Musculoskeletal Manifestations and Associated Complications of Malignancy

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Abstract: The study included 215 patients with malignancy at *Zagazig* university hospitals 100 of them had solid tumors and 115 had hematological type. All legible patients were subjected to full history taking and clinical examination (general, musculoskeletal, neurological, spine, skin). Laboratory workup including: (ESR, CRP, CBC, LFT, KFT, serum calcium, serum phosphorus, serum uric acid,alkaline phosphatase and some patients subjected to ANCA, anti-dsDNA, Anti-CCP and antiphospholipids antibodies (IgG and IgM) according to their clinical condition). Radiology and imaging workup including: (X-ray- DEXA- bone scan). Results: There was significant increase in hematological more than solid tumors as regards arthritis and arthralgia. Arthritis detected in (32.17%) and arthralgia detected in (38.26%) of patients with hematological tumors. there was significant increase in hematological more than solid tumors as regards drugs causing arthritis; it was detected in (21.67%) of patients with hematological tumors. There is significant increase in solid more than hematological tumors as regards frozen shoulder, lymphedema and hypertrophic osteoarthropathy; they were detected in (30%, 24%, 8%) respectively, in patients with solid tumors. there is significant increase in solid more than hematological tumors as regards upper motor neuron lesions and brachial plexopathies and their percentages were (13% and 10%) respectively, in patients with solid tumors. While there is significant increase in hematological tumors more than solid tumors as regards mixed peripheral neuropathy and drug causing peripheral neuropathy; they were detected in (7% and 15.7%) respectively, in patients with hematological tumors. Also, we found that there is significant increase in solid more than hematological tumors as regards osteoporosis; it was detected in 60% in patients with solid tumors and as regards drugs causing osteoporosis; it was detected in 53% in patients with solid tumors.
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Keyword; Musculoskeletal**,** malignancy, complications

1. Introduction

The association between malignancy and musculoskeletal or rheumatic disease is complex and interesting [(1)]. Some malignancies have rheumatological symptoms and may be present with joint, muscle and soft tissue manifestations [(2)]. Malignancy can be associated with a number of musculoskeletal manifestations that may be caused by direct tumor invasion into bones and joints, as a paraneoplastic syndrome, and through altered immune surveillance [(3)]. Remission of many tumors was associated with improvement in rheumatic symptoms [(4)]. Various musculoskeletal or other connective tissue disorders may arise as the result of treatment of malignant diseases. Arthralgia or arthritis may follow, or less often occur during adjuvant chemotherapy. These phenomena are referred to as post chemotherapy rheumatism or chemotherapy-related arthropathy, respectively [(5)]. Patients with cancer may not only be at risk for primary osteoporosis, but for secondary osteoporosis related to cancer therapies particularly therapies that impair gonadal function, lead to loss of serum estrogen, and negatively affect bone turnover[(6)].

Aim of the Work: is to detect musculoskeletal manifestations, and associated complications including osteoporosis, neurologic complications in patients with malignancy.

2. Patients and Methods

Study population:

According to power 80%, Confidence Interval (C.I) 95%, frequency of malignancy in Egypt 100 patients/100000 populations (Health Organization Statistics), population size of Sharkia Governorate 5,34 millions(central agency for statistics and mobilization). So, population size of malignancy in Sharkia Governorate is (5340), so, sample size is 215 of patients above the age of 19 years. This study was done from Jan 2013 to Jan 2014 This work was performed to study musculoskeletal manifestations and associated complications in patients with malignancy from clinical Oncology Department, hematology Department and Pain Clinic of Zagazig University Hospitals.Patients were divided into two groups:

1) **Group I:** 100 patients with different solid tumors,

2) **Group II:** 115 patients with different hematological tumors.

Inclusion criteria:[7]

- Histologically proven cancer: solid and hematological malignancy.
- Treatment by Chemotherapy, radiotherapy or hormonal therapy.
- History of bone pain persists in spite of normal bone scan and alkaline phosphatase and without local tenderness.

Exclusion criteria: [7]

- Patients with primary connective tissue diseases as: Rheumatoid arthritis, Systemic Lupus Erythromatosis, Primary Anti-phospholipid syndrome, Primary vasculitis., Mixed cryoglobulinemia, and Systemic sclerosis.
- Patients with arthralgia immediately following chemotherapy within two weeks.

METHODS: All patients were subjected to: **(1)A detailed history** taking including joint complaint**,** methods of treatment**:** Drugs were cyclophosphamides, oncovin,vinblastin, doxorubicin, ebirubcin, oxaliplatin, bleomycine 5-fluorouracil, cisplatin, methotrexate, Ifosphamide tamoxifen, and aromatase inhibitors, corticosteroides

(2)Associated Symptoms as: History suggesting of vasculitis, Reynaud's phenomena, nodules, or nail changes.

(3) General constitutional symptoms: It includes fever, malaise and weight loss.

(4) History suggesting osteoporosis and its complications as: Back pain and non-traumatic fracture.

(5)Neurological symptoms: They include symptoms suggesting cranial nerves affection, symptoms suggesting increased intracranial tension, motor weakness (in upper and lower limbs: distal, proximal, flexors and extensors), sensory affection, sphincteric disorders.

2-Examination:

1-General Examination:

2- Musculoskeletal Examination **(8).**

Grading of tenderness: **(9),** Grades of clubbing of fingers and toes **(10):**

3-Examination of the spine:

a- Straight leg raising test **(11)**

b- Femoral stretch test **(12).**

3- Neurological examination (13) including: Examination of cranial nerves., Examination of motor system, sensory system. And measurement of mid arm circumference

3-Investigations:

- CBC,LFT,KFT, ESR [14]
- C-reactive protein (CRP) [15]
- Anti-CCP_2 titer [16]
- ANCA [17]
- Anti-dsDNA antibodies titer [18]
- Antiphospholipid antibodies titre [19]

4-Imaging study:-Plain x- ray: - According to site of joint affection.

-Chest x-ray: postroanterior view.

-If fracture occurred to detect if present due to: osteoporotic fracture or fracture due to secondaries (all secondaries are osteolytic except prostatic secondaries are osteoslerotic).

- Dual energy X-ray absorptiometry (DEXA study): It is used to detect presence or absence of associated of low bone mineral density (BMD) detected at hips and lumbar spine was done for risky patients. T scores: The WHO definitions [20]

-Bone scan: By Tc 99m technetium methylene diphosphonates [21]**.**

Statistical Methods The following statistical methods were used for analysis of results of the present study (22).

For data summarization

A -quantitative data; 1-measure for central tendency: - arithmetic mean (x_)

2-median: Used for summarization of skewed data because it's insensitive to extreme value median = ((n-1) ÷2)

3- Measures of dispersion (standard deviation) it's the positive square root of the variance

$$(SD) = \sqrt{\frac{\sum X^2 - \frac{(\sum X)^2}{n}}{n-1}}$$

5- The range shows the difference between the largest and the smallest values in the observations

B-Qualitative data Chi square(x^2) is a test of association between a factor or attribute and an outcome. Used only for qualitative data, compares independent samples.

$x^2=\sum(O-E)^2 \div E$.

O=observed number in each cell

E= expected number in each cell.

$\sum$= the sum

Our results showed the following: There is there is significant increase in hematological more than solid tumors as regards arthritis and arthralgia. Arthritis detected in (32.17%) and arthralgia detected in (38.26%) of patients with hematological tumors. Also, there is significant increase in hematological more than solid tumors as regards drugs causing arthritis; it was detected in (21.67%) of patients with hematological tumors.

There is significant increase in solid more than hematological tumors as regards frozen shoulder, lymphedema and hypertrophic osteoarthropathy; they were detected in (30%, 24%, 8%) respectively, in patients with solid tumors.

In our study, we found that there is significant increase in solid more than hematological tumors as regards upper motor neuron lesions and brachial plexopathies and their percentages were (13% and 10%) respectively, in patients with solid tumors. While there is significant increase in hematological tumors more than solid tumors as regards mixed peripheral neuropathy and drug causing peripheral neuropathy; they were detected in (7% and 15.7%) respectively, in patients with hematological tumors. Also, we found that there is significant increase in solid more than hematological tumors as regards osteoporosis; it was detected in 60% in patients with solid tumors and as regards drugs causing osteoporosis; it was detected in 53% in patients with solid tumors.

3. Results

Table (1): Sociodemographic data of patients

	Solid tumors (n=100)	Hematological tumors (n=115)	x^2	*p*
Age in years				
Range	(19-75)	(19-72)	4.76	0.00*
Mean ±SD	(51.4±12.5)	(41.8±16.6)		
Sex				
Males: N (%)	46 (46)	70 (61.4)	5.8	0.02*
Females: N (%)	54 (54)	45 (38.6)		
Disease duration				
Range	(1month-9year)	(1month-2year)	374.0	0.00*
Mean ±SD	(4.1±3.5)	(0.58±0.39)		

Table (2): Number and percentage of different types of solid tumors.

Type of tumor	Number of patients (100)	Percentage (%)
Breast	36	36.0
Lung	14	14.0
Hepatic	11	11.0
Gastrointestinal tract	10	10.0
Genital tract	8	8.0
Brain	6	6.0
Urinary	5	5.0
Others	10	10.0

Table (3): musculoskeletal manifestations.

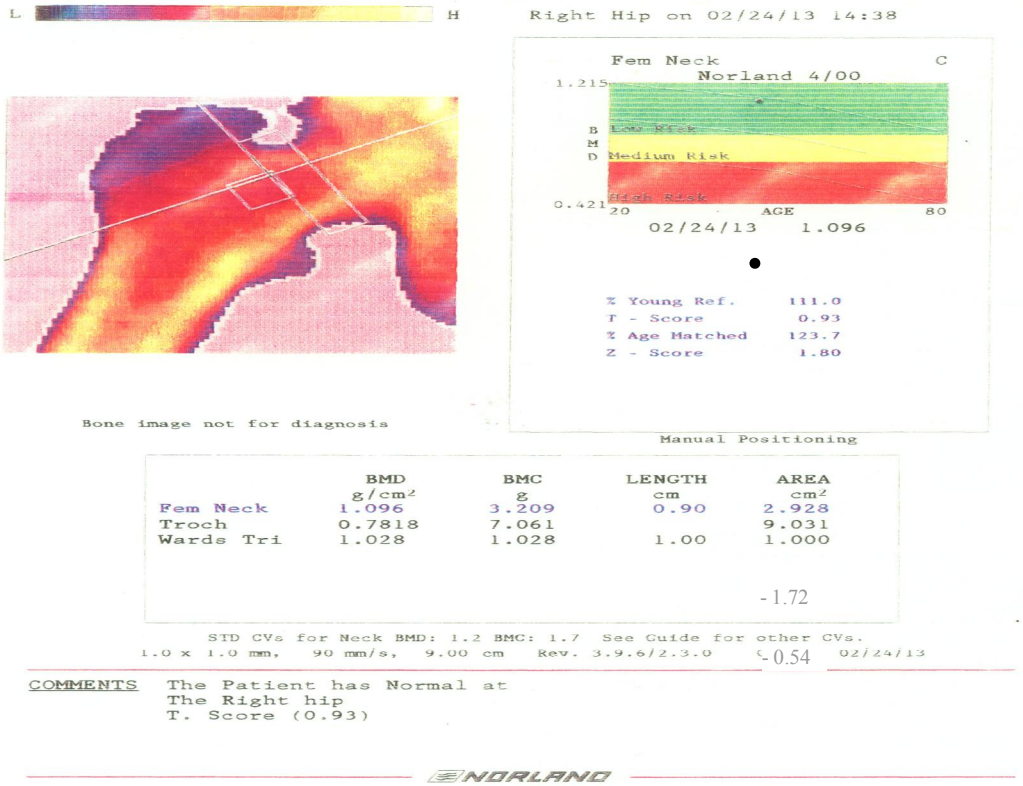
	Solid tumors n (100)	(%)	Hematological tumors n (115)	(%)	x^2	*p*
Arthritis						
Monoarthritis	8	(8.%)	13	(11.3%)	8.69	
Oligoarthritis	4	(4.%)	2	(1.7%)		0.01*
Polyarthritis	8	(8.%)	22	(19.1%)		
No arthritis	80	(80%.)	78	(67.9%)		
Arthralgia						
Oligoarthralgia	10	(10. %)	2	(1.7%)	7.53	0.00*
Polyarthralgia	21	(21. %)	42	(36.5%)		
No arthralgia	69	(69. %)	71	(70.4%)		
Therapy induced:						
Arthritis	8	(8.%)	25	(21.7%)	8.69	0.01*
arthralgia	20	(20.0%)	21	(18.26%)	0.06	0.80
Frozen shoulder	30	(30. %)	9	(7.8%)	7.2	0.00*
Lymphedema	24	(24. %)	0	(0. %)	17.2	0.00*
Hypertrophic Osteoarthropathy (HOA)	8	(8. %)	0	(0. %)	.39	0.00*

Table (4): Number and percentage of osteopenia, osteoporosis,and drug causing osteoporosis of patients.

	Solid tumors		Hematological N		x^2	*p*
	n (100)	(%)	n (115)	(%)		
Osteopenia	20	(20.0)	22	(19.1)	0.24	0.62
Osteoporosis	60	(60.0)	60	(52.2)	23.4	0.00*
Drug causing osteoporosis	53	(53.0)	49	(42.6)	15.6	0.00*

Table (5): neurological complications of patients.

Type of lesion	Solid tumors		Hematological tumors		x^2	*p* value
	n (100)	(%)	n (115)	(%)		
Cranial nerves lesion	9	9	13	11.3		
7th	9	9	11			
	UMNL		3 UMNL	23.07	0.36	0.55
			8 LMNL	61.53		
7th & 8th	-	-	2 LMNL	15.4		
UMNL	13	13	4	3.5	6.47	0.01*
Peripheral neuropathy						
Sensory	25	25	28	24.3	0.26	0.50
Sensory, motor	0	0	8	7	7.36	0.01*
Brachial Plexopathy	10	10	2	1.7	5.91	0.01*
Therapy related complications						
Peripheral neuropathy	10	10	18	(15.7)	8.69	0.01*
UMNL	0	0	2	(1.7)	0.06	0.80



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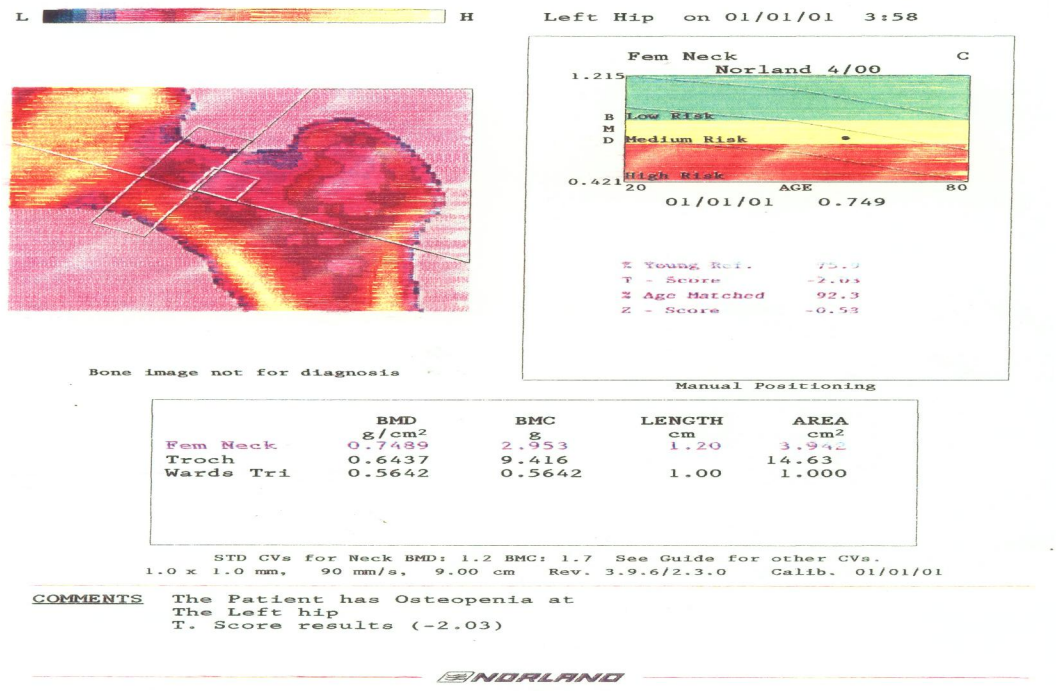

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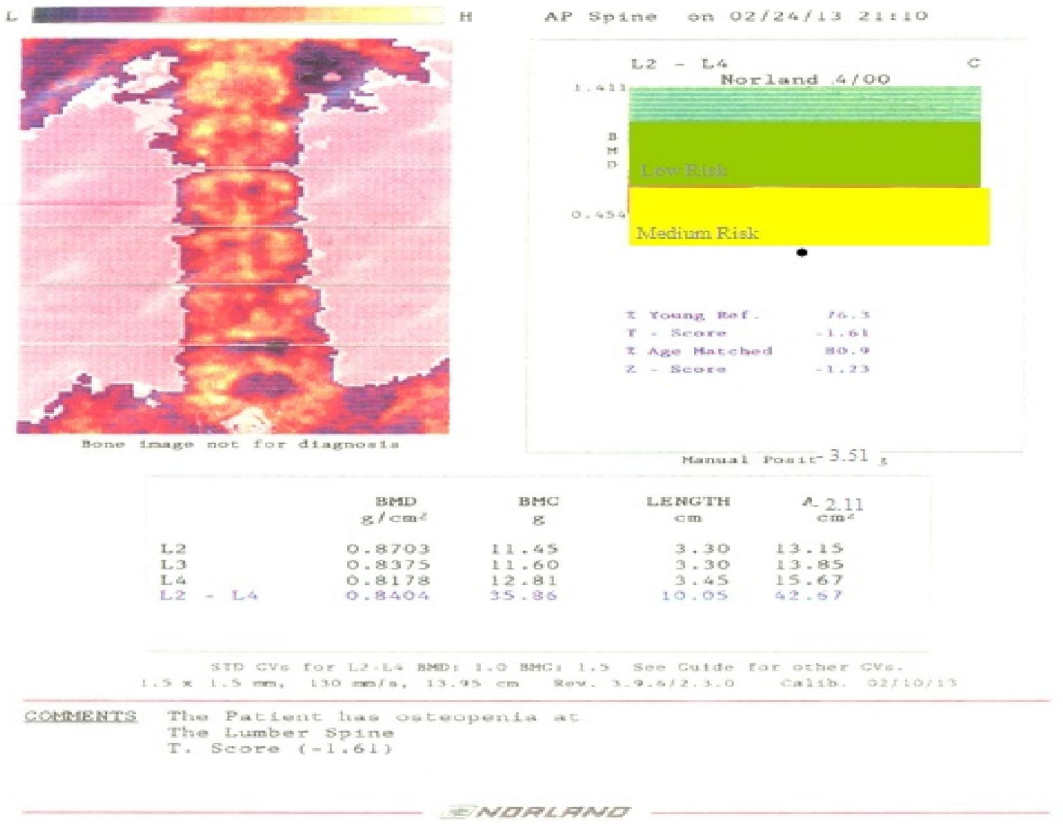

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Fig. (1: A, B, C): Osteoporosis in female patient, 49 years old with estrogen receptor positive cancer breast on aromatase inhibitor.

Table (6): Anti-phospholipids syndrome and positive anti- phospholipids antibodies of the patients in G1 and G2.

	G1 Solid tumors n (100)	(%)	G2 Hematological tumors n (115)	(%)	x^2	*p*
Anti-phospholipids syndrome	12	(12.0)	14	(12.17)	1.88	0.17
Positive anti-phospholipids antibodies	6	(50.0)	8	(57.14)	15.1	0.00*

4. Discussion

Several musculoskeletal manifestations were detected in the patients with malignancy in the present study. In agreement with the present results is the study of Yamashita *et al.,* that the association between musculoskeletal features and malignancy is well-known, and rheumatologists may experience several problems with the various rheumatological manifestations [(23)]

.Additionally**,** Gheita *et al* reported that malignant neoplasms are associated with a wide variety of rheumatological syndromes [(7)].

In the present study, arthritis was found in (20 and 32.17%) of the patients with solid and hematological tumors respectively, arthralgia was detected in (31% and 38.26%) patients with solid and hematological tumors respectively, and hypertrophic osteoarthropathy (HOA) in (8%) of patients with lung cancer. The most commonly involved joints were small joints of the hands in upper limbs and ankles and knees in lower limbs. In accordance with these results are the findings of Dabrowska-Zimoń and Brzosko they reported that the most frequently recognized rheumatological syndromes associated with malignancy are polyarthritis and HOA [(24)]. Also, arthritis was detected in (39.36%) of patient in Rugiene *et al.* [(25)]. another study by Oztürkcan *et al.* reported that HOA occurred in 2.27% of patients with lung cancer [(26)]. Also Fridlington *et al.,* reported HOA cases (1.3%) of studied patients with malignancy [(27)]

In this study, frozen shoulder was present in (9 and 30%) of patients with hematological and solid tumors respectively. It was very common in patients with breast cancer. Causes of frozen shoulder were local incisional pain from breast or axillary surgery, radiculopathy, synovitis, local tumor recurrence, bony metastases, radiation, and lymphedema these causes commonly limit shoulder motion either voluntarily or subconsciously as a patient attempts to avoid painful maneuvers**,** Sano *et al.* [(28)]**.** In agreement with these results are the findings of Gheita *et al.* [(7)]**,** they reported that frozen shoulder was detected in (15%) of studied patients. A painful "frozen shoulder" with disability may be seen after painful conditions as tumors [(29)]. Moreover, frozen shoulder following breast cancer surgery is addressed in (20-23%), Cheville and Tchou, [(30)].

Lymphedema in our study was detected in (24%) of studied patients with cancer breast. In agreement with these results are the findings of Schünemann and Willich , [(31)] who reported that (27%) of patients with cancer breast developed secondary lymphedema of the arm after primary therapy of cancer breast consisted of operation alone and additional irradiation increased this rate, however, reduction of the lymphedema rates can be done by minimization of the aggressiveness of the treatment.

Some musculoskeletal complications due to cancer therapies were detected in this study. Arthritis was detected in (15.34%) of studied patients, (8% and 21.7%) of patients with solid and hematological tumors respectively. Arthralgia was detected in (19.06%) of patients, (20%-17.39%) of patients with solid and hematological tumors respectively. Arthralgia occurred in (22.22%) of patients, but arthritis occurred in (66.6%) of patients on chemotherapy Kim *et al.,* [(5)]. However; Abu-Shakra *et al.,* [(32)] reported that musculoskeletal complications due to cancer therapies developed in (1.32%) of the studied patients

In this study, neurological complications were detected in (15%- and 25%) of the studied patients in form of cranial nerves affection, upper motor neuron lesions, peripheral neuropathies and plexopathies. In agreement with the result of Rubin 2005 [(33)]**,** they reported that the neurological complications occur in up to (20%) of cancer patients, they resulted from the direct space occupying effects of cancer, malnutrition, iatrogenic and paraneoplastic syndromes.

The 7th cranial nerve affection explained by Casciato [(34)]:may be of upper motor neuron lesion in patients with solid tumors due to primary brain tumor or due to brain metastasis secondary to cancer lung and breast and in patients with hematological tumors due to metastatic meningitis secondary to leukemia,lymphoma or intracranial thrombosis secondary to treatment with L-asparginase and may be of lower motor neuron lesion in patients with

hematological malignancy secondary to lymphoma and leukemic infiltration of the nerve and secondary to chronic mastoditis. Also, Casciato [34] explained that peripheral neuropathies with malignancy occur as a part of paraneoplastic syndromes or due to chemotherapy and brachial plexopathy occur either due to metastasis to brachial plexus from lung cancer, breast cancer and lymphoma or due to radiation,

The bone mineral density (DEXA) T-score was significantly reduced in studied patients being more evident in the spine. The bone loss was higher in solid more than hematological tumors. Reduced bone mineral density was detected in (77.67%) of the studied patients (80% and 75.65%) of patients with solid and hematological tumors, respectively).These findings were in accordance with many clinical studies confirming rising of osteoporosis with malignancy. In harmony with these results, a study done by Camacho *et al.,* [35] who found that bone loss in (78%) of the breast cancer patients. However, in a study done by Spanikova and Spanik [36], the rate of osteoporosis was (53, 75%) in the group of patients on follow-up without hormonal therapy. Chemotherapy induced osteoporosis was detected in (47.44%) of studied patients (53%-42.6% of patients with solid and hematological tumors respectively). These drugs included aromatase inhibitors (e.g. anastrazole and letrozole), steroids, adriamycin. Radiotherapy or combined therapies also can cause osteoporosis. In agreement with these results is study done by Spanikova and Spanik [36], they found that (43.35%) of patients with cancer breast on chemotherapy had bone mineral density in levels of osteoporosis. However, higher rate was detected in the study of Al Amri and Ali [37], that reported that cancer chemotherapy induced osteoporosis was detected in (59, 67%) of the studied patients as all patients were with age ≥50 years and on chemotherapy causing osteoporosis.

In the present study, anti-phospholipids antibodies were done for patients with manifestations suggesting Anti-phospholipids syndrome. Anti-phospholipids syndrome was present in (12.09%) of studied patients, (12% and 12.17%) of patients with solid and hematological tumors respectively and positive anti-phospholipids antibodies were detected in (53.84%) of cancer patients with Anti-phospholipids syndrome (6.51% of the studied patients). In accordance with these results were findings of Abu-Shakra *et al.,* [32], they reported that Anti-phospholipids syndrome was detected in (22%) of their patients and positive anti-phospholipids antibodies were reported in (2-12%) of the sera of patients with cancer and this autoantibody activity is the result of malignant transformation of B cells that produce auto antibodies.

The mechanisms whereby the neoplasm leads to rheumatic symptoms are: direct invasion of the musculoskeletal system, synovial reaction of juxta-articular bone or capsular carcinomatous, secondary gout, and paraneoplastic manifestations. Paraneoplastic rheumatic disorders are induced by malignancy through hormones, peptides, autocrine and paracrine mediators, antibodies and cytotoxic lymphocytes, [38].

Conclusions

- Rheumatic manifestations occurring during malignancies and following the treatment represent a significant percentage of symptoms and signs. The immunology profile does not help in discriminating between these musculoskeletal manifestations and primary connective tissue diseases. The major challenge for the clinical rheumatology practice is to find the clues helpful to differentiate between autoimmune rheumatic diseases and rheumatic symptoms induced by malignancy. Often, clear distinctions cannot be made just on clinical examination, but wide laboratory and radiology workups are required. However, rheumatic symptoms induced by malignancy can be suspected by:
- Old age at onset.
- Predominance in unusual sex.
- Atypical presentation.
- Negative family history.
- Absence of rheumatoid nodules.
- Unexplained anorexia and weight loss suggesting malignant cachexia.
- Poor response to conventional therapy.
- Improvement of most of these manifestations after diagnosis and adequate treatment of the causative tumor
- Another clue to diagnose occult neoplasias in clinically suspected paraneoplastic syndrome is to screen an appropriate link between some of these manifestations and some tumors. Tide link has been described between hypertrophic osteoarthropathy and cancer lung. A connection of arthritis with lymphoprolipherative diseases, breast, gastrointestinal and genital cancers has been also detected. Hematological malignancy should be suspected in patients presenting with vasculitis or lupus-like features. Brain tumors, either primary or secondary, should be suspected in patients presenting with picture of upper motor neuron lesion of gradual onset, progressive course and without obvious cause. Another link between peripheral neuropathy and malignancy especially hematological tumors has been described.
- A variety of cancer and cancer therapy related neurological complications are diagnosed either at initial presentation or at follow-up. Patients

with malignancy and on chemotherapy are at a significant risk of osteopenia and osteoporosis and they represent about 75% of our studied patients.

Recommendations

All malignant patients should undergo the following:

- Complete periodic musculoskeletal examination for early prediction of any related signs.
- Complete periodic neurological examination and confirmation of findings by different methods e.g. nerve conduction, imaging studies
- In all patients with rheumatic or neurological manifestations, malignancy should be suspected as a cause especially, if patients presented with old age, male predominance, and atypical presentation and associated malignant features.
- Bone mineral density measurements should be done once diagnosis is established and regular DEXA should be done for early detection of osteoporosis, especially in patients with solid tumors. So, early treatment is helpful to prevent complications of osteoporosis.

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