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## Original article

# Signs and symptoms of rheumatic diseases as first manifestation of pediatric cancer: diagnosis and prognosis implications



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## ABSTRACT

**Objective:** To assess the prevalence and describe the clinical, laboratory and radiological findings, treatment and outcome of children with cancer initially referred to a tertiary outpatient pediatric rheumatology clinic.

**Methods:** Retrospective analysis of medical records from patients identified in a list of 250 new patients attending the tertiary Pediatric Rheumatology Clinic, Ribeirão Preto Medical School hospital, University of São Paulo, from July 2013 to July 2015, whose final diagnosis was cancer.

**Results:** Of 250 patients seen during the study period, 5 (2%) had a cancer diagnosis. Among them, 80% had constitutional symptoms, especially weight loss and asthenia, and 60% had arthritis. Initially, all patients had at least one alteration in their blood count, lactate dehydrogenase was increased in 80% and a bone marrow smear was conclusive in 60% of patients. Bone and intestine biopsies were necessary for the diagnosis in 2 patients. JIA was the most common initial diagnosis. The definitive diagnosis was acute lymphoblastic leukemia (2 patients), M3 acute myeloid leukemia, lymphoma, and neuroblastoma (one case each). Of 5 patients studied, 3 (60%) are in remission and 2 (40%) died, one of them with prior use of steroids.

**Conclusion:** The constitutional and musculoskeletal symptoms common to rheumatic and neoplastic diseases can delay the diagnosis and consequently worsen the prognosis of neoplasms. Initial blood count and bone marrow smear may be normal in the initial framework of neoplasms. Thus, the clinical follow-up of these cases becomes imperative and the treatment, mainly with corticosteroids, should be delayed until diagnostic definition.

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## Sinais e sintomas sugestivos de doenças reumáticas como primeira manifestação de doenças neoplásicas na infância: implicações no diagnóstico e prognóstico

### R E S U M O

#### Palavras-chave:

Doenças reumáticas, Pediatria  
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**Objetivo:** Avaliar a prevalência e descrever as principais manifestações clínicas, exames complementares, tratamento e evolução de crianças com doenças neoplásicas atendidas inicialmente em um serviço terciário de reumatologia pediátrica.

**Métodos:** Analisamos retrospectivamente o prontuário médico de pacientes com diagnóstico definitivo de neoplasia, identificados entre 250 casos novos atendidos no ambulatório de reumatologia pediátrica do Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto-USP, no período de julho de 2013 a julho de 2015.

**Resultados:** Dos 250 pacientes recebidos pelo ambulatório no período do estudo, 5 (2%) tiveram diagnóstico de neoplasia. Desses 5 pacientes, 80% apresentavam sintomas constitucionais, principalmente perda de peso e astenia e 60% artrite. Inicialmente, todos apresentavam pelo menos uma série alterada no hemograma, 80% aumento da desidrogenase láctica (LDH) e 60% mielograma confirmatório. Dois pacientes necessitaram de biópsia, óssea e intestino, para o diagnóstico final. Artrite idiopática juvenil foi o diagnóstico inicial mais frequente. Os diagnósticos definitivos foram leucemia linfóide aguda (2 casos), leucemia mielóide aguda-M3, neuroblastoma e linfoma (1 caso cada). Dos pacientes estudados 3 (60%) estão em remissão. Dois pacientes foram a óbito (40%), um deles com uso prévio de corticoide.

**Conclusão:** Os sintomas constitucionais e musculoesqueléticos comuns às doenças reumáticas e neoplásicas podem retardar o diagnóstico e consequentemente agravar o prognóstico das neoplasias. O hemograma inicial, assim como o mielograma, podem estar normais no quadro inicial das neoplasias. Dessa forma, o seguimento clínico evolutivo destes casos torna-se imperativo e o tratamento, principalmente com corticoides, deve ser retardado até definição diagnóstica.

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## Introduction

Systemic symptoms related to rheumatic diseases, such as fever of unknown origin, exanthema, vasculitis, lymphadenopathy and hepatosplenomegaly, with or without association with musculoskeletal complaints such as arthritis, arthralgia and myositis, may also correspond to the first symptoms of neoplastic diseases. Thus, in many cases, neoplastic diseases are initially diagnosed as a rheumatic disease, which prolongs the time elapsed until the establishment of a correct diagnosis, delays the beginning of treatment and compromises the prognosis.<sup>1-3</sup>

The musculoskeletal manifestations that have been associated with neoplasias are, mainly, diffuse bone pain, arthritis, arthralgia, and myalgia. The characteristics of the pain help in the establishment of a correct diagnosis. In lymphoproliferative diseases, bone pain is initially classified as intermittent (especially in the metaphyseal region), with progression to a continuous and preferably nocturnal pain.<sup>4</sup> On the other hand, in rheumatic diseases, for example, juvenile idiopathic arthritis, the patient suffers from a pain of low-to-moderate intensity, which occurs mainly in the morning and is accompanied by a characteristic stiffness.<sup>3</sup>

Several neoplastic diseases may be associated with musculoskeletal complaints: primary tumor of bone, cartilaginous,

fibrous, connective tissue, or mixed origin with direct invasion of bone, joint or muscle tissue; metaphyseal bone tumor; malignant infiltration of the bone marrow; and paraneoplastic syndromes induced by distant tumors via inflammatory mediators.<sup>5,6</sup>

When these symptoms predominate at the beginning of the disease, one must proceed with the differential diagnosis of juvenile idiopathic arthritis (JIA), rheumatic fever (RF), systemic lupus erythematosus (SLE), and septic or reactive arthritis, among other diagnoses of rheumatic diseases.<sup>6</sup>

The aim of this study was to evaluate the prevalence and to describe the main clinical manifestations, complementary exams, treatment, and evolution of children with neoplastic diseases initially attended at a tertiary pediatric rheumatology unit.

## Methods

We retrospectively analyzed the medical records of patients with a definitive diagnosis of malignancies, identified among 250 cases seen for the first time in the pediatric rheumatology outpatient clinic of the Hospital das Clínicas of the Medical School of Ribeirão Preto-University of São Paulo (HCFMRP-USP) in the period from July 2013 to July 2015. The following characteristics of the included patients were recorded: age at onset

of symptoms, time elapsed between the onset of symptoms and the diagnosis of malignancy, initial signs and symptoms, laboratory tests, such as: blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), lactate dehydrogenase (LDH), specific antibodies; and alterations found in radiological exams, treatments performed, and initial (rheumatic disease) and final (cancer) diagnosis.

## Results

Of a total of 250 patients referred to the pediatric rheumatology outpatient clinic in 2 years, in fact 5 (2%) were cancer patients.

The demographic, clinical, and laboratory characteristics of each patient are described in [Table 1](#).

The time elapsed between the onset of the signs and symptoms and the diagnosis ranged from 7 days to 3 months. Weight loss and asthenia were the most observed systemic manifestations. Juvenile idiopathic arthritis (JIA) and acute lymphoblastic leukemia (ALL) were, respectively, the most prevalent initial and definitive diagnoses.

In addition to the musculoskeletal manifestations presented in [Table 1](#), at the initial physical examination, one patient suffered from adenomegaly and two patients had hepatomegaly and splenomegaly. No cutaneous manifestations were observed.

Patient 4 was admitted to the service taking corticosteroids, 2 mg/kg/day for 30 days; this medication was progressively tapered from the first consultation.

All patients had some change in their blood count: four had hemoglobin < 12 g/dL, two had leukopenia (white blood cells < 4000/mm<sup>3</sup>), two had total leukocytes > 10,000/mm<sup>3</sup>, and one patient showed thrombocytopenia (platelets < 150,000/mm<sup>3</sup>). Serum LDH levels were increased in four cases (mean = 1349 U/L). The autoantibodies initially requested, according to the initial diagnostic suspicion, were negative for their respective diagnoses, i.e. – juvenile idiopathic arthritis, antiphospholipid syndrome, and polyarteritis nodosa.

The imaging studies are shown in [Table 2](#). Only one patient had a vertebral lytic lesion on the plain radiograph. Other findings were more nonspecific, for example, signs suggestive of osteopenia, stroke, and synovial thickening. In one patient, deep venous thrombosis (DVT) of the femoropopliteal vein was diagnosed by Doppler ultrasound of the lower limbs. Chest tomography was performed in 2 patients, revealing compressive vertebral fractures and poorly defined nodular opacities in the left lung in each case, respectively. Magnetic resonance was requested in one patient; the examination showed a tumor mass compatible with malignant neoplasm of the hip.

Bone marrow aspiration was performed in all patients within the first month of investigation. Three patients presented medullary alterations compatible with cytologic and immunophenotyping diagnoses: acute lymphocytic leukemia in two patients, acute myeloid leukemia in one patient. But in two patients it was not possible to establish a diagnosis based on the bone marrow, either because there was no alteration, or because the study showed infiltration by neoplastic cells of unidentified etiology. Subsequently, an excisional biopsy was obtained in these patients, at which time T-cell non-Hodgkin's

lymphoma (bowel biopsy) and neuroblastoma (bone biopsy) were respectively diagnosed.

Two patients were treated and are currently in post-chemotherapy surveillance (patients 1 and 5), one is still on chemotherapy (patient 2), and two patients died during treatment (patients 3 and 4), including that patient initially treated with corticosteroids.

## Discussion

It is not uncommon the presence of musculoskeletal involvement as one of the manifestations of neoplasms, particularly leukemia. Brix et al.,<sup>7</sup> in a retrospective evaluation of 286 children, and Robazzi et al.,<sup>8</sup> studying 406 children seen in oncology outpatient clinics and diagnosed with acute leukemia, found frequencies of joint involvement of 18.5% and 54.7% of the cases, respectively. Rheumatic diseases, mainly JIA, were the initial suspicion in 68% of the cases of leukemia with arthritis evaluated by Brix et al.<sup>7</sup> Rheumatologic symptoms, as initial and isolated manifestations of malignancies, but initially referred to the rheumatologist, are less frequent, but no less worrying, and these can lead to a diagnostic error, with significant worsening of the patient's prognosis. In our study, in a two-year period, 2% of the children referred to the rheumatology outpatient clinic with a diagnostic hypothesis of rheumatic disease were, in fact, carriers of neoplastic disease. This prevalence is higher than that observed in other studies, as in Trapani et al.<sup>6</sup> (less than 1%) and in Gonçalves et al.<sup>9</sup> (0.25%).

The musculoskeletal manifestations of neoplasms can be explained by the direct invasion of tumors in bones and joints and also by paraneoplastic syndromes and immunological alterations, with symptoms at sites different from those of the primary tumor.<sup>10,11</sup>

Primary tumors, such as osteosarcoma and Ewing's sarcoma, are primarily responsible for the direct effects found. The localization of the tumor in long bones, with compression of adjacent structures, leukemic infiltration of synovial tissues, intra-articular bleeding secondary to thrombocytopenia, and synovial reaction by periosteal or capsular infiltration are some of the factors that justify the musculoskeletal symptoms. Even in benign tumors, such as the fibrous cortical defect, the replacement of the bone by fibrous tissue can cause pain, deformity, and spontaneous fractures.<sup>8,10</sup>

Paraneoplastic rheumatic syndromes can be induced by hormones, peptides, autocrine and paracrine mediators, and by cytotoxic lymphocytes. Inflammatory myopathies and vasculitic syndromes may precede, appear concomitantly, or follow malignant hematological diseases. Malignancies may also induce the formation of antibodies, including antiphospholipid antibodies, with manifestations very similar to the antiphospholipid syndrome (APS), including thrombosis.<sup>10,11</sup>

The musculoskeletal symptoms related to tumors may also arise secondarily to bone metastases. Ewing's sarcoma and neuroblastoma (NB) are the tumors most related to bone metastasis in childhood. The clinical picture of NB depends on the size and location of the tumor, and also on the presence of metastases. At the time of the diagnosis, about 50% of the children with NB exhibit metastases in lymph nodes, liver,

**Table 1 – Clinical characteristics, initial external diagnosis, initial treatment, final diagnosis, time elapsed between the initial and final diagnosis, and outcome of five oncologic patients initially referred to the rheumatologist.**

| Patient (gender)                                 | 1 (F)   | 2 (M)   | 3 (M)   | 4 (M)  | 5 (F)  |
|--|---|---|---|--|--|
| Age of onset of symptoms (years)                 | 7   | 7   | 12  | 4  | 15   |
| Constitutional symptoms                          | Asthenia and weight loss                            | –   | Asthenia, weight loss and fever   | Asthenia, weight loss and fever                            | Asthenia, weight loss, fever and amenorrhea.     |
| Pain   | Scapula, knees, right hallux, feet and lumbar spine | Medial face of the left thigh   | Abdominal   | Cervical, lumbar, knee and left elbow.                     | Shoulders and knees                              |
| Arthritis  | Right hallux<br>Metacarpophalangeals                | –   | –   | Knees, ankles, left elbow.                                 | Right knee                                       |
| First tests                                      |   |   |   |  |  |
| Hemoglobin (g/dl)                                | 10.5  | 12.2  | 11.1  | 8.2  | 8.7  |
| Leukocytes (n/mm <sup>3</sup> ) and differential | 4800 (40% segmented; 53% lymphocytes)               | 2800 (12% segmented, 78% lymphocytes)                                   | 6400 (5% band, 86% segmented, 11% lymphocytes)  | 17,800 (2% metamyelocytes, 53% segmented, 44% lymphocytes) | 11,500 (6% band; 76% segmented; 19% lymphocytes) |
| Platelets (p/mm <sup>3</sup> )                   | 186,000   | 87,000  | 233,000   | 293,000  | 389,000  |
| LDH (U/L)  | 325   | 490   | 1844  | 2080   | 2006   |
| % increase                                       | normal  | upper limit   | 4×  | 4.5×   | 4.3×   |
| CRP (mg/dl)                                      | 0.81  | 13.4  | 8.64  | 3.67   | 10.32  |
| ESR  | 36  | 17  | 9   | 34   | 54   |
| Autoantibodies                                   | ANA and RF non-reactive                             | Anticardiolipin, Lupus Anticoagulant, and Anti-β2 glycoprotein negative | ANA, Anti Ro, Anti-La, IgG and IgM ANCA non-reactive. Anti-cardiolipin IgM positive (10.4) and IgG negative | ANA and RF non-reactive                                    | ANA non-reactive                                 |
| Initial diagnosis                                | Juvenile idiopathic arthritis                       | APS<br>Femoropopliteal DVT  | Vasculitis (PAN)  | Juvenile idiopathic arthritis                              | Juvenile idiopathic arthritis                    |
| First treatment                                  | NSAIDs  | Enoxaparin  | Human Immunoglobulin  | Corticosteroid   | NSAIDs, opioids                                  |
| Final diagnosis                                  | Acute lymphoid leukemia                             | Acute myeloid leukemia, subtype M3                                      | T-cell non-Hodgkin's lymphoma   | Neuroblastoma  | Acute lymphoid leukemia                          |
| Time to final diagnosis                          | 28 days   | 13 days   | 3 months and 11 days  | 1 month and 18 days  | 7 days   |
| Outcome  | Full 1st remission                                  | Alive in remission  | Death due to illness  | Death due to illness                                       | Full 1st remission                               |

F, female; M, male; APS, antiphospholipid syndrome; PAN, polyarteritis nodosa; NSAID, non-hormonal anti-inflammatory drug; DVT, deep venous thrombosis; ANA, anti-nuclear antibodies; RF, rheumatoid factor; ANCA, anti-neutrophil cytoplasmic antibodies; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LDH, lactic dehydrogenase. Normal values of laboratory tests: hemoglobin >12; leukocytes >4000; platelets >150,000/mm<sup>3</sup>; CRP <0.6 mg/dl; ESR <10; LDH >230 and <460 U/L.

bone, and bone marrow. Bone and bone marrow impairment cause severe pain and irritability.<sup>12</sup> The patient with NB, who had been referred to the hospital with an initial diagnosis of JIA and who was taking steroids, had a metastatic neuroblastoma. Although the occurrence of neuroblastoma together with polyarthritis has been previously described, the frequency with which this association occurs remains unknown.<sup>9,13</sup>

Thus, the differential diagnosis of malignancies should always be included in the diagnostic propaedeutics of patients referred to the rheumatologist with musculoskeletal signs and symptoms.<sup>9</sup>

Systemic and constitutional symptoms are common both in the initial presentation of malignancies and of rheumatic diseases, and this turns into a difficult task the differential diagnosis and results in delayed diagnosis – in our study, up to 3 months. An example of such symptoms is fever, which may be the only manifestation of the initial presentation of several rheumatic diseases and tumors; this symptom may persist in isolation for a long time as a fever of undetermined origin. This is a frequent observation in the systemic form of juvenile idiopathic arthritis, systemic lupus erythematosus, and in some vasculitides.<sup>14</sup>

**Table 2 – Imaging, bone marrow examination and biopsy studies of five oncologic patients initially referred to the rheumatologist.**

| Patient | X-ray of long bones                             | X-Ray of joints   | X-Ray of other locations             | US  | CT   | MRI   | Bone marrow                                     | Biopsy                             |
|---------|---|---|--------------------------------------|---|--|---|---|------------------------------------|
| 1       | Osteopenia                                      | Fists, hands, ankles, knees: normal<br>Vertebrae: Lytic lesions   | Thorax: fracture of vertebral bodies | Joints: normal  | Spine: compressive fracture of vertebral bodies  |   | ALL   |                                    |
| 2       |   |   | Thorax: normal                       | Lower limbs: Left femoropopliteal DVT   |  |   | AML – M3  |                                    |
| 3       |   |   | Thorax: bilateral pleural effusion   |   | Abdomen: ascites, hepatosplenomegaly<br>Thorax: poorly defined nodular opacity in the left lung. Bilateral consolidation |   | Normal  | Bowel: T-cell non-Hodgkin lymphoma |
| 4       | Osteopenia<br>Irregularity in left femoral head | Elbows, knees and ankles: joint effusion and synovial thickening. |                                      | Abdomen: normal<br><br>Joints: joint effusion/synovial thickening, no signs of active inflammatory process.<br>Joint: joint effusion. |  | Hip: diffuse alteration of bone marrow, anterior and posterior neoplastic lesion, infiltrating musculature. | Leukemic cells; immunophenotyping: inconclusive | Bone: Neuroblastoma                |
| 5       | Without changes                                 | Without changes   |                                      |   |  |   | ALL   |                                    |

US, ultrasound; CT, computed tomography; MRI, magnetic resonance imaging; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia – M3 promyelocytic; DVT, deep venous thrombosis.

In our study, 80% of the patients presented constitutional symptoms in the initial clinical presentation, characterized by fever, weight loss, and asthenia. In particular, a patient with a final diagnosis of T-cell non-Hodgkin's lymphoma, who clinically may be associated with a triad of symptoms called B symptoms (weight loss without apparent reason, night sweats, and fever),<sup>15</sup> was initially diagnosed as a case of polyarteritis nodosa (PAN) in its systemic form. This patient also presented a positive PCR for tuberculosis in pleural fluid, which made the diagnosis an even more difficult task, illustrating the similar initial symptomatology between neoplasms, infections, and rheumatic disease.<sup>16</sup> Also in our study, two patients had a diagnosis of ALL, the most common cancer in childhood, and the occurrence of constitutional symptoms such as fatigue, lethargy, weight loss, and fever at the onset of the condition is described in up to 100% of the cases.<sup>3,8,17</sup> In addition to fever and weight loss, proptosis and periorbital ecchymosis (the sign of the raccoon) are also common findings in cases of disseminated NB disease (i.e. the diagnosis of one of the patients).<sup>18</sup>

In myeloproliferative diseases and in bone tumors, bone pain is mainly referred to the metaphysis of long bones, occurring characteristically at night.<sup>6</sup> For the most part, in the initial phase, the pain is intermittent, with a tendency to become intense and persistent, generally being out of proportion in the face of the physical examination findings.<sup>19</sup> In cases of ALL, bone pain is present in 34% of patients, arthritis can occur in up to 1/4 of cases, and arthralgia may also be present.<sup>3,8,17</sup> The myeloproliferative diseases observed in this study were ALL, AML, and non-Hodgkin's lymphoma. In these patients, the pattern of musculoskeletal pain was variable, but a pain out of proportion in the face of the physical examination findings was often noted (3 of 5 cases).

Bleeding, coagulopathies, leukostasis, and tumor lysis syndrome are possible complications of AML, being frequent causes of mortality.<sup>20</sup> In the case herein described, the patient was diagnosed with the M3 subtype – acute promyelocytic leukemia (APL).<sup>21</sup> AML M3 corresponds to about 20% of all AMLs, and differs from other subtypes because it is strongly associated with the presence of coagulopathy and disseminated intravascular coagulation (DIC) in up to 90% of cases.<sup>22</sup> Due to the hemorrhagic and thrombotic events associated with the condition, the main differential diagnoses are with APS, protein C deficiency, and protein S deficiency. Regarding the patient described with DVT, despite the presence of thrombocytopenia in the initial hematological examination, the investigation was directed toward a congenital thrombophilia; later, this patient was referred to the pediatric rheumatology discipline for APS investigation. Considering that APS may also be associated with the presence of thrombocytopenia, the patient was investigated for this pathology. The bone marrow examination was performed only after the patient's progression to a severe neutropenia.

Although non-specific, laboratory tests such as the blood count and inflammatory tests may present alterations that give rise to the need to expand the diagnostic investigation. A high erythrocyte sedimentation rate (ESR) in the presence of a normal or decreased platelet count may cause the physician to suspect of an infiltrative process.<sup>14</sup> In this study, all patients had elevated ESR at baseline examinations; four of them had

normal platelets, and only one exhibited thrombocytopenia. In neoplastic diseases, the finding of early anemia, particularly normocytic anemia, is common. In rheumatic diseases, one may find less intense anemias as a result of the chronic inflammatory process. In relation to the white series, the findings of lymphocytosis and/or leucopenia and, less frequently, leukocytosis predominate in neoplastic patients; in rheumatic diseases, a predominance of leukocytosis and neutrophilia is noted. Thrombocytopenia is found quite frequently in neoplasms with bone marrow involvement, whereas thrombocytosis is more common in rheumatic diseases.<sup>14</sup> However, the initial blood count in patients with bone pain, even in those with leukemia, may be normal. Thus, it is extremely critical for the diagnosis that these patients are monitored with serial blood counts.

Jones et al. described three main predictive factors for ALL: the presence of leucopenia and thrombocytopenia and a history of nocturnal awakenings caused by pain. The combination of any cytopenia in peripheral blood, including anemia, in association with nocturnal bone pain, increases the diagnostic sensitivity; the presence of two low hematological values, together with nocturnal bone pain, resulted in 100% sensitivity and 85% specificity for neoplastic disease.<sup>23</sup> In our study, three patients had nocturnal bone pain at the onset of symptoms, and all of these were anemic (patients 1, 4 and 5). The final diagnoses of these patients were: neuroblastoma with bone marrow infiltration (1 case) and ALL (2 cases). A fourth patient had leukopenia and received a final diagnosis of AML M3.

Increases of LDH may aid in diagnostic differentiation since the presence of elevation in this marker (more than 5 times the normal value) is often associated with neoplastic disease.<sup>23</sup> However, a normal LDH value does not rule out the possibility of malignancy.<sup>2</sup> In the present study, three patients had high LDH; in one of the remaining patients the result was normal, and in the other, the LDH was slightly above normal. Similarly, the elevation of serum uric acid may be a marker of neoplastic diseases.<sup>24</sup> Brix et al. found increases in uric acid levels in 17% of patients with ALL with joint involvement, and in 30% of patients without joint involvement; in these patients, LDH was increased in 70% of the cases. In our study, serum uric acid dosages were not performed.<sup>7</sup>

A positive antinuclear antibody is not a suitable marker to differentiate between these two groups of diseases, due to its non-specificity, and also because it may be present in non-rheumatic diseases, among them malignancies.<sup>25</sup> In our study, no patient was positive for this autoantibody. The other autoantibodies associated with rheumatic diseases are also subject to false-positive and false-negative results. Thus, it is critical to correctly follow the diagnostic criteria of each disease; on the other hand, these tests must be repeated at regular intervals (3 months), in order to confirm the persistence of the antibodies, for the purpose of diagnosis and classification of these diseases. One patient described in the present study was reagent to anticardiolipin (IgM) at low titers; this test was not repeated because the final diagnosis occurred before the time required for a new dosage.

Radiological findings in children with myeloproliferative diseases and musculoskeletal complaints may reveal several changes that aid in diagnosis. In myeloproliferative diseases,

generalized bone rarefaction, cortical and periosteal osteolytic lesions, radiolucent bands, and growth arrest lines are common findings. Osteopenia and joint effusions can be found in both rheumatic and myeloproliferative diseases.<sup>26,27</sup> Two patients with diagnoses of ALL and neuroblastoma, respectively, had osteopenia at the onset of the disease. The patient with neuroblastoma and one of the patients with ALL had joint effusion. Other imaging tests (ultrasound, MRI, and tomography) may aid in the diagnostic investigation.

The first analyses of the bone marrow may also fail to establish the diagnosis, especially in cases of leukemia.<sup>28</sup> All patients in the present study had bone marrow examinations. One of these patients had inconclusive results on two serial exams. This patient had been medicated with corticosteroids to treat the rheumatic disease, suspected in another unit, before the exam. It is known that the use of this pharmacological class may hinder or delay the diagnosis of malignancy, as it alleviates the symptoms and may alter the cytology and histology of the bone marrow.<sup>1</sup> This patient in question was diagnosed with neuroblastoma only after a bone biopsy. To begin a treatment with corticosteroids, it is imperative to have a correct diagnosis, since the use of this medication worsens the prognosis of neoplastic diseases, particularly ALL.<sup>6</sup>

## Conclusion

The group of neoplastic diseases should be included in the differential diagnosis of rheumatic diseases. Severe nocturnal bone pain, hepatosplenomegaly, lymphadenomegaly, daily fever, weight loss, and asthenia are findings suggestive of neoplasia. Laboratory tests, for example, complete blood count and LDH, and more specifically a bone marrow evaluation and imaging tests, are fundamental procedures that help in the early diagnosis. However, if such procedures have normal results in the first sample, they should be performed serially, thus avoiding the initiation of an inadequate treatment and delays in establishing the diagnosis. In the case of diagnostic doubt, corticosteroid therapy should be proscribed, since, specifically in the case of neoplastic diseases, this treatment is strongly associated with a worse prognosis.

## Conflicts of interest

The authors declare no conflicts of interest.

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