Rheumatologic Manifestations of Malignancy

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KEYWORDS

• Musculoskeletal • Malignancy • Mimics • Paraneoplastic • Lymphoma
• Pitting edema • Fasciitis • Autoimmune

KEY POINTS

- Autoimmune conditions and their treatments may be associated with an increased risk of certain malignancies.
- The lack of response to conventional treatment of a rheumatic syndrome (such as polymyalgia rheumatica or inflammatory polyarthritis) should raise the suspicion for a paraneoplastic etiology.
- Conditions such as palmar fasciitis with polyarthritis, hypertrophic osteoarthropathy, multicentric reticulohistiocytosis, and dermatomyositis have well-documented evidence for association with underlying malignancy.
- A higher incidence of non-Hodgkin's lymphoma and other hematologic and lymphoproliferative diseases is seen in patients with primary Sjögren's syndrome, systemic sclerosis, rheumatoid arthritis, and lupus, among others.

INTRODUCTION

Kankeleit[1] noted one of the earliest associations between cancer and polymyositis in 1916. Since then, a variety of clinical and epidemiologic associations between musculoskeletal symptoms and underlying malignancies have been described. However, determining causality between these conditions and malignancy remains challenging.

Certain malignancies occur with higher incidence in patients with autoimmune disorders. Mechanistically, this may relate to malignant transformation that can occur as a result of immune dysregulation in the later phase of certain autoimmune conditions. For example, non-Hodgkin's lymphomas (NHLs) are reported with higher frequency in patients with primary Sjögren's syndrome, rheumatoid arthritis (RA), and possibly in systemic lupus erythematosus (SLE).[2]

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Many clinical presentations mimic rheumatologic conditions, which, in reality, are direct signs of the musculoskeletal spread of the underlying cancer or a paraneoplastic syndrome associated with it. These paraneoplastic rheumatic syndromes are not directly caused by local or distant spread of the tumor but are actually induced through a complex interaction of humoral and cytotoxic immune mechanisms, autocrine and paracrine mediators, and signaling pathways.

Certain conditions, such as hypertrophic osteoarthropathy (HOA), dermatomyositis, and palmar fasciitis with polyarthritis have well-documented associations with cancer. However, a growing body of literature describes other conditions, including but not limited to, remitting seronegative symmetric synovitis with pitting edema (RS3PE), carcinogenic polyarthritis, multicentric reticulohistiocytosis (MRH), leukocytoclastic vasculitis (LCV), scleroderma and the scleroderma mimics, eosinophilic fasciitis, and erythromelalgia, which will be further discussed below.

It is difficult at times to discern association from coincidence, as some of these associations are merely based on case reports or small series. Another limitation is that some reports are subject to a "Berkson's bias," which occurs when patients, but not controls, are drawn from a hospital referral population. In this situation, the possibility of recognition of a hospitalized patient with both a primary rheumatic disorder and malignancy is much higher than for a patient with a rheumatic disorder alone. Finally, some reported associations are based on standardized incidence ratios (SIRs) and odds ratios, which reflect correlation between 2 disorders and not necessarily causality.[3]

In 1965, Sir Austin Bradford Hill proposed criteria to guide establishing an argument for causation.[4] These criteria may be used to determine if a given rheumatic condition can be attributed to the presence of an underlying malignancy. The summary of Bradford Hill's criteria are as follows: strength of association between the causative agent and the outcome, temporal sequence of the 2 conditions, consistency of results even when different methodology is used, theoretic plausibility, coherence (which means if the association makes theoretic sense), specificity in the causes, dose-response relationship, experimental evidence, and similar evidence from analogous conditions.[5]

The emphasis of this article is to raise awareness of those musculoskeletal conditions that should alert the clinician to a search for an occult malignancy. However, a comprehensive review of the primary and metastatic tumors of the musculoskeletal system is beyond the scope of this report.

CLINICAL CLUES FOR PRESENCE OF AN OCCULT MALIGNANCY

Several features can raise suspicion for the presence of an occult malignancy in an older patient with musculoskeletal complaints. Some of these include personal or family history of malignancy, prior exposure to carcinogenic medications or environmental pollutants, constitutional symptoms, unusual clinical picture for the rheumatic syndrome, and atypical or no response to conventional therapy.

There are other alarming presentations that may also trigger more intense search for occult malignancy, such as sudden-onset asymmetric polyarthritis presenting in the elderly, rheumatoid arthritis with monoclonal gammopathy, Sjögren's syndrome with increasing globulin-albumin gap, hypertrophic osteoarthropathy, dermatomyositis, polymyalgia rheumatica unresponsive to prednisone therapy, eosinophilic fasciitis poorly responsive to corticosteroid therapy, erythema nodosum lasting more than 6 months, and the new onset of Raynaud's phenomenon or cutaneous leukocytoclastic vasculitis after age 50 years.[6]