct since it relies on the anamnesis taken by the physician, rather than the official records of the patients. The pain character (e.g., constant, nocturnal, an neuropathic) was not categorized. The tumor localization, the histological type of osteosarcoma, and the type of chemotherapy regimen were not same in all patients, which might be interfering with the reliability of the results regarding the survival and recurrence rates.

Conclusion

The symptom of pain without swelling can be overlooked by patients, their parents, and doctors. This may result in a late diagnosis of osteosarcoma, and despite the fact that our study could not confirm it statistically, it may play a role in the local control of tumor and survival. Healthcare providers should pay more attention when they encounter pain in adolescents near a major joint that is prolonged (even in patients with trauma history), and they should be using other advanced diagnostic tools to rule out malignancies since it might be a sign of a devastating situation. Also, the patients should be informed about the importance of pain, whenever possible. It should be kept in mind that pain killers might not be the solution always.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine (Date: August 3, 2021, Number: 152321).

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