Rheumatologic Manifestations of Malignant Diseases

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ABSTRACT:

Objective: Although the case-effect relationship remains inferential in many cases, the study aims to demonstrate the association between rheumatic manifestations and malignancy. **Methods**: During the fallow-up of the patients with rheumatic diseases, any patient included in the study when malignant diseases was documented. The study population includes 10 patients (6) female and 4 males), average age was 40 year (5-75 years).

Results: In 10 patients with rheumatic diseases the following association were found : Lupus-like syndrome and breast carcinoma , polymalgia rheumatic and pulmonary carcinoma, miscellaneous arthropathies and multiple myeloma, pyogenic arthritis and colonic carcinoma, reflex sympathetic dystrophy and pulmonary carcinoma , osteomalacia and osteogenic sarcoma , carcinomatous polyarthritis and leukemia and stomach carcinoma.

Conclusions: A wide range of neoplasia may be associated with rheumatic findings .As these patients may first present to the rheumatologist; heshould be enabling earlier recognition and diagnosis,

Introduction;

An association between rheumatic manifestations and neoplasia has been observed by physicians for nearly a century. Reports and reviews of this observation have increased dramatically in recent years. (1). The connective tissue disease may precede the development of a predictable malignancy. Awareness that an underlying malignancy may produce certain musculoskeletal symptoms may allow earlier recognition of an other wise occult, potentially curable

malignancy. Conversely, knowledge that a connective tissue disease process may predispose the individual to cancer may provide early recognition of a predictable malignancy .Musculoskeletal manifestations of malignancy may be due to direct involvement by tumor or to the remote effects of tumor (paraneoplastic syndromes). Humoral factors, such as tumor-produced hormones, as well as, immunoglobulin may explain the indirect involvement. Two thirds of paraneoplastic syndromes are equally divided among rheumatologic, hematologic and neuromuscular disorders. Rarely, situations arise in which complications of rheumatic disease mimic malignancy (2). Less commonly, malignancy may mimic a rheumatic disease, for example, malignant angioendotheliomatosis presenting as primary angitis of central nervous system or systemic vasculitis.(3,4). Although it is important to exclude infection, in unilateral sacroiliitis, malignancy must be considered (5). The association of musculoskeletal syndromes with malignancy also includes the development of malignancy in the setting of preexisting connective tissue disease for example: rheumatoid arthritis, Jorgen's syndrome and scleroderma. The type of connective tissue disorder and the organ system involved often dictate the type of malignancy expected (6). Immunosuppressive therapy has been used effectively in the treatment of autoimmune and rheumatic diseases because immune mechanism is thought to be fundamental to the pathogenesis of the disease. The drugs commonly used include cyclophosphamide, chlorambucil, azathioprine and methotrexate. Baker et al, have shown that prolonged daily treatment of rheumatoid arthritis with cyclophosphamide was associated with an increased risk of cancer of the urinary bladder, skin or hematopoietic system. (7). Glucocorticoids have been implicated in the development of continuous Kaposi's sarcoma, with regression of the malignancy on discontinuation of steroid therapy (8). Certain rheumatic disorder may evolve as a result of cancer therapy. This may be an exacerbation of preceding rheumatic disorder through generalized enhancement of immunologic reactivity (9).Tamoxifen therapy may result in vacuities or arthritis treatment with, interleukin-2 may result in spondyloarthritisor inflammatory arthritis, interferon-a therapy may result in seropostive nodular rheuteumatoid arthritis (10,11). Deep radiation therapy in the treatment of ankylosing spondylitis is virtually no longer used, in large part because of the increased awareness that such therapy might result in leukemia and basal cell carcinoma.(12).

Methods: In the department of Rheumatology, Al- Sadder Teaching Hospital in Missan, patients with rheumatic diseases were followed up, when malignant disease has been developed in these patient they are included in our study. The study subjects consisted of(10) patients (6 female and 4 male). Their ages ranged

from (5-75) years, with an average of 40 years. The investigations, carried out included: CBC, ESR, CRP, Rheumatoid factors, ANA, S. urate, S. calcium,S.phosphate, alkaline phosphate, urine for bense Jones protein, synovial fluid (sent for analysis, Gram stain, for culture and sensitivity), blood film, MRI, radiographs when indicated.

Results: From (10) patients in our study (six females and 4 males), the frequent malignancy found was breast carcinoma ,bronchogenic carcinoma and gastro-intestinal tumor which occur in 6 patients,while estrogenic sarcoma, leukemia and multiple myeloma occur in the remaining (4) patients as in(Table(I)).

Table-1-Association between malignancies and connective tissue diseases among patients.

Malignancy	Patients with connective tissue dis.
Breast carcinoma, bronchogenic carcinoma and gastro-intestinal tumor	6 60%
osteogenic sarcoma, leukemia and multiple myeloma	4 40%
Total	10

Table-2 Connective tissue syndrome and the most common malignancy associated with

Connective Tissue Syndrome	**Malignancy**
Lupus-like syndrome	Breast carcinoma
Polymyagia Rheumatica	Pulmonary tumor, Bladder tumor
Miscellaneous Arthropathy	Multiple myeloma,
Pyogenic Arthritis	Colonic carcinoma
Reflex sympathetic Dystrophy	Pulamonary tumor
Osteomalacia	Osteogenic sarcoma
Carcinomatous polyarthritis:	
Rheumatoid Arthritis - like JRA - like	Stomach carcinoma Leukemia's

The patient with JRA was (5) years old while the patient with polymyolgia rheumatic was the oldest one (75) years old. The NASAIDs were used in all patients, while steroid used in 5 patients. Chloroquin, methotrexate, antibiotic, calcium and vit. D. used in 5 patients one types of medication for each. Rheumatoid factors was positive in one patient with polymyalgia rheumatic.ESR was above (100) in 5 patients. No patient show haemoarthrosis.There was no family history of rheumatic disease in our study patients. Asymmetrical joint involvement reported in patient with lupus disease, miscellaneous and carcinomatous arthritis. Seven patients were above (50) years at the onset of disease.

Table-3- Disease, patient age and their treatment.

Disease	Age (year)	Treatment
Lupus-like syndrome (2patients	30	NSAIDs +steroid
	52	NSAIDs+chloroquin+steroid
	75	NSAIDs +steroid
Polymylgia Rheumatica	62	NSAIDs +steroid
2 patient	30	NSAIDs
Miscellaneous Arthropathy	60	NSAIDs +steroid
PyogenicArthritis	58	NSAIDs +steroid
Reflex Sympathetic Dystrophy	50	NSAIDs+calicum+vit. D
Osteomalacia		
Carcinomatous polyarthritis:	53	NSAIDs+methotrexate
RA - like JRA - like	5	NSAIDs

Discussion;

All the study population was from Missan in south of Iraq, in this area where the rate of malignant disease shows significant increase. Lupus - like syndrome reported in (2 female patients, the first one was 30 years old, the second was 52). They present with Asymmetrical polyarthritis ,Raynuond s phenomena, pleural

effusion, and ANA was positive in one patient, this is similar to Freundich. study(13). They developed malignant disease after (6-9) months after their musculoskeletal complains. Steroid was received by both patients and there is no reports to show that it might cause breast causer. Two patients were above 60years, presenting with polymyalgia rheumatoid, ESR above (100 mm/hr),rheumatoid factor was positive in one patient (75years old) .The incidence of rheumatoid factors increased with age and in variety of disease status and it is positive 1-5 % of normal subject. (14). The largest investigation has been conducted in Norway with 185 case of polymalgia rheumatic, 14.6 % had cancer including 14 different neoplasms (15). In our study, the neoplasm was found in an average 1-1.2 years after the onset of polymalgia rheumatoid while the other study the average was 4-6 years (16). So when a person is above fifty present with myalgia, proximal muscle weakness and weight loss, both polymyalgia rheumatica and cancer should be considered(17). Pyogenic arthritis of the knee has been developed in 65 years male patient with poor response to conventional therapy and daily aspiration and surgical arthrotomy.

The cultures of both blood and synovial fluid were negative in our study. Other study shows that isolation of clostridium septicum from infected joint warrants a careful search for underlying malignant disease particularly colonic carcinoma (18). Whether an unusual enteric bacteria or its complications develop, the clinician should consider the possibility of malignant source (19).Patient who is 60 years old with history of mild trauma to the right hand, developed reflex sympathetic dystrophy and pulmonary tumor was documented after 9 months, with failure to respond to conventional therapy. This finding is similar to other study which showed that shoulder-hand syndrome may also be seen with tumor of the lung which is localized to the superior sulcus-pancost s syndrome (20). Other study shows that ovarian cancer is the most frequently associated malignancy (21) .Osteomalacia developed in 26 years old male presented with deterioration of gait. Osteogenic sarcoma of the female diagnosed after 7 months for the onset of osteomalacia, other study osteomalacia was associated with solid tissue tumor. Although benign tumor is characteristically associated with osteomalacia, malignant tumor has been reported (22). MRI skeletal survey is a very powerful method for detecting the responsible tumor because the most frequent causes for oncogenic osteomalacia are tumors in bone or soft tissue (23). Fifty –three-years old female presented with rheumatoid arthritis like disease, with several features suggesting the possibility of malignancy, these include late age at onset of arthritis, asymmetric joint involvement, explosive onset, sparing of wrists joint, absence of rheumatoid nodules and absence of rheumatoid factors,

Caldwell in his study shows that polyarthritis resembling rheumatoid arthritis may be the presenting manifestation of malignancy and %80 of women with this syndrome have had breast carcinoma (24) , while in our study stomach carcinoma was documented. Five- year-old female patient presented with polyarticular arthritis, ANA-positive. Response to NSAIDS, occurs first, then sever joint pain that disproportionate to the degree of arthritis was developed alter 5 months the second peripheral blood smear is diagnostic of leukemia. Our study is similar to Spilberg and Meyer study in which polyarthritis may be the presenting manifestation in childhood leukemia and acute lymphocytic leukemia is predominant (25). Sehaller in his study shows that of 13 children, 2 to 14 years of age,who presented for rheumatologial evaluation and proved to have malignancy, 10 had leukemia and other soft tissue sarcoma .(26). Miscellaneous arthropathy in patient with seronegative rapidly progressive sacroilitis,and enthesopathies after nine months of multiple myeloma was diagnosed.Among skeletal neoplasm's in adult, multiple myeloma is the most likely to be present problem in rheumatological differential diagnosis because this disease occurs mainly after the age of 55 years, so that complaint of skeletal pain may initially be minimized as symptoms of degenerative disease of joint or intervertebral disc.(27).In other study patients with chronic rheumatoid arthritis are at risk of development of multiple myeloma.(28).Roldan showed that non-Hodgkin lymphoma subsequently developed in a patient with miscellaneous arthropathies(29).

Conclusion

In conclusion, rheumatoid symptoms and manifestations may be clues to the existence of cancer. Recognition of these manifestations is necessary for efficient diagnostic evaluation of many patients.

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