Role of Power Doppler Ultrasonography in Detection of Subclinical Hyperuricemia in Patients with Non-Hodgkin's Lymphoma

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ABSTRACT

Objective: This study aimed to detect incidence of subclinical arthritis in patients with NHL and the diagnostic ability of PDUS in detecting subclinical hyperuricemia. Methods: We studied 100 NHL patients (divided into 2 groups depending on the presence of the double contour (DC) sign detected by PDUS) and 100 controls in a cross sectional study. Demographic, clinical and serological data were evaluated. PDUS was done to all patients and controls. Results: There was a statistically significant difference between the two groups regarding the presence of subclinical hyperuricemia in group (1)(p=0.008) who had higher s. creatinine and gouty nephropathy (p=0.002 and p=0.001 respectively). Conclusion: PDUS can detect subclinical hyperuricemia and subsequent inflammatory arthritis in NHL patients; also it serves as a non-invasive, bedside tool.

Key words: Hyperuricemia; gouty nephropathy; NHL and PDUS

Introduction

The MSU crystal deposition can be clinically expressed as gouty arthritis, tophi formation, urate nephropathy or urolithiasis[1].

Serum urate (SU) concentration represents the balance between the breakdown of purines and the rate of uric acid renal excretion. The solubility threshold is approximately 7 mg/dl, and when exceeded level of interstitial fluids become oversaturated, which in turn increases the likelihood of monosodium urate (MSU) crystal tissue deposition [2].

Increased turnover of malignant cells results in an increase in cell lysis, catabolism of nucleic acids, and release of purine metabolites. Renal insufficiency develops as a consequence of hyperuricemia and is characterized by urine supersaturated with uric acid and crystallization of uric acid in the renal tubules and distal collecting system [3]. Tumor lysis syndrome (TLS), a potentially life-threatening complication characterized by hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalemia can result in acute renal failure. Patients with myeloproliferative disorders, lymphoid malignancies, or solid tumors with large tumor burdens are at increased risk of TLS as a consequence of chemotherapy, corticosteroids, radiation therapy, or stem cell transplantation [4].

Non- Hodgkin's lymphomas (NHL) are the most common occurring hematological malignancies in the world. They represent about 4% of all new cancer cases and are the fifth leading cause of cancer death [5]. The etiology of NHL is unknown although several genetic factors, environmental and infectious agents have been associated with the development of lymphoma as the association with EPV, HIV and HCV cannot be neglected[6].

The treatment of NHL includes chemotherapy with different regimens according to the type of NHL, involved field radiotherapy and the recent target theory as Anti-CD 20 (rituximab) and Anti-CD 52 (alemtuzumab) antibodies [7].

Ultrasound (US) has been demonstrated to be a valid imaging modality to detect musculoskeletal involvement in patients with gout [8,9]. The main US findings related to MSU crystal deposition include hyperechoic enhancement of the superficial margin of the hyaline cartilage ; double contour (DC) sign, hyperechoic spots within tendons and soft tissues, tophi and bone erosions [10]. Additionally, an increase of blood flow surrounding the MSU deposits detected by power Doppler (PD) has been described as an indicator of inflammatory activity [11,12].

Materials and Methods

One hundred Egyptian patients diagnosed as NHL were consecutively recruited from oncology department of Cairo university hospitals (46% males and 54% females,) were included in the present study. They were classified into 2 groups, according to the presence of (DC) sign detected by power Doppler ultrasonography (PDUS); group (1) had DC sign (47/100) (47%), and group (2) had no DC sign (53/100) (53%). Four NHL patients (8.5%) in group (1) gave a past history of acute gouty arthritis that was diagnosed according to the criteria for the classification of acute gouty arthritis [13].

All patients were asked to complete a questionnaire on demographics and medications used. All subjects were informed about the aim of the study and gave their consent. Patients were musculoskeletally examined in the rheumatology and rehabilitation department, Cairo university hospitals. Blood was drawn at the time of the study for analyses which included the following: complete blood picture, serum creatinine, fasting blood sugar, serum uric acid, K, P and Ca and liver functions were tested for all enrolled cases. Plain X-ray was done for all enrolled patients.

Power Doppler ultrasonography examination

All subjects subsequently underwent a structural musculoskeletal US evaluation of both knees and 1st MTP joints by two experienced observers. Bilateral knee joints (transverse suprapattellar view of the femoral cartilage in maximal flexion) and bilateral 1st MTP joints (longitudinal dorsal and medial views) were examined to evaluate the double contour sign and effusion, but no tendon US was performed. Double contour sign was defined as a hyper echoic band over the femoral articular cartilage or metatarsal head cartilage using a 12.5 MHz linear probe (Philips-ATL®, HDI 5000, Philips®, Bothell, WA, USA). Blood flow was examined with a pulse repetition frequency of 750 KHz and a Doppler frequency between 6 and 8 MHz. Attention was given not to compress the tissues under examination to avoid a "blanching" of the PD signal due to the transducer pressure.

Statistical analysis

Computer software package SPSS 15 was used in the analysis for quantitative variables, mean (as a measure of central tendency) and standard deviation (as measures of variability). Frequency and percentages were presented for qualitative variables.

ANOVA test was used to estimate differences in quantitative variables. Chi-square and Fisher-exact tests were used to estimate differences in qualitative variables. P Value < 0.05 is significant [14].

Kappa statistics were calculated to determine the proportion of inter- and intra-observer agreement beyond that expected by chance. The method for estimating an overall kappa value in cases of multiple observers and categories is based on the work of Landis and Koch (1) A value of $\kappa = 1.0$ corresponds to complete agreement; 0, no agreement; and less than 0, disagreement. Landis and Koch suggested that a kappa value ≤ 0.20 indicates slight agreement; 0.21-0.40, fair agreement; 0.41-0.60, moderate agreement; 0.61-0.80, substantial agreement; and 0.81-1.00, almost perfect agreement [15].

Results

Figure 1: the right side shows longitudinal view of the 1st metatarsophalangeal joint, and left side shows transverse view of knee joint, both show the double contour sign (arrow)

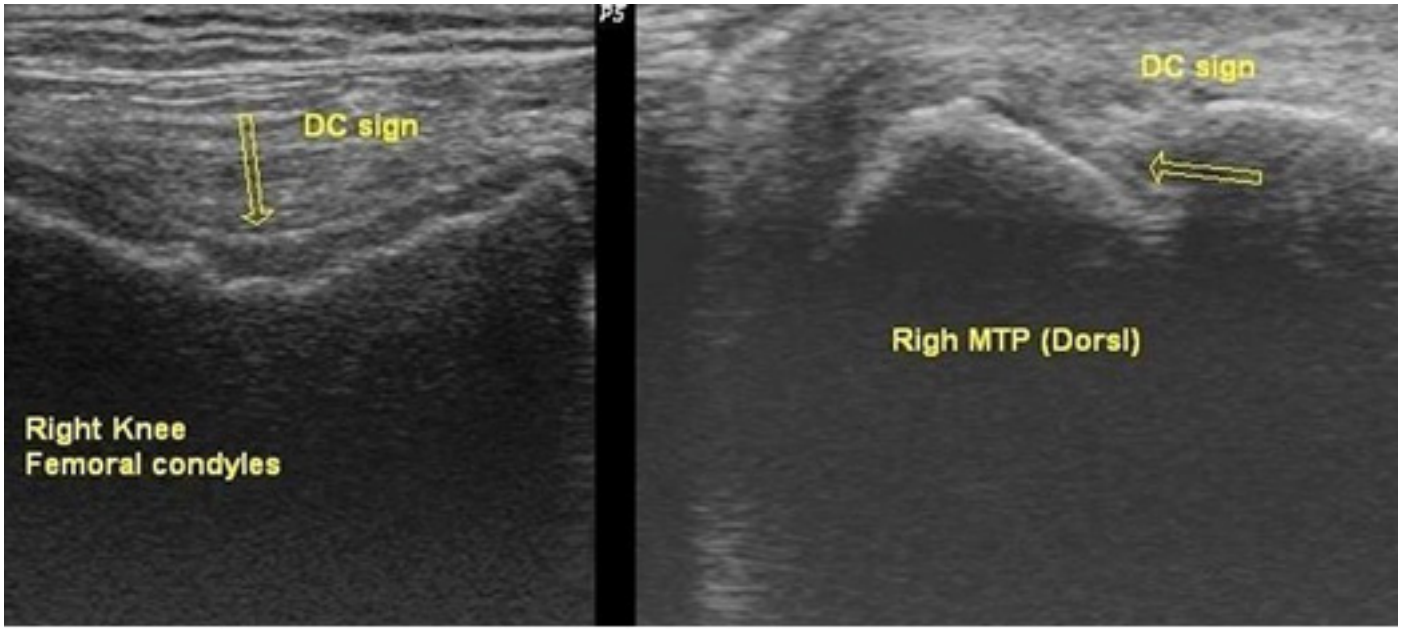

Figure 2: the right side shows longitudinal view of the 1st metatarsophalangeal joint with mild effusion and punched out erosion (arrow), and left side shows longitudinal view of knee joint with effusion and synovial hyper-vascularity (arrow)

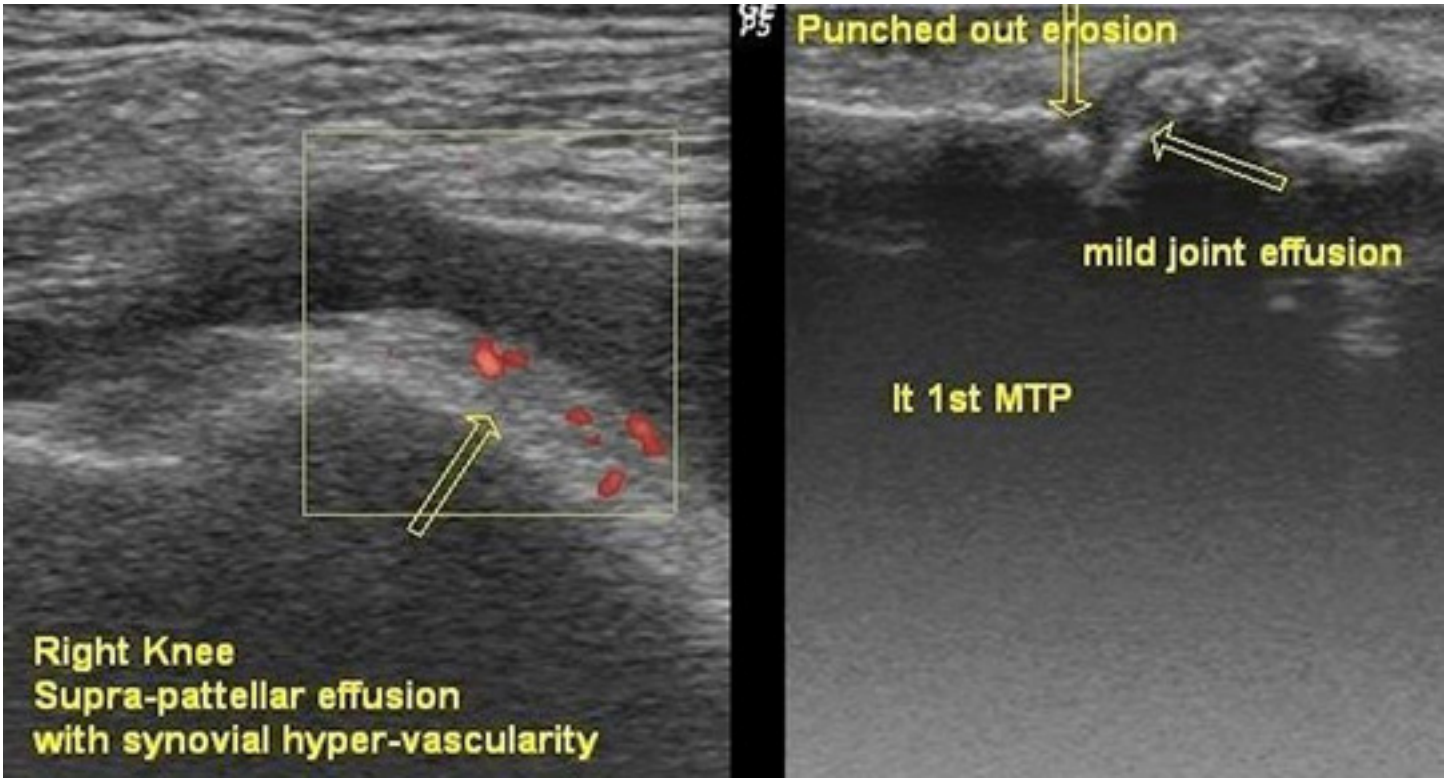

Figure 3: shows that patients in group (1) had significantly higher SUA than those of group (2) (P0.008)

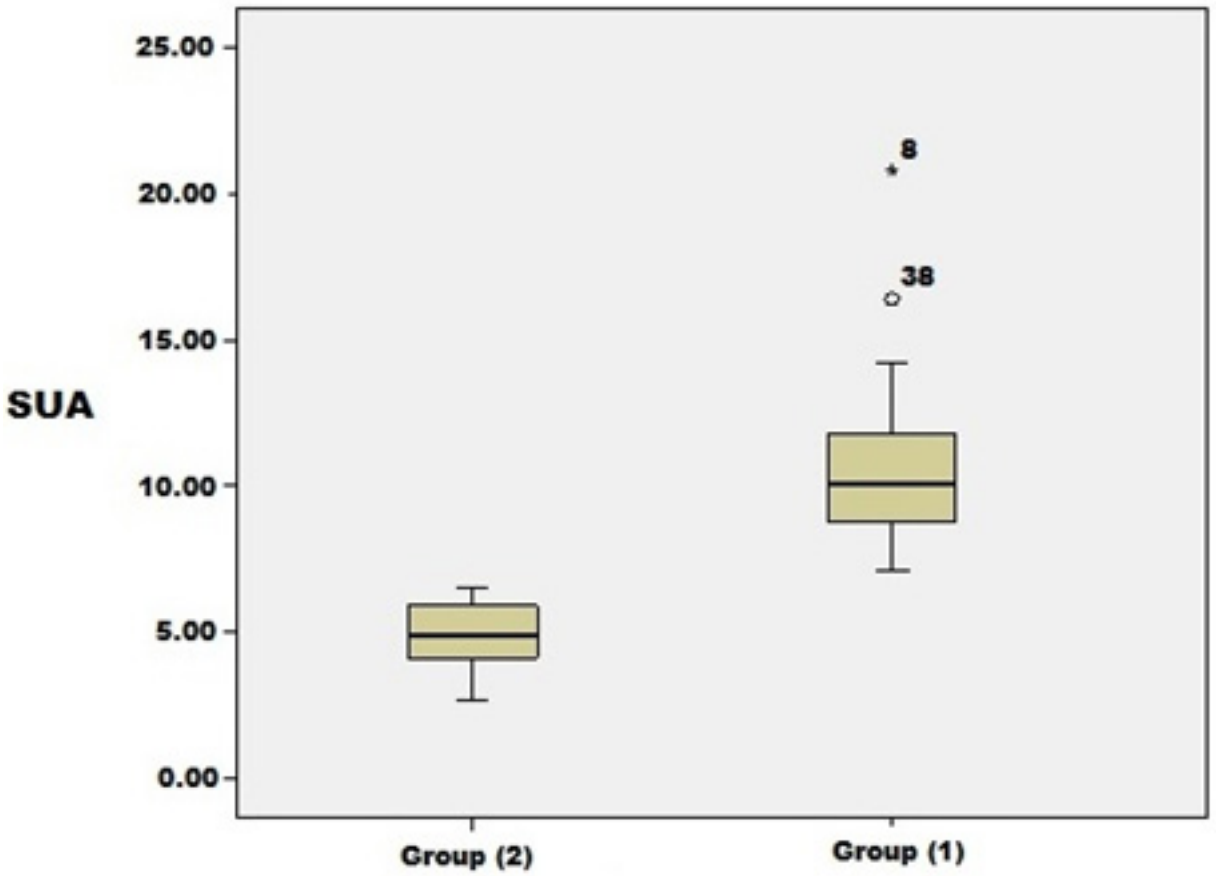

Figure 4: shows that patients in group (1) significantly had higher serum creatinine (P0.002)

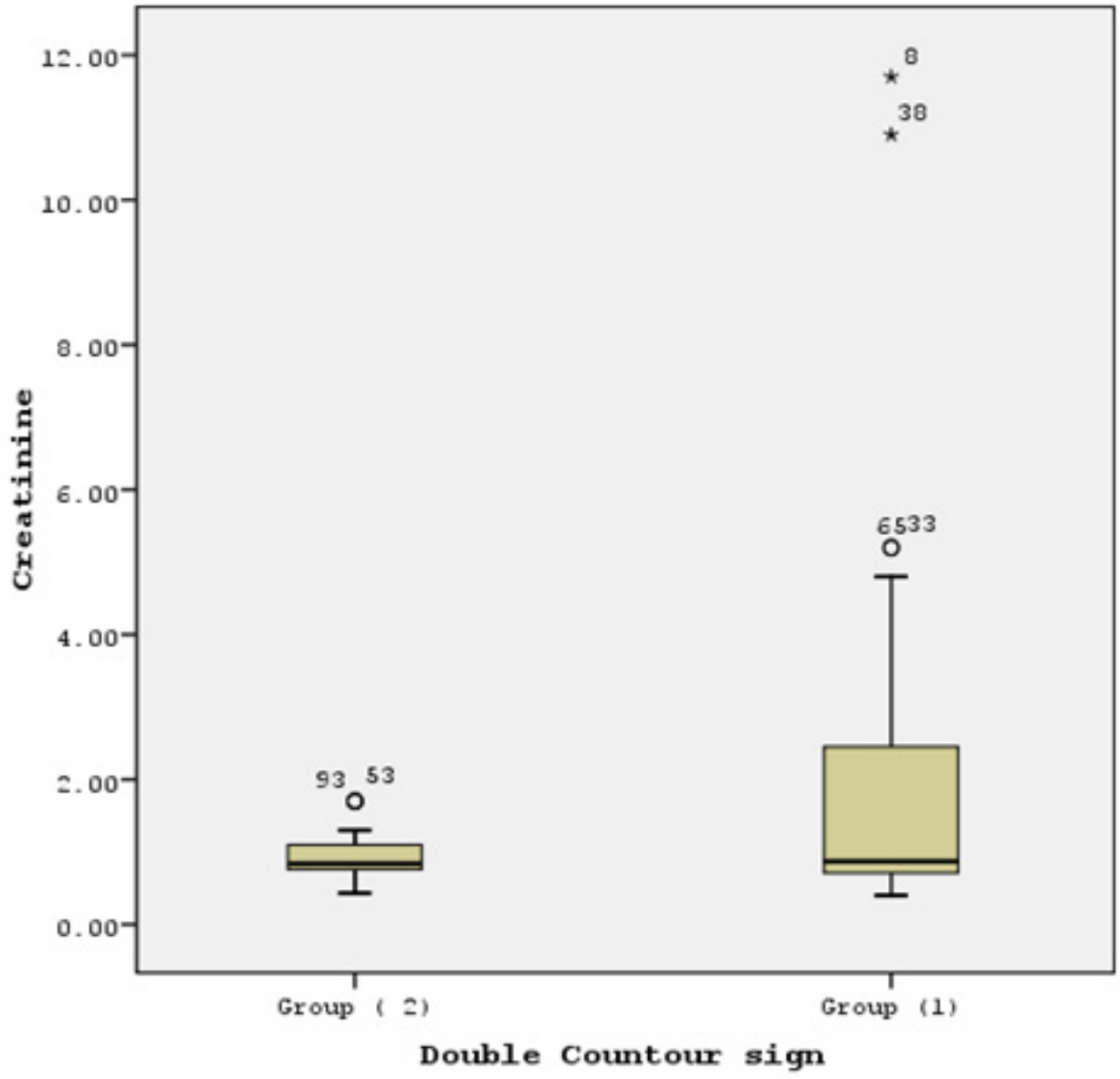

Table 1: Demographics and medications used by the studied patients

	Group (1)	Group (2)	Controls	P value
Age (years) (Mean ±SD)	47.1 ±13.4	44.8 ±13.3	45.2±11.5	0.2
Disease duration (years) (Mean ±SD)	5.1±2.4	4.7±2.9	0±0	0.3
Patients on allopurinol therapy No. (%)	44.7 ± 71.7	233.9 ± 91.9	0 (0%)	<0.001
Chemotherapy cycles (Mean ±SD)	3±1.9	4±1.8	0±0	<0.001

* Statistically significant value ($p < 0.05$)

Table 2: Clinical, laboratory and PDUS data of the current patients and controls

	Group (1)	Group (2)	Controls	P value
Gouty nephropathy No. (%)	12/47(25.5%)	1/53 (1.9%)	0 (0%)	<0.001
Enlarged Lymph nodes No. (%)	18/47 (38.3%)	1/53 (1.9%)	0 (0%)	<0.001
SUA	10.5± 2.6	4.9± 1.1	10.5± 2.2	0.008
Serum Ca(mg/dl) (Mean ±SD)	8.2± 1.2	9.1± 0.6	8.9±0.2	0.003
Serum P(mg/dl) (Mean ±SD)	5.2±2.8	4.3±1.6	3.6±1.4	0.003
Serum K(mg/dl) (Mean ±SD)	5.1±2.2	4.1±0.4	3.9± 0.3	0.007
Serum creatinine(mg/dl) (Mean ±SD)	1.9± 2.5	0.9± 0.3	10.5± 2.2	0.002
HGB (g/dl) (mean± SD)	11.2± 1.1	11.5± 1	10.5± 2.2	0.6
TLC (103/mm3) (mean± SD)	8.7± 2.5	7.6± 3.1	9± 0.7	0.7
Platelets (103/mm3) (mean±SD)	155.7±28	170±25.4	168± 17	0.4
FBS (mg/dl) (mean±SD)	90.2± 10.5	88.1± 13	95± 12	0.7
Synovial hyper vascularity No (%)	20/47 (62.6%)	2/53(3.8%)	0 (0%)	<0.001
Soft tissue edema No (%)	16/47 (34%)	2/53(3.8%)	0 (0%)	<0.001
Bone erosions No (%)	3/47 (6.4%)	0/53(0%)	0 (0%)	0.1
Joint effusion No (%)	16/47 (34%)	0/53(3.8%)	0 (0%)	<0.001

SUA: serum uric acid, Ca: calcium , P : phosphorus , K : potassium, HGB: hemoglobin, TLC: total leukocyte count, FBS : fasting blood sugar, FBS: fasting blood sugar .

* Statistically significant value (p< 0.05)

One hundred NHL patients (46% were males and 54% were females) and100 age matched healthy controls with a mean age of 45.2±11.5years were examined during this study. They were classified into two groups according to the presence of the DC sign as shown in Figure 1; inter and intra-reader analysis is 0.71 and 0.74 respectively. Demographics and medications received are shown in Table 1. All patients were on chemotherapy.

Clinical examination revealed MTP joint swelling only in four patients in group 1 (4/47 (8.5%)) and absent in group 2. Joint pain was found in seven patients; five of them complained of MTP joints pain and 2 of them complained of knee joint pain (6/47 (12.8%) in group 1 and 1/53 (18.9%) in group 2.

Tumor lysis syndrome was present in 10/47 (21.3%) NHL patients in group 1 and absent in group 2) (P< 0.001). PDUS detected synovial hyper vascularity in (62.6%) in group 1 and joint effusion in (34%) in group 1 as shown in Figure 2; other clinical, laboratory and PDUS parameters are shown in Table 2.

On comparing the two examined groups, it was found that patients in group 1 had higher SUA (p=0.008) as shown in Figure 3, and higher serum creatinine (P0.002) as shown in Figure 4. Gouty nephropathy was present in group 1 in 12/47 (25.5%); two of them (16.7%) were on hemodialysis but only 1/53 (1.9%) in group 2 had gouty nephropathy with highly significant difference (P<0.001).

In group 1 only 16/47 (34%) were taking allopurinol, in comparison to 49/53 (92.5%) in group 2 with highly significant difference (p<0.001) (odds ratio =0.04 and 95% CI ranging between 0.01-0.13).

There was a past history of acute gouty arthritis in 4/47 (8.5%) in group 1 and absent in group 2 with significant difference (P0.04). Plain -X ray radiography of the patients with past history of acute gouty arthritis revealed soft tissue edema.

Discussion

Gout is one of the commonest forms of inflammatory arthritis. The prevalence appears to be rapidly increasing worldwide [16]. It is mediated by the crystallization of uric acid within the joints [17]. Urate crystals are deposited predominantly in the superficial portions of the articular cartilage. These characteristic cartilaginous deposits are not readily demonstrated with conventional diagnostic imaging modalities[18] . Articular chondrocalcinosis is also a common crystal deposition joint disease in which calcium pyrophosphate dihydrate (CPPD) crystals deposit within the joint cartilage and fibrocartilage. It appears by US as punctate hyper echoic dots within the cartilage resembling "rosary beads"[19].

Treatment of NHL results in metabolic disturbances that require urgent treatment, among these, hyperuricemia has emerged as an important complication associated with the use of newer therapeutic agents. Allopurinol, a xanthine oxidase inhibitor, has traditionally been used to treat hyperuricemia; it blocks the production of uric acid from xanthine and hypoxanthine without affecting the breakdown of already formed uric acid, and at the same time prevents new production [20]. This coincides with the results in the present study as the number of patients on allopurinol therapy is much higher in group 2 who presented with lesser complications of (SUA).

In the current study, on comparing the two groups it was found that patients with DC sign had significant hyperuricemia than those without DC sign (P0.008). Double contour sign represents SUA crystals deposition in the hyaline cartilages [21]. As confirmation of the presence of MSU in the hyaline cartilage, Thiele and Schlesinger [22] demonstrated the disappearance of the double contour sign in patients with gout successfully treated with urate-lowering agents who had maintained SU levels below 6 mg/dl for at least 7 months [23]. This may strengthen the need for treatment necessity in asymptomatic individuals with hyperuricemia and indisputable US features of MSU crystal tissue deposition such as the double contour sign or the presence of tophi [24].

PDUS detected synovial hyper vascularity in (62.6%) in group 1 and (3.8%) in group 2 and soft tissue edema in (34%) in group 1 and (34%) in group 2 with highly significant difference (P<0.001); joint effusion was detected in (34%) in group 1 and was absent in group 2 with highly significant difference (P<0.001). This strengthens the importance of use of PDUS in detecting the subclinical attacks arthritis [23].

On comparing the two examined groups, it was found that patients in group 1 had higher serum creatinine (P0.002), as gouty nephropathy was present in group 1 in12/47; (25.5%) two of them (16.7%) are on hemodialysis, but only 1/53 (1.9%) in group 2 with highly significant difference (P<0.001).

In group 1 only 16/47 (34%) were taking allopurinol, in comparison to 49/53 (92.5%) in group 2 with highly significant difference (P<0.001) (odds ratio =0.04 and 95% CI ranging between 0.01-0.13). It was found that allopurinol blocks the formation of uric acid by inhibiting the enzyme xanthine oxidase, thus causing an increase in plasma concentrations of the uric acid precursors hypoxanthine and xanthine. Patients at high risk for tumor lysis still need to excrete the preexisting uric acid that is not targeted by allopurinol. Allopurinol also inhibits de novo purine synthesis, further lowering uric acid concentrations [25].

Conclusion

PDUS can detect the subclinical hyperuricemia and the attacks of subclinical arthritis. Also the use of allopurinol therapy decreases the SUA level in NHL patients and subsequently the incidence of gouty arthritis and gouty nephropathy.

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