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Aspects regarding musculoskeletal pain in pediatric patients with malignancy

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ABSTRACT

Introduction. Musculoskeletal pain is among the most common complaints of children and most episodes are self-limiting. However, in some cases, it is the first sign of malignancy.
Objectives. Evaluation of the frequency and characteristics of musculoskeletal complaints as initial symptoms present in children with newly diagnosed cancer.
Material and methods. Retrospective study that included 231 children with various malignancies diagnosed in the Pediatric Clinic I, Targu Mures, during 2000-2015. The collected data were: age at diagnosis, clinical features, laboratory findings and final diagnoses.
Results. 23% of children with cancer had musculoskeletal symptoms at initial presentation. The average time between the onset and final diagnosis was 60 days. The most common complaints were arthralgia (50%) involving large joints. Juvenile rheumatoid arthritis has been the most common initial diagnosis in 7 of 54 patients (13%). Anemia was the most frequent hematological initial finding. All patients had elevated erythrocyte sedimentation rate (ESR) and lactate dehydrogenase (LDH). Malignancies diagnosed were: acute lymphoblastic leukemia and myeloid leukemia, lymphomas and solid tumors.
Conclusions. Early diagnosis of cancer and adequate treatment are essential to improving the prognosis and can be done including cancer in the differential diagnosis of rheumatic diseases in children who initially accuse musculoskeletal pain.

Keywords: musculoskeletal pain, children, malignancy

Abbreviations:
ALL – acute lymphoblastic leukemia
AML – acute myeloid leukemia
CRP– C reactive protein
CT– computer tomography
ESR – erythrocyte sedimentation rate
LDH – lactic dehydrogenases
MRI – magnetic resonance imaging
NSAIDs – nonsteroidal anti-inflammatory drugs

INTRODUCTION

Transient joint pains in the limbs are common among children, and most cases resolve without any treatment. These pains are mostly labeled as benign „growth pains" or they appear due to hyper mobile joints (1). Rarely these pain accusations prove to be of organic origin, and occasionally associated with malignancy as the initial manifestation of the disease. Acute lymphoblastic leukemia is the most common malignancy of childhood, including 25-30% of all malignant pediatric tumors and is the most common cancer associated with onset musculoskeletal pain (2). Musculoskeletal manifestations that are associated with cancers include diffuse bone pain, arthritis, arthralgia and myalgia. The pain features are useful for the orientation of the physician in accurate diagnosis. In lymphoproliferative diseases, bone pain is initially described as intermittent and gradually becomes continuous, intense and mostly nocturnal. Instead, the pain of rheumatic diseases has a low or moderate intensity, occurs mainly in the morning and is accompanied by a characteristic stiffness. Musculoskeletal pain associated with neoplasia is due to infiltration of the joint or muscle, intra or periarticular hemorrhage, or as paraneoplastic effect mediated by hu-

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moral factors (3). When these symptoms are predominant at the onset of the disease, differential diagnosis includes juvenile rheumatoid arthritis, rheumatic fever, septic or reactive arthritis and systemic lupus erythematosus (4).

The objectives of this study were to evaluate retrospectively the frequency and type of malignancy in children who initially accused musculoskeletal pain and characteristics of clinical and laboratory abnormalities that may suggest such malignancies.

MATERIAL AND METHOD

We performed a retrospective study in which we included 231 children with various malignancies who were diagnosed and treated in the Pediatric Clinic I Targu Mures-Compartment of Hemato-Oncology during 2000-2015.

The collected data were: age at diagnosis, the time interval between the onset of manifestations and diagnosis of neoplasia, early signs and symptoms; laboratory tests (complete blood count, ESR, CRP, LDH, cupremia, ferritin) and imaging investigations performed at admission, initial treatment followed and also the final diagnosis (such neoplasia). The type of musculoskeletal pain was also noted: artromyalgia, arthralgia, arthritis, bone pain, and pain characteristics (morning pain, nocturnal pain and ache).

RESULTS

Of the 231 patients diagnosed and treated with various malignancies from 2000 to 2015 period, 54 patients (23%) had at the disease onset musculoskeletal symptoms. The gender distribution of the 54 patients showed a slight predominance of males (33 patients) compared to females (21 patients). Patient age ranged from 3 to 18 years, with an average age of 8.4 years.

The symptoms associated with neoplasia were present at the onset of illness in a large number of patients; so the 54 patients with musculoskeletal pain had at the onset of illness associated mucocutaneous pallor (44 patients), fever (33), tiredness (27), night sweats (5), vomiting (6), irritability (21) lymphadenopathy (27), abdominal pain (12), weight loss (19), other symptoms (35). Musculoskeletal manifestations were: arthromyalgia in 8 patients, arthralgia in 32 patients, and 45 patients had bone pain. Monitoring the locations of arthralgia type of pain, of the 54 patients, 24% had associated arthralgia of the shoulder, 17% back pain, 10% arthralgia hip, 12% in the knee, ankle 9%, elbow 5% and 2.5% in the temporomandibular joint, and there were also multiple impairment in the same case. It was found that musculoskeletal pain is predominantly nocturnal, more than half of the patients, 54%, accusing nocturnal pain, while 31% did not characterize the pain, 11% had morning pain and 4% continuous pain (Table 1).

TABLE 1. *Distribution of patients regarding pain character*

Pain character	Nocturnal pain	Morning pain	Continuous pain	Unspecified pain as time of day
Number of patients	29	6	2	17
Percent (%)	54%	11%	4%	31%

Before presentation to oncology pediatric specialist, most patients were diagnosed with upper airways infection or juvenile rheumatoid arthritis and thus 24 patients had various nonsteroidal anti-inflammatory drugs (NSAIDs), 10 patients were treated with anti-inflammatory steroids for pain relief, the rest being treated with other drugs.

Evaluation of laboratory tests and imaging investigations at the Pediatric Oncology Compartment are presented in Fig. 1.

The most common final diagnosis was acute lymphoblastic leukemia (33 patients). Other malignant diagnoses were represented by: acute myeloid leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, neuroblastoma, nephroblastoma, Ewing sarcoma, rhabdomyosarcoma, ameloblastoma and histiocytosis (Fig. 2).

We've also analyzed the number of days from onset of symptoms to final oncological diagnosis, averaging to 60 days. The study shows that the fastest diagnose were in nephroblastoma cases (14 days). Oncologic diagnosis has been specified for neuroblastoma and histiocytosis in about 50 days, for rhabdomyosarcoma, lymphoma and non-Hodgkin's lymphoma in 60 days, an average of 75 days for acute leukemia, and the late diagnosed cases being Hodgkin lymphoma and Ewing's sarcoma (100-160 days).

DISCUSSIONS

Musculoskeletal pain is common in children, especially those of school age and often resolves without any treatment. Although the most often the cause is benign, malignant etiology should always be excluded. In malignancies, musculoskeletal pain occurs by tumor cells infiltrating the synovium, periosteum or bone marrow, but also secondary storage of uric acid or immune complexes; intra-

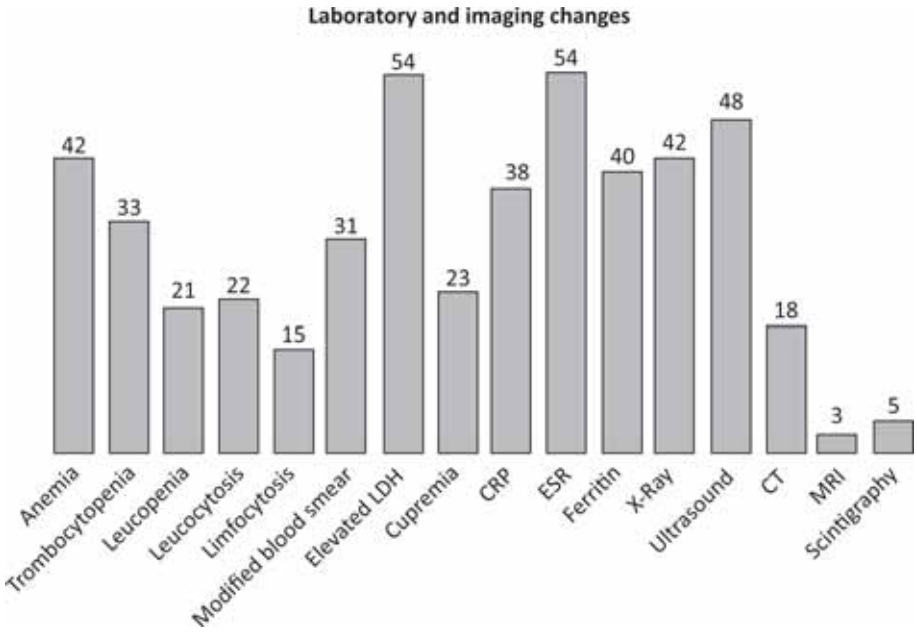

FIGURE 1. *Patients with musculoskeletal pain and changes in laboratory investigations*

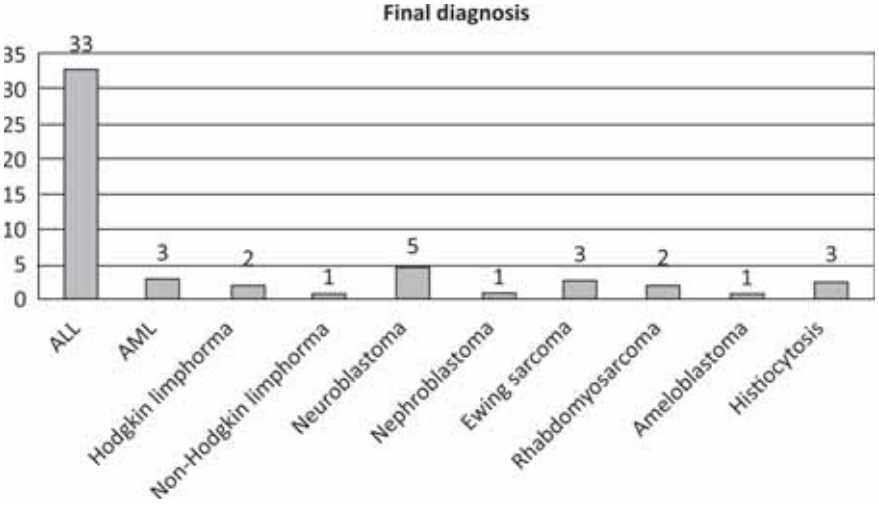

FIGURE 2. *Oncologic diagnosis of patients with musculoskeletal pain*

articular bleeding secondary to thrombocytopenia is a factor less frequent (3).

In our study, musculoskeletal symptoms were present at onset in 23% of patients with oncologic pathology, most commonly in patients with leukemias. In one study on 61 patients with leukemia, Cassia Maria bridge et al (5) reported the presence of musculoskeletal complaints in 62% of patients, particularly in the large joints of the limbs.

Medical history is very important and provides details on the nature of pain. Thus, predominantly nocturnal pain or continuous pain suggests a malignant process; metaphyseal bone pain or pain in the large joints can be a warning sign. In our study, pain was most frequent nocturnal in the large joints (shoulder, knee, hip) or backbone. Intense night pain that awakens the child from sleep is not typical for juvenile rheumatoid arthritis orienting towards a malignant disease (1). Fever, pallor, bone pain and nocturnal pain are symptoms that commonly occur in leukemia (6). Similar to literature, in the present study nearly three quarters of patients with rheumatic pains and fever associated pallor and fatigue.

We have analyzed the number of days from onset of symptoms to final oncological diagnosis. The average number of days was 63 days, the earliest diagnosed cases being nephroblastoma in about 14 days, and most delayed diagnoses were of Hodgkin lymphoma (108 days) and Ewing's sarcoma (155 days). Some studies show similar diagnosis of malignant disease in about 2 months of the onset of

musculoskeletal complaints (7), and some even in 5 months (3). The delay might be due to the lack of clinical findings suggesting neoplasia and the use of steroid therapy for a short period of time. The patient population studied, corticosteroid therapy was administered to 10 patients with musculoskeletal pain and NSAID medication to 24 patients. These treatments have been shown to be useful for temporary relief of pain and neoplasia is diagnosed only after recurrence of chronic pain. The steroid danger is that it can mask the symptoms and abnormal laboratory tests, thus the correct diagnosis is late.

Uncharacteristic clinical features and the administered treatment can cause difficulties in final diagnosis; in our study musculoskeletal complaints were initially labeled as frequent respiratory tract infections or within a rheumatoid arthritis context.

There are a number of articles that have reported cases of symptomatic osteoarticular onset of lymphoproliferative diseases, initially interpreted as in some rheumatic diseases (7-11).

Regarding laboratory analysis, in our study anemia was the most common hematological finding followed by thrombocytopenia in oncological patients. We would like to emphasize the presence of thrombocytopenia in patients with leukemia and that most often patients with juvenile rheumatoid arthritis present thrombocytosis, resulting in stimulation of megakaryocytes by the Interleukin-6 (12). Barbosa et al accentuates the importance of increased levels of LDH (5); having in the group of malignancies values of 2.2 times higher than normal, while in rheumatoid arthritis group only of 0.8 times the normal value. In our study, we found that LDH and ESR were elevated in all patients with neoplasia and rheumatic pain, a finding that is similar to other studies (1,3,13,14).

Inflammatory markers, although nonspecific, are typically elevated in cancer patients, as observed in the present study and can be used as an important screening test for children with onset musculoskeletal pain of malignant disease.

It is essential to raise awareness of the possibility of existence of a neoplastic disease in children presenting musculoskeletal complaints. Thus, our study aims to point out the need to include malignant tumors in the differential diagnosis of unexplained musculoskeletal pain.

CONCLUSIONS

Early diagnosis is a decisive factor in the treatment of oncological diseases and evolution. A malignancy must always be excluded in children with musculoskeletal complaints. Clinical uncharacteristic and nonspecific laboratory analyzes can cause final diagnosis problems, so we emphasize on the importance of conducting rigorous hemato-oncological investigations in these patients.

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