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CLINICAL STUDY

Systemic malignancies presenting as primary osteolytic lesion

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Abstract: The tumor formation may be the earliest manifestation preceeding other symptoms, signs and bone marrow evidence of systemic malignancy – leukemia/lymphoma. Here we present three cases of systemic malignancy in which bone lesions were the first manifested signs of the disease. All three cases were thought to be orthopedic cases and had been treated as so without genuing improvement. We would like to draw an attention to children who present with multifocal musculoskeletal pain and the importance of whole-body scaning. We describe interesting cases of diffuse large cell lymphoma and leukemia that initially presented as primary osteolytic bone lesion and discuss the differential diagnosis, literature review of non-Hodgkin's lymphoma arising in bone as the primary site *(Tab. 1, Fig. 3, Ref. 18).* Full Text (Free, PDF) *www.bmj.sk.*
Key words: acute lymphoblastic leukemia, non-Hodgkin's lymphoma, primary osteolytic lesion, compression fractures, diffuse large B-cell lymphoma.

Lymphoblastic lymphoma is a neoplasm of precursors lymphoid cells morphologically indistinguishable from those of acute lymphoblastic leukemia. It usually manifests in the lymph nodes, skin and other organs. Primary non-Hodgkin's lymphoma (HNL) of bone is a rare disorder representing less than 1 % of all non-Hodgkin's lymphomas, 3–5 % of all bone tumors and 5 % of all extranodal non-Hodgkin's lymphomas. In recent years more case reports of precursor B-cell lymphoblastic lymphoma (P-BLL) / leukemia presenting as a lytic bone lesions have appeared in the literature (1). Bone involvement is also common in acute lymphoblastic leukemia. About one third patients present with bone pain and approximately one half of them have bone involvement, which could include osteopenia, osteolytic lesions and pathological fractures (2). Presence of frank osteolytic lesion with or without hypercalcemia is infrequent. These patients are used to be misdiagnosed especially when blasts are absent in differential blood count and even in bone marrow aspirate. It could be of T or B-phenotype. Both phenotypes have the same prognosis as systemic manifestation of acute lymphoblastic leukemia, when treated in conventional protocols (3). Non-Hodgkin's lymphoma arising in bone as the primary site is unusual too. The peak incidence is in the fifth decade of life, with a predominance of male patients and most lesions occuring in the lower part of the body. Approximately half of NHLs arising in bone occur in the long bones, with pelvic and vertebral lesions making up another 25 % of cases (4). Clinical presentation include localized bone pain and occasionally a palpable mass. Radiological studies usually demonstrate an osteolytic lesion (5). Pathologic appearance of NHL arising in bone has demonstrated a wide spectrum of histologic subtypes. Most of them were classified as intermediate-grade or aggressive B-cell lymphomas (6). The most common histologic subtype is diffuse large B-cell lymphoma (DLBCL), although other histologic subtypes including CD30-positive anaplastic large-cell lymphoma (predominantly of T-cell type), Burkitt's lymphomas, and lymphoblastic lymphomas have also been described (7). The diagnosis of NHL and lymphoblastic leukemia arising in bone is a little bit difficult because of the broad spectrum of differencial diagnosis (bone tumors, metastatic tumors, infectious and traumatic affections), so biopsy for histological analysis is a gold stone in diagnosis (8). The extent of disease should be always determined by clinical staging methods. Radiological studies include chest x-ray, computed tomogra-

Tab. 1. Clinical staging of pediatric NHL according to St. Jude hospital.

Stage of disease	Involved compartments (regions)
Stage I	When one lymph nodes region or extranodal manifestation in one side of diaphragm is affected
Stage II	When more than one lymph nodes region are affected with or without extranodal propagation at the same side of diaphragm
Stage III	When both sides of diaphragm are involved or epidural, multiarticular, mediastinum, thymus, pleura, all accept resectable abdominal manifestation
Stage IV	When bone marrow is positive for blasts, and or CNS involvement

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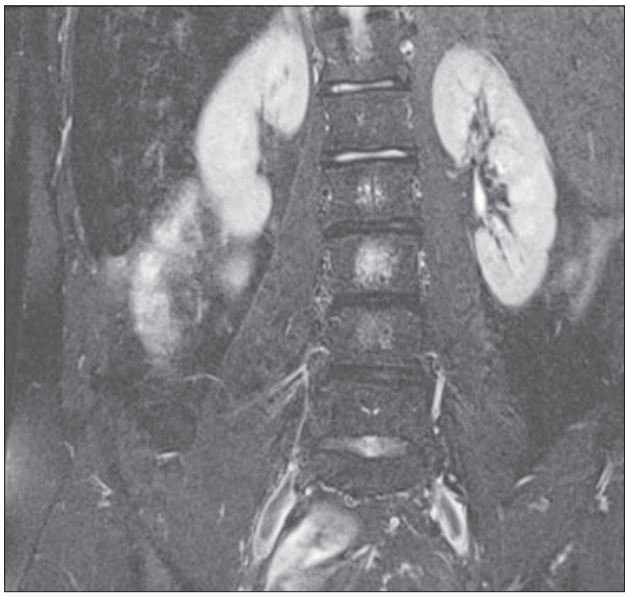

Fig. 1A. MRI of spinal cord shows ostoelytic changes of Th12, L3, hypoechogeneic cortical lesions of both kidneys.

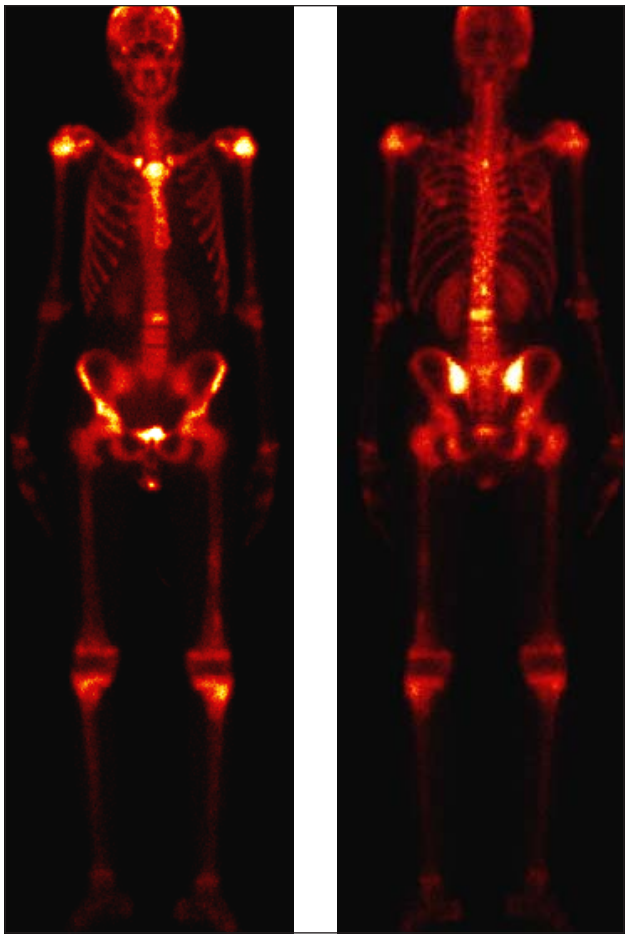

Fig. 1B. Tc99-scintigraphy with high acommulation at the skull, right clavicle, bilateral humers, L3 of spinal cord, pelvis bones and bilateral femurs.

phy (CT) scan and/or abdominal/ pelvic ultrasound, MRI, Tc99-scintigraphy and PET-scaning, are essential (9). CSF examination for cytology and bone marrow examination (aspirate with or without biopsy) for cytomorphology and histopathology, are of high value (10). According to the St. Jude clinical staging of pediatric NHL (Tab. 1), clinical stage of the disease will be determined. Treatment modals are chemotherapy and radiotherapy according to the stage of disease and protocol in use (11). We would like to report two cases of acute lymphoblastic leukemia and one case of non-Hodgkin's lymphoma, manifested primary as bone lesions.

Case reports

Case 1

17-years old boy was in close followup in orthopedic clinic for scoliosis since birth. Two months before admission to the oncology department, he was complaining of backache in lumbar area with subfebrility and febrility on and off, for which he was admitted to the clinic of infectious disease. Since all investigations done were negative, he was transferred to the general pediatric ward, where broad spectrum of investigations was also done without significant findings. In abdominal CT spondylitis of the vertebral body L3 was detected. It was also found in abdominal MRI beside diffuse osteolytic changes of lumbosacral area, pelvis and hypoechogeneic cortical lesions of both kidneys (Fig. 1A). In this point a suspicion of systemic malignancy was raised. Tc99-scintigraphy of the whole body bones showed high accumulation at the skull, right clavicle, bilateral humers, L3 of spinal cord, pelvis bones and bilateral femours. The viability of these lesions was confirmed by 18FDG-PET (Fig. 1B, 1C). Then the patient was transferred to our clinic for diagnosis and further management. On admission physical examination and systemic

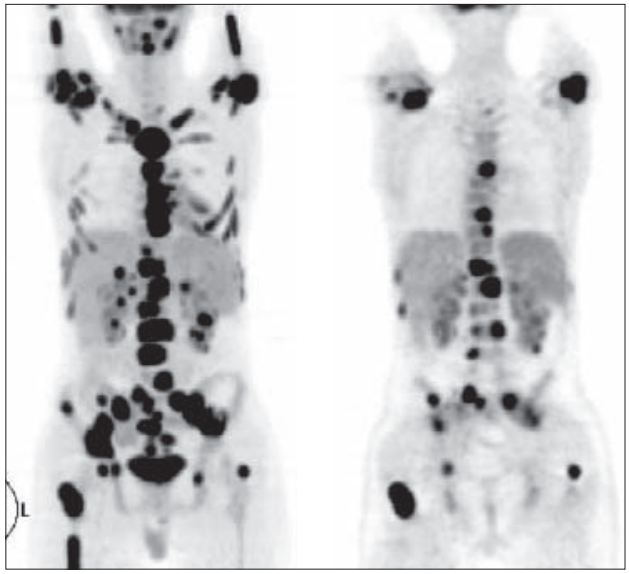

Fig. 1Ca. Initial (at diagnosis) ^{18}FDG-PET shows vaible lesions in the sternum. The thaoraxic and lumber vertebrae of cord, and bilateral scapulae, humers, femurs, pelvis bones.

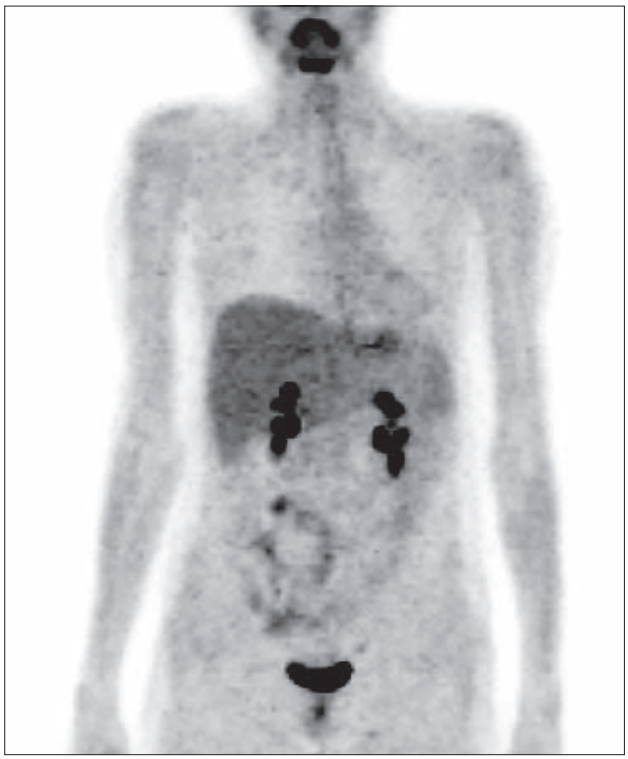

Fig. 1Cb. ^{18}FDG-PET before maintenance phase of chemotherapy.

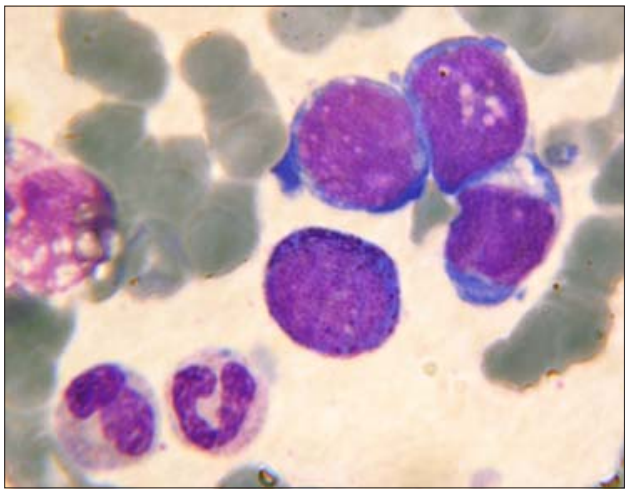

Fig. 1D. Bone marrow smear shows precursor B-lymphoblast.

review, complete hemogram and biochemistry were within normal limits. Differential blood count and bone marrow aspirate were without malignant cells. Bilateral femoral – XR showed osteolytic lesion in the distal metaphysis of the left femour. USG of urogenital system illustrated picture of hypoechogeneic lesion in the cortex of the right kidney, left kidney was intact. Having all these investigations being made, an open biopsy of L3 for histology was indicated and DLBCL was diagnosed. According to all staging investigations, clinical stage IV with primary affection of axial skeleton was established. Later bone marrow aspirate was found to be positive for lymphoblasts (20 %) (Fig. 1D), CSF was negative for malignant cells. Patient was treated according to the conventional protocol for lymphoblastic lymphoma (BFM-LB04), achieved complete remission of the disease and he is doing well now.

Case 2

12-years old girl was diagnosed in May 2003 as a case of coxisynovitis, treated by nonsteroid-antinflammatary drugs. In January 2004 she experienced compression fracture of Th7 vertebral body which was detected by CXR. There was a severe osteoporosis in densitometry. Two months later multiple compression fractures of Th7, Th8, Th9, Th12 and L2, L4, L5 vertebral bodies were detected at MRI (Fig. 2A). Complete hemogram and biochemistry were within normal limits accept of transient hypercalcemia, which was treated by biphosphanate preparations. Differential blood count was negative for malignant or atypical cells, and serological tests also were negative. In September 2007 because of Mantoux II test was found to be positive and ESR was raised, the patient was transferred to the chest disease clinic for further investigations and management, in the bone marrow aspiration 3.6 % of blasts was found, but by immunophenotyping malignant character of them was excluded. Trephine biopsy followed, and small blue cells were revealed. One month later in April 2004 she was admitted to our clinic in good condi-

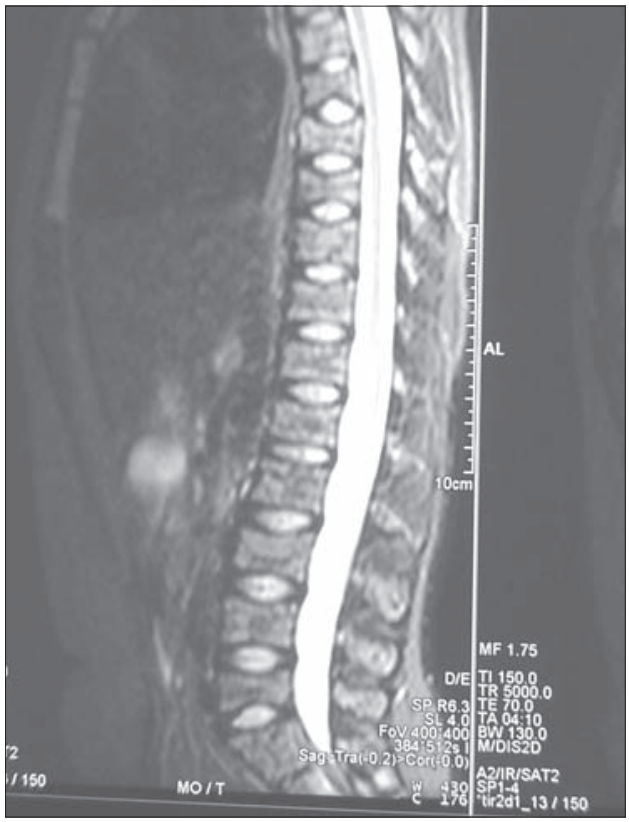

Fig. 2A. MRI shows compression fractures of vertebral bodies Th7, Th8, Th9, Th12 and L2, L4, L5.

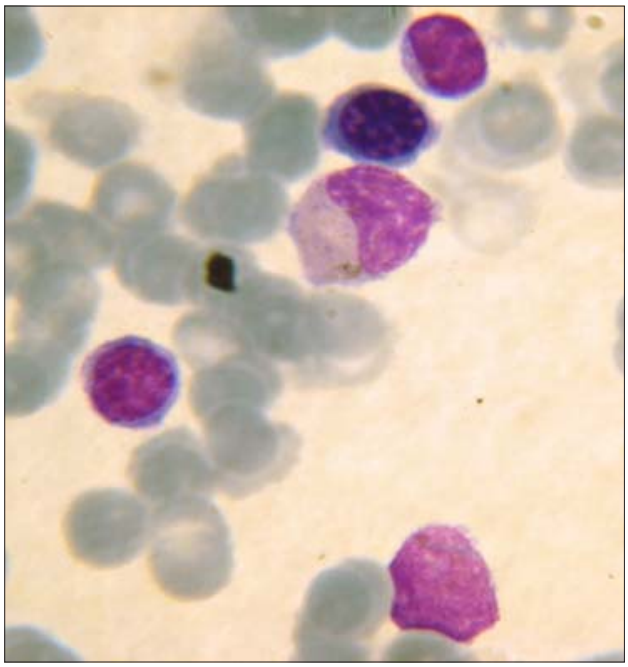

Fig. 2B. Bone marrow smear shows precursor B-lymphoblasts.

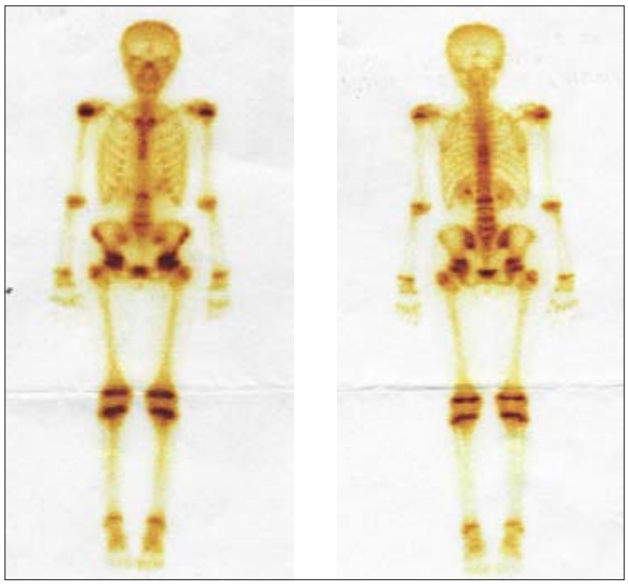

Fig. 2C. Initial Tc99-scintigraphy with high acommulation at both shoulder joints, spinal cord, pelvis bones, and bilateral hip and knee joints.

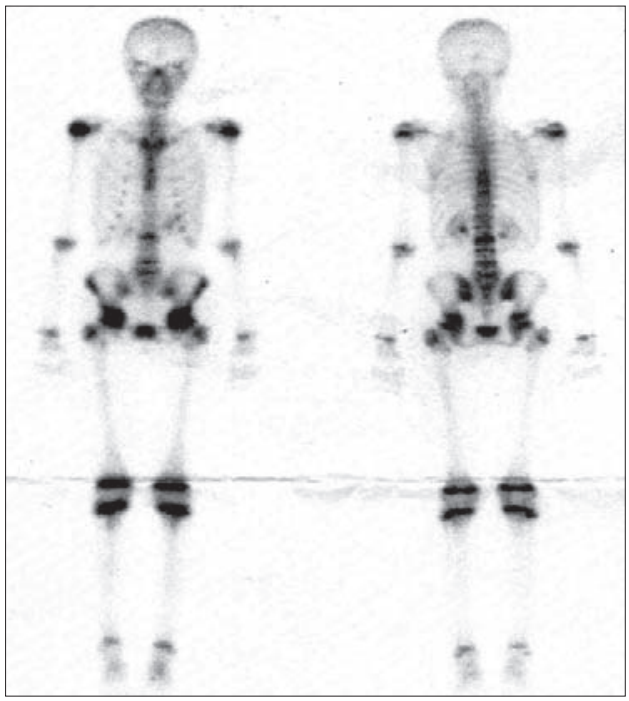

Fig. 2Da. Initial ^{18}FDG-PET-shows viable lesions of both shoulder joints, thaoraxic and lumber area of the spinal cord, pelvis bones, and bilateral hip and knee joints.

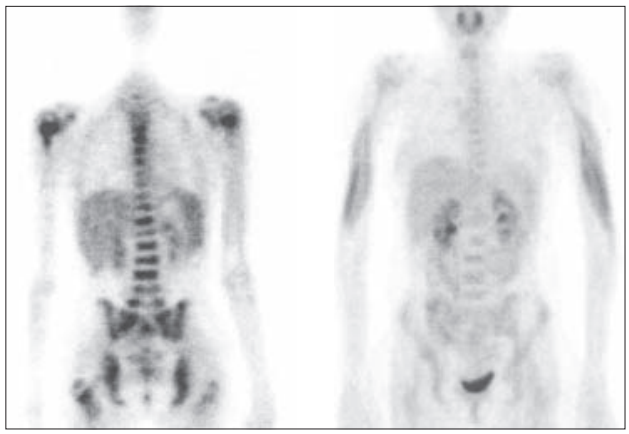

Fig. 2Db. 18 FDG-PET during treatment.

tion. Right iliac crest bone marrow aspiration showed 24.8 % of blasts with L1 morphology, pre-B phenotype vs 5.4 % of the same phenotype from the left iliac crest. One week later, bone marrow aspiration was repeated with 45.6 % lymphoblastic infiltration of the same phenotype (Fig. 2B). CSF was negative for malignant cells. On the CXR mediastinal mass and diffuse chest skeletal changes (osteoporosis) were showed. Abdominal CT--scan showed hyperdense liver and spleen and fluid in douglas pauch. Sphenoidal sinus changes were showed on brain CT, which might be due to skeletal destruction. Right iliac crest lesion 18 x 5x7 cm and upper mentioned compression fractures were detected at Tc99-scintigraphy (Fig. 2C). The viability of some bone lesions was confirmed by 18FDG-PET (Fig. 2D). Patient was treated according to the BFM ALLIC-2002 protocol for treatment of acute lymphoblastic leukemia and achieved complete remission. The treatment was finished in April 2006. While she was in follow up, relapse of the disease was diagnosed in March 2008, treated according to the protocol for ALL relapse. She achieved second complete remission and in December 2008 she had allogeneic stem cell transplantation (SCT) from HLA-iden-

tical sibling. In this time she is still in the transplantation unit because of infectious complications.

Case 3

7-years old boy injured his back two months prior to admission, in December 2007. He started to have backpain when he injured to the same lumbosacral area for the second time. He was admitted to the orthopedic clinic as lumbosacral vertebroalgic syndrome with normocytic anemia and thrombocytopenia. Analgetics with substitution of depleted blood fractions had been given to him, and then discharged. One week later the patient was readmitted with severe intensive lumbosacral pain. Complete hemogram was done with a picture of normocytic anemia and thrombocytopenia. Therefore he was transferred to our clinic in February 2008 for differential diagnosis and further management. At admission he had backache, and on examination there was tenderness at lumbosacral area. Systemic review was within normal limits. In complete hemogram there was normocytic anemia and thrombocytopenia, without malignant cells in differential blood count. Biochemistry was normal accept of hypercalcemia, in treatment of which biphosphonate preparation was used. Bone marrow aspiration was indicated, which revealed 90 % of blasts. Immunophenotyping the diagnosis of common ALL-B--fenotyp was confirmed (Fig. 3A). CSF was negative for malignant cells.

Dorsal MRI which was done before, demonstrated atypical changes on the vertebral bodies of Th7, L2, L3. They could be as a result of an old undiagnosed fractures or diffuse structural changes which may have hematological origin (Fig. 3B). Patient was treated according to the conventional protocol for ALL, achieved complete remission and he is by this time in maintenance phase of the treatment.

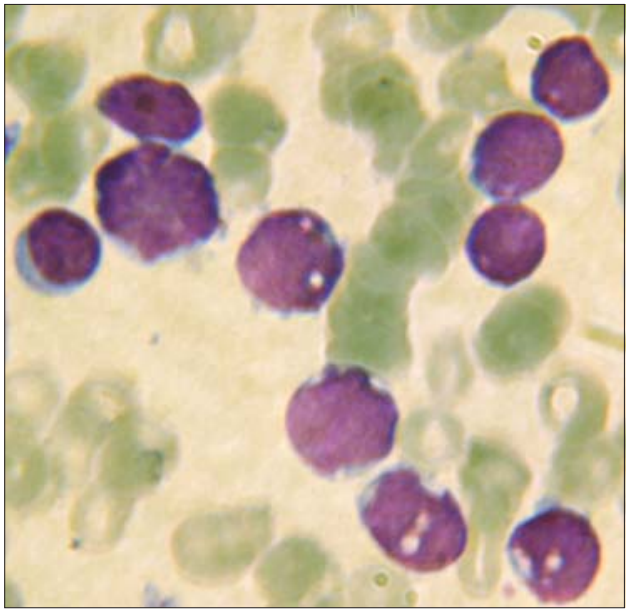

Fig. 3A. Bone marrow smear shows precursor B-lymphoblast.

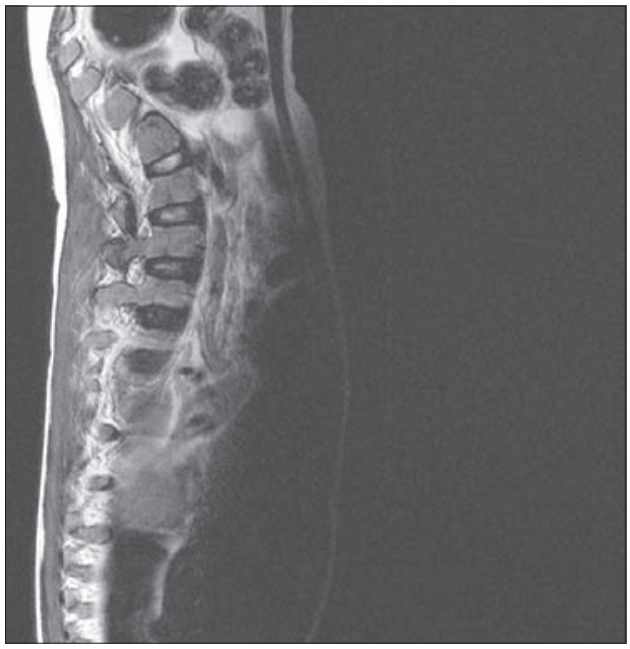

Fig. 3B. Spinal cord MRI shows atypical changes of vertebral bodies of Th7, L2, L3.

Comments

NHL arising in bone has been described predominantly as occurring in adults, but it also occurs in children and adolescents. Reports of survival in adults have been variable, with overall survival rates ranging from 40 % to 90 %, and therapy often including irradiation (12). In children and adolescents, there have been a few studies with only small numbers of patients with NHL arising in bone and limited documentation of phenotype (13). NHL arising in bone seems to be of low frequency (1 % to 2 %) on the basis of studies from single institutions containing the largest numbers of NHL patients. These studies in young patients, with heterogeneous types of NHL, have reported variable survival rates ranging from 40 % to 100 % (14). Comparison of results among these studies is limited because of the variable treatment regimens used even within single reports. In general patients with localized disease had a good outcome ranged from 75 % to 100 % compared with those with disseminated disease with outcome ranged from 25 % to 71 % (15). In many studies it was confirmed that the histologic types of NHL restricted to bone with either localized or disseminated disease are predominantly the large-cell lymphomas, along with a substantial proportion of lymphoblastic lymphomas. There are only few small noncleaved-cell lymphomas. The large cell lymphomas occur more often as localized disease, whereas the lymphoblastic lymphomas more frequently present as disseminated disease (16). If the disease presents itself as in our patient (case 1) diagnosis may delay, mainly when bone marrow aspirate analysis doesn't reveal malignant cells. Bone scanning survey may be useful as in our case (18FDG-PET/Tc99 scintigraphy), which showed osteolytic le-

sions and multiple lesions in both kidneys. By this point the decision of biopsy was not so difficult to be made.

In case of lymphoblastic leukemia arising primary in bone as osteolytic lesion, many reports had appeared in literature. Some of them presented with hypercalcemia, which used to be accompanied by high level of parathormon related peptide (PTHrP), prostaglandin E, or interleukins. In such cases the first option treatment to overcome hypercalcemia is saline with diuretics. If hypercalcemia is refracter the second line of treatment are biphosphonates (17). In some cases it was frank transient hypercalcemia as in our cases (18).

For our 2nd case positive Mantoux II test and high ESR wrongly directed the diagnostic work-up, but fortunately the compression fractures that had been detected before by RTG image, and Tc99.scintigraphy were saved the situation. RTG, USG, MR.images detected diffuse lesions in the bone marrow of both femours, pelvis and lumbar vertebrae. BM aspiration was ordered followed by trephine biopsy. The findings of bone marrow infiltration with 3.6 %, 24.8 % and 45.6 % of blasts in interval of one month and one week respectively might indicate that the bone marrow infiltration take place later, while there were bone lesions elsewhere on axial skeleton (thoracic and lumbar vertebrae and bones of the pelvis).

In the 3rd case unfortunately the general condition of patients didn't allow to performe whole body bone scintigraphy scanning. But from the character of change (diffuse) of the bone lesions, demonstrated by MR image, a suspicision of hematological origin of these lesions was raised, and confirmed by bone marrow aspirate analysis.

Conclusion

Skeletal pain in children can have multiple etiologies, including trauma, infection, and malignancy. The ethiology of unexplained musculoskeletal (bone) pain having being excluded infectious and traumatic ethiology, should be always taken as serious as it could actually be. Bone manifestation of lymphoblastic leukemia/ lymphoma should be taken in mind in otherwise unexplained bone pain or lesion although it is a rare identity. Leukemia, the most common malignancy in children, will usually manifest itself with characteristic clinical and laboratory findings, leading to the correct diagnosis. Occasionally, however, the primary presenting feature in leukemia is persistent, often multifocal, musculoskeletal pain. In an attempt to workout the etiology of the pain, children who present in this fashion may undergo bone scanning and the gold stone of diagnosis is biopsy of lesion for histology.

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