RHEUMATIC MANIFESTATIONS AND MALIGNANCY

Essay

Submitted for Partial Fulfillment of the Master Degree in Rheumatology and Rehabilitation

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2009

ACKNOWLEDGEMENT

I would like to express my sincere appreciation and gratitude for my professors for their enthusiastic and continuous assistance and cooperation.

I wish to express my appreciation and thanks to eminent Prof. Dr. Samia Zaki Hassan, Professor of Rheumatology & Rehabilitation, Faculty of Medicine, Cairo University, because she shared actively in planning and building up of this research. I have got great benefits from her great experience.

I like to thank Dr. Hania Salah Zayed, lecturer of Rheumatoloty & Rehabilitation, Faculty of Medicine, Cairo University, for the great effort she made to produce this study in the best form. She guided my research with enthusiasm and valuable advice.

At last, I cannot forget the person who was always behind my success. This is my husband, the one who assisted, in numerous ways, in taking care of this research and tolerated a lot for it to be born.

Abstract

The relationship between malignancy and rheumatic manifestations is complex. The purpose of this review is to highlight the associations between rheumatic disorders and cancer. This review focuses on paraneoplastic rheumatic disorders which are associated with an occult malignancy, the risk of malignant transformation in rheumatic diseases, the malignant potential of antirheumatic drugs as well as rheumatic complications of drugs used to treat cancers. The clinician must be aware of the associations between malignancy and rheumatic diseases for proper diagnosis and management.

Key Words: (Paraneoplastic rheumatic syndromes- Rheumatic diseases- Malignancy- Antirheumatic drugs- Antineoplastic drugs).

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List of abbreviation

EBV	Epstein barr virus
SS	Sjögren's syndrome
TNF	Tumour necrosis factor
DM	Dermatomyositis
DNA	Deoxy ribonucleic acid
ANA	Antinuclear antibody
PDGf	Platelet derived growth factor
SLE	Systemic lupus erythematosus
RA	Rheumatoid arthritis
PGE_2	Prostaglandin E_2
HOA	Hypertrophic Osteoarthropathy
VEGF	Vascular endothelial growth factor
Ig	Immunoglobulin
HCV	Hepatitis C virus

C3 & C4	Complement
FPS	Fasciitis Panniculitis Syndrome
ESR	Erythrocyte sedimentation rate
PR	Polymyalgia rheumatica
NHL	Non Hodgkin's lymphoma
NAA	Natural auto-antibodies
PM	Polymyositis
POEMS	Polyneuropathy, Organomegaly, Endocrinopathy, M- proteins and Skin changes
TGF.b	Transforming growth factor beta
SIR	Standardized incidence ratio
RF	Rheumatoid factor
SSA- SSB	Anti-Ro and Anti-La antibodies
BCL-2	B- cell lymphoma proto-oncogene
OA	Osteoarthritis
NSAIDs	Non steroidal anti-inflammatory drugs
EULAR	European League Against Rheumatism

MESNA	Mercapto ethane Sulphonate Sodium
I-V	Intra-venous
MTX	Methotrexate
DMARDs	Disease modifying anti-rheumatic drugs
CD5	Cluster of differentiation found on subset of Igm secretory B- cells and on T- cells.
NK	Natural Killer cells
BCL	B-cell lymphoma
US	United States
SEER	Surveillance, Epidemiology and End Results
m- RNA	Messenger Ribonucleic acid
CMF	Cyclophosphamide, Methotrexate, 5-florouracil
RDs	Rheumatic diseases
LN	Lymph node
CA125	Cancer antigen 125
CT	Computed Tomography

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INTRODUCTION

The association between malignancy and musculoskeletal or rheumatic disease is complex and intriguing ***(Misra and Agarwal, 2004***).

The clinical and temporal relation between various rheumatic syndromes and malignant neoplasms can take several forms:

A- Rheumatic syndrome as a manifestation of an established or occult malignancy.

B- Malignancy occuring in the setting of an established rheumatic disease.

C- Malignancy as a complication of anti-rheumatic therapy.

D- Rheumatic syndrome as a complication of antineoplastic therapy ***(Kaell, 2006).***

Paraneoplastic syndromes can occasionally be the first presentation of an underlying malignancy. Old age of onset, atypical features of rheumatic disease and absence of response to antirheumatic therapy may be suggestive of a paraneoplastic process. ***(Chakravarty and Genovese, 2005).***

Several rheumatic syndromes can occur as a paramalignant syndrome accompanying various solid and haematologic malignancies such as hypertrophic osteoarthropathy, polyarthritis, dermatomyositis, palpable purura, vasculitis and others ***(Kaell, 2006)***.

Malignancy may develop in the setting of established connective tissue diseases. Several factors including the autoimmune disease itself, viral factors e.g. Epstien Barr Virus (EBV) and others have been implicated in the pathogenesis of tumour development. However, it is difficult to separate whether it is disease drived mechanism or from the potential oncogenic properties of immunosuppressive drugs used in treatment ***(Szekanecz E. et al, 2006)***.

For example, there is increased incidence of alveolar cell carcinoma, non melanoma skin cancer and adenocarcinoma of the oesophagus in patients with systemic sclerosis. Patients with Sjögren's syndrome (SS) have higher risk for lymphoproliferative disorders while patient with dermatonyositis (DM) have an increased risk of ovarian, lung and gastric tumours ***(Chakravarty and Genovese, 2005.)***

Immunosuppresive and cytotoxic drugs such as methotrexate, cyclophosphamide, azathioprine & anti tumour necrosis factor (TNF) biologicals may also lead to development of tumours especially leukemias and lymphomas.

Cyclophosphamide can cause bladder and skin cancer in addition ***(Chakravarty and Genovese, 2005).***

On the other hand, rheumatic syndromes may occur as a complication of antineoplastic therapy with incidence ranging from 1% to 25%. For example, Anthracylin may cause transient arthritis, busulfan sicca syndrome, Bleomycin scleroderma like features and cisplatin Raynaud's phenomenon ***(Kaell, 2006)***.

Aim of the work:

The aim of this study is to discuss current reviews on the relation between rheumatic syndromes and malignancy as regards pathogenesis and early proper diagnosis.

Rheumatic syndromes as a manifestation of an underlying malignancy

Musculoskeletal syndromes in relation to malignancy can develop either due to a primary tumour involving bone e.g. chondrosarcoma and osteogenic sarcoma presenting as monoarticular pain, or due to metastases to the musculoskeletal system from a solid neoplasm e.g. breast and lung cancer and in haematological malignancies e.g.. leukaemia due to synovial infiltration and lymphoma due to lymphomatous infiltration of juxta-articular bone ***(Kaell, 2006)***.

Chakravarty and Genovese (2005) reported that musculoskeletal syndromes can also develop as a paraneoplastic process and can be the first presentation of an underlying malignancy**.**

In the case of paraneoplastic rheumatic disorders, the tumour is at distance from the joint and the articular and periarticular regions are not affected by the cancer. The symptoms may present as well defined autoimmune disorders. Paraneoplastic musculoskeletal symptoms may precede the development of malignant disease for years but the two conditions may also occur simultaneously (***Szekanecz et al., 2006)***.

Pathogenesis of paraneoplastic syndromes:

The main distinguishing feature between tumour-associated with rheumatic diseases and paraneoplastic rheumatic syndromes is the fact that surgical removal or pharmacological treatment in the first case has no influence on rheumatic symptoms, whereas it almost results in the disappearance of symptoms in paraneoplastic diseases. These observations have prompted oncologists and rheumatologists to investigate the pathogenetic mechanisms of the rheumatic manifestations of cancer leading to three distinct working hypotheses:

a) Both the malignancy and the paraneoplastic syndromes are independent effects of a common causal factor as a viral infection or exposure to drugs or physical stimuli (e.g. ultra violet radiation).

b) Paraneoplastic syndromes are a direct effect of mediators produced by tumour cells, which trigger inflammation in the tissues where rheumatic diseases manifest.

c) Paraneoplastic rheumatic syndromes are mediated by a hypersensitivity reaction due to either tumoural expression of antigens shared by the cells targeted by the autoimmune diseases or to the release of intracellular antigens from apoptotic tumour cells. Supporting this third hypothesis is the demonstration of auto-antibodies to nuclear proteins and to double stranded deoxyribonucleic acid (DNA).