Journal of Advances in Medicine and Medical Research

32(16): 39-48, 2020; Article no.JAMMR.61020
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Role of MRI in the Detection and Monitoring of Lower Limb Osteonecrosis after Chemotherapy in Pediatric Patients with Acute Lymphoblastic Leukaemia

Aliaa M. Maarek[1*], Mohammed M. Dawoud[1], Tarek A. Rafat[2] and Khaled I. Elshafey[1]

[1]Radiodiagnosis Department, Faculty of Medicine, Tanta University, Egypt.
[2]Department of Radio-diagnosis, National cancer institute, Egypt.

Authors' contributions

This work was carried out in collaboration among all authors. Author AMM designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors MMD and TAR managed the analyses of the study. Author KIE managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2020/v32i1630627
Editor(s):
(1) Dr. Ashish Anand, G.V. Montgomery Veteran Affairs Medical Center and University of Mississippi Medical Center and William Carey School of Osteopathic Medicine, USA.
Reviewers:
(1) Gisele Pereira de Carvalho, Universidade Federal de Ciências da Saúde de Porto Alegre – UFCSPA, Brazil.
(2) Ben Taylor, Grant Medical Center, USA.
Complete Peer review History: http://www.sdiarticle4.com/review-history/61020

Original Research Article

Received 01 July 2020
Accepted 06 September 2020
Published 14 September 2020

ABSTRACT

Background: Magnetic resonance imaging (MRI) is the technique that demonstrated the highest sensitivity and specificity in the early diagnosis of osteonecrosis. It allows detecting initial typical signal intensity alterations of the bone marrow when other examinations showed nonspecific findings or even no alterations at all. The aim of this study is to assess the role of magnetic resonance imaging in detection and monitoring osteonecrotic lesions in pediatric patient with acute lymphoblastic leukemia after chemotherapy.
Materials and Methods: This prospective study was performed on 30 pediatric patients ranged from 4 to 18 years with acute lymphoblastic leukemia on chemotherapy or after 3months from ending chemotherapy with symptoms suspicious for osteonecrosis (i.e., articular pain). All patients were explained about the procedure to be done. MRI study of whole lower limbs was done for all patients.

**Corresponding author: E-mail: Maarek@gmail.com;*

Results: In the present study all patients were symptomatic. 24\30 patients (80%) had hip pain, 25\30 patients (83.3%) had knee pain and 8\30 patients (26.7%) had limping. We reported that knee pain was the most common complaint representing 83.3% of patients. 11\30 patients (36.7%) had no MRI findings. 19\30 patients (63.3%) had different positive findings; 4 patients (13.3%) had non -articular osteonecrosis (ON) only with no joint involvement (bone infarction), 2 patients (6.7%) had avascular necrosis of femoral head epiphysis without bone infarction and 13 patients (43.3%) had combined bone infarction and avascular necrosis with Joint involvement. Follow up by MRI was done for all patients (30 patients), 27 patients showed no change in MRI findings, one patient progressed from avascular necrosis of the femoral head epiphysis without deformity to avascular necrosis of the femoral head epiphysis with deformity. The other two patient showed regressive course.

Conclusion: We concluded that MRI study is mandatory for early detection and monitoring of lower limb osteonecrosis in pediatric patients with acute lymphoblastic leukemia under or after chemotherapy. The radiologist and clinician must do MRI lower limbs routinely and follow up MRI after 4-6 months to first MRI due to some patients had regressive or progressive findings.

Keywords: Osteonecrosis; lymphoblastic leukaemia; Magnetic Resonance Imaging (MRI); MRI.

1. INTRODUCTION

Acute lymphoblastic leukemia (ALL) survival rates in pediatric patients have significantly increased (up to 90 %) due to improvement of therapy regimens but several complications due to treatment related toxicity emerged in the middle and late terms. One of the most common complications is osteonecrosis (ON) characterized by the death of bone marrow elements and typically affects weight bearing limbs [1-2].

Osteonecrosis (ON), similar to ischemia in other organ systems, results from a reduction or complete loss of blood supply to bone. [3] Osteonecrosis was defined by development of pain in bones and joints while patient on treatment or within 1 year of completion of treatment and confirmed by magnetic resonance imaging (MRI) [4].

Several imaging techniques have been employed in order to properly identify osteonecrosis. Conventional radiography and even multidetector computed tomography (MDCT) used at baseline but had high radiation dose and lack sensitivity in the prompt detection of osteonecrosis. Nuclear medicine techniques (i.e., scintigraphy) may allow an early detection of metabolic alterations in affected bones but are not specific and provide a rough depiction of morphology [5-6].

Magnetic resonance imaging (MRI) is the technique that demonstrated the highest sensitivity and specificity in the early diagnosis of osteonecrosis. It allows detecting initial typical signal intensity alterations of the bone marrow when other examinations showed nonspecific findings or even no alterations at all [7]. MRI features currently considered typical of osteonecrosis are well-circumscribed geographic areas with margins of low signal on T1-weighted and high signal on T2-weighted images (viable tissue). The “double-line” sign, consisting of an outer low signal and high signal circumscribing the area on T2 weighted sequences is also considered diagnostic of osteonecrosis [8].

The aim of this study is to assess the role of magnetic resonance imaging in detection and monitoring osteonecrotic lesions in pediatric patient with acute lymphoblastic leukemia after chemotherapy.

2. SUBJECTS AND METHODS

This prospective study was performed on 30 pediatric patients ranged from 4 to 18 years with acute lymphoblastic leukemia on chemotherapy or after 3months from ending chemotherapy with symptoms suspicious for osteonecrosis (i.e., articular pain)., referred to Radiodiagnosis and Imaging Department of Tanta University hospital and to Oncology Department of National Institute of Oncology from September 2017 to March 2019.

The exclusion criteria included: Patients were less than 1year and more than 18 years, General MRI contraindications (presence of metallic foreign bodies).

History, clinical examination and laboratory investigations were conducted. All patients were explained about the procedure to be done. MRI

study of whole lower limbs was done for all patients (30), obtained using a closed MRI machine (General Electric SIGNA) HS (high speed) with magnets of intensity field 1.5 T. The Sequences (T1-weighted and STIR on coronal planes for both hips and knees.) were acquired on the coronal plane from the hips to the ankle with two or three stacks depending on patient's height. Field of view (FOV) was adapted to the major circumference of every patient. The mean acquisition time was about 15–20 min.

- Position: The patient was positioned supine with headfirst.

- Coil: Q-Body

2.1 Imaging Acquisition

- Coronal T1 weighted (TR/TE, 500/10 ms) with slice thickness 3-6.5 mm, gap 1 mm, FOV 32-80 cm and matrix 256 x 256.

- Coronal STIR weighted with slice thickness 3 -6.5 mm, gap 1mm, FOV 40-80 cm and matrix 256 x 256.

In 19 cases approved to have osteonecrosis after coronal T1 and STAIR MRI, we did additional sequences to be more accurate for follow up and staging:

- Sagittal T2 weighted with slice thickness 1 -3 mm, gap 1mm, FOV 40-50 cm and matrix 256 x 256.

- Coronal T2 weighted with slice thickness 1 -3 mm, gap 1mm, FOV 40-50 cm and matrix 256 x 256.

- Axial T1 weighted (TR/TE, 500/10 ms) with slice thickness 3 mm, gap 1 mm, FOV 32-42 cm and matrix 256 x 256.

- Axial T2 weighted (TR/TE, 3300/100 ms) with slice thickness 3 mm, gap 1 mm, FOV 32-42 cm and matrix 256 x 256.

- Sagittal T1 weighted with slice thickness 1 -3 mm, gap 1mm, FOV 40-50 cm and matrix 256 x 256.

2.2 Statistical Analysis

The sample size was calculated using Epi-Info software statistical package created by World Health organization and center for Disease Control and Prevention, Atlanta, Georgia, USA version 2002. The criteria used for sample size calculation (n>25) were 95% confidence limit, 80% power of the study.

Analysis of data were performed by SPSS v25 (SPSS Inc., Chicago, IL, USA). Quantitative parametric variables (e.g. age) were presented as mean and standard deviation (SD). Qualitative variables were presented as frequency and percentage. P value < 0.05 was considered significant.

3. RESULTS

As regards demographic data (age and gender) in the present study that included 30 patients, showing 16 (53.4%) of them were males and 14 (46.6%) of them were females, their ages ranged from 4 to 18 years with a mean age of 12.7 years. The most affected age group was from 10 to less than 15 years old included 15 patents representing 50% of all patients. Twenty-two (73.3%) patient were on chemotherapy and 8 (26.7%) patients previously had chemotherapy. Table (1).

All patients in the current study were symptomatic, 24\30 patients (80%) had hip pain, 25\30 patients (83.3%) had knee pain and 8\30 patients (26.7%) had limping. We reported that knee pain was the most common complaint representing 83.3% of patients. Fig. (1).

Table 1. Age and sex distribution in the studied patients

Age in years	Sex				Total	
	Male		Female			
	Number	Percentage%	Number	Percentage%	Number	Percentage%
1 -<5	1	3.3	1	3.3	2	6.6
5 -<10	2	6.7	3	10	5	16.7
10 -<15	8	26.7	7	23.3	15	50
15 – 18	5	16.7	3	10	8	26.7
Total	16	53.4	14	46.6	30	100

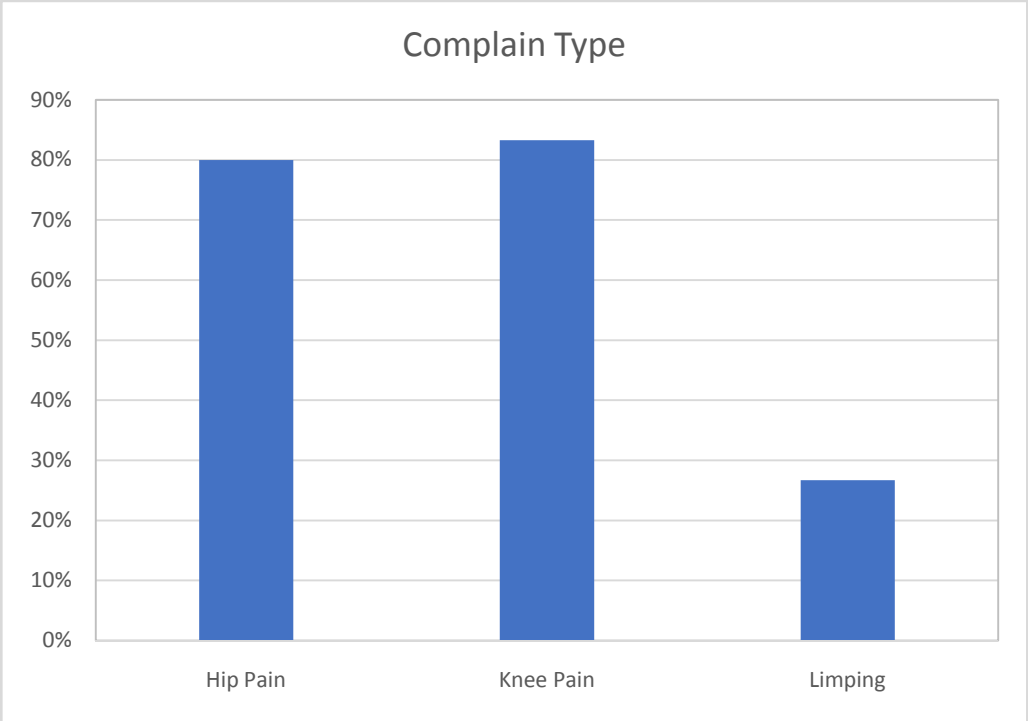

Fig. 1. Type and distribution of complain in the studied patients

MRI study of whole lower limbs was done for all patients. 11\30 patients (36.7%) had no findings. 19\30 patients (63.3%) had different positive findings; 4 patients (13.3%) had bone infarction only, 2 patients (6.7%) had avascular necrosis of femoral head epiphysis and 13 patients (43.3%) had combined bone infarction and avascular necrosis(osteonecrosis). After following up MRI since 3-6months, we had 70 ON lesions in 30 patients in different site in both lower limbs. 30 patients had followed up with MRI, in 11 patients (36.7%) after following up MRI had not findings. In 19 patients (63.3%) after following up MRI had different findings, 4 Patients (13.3%) had bone infarction only, 3 patients had avascular necrosis only, 12 patients had osteonecrosis (avascular necrosis and bone infarction). Table (2).

In the present study we detected 72 ON lesions seen in 19 patients in lower limbs bilaterally: 23 avascular necrotic lesions seen involving hip and knee joints and 49 bone infarction lesions without joint involvement .16 avascular necrotic lesions seen in femoral head epiphysis and 7 avascular necrotic lesions seen in tibial condyles reaching to its articular surface. We had 20 avascular necrotic lesions without joint deformity and 3 avascular necrotic lesions with joint deformity inform of collapse and contour irregularity of the femoral head epiphysis. After following up MRI We had 23 lesions avascular necrotic (with or without deformity) in different sites. The majority showed AN in two joints.16 lesions in head of femur (hip joint) ,7 lesions in tibia (knee joint). We had 19 avascular necrotic lesions without joint deformity and 4 avascular necrotic lesions with joint deformity inform of collapse and contour irregularity of the femoral head epiphysis. Table (3).

The most common site of bone infarction in lower limbs seen at femoral diaphysis (16 lesions) followed by femoral condyles (13 lesions), tibial diaphysis (7 lesions), tibial plateau (7 lesions), pelvic bones (3 lesions), patellae (1 lesion), fibula (1 lesion) and tarsal bones (1 lesion). After following up MRI We had 48 bone infarction lesions, the most common site of bone infarction in lower limb is Femoral diaphyses (14 lesions) and Femoral condyles (13 lesions), followed by Tibial diaphyses(7 lesions), Tibial plateaus (7 lesions), Pelvic bones (3 lesions), Patellae (1 lesion), Fibulae (1 lesion), Ankles and feet (1 lesion).Table (4).

17\22 (77.3%) patients were on chemotherapy had osteonecrosis (ON) while 2\8 (25%) patients were finished chemotherapy had osteonecrosis. Patients were on chemotherapy had 22 avascular necrotic lesions and 46 bone infarction

lesions, also patients were finished chemotherapy had one avascular necrotic lesion 3 bone infarction lesions. Table (5).

In male patients (16\30); 10 patients had ON and 6 patients had no findings, while in female patients (14\30); 9 patients had ON and 5 patients had no findings. The incidence of ON in patients <10 years was 6.7%, whereas for patients ≥10 years was 36.7% and 20% for patients ≥15 years. These findings were listed in Table (6).

Table 2. Summary of MRI findings and after following up

Findings of MRI findings	Number	Percentage %
No finding	11	36.7
Bone infarction only	4	13.3
Avascular necrosis only	2	6.7
Osteonecrosis	13	43.3
Findings after following up	**Number**	**Percentage %**
No finding	11	36.7
Bone infarction only	4	13.3
Avascular necrosis only	3	10
Osteonecrosis	12	40

Table 3. Summary of Avascular necrotic lesions and after following up MRI

Avascular necrotic lesion	Femoral head epiphysis	Tibial condyles
without joint deformity	14	6
with joint deformity	2	1
Avascular necrotic lesion	**Femoral head epiphysis**	**Tibial condyles**
without joint deformity	13	6
with joint deformity	3	1

Table 4. Distribution of bone infarctions in lower limb and after following up

Bone infarctions in lower limb	Number of lesions	Percentage %
Pelvic bones	3	4.1
Femoral diaphyses	16	22.2
Femoral condyles	13	18.1
Patellae	1	1.4
Tibial plateaus	7	9.7
Tibial diaphyses	7	9.7
Fibulae	1	1.4
Ankles and feet	1	1.4
Bone infarction lesions after following up MRI	**Number of lesions**	**Percentage %**
Pelvic bones	3	4.2
Femoral diaphyses	14	20
Femoral condyles	13	18.6
Patellae	1	1.4
Tibial plateaus	7	10
Tibial diaphyses	7	10
Fibulae	1	1.4
Ankles and feet	1	1.4

Table 5. Summary of lesions on or previously on chemotherapy

Osteonecrotic lesions	Patients on chemotherapy	Patients previously on chemotherapy
Avascular necrosis	22	3
Bone infarction	46	1

Table 6. Incidence of ON lesions according to age and sex of the studied patients

Age in years	Sex							
	Male				Female			
	No finding		ON		No finding		ON	
	N.	%	N.	%	N.	%	N.	%
1 -<5	1	3.3	0	0	1	3.3	0	0
5 -<10	1	3.3	1	3.3	2	6.7	1	3.3
10 -<15	3	10	5	16.7	1	3.3	6	20
15-< 18	1	3.3	4	13.3	1	3.3	2	6.7
Total	6	20	10	33.3	5	16.7	9	30

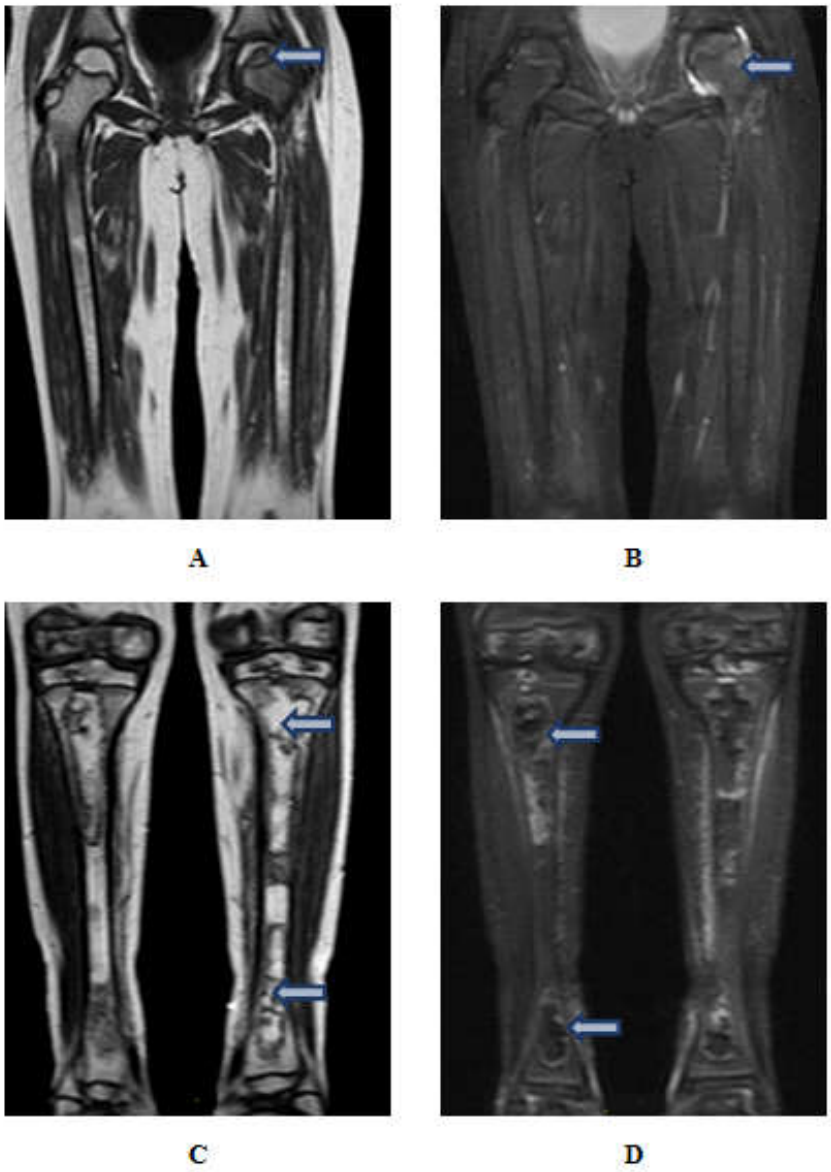

Fig. 2. Coronal T1-weighted (A, C) and Coronal STIR (B, D) revealed Ill-defined area of abnormal signal intensity seen involving the left femoral head epiphysis of low signal in T1WI and intermediate to low signal in STIR WI . Multiple geographic areas of abnormal bone marrow signal intensity noted in both upper femoral shafts, bilateral tibial plateau, proximal and distal tibial shafts being of low T1 signal intensity and high signal intensity on STIR

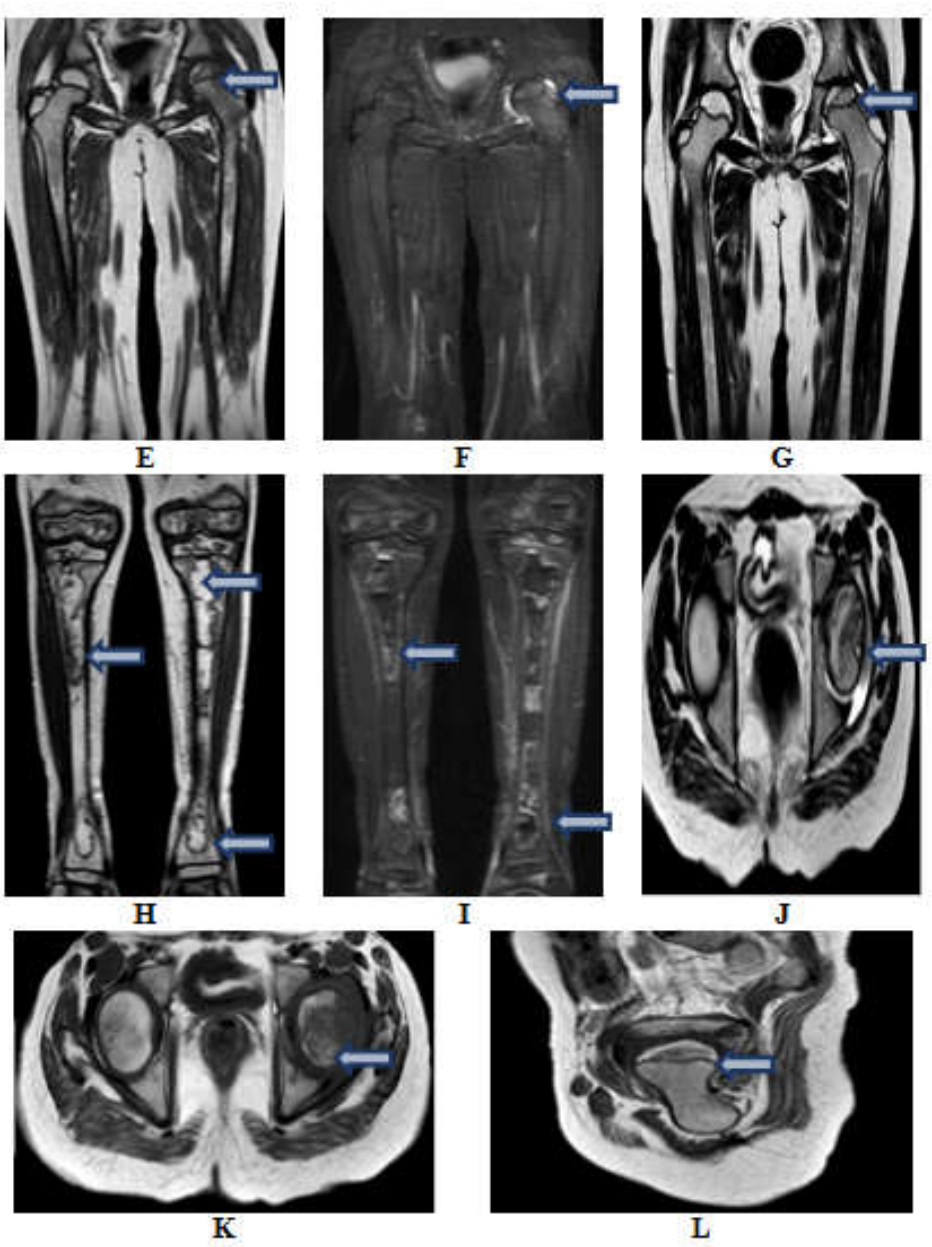

Fig. 3. Coronal T1-weighted (E, H), coronal STIR (F, I), coronal T2-weighted (G), axial T2-weighted (J), axial T1-weighted (K) and sagittal T1-weighted (L) revealed: Loss of the normal spherical configuration the left femoral capital epiphysis being partially collapsed at its superior aspect with irregular articular surface and subchondral fissuring. Also, there is replacement of the normal high T1 and T2 signal by a geographic area of low T1 and T2 lesions and high signal on STIR. Geographic areas of abnormal marrow signal are noted in both upper femoral shafts, bilateral tibial plateau, proximal and distal tibial shafts being of low T1 and T2 signal intensity and high signal intensity on STIR

One of our cases a 13 years old male patient with ALL presented with bilateral hip, knee pain and limping after chemotherapy. Diagnosis: the current MRI findings consistent with early avascular necrosis of the left femoral capital epiphysis, multiple bone infarctions at upper femoral shafts, tibial plateau, proximal and distal tibial shafts on both sides. Fig. (2).

Follow up of patient after 6 weeks. Diagnosis: the current MRI findings consistent with avascular necrosis of the left femoral capital epiphysis,

multiple bone infarctions at upper femoral shafts, tibial plateau, proximal and distal tibial shafts on both sides (progressive course). Fig. (3).

4. DISCUSSION

Morbidity after ALL varies considerably with treatment received. Osteonecrosis (ON) is one of the most debilitating complications seen during or after treatment for ALL and is mostly an iatrogenic complication that has been attributed to increased use of glucocorticoids and chemotherapy .MRI can detect bone ischemia and osteonecrosis at an early stage, when results of most other imaging modalities are negative and when the patient is still asymptomatic [9].

In the present study 16 patients (53.3%) were males while 14 (46.7%) were females. The age of our selected patents ranged from 4 to 17 years with a mean of 12.2 years, which agreed with study done by Ribeiro et al [10], they reported 10 male and 7 female with ON in the studied ALL patients after chemotherapy with median age of 11.5 years.

In the present study we noticed that knee pain was the most common complaint representing 83.3% of all patients followed by hip pain representing 80% and then limping representing 26.7%, which agreed with study done by Ribeiro et al [10], they reported that knee joint pain was the most common symptom that occurred in 14 patients.

In the current study MRI was done of all patients (30 patients); 11 patients were negative (36.7 %), 4 patients (13.3%) had only non-articular osteonecrosis (bone infarction), 2 patients (6.7%) had avascular necrosis of femoral head epiphysis without bone infarction and 13 patients (43.3%) had combined articular and non-articular osteonecrosis.

We reported that non-articular osteonecrosis more common than articular osteonecrosis, which agreed with study done by Ippolito D. et al. [11], as their study included 45 patients, 13 cases were negative (29 %), 15 patients with non-articular ON (33 %), 12 patients with articular ON (27 %), 5 patients had ON with deformity (11 %).

In the present study, we detected 72 ON lesions seen in 19 patients in lower limbs bilaterally; 23 ON lesions seen involving hip and knee joints and 49 ON lesions without joint involvement (bone infarction). 16 ON lesions seen in femoral head epiphysis and 7 ON lesions seen in tibial condyles reaching to its articular surface. We had 20 ON lesion without joint deformity and 3 ON lesions with joint deformity inform of collapse and contour irregularity of the femoral head epiphysis.

According to Ojala et al. [12], they detected nine of the 24 patients (38%) had ON, two of the patients had a single osteonecrotic lesion, whereas seven had multiple areas of osteonecrosis. The lesions of six patients were metaphyseal, and three had both metaphyseal and epiphyseal osteonecrosis. None of the lesions affected cartilaginous surfaces. The largest lesions were 10–18cm in diameter.

We agreed with Ojala et al. [12], they reported the most common site of bone infarction in lower limb was femoral diaphysis (8 lesions) followed by femoral condyles (5lesions), tibial plateau (4 lesions),) tarsal bones (3 lesion) and tibial diaphysis (1 lesions).

In the present study, the incidence of ON for patients <10 years is 6.7%, whereas for patients ≥10 years was 36.7% and 20% for patients ≥15 years. The majority showed ON in two or more joints.

In the study done by Burger B et al. [13], the incidence for patients <10 years is 0.2%, whereas for patients ≥10 years was 8.9% and 16.7% for patients ≥15 years.

Follow up of all patients in the present study (30 patients) was done by MRI, the median duration of follow up was 6 months (range 4-8 months). 27 patients showed no change in MRI findings, one patient progressed from avascular necrosis of the femoral head epiphysis without deformity to avascular necrosis of the femoral head epiphysis with deformity. The other two patients showed regressive course. According to study reported by Sansgiri et al. [14], 481 patients, they identified 21 cases with subtle poorly defined geographically delineated MRI signal abnormalities in knees or hips, or both, that progressed over a median of 4 months (range, 1.6- 18.5 months) to MRI signs of osteonecrosis. Articular surface collapse developed in three hips (two patients) and three knees (three patients). The median duration of follow-up was 27 months.

In the study done by Engelbrecht et al [15], follow up examinations revealed a regression in 19 ON,

no change in 43 and a progression in 4 lesions. ON within the epiphysis with joint involvement or lesions greater than 9 cm2 more frequently showed a progression of ON with final joint destruction.

According to Ojala et al. study [12], follow-up MRI examination was performed, one of them showed regression of the lesions, one patient was stationary MRI findings and the other patient showed progression in osteonecrosis.

We reported high sensitivity and specificity of MRI for early detection and follow of lower limb osteonecrosis in ALL patients after chemotherapy.

MRI is nearly 100% sensitive and specific for early osteonecrosis and is, therefore, highly effective for screening without exposing patients to ionizing radiation [10].

5. CONCLUSION

We concluded that MRI study is mandatory for early detection and monitoring of lower limb osteonecrosis in pediatric patients with acute lymphoblastic leukemia under or after chemotherapy. The radiologist and clinician must do MRI lower limbs routinely and follow up MRI after 4-6 months to first MRI due to some patients had regressive or progressive findings.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

Obtained permission from institutional ethical committee and an informed parental written consent was taken.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Pui CH, Campana D, Pei D, et al. Treating of childhood acute lymphoblastic leukemia without cranial irradiation. N Engl J Med. 2009;360:2730–41.
2. Barr RD, Sala A. Osteonecrosis in children and adolescents with Cancer, Pediatric Blood Cancer. Discussion 486. 2008;50(2):483–5
3. Chen CH, Chang JK, Lai KA, et al. Alendronate in the prevention of collapse of the femoral head in nontraumatic osteonecrosis: a two-year multicenter, prospective, randomized, double-blind, placebo-controlled study. Arthritis Rheum. 2012;64(5):1572–1578.
4. Kawedia JD, Kaste SC, Pei D, et al. Pharmacokinetic, pharmacodynamic and pharmacogenetic determinants of osteonecrosis in children with acute lymphoblastic leukemia. Blood. 2011;117(8):2340–7.
5. Fan C, Foster KB, Wallace WH, et al. Pathobiology and prevention of cancer chemotherapy-induced bone growth arrest, bone loss, and osteonecrosis. Curr Mol Med. 2011;11(2):140–51.
6. Steinberg ME, Steinberg DR. Classification systems for osteonecrosis: an overview. Orthop. Clin. North Am. 2004;35:273–283.
7. Coleman BG, Kressel HY, Dalinka MK, et al. Radiographically negative avascular necrosis: detection with MR imaging. Radiology. 1988;168(2):525.
8. Ficat RP. Idiopathic bone necrosis of the femoral head: early diagnosis and treatment. J Bone Joint Surg (Br). 1985;67(1):3–9.
9. Gayana S, Bhattacharya A, Kumar RS, et al. F-18 fluoride positron emission tomography/computed tomography in the diagnosis of avascular necrosis of the femoral head: Comparison with magnetic resonance imaging: Indian J Nucl Med. 2016;31(1):3.
10. Ribeiro RC, Fletcher BD, Kennedy W, et al. Magnetic resonance imaging detection of avascular necrosis of the bone in children receiving intensive prednisone therapy for acute lymphoblastic leukemia or non-Hodgkin lymphoma. Leukemia. 2001;15(6):891–7.
11. Ippolito D, Masetto A, Franzesi CT. et al. Lower-limb MRI in the staging and re-staging of osteonecrosis in paediatric

patients affected by acute lymphoblastic leukaemia after therapy, Skeletal Radiol. 2016;45(4):495–503.
12. Ojala AE, Paakko E, Lanning FP, et al. Osteonecrosis during the treatment of childhood acute lymphoblastic leukemia:a prospective MRI studies. Med Pediatr Oncol. 1999;32(1):11–17.
13. Burger B, Beier R, Zimmermann M., et al. Osteonecrosis: a treatment related toxicity in childhood acute lymphoblastic leukemia (ALL): experiences from trial ALL-BFM 95. Pediatr Blood Cancer. 2005;44(3):220–225.
14. Sansgiri RK, Neel MD, Soto-Fourier M, et al. Unique MRI findings as an early predictor of osteonecrosis in pediatric acute lymphoblastic leukemia. AJR. 2012;198(5):432–9.
15. Engelbrecht V, Scherer A, Bruder M, et al. MRI of aseptic osteonecrosis in children and adolescents with acute lymphoblastic leukemia [in German]. Rofo. 2000;172(4):336–341.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/61020