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Malignancies presenting as rheumatologic conditions

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Abstract

Rheumatologic manifestations are a well-known presentation in malignancies and could delay the diagnosis of malignancy if not promptly suspected. Screening for malignancies is advisable if there are other risk factors or associated with old age. The symptoms range from musculoskeletal to vasculitis and hematological manifestations. Carcinomatous Polyarthritis is more common among all the paraneoplastic manifestations. It presents as migratory polyarthritis. It is characterised by sterile synovial aspiration, absence of rheumatoid factor and Anti CCP, no response to NSAIDs, asymmetric joint involvement. Other musculoskeletal presentations include hypertrophic osteoarthropathy, tumor induced osteomalacia, acute gout, spondyloarthritis, juvenile idiopathic arthritis among others. Leukocytoclastic vasculitis is the commonest type of cutaneous vasculitis, presenting as palpable purpura. It is generally associated with hematological malignancies. Dermatomyositis is strongly associated with malignancies with a relative risk of 4.4. Severe involvement of skin and muscle suggests an underlying malignancy. Systemic sclerosis presenting as paraneoplastic manifestation although rare has been reported. Paraneoplastic scleroderma has been reported in patients with POEMS syndrome and IgA plasmacytoma. Other paraneoplastic manifestations include polyangiitis with granulomatosis, palmar fasciitis with polyarthralgia, polymyalgia rheumatica, acute febrile neutrophilic dermatosis, autoimmune hemolytic anemia, anterior uveitis, eosinophilic fasciitis, Lambert-Eaton syndrome etc. Variety of humoral factors like VEGF, PDGF, TIF-1, MMP-3 and CTGF have been implicated in the pathogenesis of different presentations. Early recognition of atypical rheumatologic presentation and a subsequent screening for malignancies with appropriate treatment could result in complete remission.

Keywords: Rheumatology, Malignancies, Rheumatologic manifestations.

INTRODUCTION

Malignancies present with a wide array of symptoms including musculoskeletal symptoms and other symptoms which may mimic rheumatologic conditions [1]. The underlying mechanisms for symptoms could include metastasis, local invasion by tumour, response of synovium to juxta articular masses.2 Paraneoplastic syndromes have also been known to produce symptoms mimicking a rheumatologic condition, where in the tumour is in a distant place and there is no evidence of metastasis, to the said locality of symptoms [1,2]. The symptoms usually present as a polyarthritis. Other symptoms which have been reported include polymyositis/dermatomyositis, hypertrophic pulmonary osteoarthropathy, Vasculitis, Cutaneous leukocytoclastic vasculitis, Henoch- Schönlein purpura etc [3]. Among the paraneoplastic manifestations, Carcinomatous Polyarthritis (CP) is generally misleading as it can also present with a high rheumatoid factor (RF) titre [2].

The identification of these rheumatologic presentations earlier becomes crucial in view of the underlying malignancy and the need for effective and early management [4]. There are reports of paraneoplastic manifestations presenting before cancer [5]. Diagnosis of the paraneoplastic conditions can be challenging in the presence of an occult malignancy [1]. Screening for cancer is warranted in the setting of old age and if there are other risk factors [5].

Carcinomatous Polyarthritis

Migratory polyarthritis is a relatively common condition encountered in daily practice. It can be due to crystal induced arthropathy, infectious polyarthritis like Lyme disease and chlamydia. Other differential diagnosis includes reactive arthritis, palindromic rheumatioid arthritis and autoimmune diseases. Less frequently underlying malignancy (metastatic or paraneoplastic) could lead to migratory polyarthtritis [1]. Carcinomatous polyarthritis is migratory polyarthritis due to paraneoplastic manifestation of malignancy.

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It was first described in 1953 by Lansbury [2]. Malignancies commonly presenting with CP are tumors of lung, breast, gastric, ovaries, pancreas, hematologic, renal and adrenal glands [1,2]. The age in patients presenting with CP generally correlated to the associated malignancy. There was no gender predilection noted [1]. CP is a diagnosis of exclusion [1]. Historically the following criteria needs to be fulfilled to be labelled as CP: the polyarthritis should present during the course of a malignant illness or identified prior to the diagnosis of a malignancy, symptoms should not be attributable to a direct invasion of the tumor and the symptoms should improve with treatment of the underlying malignancy [2].

Other features that distinguish CP from its differential diagnosis are sterile synovial aspiration with no crystals, absence of rheumatoid factor and anti cyclic citrullinated peptide antibody, asymmetric joint involvement, lack of response to NSAIDs, sudden onset, absence of characteristic radiographic lesions [1,2]. The pathogenesis of CP is unclear, circulating immune complexes has been postulated to be one of the possible mechanisms [6].

Hypertrophic osteoarthropathy

Hypertrophic osteoarthropathy (HOA) is characterised by subperiosteal new bone formation on the shafts of phalanges, periostosis, synovial effusions involving large joints. It presents with pain and swelling of the affected joints and bones [5]. HOA can be recognised with triad of clubbing of nails, symmetric polyarthritis and periostitis of long tubular bones [3]. HOA could be secondary to pulmonary disease of which more than 70% of HOA are associated with lung cancer [3]. Periostitis is the classical feature of HOA on X rays and generally involves tibia and fibula and hence can be distinguished easily from osteoarthritis and other rheumatological etiologies [3]. The factors that are postulated to play a role in pathogenesis of HOA include vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), prostaglandin E2 [5].

Leukocytoclastic vasculitis

Cutaneous vasculitis may be associated with malignancies. There is no clear proportion available in terms of its association. Gibson et al have reported about 8% of cutaneous vasculitis subjects had an associated vasculitis [7]. Among the paraneoplastic cutaneous vasculitis histologically leukocytoclastic vasculitis was the most common [8]. It presents as palpable purpura in lower extremities associated with pain, burning sensation and pruritus. It is most commonly associated with hematological malignancies, followed by lung, prostate, renal, breast, head and neck and endometrial cancers [5,8]. Possible mechanisms include impaired clearance of normal immune complexes, production of immunoglobulins against an abnormal circulating antigen or normal endothelium or production of immunoglobulins against vascular antigens that produce in situ immune complex deposition [8].

Although cutaneous vasculitis is not commonly associated with malignancies, it is advisable to screen for malignancies in the setting of unknown origin of fever, recurrent unexplained relapses of purpura, lymphadenopathy, organomegaly, constitutional syndrome, high ESR, doubtful lung mass, cytopenias or presence of immature cells on peripheral smear especially with advanced age [8].

Dermatomyositis

Dermatomyositis (DM) is strongly associated with malignancies. It has a relative risk of 4.4. for developing malignancies in the subsequent two years of onset [9]. Malignancies commonly associated with DM are carcinomas of nasopharynx, breast, lung, ovary and colon [3]. They present with classical dermatologic signs of DM including heliotrope rash, Gottorn's papules, poikilodermatous eruptions which are photosensitive, erythematous rash on face, neck, chest, back and shoulders (Shawl sign) and periungual telangiectasia [3,5]. The severe the involvement of skin and muscle often suggests an underlying malignancy [3]. "Cross Over" immunity is a model proposed as possible mechanism for DM in the setting of malignancy where in the antibodies generated against the tumor might cross react with the antigens on skin and muscle [3]. The treatment of choice for DM is glucocorticoids, when DM ia paraneoplastic treating the primary tumor results sometimes in complete recovery of DM [5]. There are reports where in DM has recurred after 10 years without any malignancy after successful treatment of small cell lung cancer [10]. In contrast to DM, polymyositis is not a commonly associated with malignancy [5].

Systemic Sclerosis

Systemic sclerosis (SSc) is associated with an increased risk of developing malignancies by 2.1-fold and a relative risk of 8.3 for lung cancer.9 However SSc presenting as a paraneoplastic manifestation of malignancies is quite rare. There are reports of malignancy triggering a rheumatologic condition which is not paraneoplastic in nature. Paraneoplastic SSc may lack the immunological markers that are hallmark of systemic sclerosis. The pathogenesis of paraneoplastic SSc could be secondary to autoimmunity induced by cancer [11].

Paraneoplastic scleroderma has been described in patients with POEMS syndrome. It is seen in patients with IgA plasmacytoma and is characterised by presence of scleroderma like features along with polyneuropathy, hepatosplenomegaly, osteolytic lesions and lymphadenopathy [9].

Polyangiitis with Granulomatosis

Patients with polyangiitis with granulomatosis may present with peripheral nervous system involvement in the form mononeuritis multiplex or mixed polyneuropathy in 15-40% of cases. Lymphoproliferative malignancies and myelodysplastic syndromes are the type of cancers generally presenting as polyangiitis. Immune complex formation and low complements as a result of consumption are less likely to be seen in cases of paraneoplastic polyangiitis [12].

Palmar fasciitis with polyarthralgia (PFPAS)

This is one among the rare presentations noted commonly in carcinoma of breast, gastric cancers, ovarian cancers. It is also noted in cancers of lung, uterus, prostate [13]. The underlying mechanism is not clearly understood, however, it has been identified that there is an increase in the fibrotic activity mainly in the hand due to the activity of transforming growth factor beta and connective tissue growth factors [14]. Biopsy of the palmar fascia may reveal nodules or whorls of fibroblasts surrounded by dense connective tissue [15].

Polymyalgia Rheumatica (PMR)

Generally observed with carcinoma lung [3]. It presents as limb girdle pain and stiffness. It is also seen in hematologic malignancies, myelodysplastic syndromes, carcinoma colon, prostate and breast. PMR is associated with increased inflammatory markers like high erythrocyte sedimentation rate and c- reactive protein [5]. PMR responds to steroids and methotrexate.

Tumor induced osteomalacia

It is also called oncogenic hypophosphatemic osteomalacia. It is a rare form of renal phosphate wasting syndrome. It results in severe hypophosphatemia [14]. It also affects the vitamin D metabolism and results in osteomalacia. It is classically associated with benign mesenchymal tumors. Increased levels of fibroblast growth factor-23(FGF-23) and/or the frizzled-4 protein produced by the tumor are postulated to be the possible etiology. It could be challenging to localise the tumor which could arise from bone or soft tissue anywhere in the body.

Other musculoskeletal manifestations

Acute gout secondary to hyperuricemia, sacroilitis and features mimicking spondyloarthritis, juvenile idiopathic arthritis, remitting seronegative symmetrical synovitis with pitting oedema (R3SPE) have all been reported previously. Although there are a handful of such case reports, we would like to emphasise that there is a myriad of manifestations and presence of any atypical feature should alert the consulting physician to look deeply for associated malignancies [13].

Acute febrile neutrophilic dermatosis (Sweet syndrome)

Sweet syndrome presents as sudden painful eruptions of erythematous nodules, papules or plaques involving the extremities, upper trunk and face associated with fever and malaise [5]. Often associated with hematologic malignancies, multiple myeloma, genitourinary, gastrointestinal and breast cancers. Skin biopsy often reveals neutrophilic infiltration of dermis [5,16]. Respond well to corticosteroids and colchicine [16]. Musculoskeletal, pulmonary and hepatic involvement can occur in Sweet syndrome [9].

Autoimmune hemolytic anemia

Autoimmune hemolytic anemia and thrombocytopenia are well established paraneoplastic manifestation of hematologic malignancies like chronic lymphocytic leukemia and B cell lymphoma. It is associated with presence of circulating antibodies against red blood cells and platelets [8,9].

Amyloidosis

About 15% of amyloidosis patients have associated malignancies which most commonly include multiple myeloma, lymphomas and other solid tumours.

They present with features suggestive of restrictive cardiomyopathy, weight loss, skin infiltration and neuropathy [15]. Amyloid arthropathy commonly affecting the knees, shoulders, wrists, small joints of hand may be associated with multiple myeloma [14].

Other rare paraneoplastic rheumatic manifestations

Anterior Uveitis is rarely noticed along with breast cancer. Behcet's disease is also noted as a paraneoplastic manifestation of breast cancer [17]. Refractory Raynaud's syndrome with digital necrosis noted in lymphoproliferative disorders, and ovarian, lung and stomach cancers. Multicentric reticulohistocytosis and panniculitis have also been noted [15]. Sympathetic dystrophy, lupus like syndrome, eosinophilic fasciitis, Lambert-Eaton syndrome, erythromelalgia and recurrent polychondritis have also been described as rare paraneoplastic rheumatic manifestations [18].

Pathophysiology and clinical features

The first case of rheumatic disease with malignancy was described way back in 1916 and the number has always seen a steady rise every year [13]. The symptoms that suggest a paraneoplastic etiology of paraneoplastic rheumatologic manifestation include asymmetric Raynaud's phenomenon which is refractory to treatment with vasodilators, presence of atypical constitutional symptoms, rapid worsening of symptoms, advanced age, previous history of cancer or family history of cancer, abnormal laboratory investigations like hypercalcemia, hypergammaglobulinemia, anemia and presence of anti RNA polymerase III antibodies, atypical distribution of articular pain, occult blood noted in stools, poor response to corticosteroids [11,12].

Pathogenesis is different for each paraneoplastic manifestation. Variety of factors are generated depending on which tumor is the underlying cause. Most accepted pathogenesis is of HOA where in VEGF and PDGF are recognised as the humoral factors responsible for periosteal proliferation which in turn results in HOA. Inflammatory arthritis with synovitis has many factors that might result in CP. Whereas, remitting seronegative symmetrical synovitis with pitting oedema (R3SPE) results due to expression of matrix metalloproteinase 3 (MMP-3). PFPAS in ovarian cancer is associated with connective tissue growth factor (CTGF) release which increases fibrotic activity and results in palmar fasciitis. Transcription intermediary factor – 1(TIF-1) has been identified as the primary humoral factor responsible for myositis in cancer associated myositis. Mesenchymal tumors producing FGF23 results in phosphaturia and subsequently resulting in tumour associated osteomalacia [19]. However the reason for a paraneoplastic manifestation to localize to particular tissue like palmar fascia or to certain bones in HOA despite the humoral factors responsible are present in systemic circulation has not clearly understood.

CONCLUSION

A wide range of autoimmune conditions may be the presenting symptoms of many malignancies. It may occur simultaneously, or the atypical nature of the rheumatologic manifestation may prompt for a search for an underlying malignancy especially when there is no response to conventional therapy. The key factor is early recognition and initiating effective treatment. This in turn could result in complete resolution of the paraneoplastic manifestations in most cases. The reappearance of the paraneoplastic symptoms could also mean the relapse of the malignancy and in some cases could be only a rheumatologic condition. Hence it is not reliable to assume that the malignancy has recurred but can serve as warning for a thorough search for same. There are many factors which are yet to be identified which result in paraneoplastic manifestations.

Further research in those lines could definitely result in a clear understanding of their pathogenesis and could open up new arenas for treatment.

Conflicts of Interest

There is no conflict of interest.

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