Paraneoplastic rheumatic disorders: a review

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Introduction

Malignant disease is associated with a wide variety of musculoskeletal disorders and, importantly, may present as such. Locomotor symptoms can result from direct invasion of bone, joint or soft tissue by primary or secondary tumour, but may also occur without direct invasion of affected tissues by malignant cells. This latter group of 'paraneoplastic' disorders includes well recognized syndromes such as hypertrophic osteoarthropathy and dermatomyositis, as well as less well defined disorders such as 'cancer arthritis'. These conditions are the subject of the present review in which we draw attention to the fact that they may be the presenting feature of cancer, at a stage when identification of the primary tumour may permit curative therapy. Secondly, we discuss possible mechanisms involved in the pathogenesis of these disorders, since we believe that they may serve as useful models of idiopathic rheumatic disorders. Paraneoplastic rheumatic disorders can be grouped into three broad categories, namely articular, muscular and systemic.

Articular disorders

Gout

Acute gout may be the presenting feature of myeloproliferative disorders, especially polycythaemia rubra vera[1], but is rarely seen in patients with solid tumours[2]. This may be related to the greater degree of hyperuricaemia in the former group, since hyperuricaemia is rarely seen in patients with solid tumours until the tumour becomes disseminated[2]. In clinical terms the features of such secondary gout do not differ from idiopathic gout, although women are affected more frequently and a family history of the disease is obtained less often than in the idiopathic form.

Cancer arthritis

An inflammatory arthropathy which resembles rheumatoid arthritis has been described in association with cancer. However, both rheumatoid arthritis and cancer are sufficiently common in the population at large for their coexistence to be unremarkable. The existence of a form of seronegative polyarthritis distinct from rheumatoid arthritis and associated specifically with cancer is suggested by a close temporal relationship between the onset of arthritis and appearance of malignancy, and improvement of the arthritis with treatment of the tumour[3-6]. Mackenzie and Scherbel[4] described 18 patients with arthritis and malignancy, 8 of whom had typical rheumatoid arthritis while the other 10 had atypical features including an explosive onset, asymmetry, and predominant lower limb involvement with sparing of the hands; only one of this latter group had circulating rheumatoid factor and none had rheumatoid nodules. The arthropathy antedated discovery of the tumour by a mean of ten months; in 8 of 11 patients in whom the tumour could be treated the arthritis improved, only to relapse in 2 of 3 cases when the tumour recurred. Sheon *et al.*[7] described 26 patients whose inflammatory arthropathy began within two years of discovery of a tumour. Four of these patients met the ARA criteria for classic or definite rheumatoid arthritis, whereas only 7 of the remaining 22 had circulating rheumatoid factor and only 3 had erosions. These authors did not find a consistent relationship between successful treatment of the malignancy and remission of the arthritis. No particular site of tumour appeared to be associated with development of arthritis, but breast cancer was by far the most common cause of an asymmetrical arthritis in women.

How might tumours give rise to arthritis? Perhaps the most obvious mechanism would be deposition of immune complexes consisting of tumour antigens and host antitumour antibodies within the joint, since circulating immune complexes are common in patients with cancer[8]. Few studies have addressed this question: Awerbuch and Brooks[9] demonstrated synovial fluid immune complexes with absent synovial fluid C3 and C4 in a patient with polyarthritis and lymphoma, whereas Bradley and Pinals[10] could detect no immunoglobulin or complement in a synovial biopsy from a patient with lung cancer, circulating immune complexes and polyarthritis. Clearly, further investigation of immune complex and complement abnormalities in synovial fluid and membrane of such patients is necessary. Similarly there are few reports of synovial pathology in cancer arthritis; a mild nonspecific synovitis with lymphocytic and plasma cell infiltration was reported in two studies[5,10]. We are aware of no reports of the immunopathological findings in cancer arthritis, but it is possible that the malignant disease results in a disorder of immunoregulation which leads to arthritis in the same way as that postulated for rheumatoid arthritis[11]. Alternatively, an antigen expressed by the tumour might resemble one present within the joints, arthritis resulting from a crossreactive immune response. Type 2 collagen or proteoglycan of articular cartilage are potential targets for such an immune response, but to date tissue-specific synovial antigens have not been identified. Recently the probable target antigen in adjuvant arthritis of rats has been identified by Cohen *et al.*[12], who generated T-cell clones reactive with mycobacterial components of adjuvant and used these to identify an articular antigen with which the clones crossreacted. A similar approach could be applied to cancer arthritis where T-cell clones raised against the host tumour

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might identify a target antigen within the joint, an immune response to which might play a role in the pathogenesis of other forms of arthritis.

Amyloid

Bone pain is a common presenting feature of multiple myeloma and osteolytic lesions are usually readily demonstrated on X-ray. Multiple myeloma may also present as amyloid arthropathy – a symmetrical polyarthritis typically affecting the hands, shoulders and knees. There may be considerable periarticular swelling, morning stiffness and nodules suggesting a diagnosis of rheumatoid arthritis, but unlike that condition swelling around the shoulders is particularly prominent: the 'shoulder pad' sign[13]. Synovial fluid is usually non-inflammatory in character[14] but amyloid deposits can be identified on synovial biopsy or in villous fragments in synovial fluid[15]. In a recent study amyloid arthropathy was dignosed in 3 of 43 patients with multiple myeloma[16]. All 3 patients also had carpal tunnel syndrome, compared with only 3 other patients in this series. Amyloid was identified in Congo Red stained synovial fluid sediment, but in only one of these cases was amyloid detected on rectal biopsy.

While amyloid arthropathy is not uncommon in multiple myeloma, it is rare in other forms of amyloidosis and has not to our knowledge been described with other types of cancer. Possibly the high concentration of paraprotein in adjacent bone marrow in myeloma favours deposition in articular tissues, the paraprotein diffusing into synovial fluid[15] whence it is taken up and processed by synovial macrophages[17] and possibly chondrocytes[16], with consequent local accumulation of amyloid fibrils.

Muscle disorders

Polymyositis and dermatomyositis

It has long been recognized that myositis may be associated with malignancy, but the magnitude of increased risk is not clear due to the lack of a large controlled study. Bohan *et al.*[18] found malignant disease in 8.5% of their series of 153 patients with myositis. Malignant disease was not seen in those patients with associated connective tissue disorders or in children, although an adolescent with myositis and malignancy has been reported[19]. This overall incidence is similar to the figure of 7.7% reported by De Vere and Bradley[20]. Most, but by no means all of the tumours were seen in elderly patients with dermatomyositis. Myositis is seen in patients with a wide variety of tumours, although Barnes[21] has suggested that tumours of the ovary and stomach are more common and those of the large bowel less common than in the general population. In nearly 70% of the patients reported by Bohan *et al.*[18] the myositis preceded appearance of the malignancy with a mean of 1.9 years (range 1 month to 6 years); in the remainder it followed the tumour by an average of 2.8 years (range 4 months to 5 years). The long interval between the onset of myositis and discovery of malignancy in some cases and the fact that in only 3 of 11 patients in this series was there any improvement in the myositis following treatment of the tumour, might suggest that in most cases the two disorders occur in persons with a shared predisposition rather than that they are causally related.

Several explanations for the association between myositis and malignancy can be advanced (Figure 1).

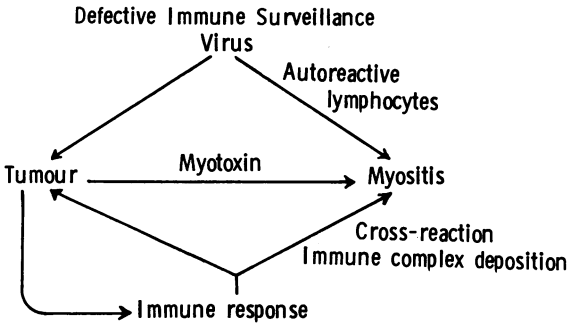

Figure 1. Possible explanations for the association between myositis and malignant disease

Perhaps the simplest is that the tumour secretes a myotoxic factor, and the myotoxic potential of serum from affected patients merits examination. Several patients have recently been reported in whom myositis appeared to be mediated by an IgG kappa paraprotein with anti-muscle specificity[22]; similar autoantibodies should be sought in patients with cancer and myositis. Immune complexes may play a pathogenic role in childhood myositis[23] and the possibility that muscle damage results from deposition of complexes of tumour and antitumour antibodies should be considered. While it is possible that a virus might contribute to induction of the tumour and also result in expansion of an autoantibody-producing clone, this seems unlikely. Dawkins and Zilko[24] have suggested that both the myositis and the tumour might result from a subtle immune defect; this could allow proliferation of a tumour with a particular surface antigen which is shared by an idiotype on an autoimmune clone of muscle-reactive lymphocytes. Alternatively the tumour antigen might resemble a muscle cell surface antigen so that an immune response to the tumour might, by crossreaction with the latter, result in myositis. Direct evidence of crossreactivity between tumour and muscle antigen or autoantibody idiotype could be obtained with monoclonal antibodies or T-cell clones raised against tumour antigen. This might lead to the identification of target antigens on the muscle cell surface and idiotypes of anti-muscle antibodies, so that immunotherapy might be possible not only in tumour-associated but also in other forms of myositis.

Polymyalgia rheumatica

Polymyalgia rheumatica (PMR) is seen in elderly patients, a group in which malignant disease is common. Although patients with PMR do not appear to be particularly susceptible to cancer[25], a syndrome resembling PMR may occasionally be the presenting feature of malignant disease. Sheon *et al.*[7] reported 5 patients in whom malignant disease was discovered within three months of the onset of PMR. One patient had leukaemia, the others tumours of colon, prostate, ovary and kidney. The authors commented that these patients represented a 'small percentage' of their total group of patients with PMR. The characteristic elevation of ESR and response to steroid therapy seen in idiopathic PMR may also be seen in patients with cancer, so that the distinction of a tumour-associated PMR syndrome from idiopathic PMR requires vigilance and attention to atypical systemic symptoms. The pathogenesis of PMR is obscure, although electronmicroscopy of muscle has revealed some nonspecific abnormalities[26]. As with myositis, the

possibility that an immune response to the tumour results in the muscle disease by a crossreactive mechanism merits examination, but clearly other mechanisms such as myotoxin secreted by the tumour could be involved.

Systemic disorders

Vasculitis

Erythema nodosum[27], Henoch-Schönlein purpura[28], cryoglobulinaemic purpura[29], necrotizing vasculitis[30], and polyarteritis nodosa[31] have all been described as the presenting feature of malignancy. While circulating immune complexes are common in patients with many types of cancer[8], it is striking that most of these cases involve patients with lymphoma, leukaemia or myeloma. This raises the possibility that patients with these conditions are predisposed to the deposition of immune complexes, possibly as a result of an interaction between malignant lymphoid cells and vascular endothelium. *In vitro* investigation of this possibility might further illuminate the mechanisms involved in the localization of immune complexes.

Panniculitis

The clinical features of panniculitis are subcutaneous nodules, usually on the lower limbs but sometimes also on the buttocks and trunk, and arthritis which may be either monarticular or polyarticular but which frequently involves the ankles[32]. Panniculitis may be the presenting feature of pancreatic carcinoma or pancreatitis and these diagnoses should be considered in patients who present with an unexplained arthritis and subcutaneous nodules. In a literature review of patients with panniculitis and pancreatic carcinoma, Hughes *et al.*[33] noted that skin rash (65%) and arthropathy (35%) were much more common presenting features of the carcinoma than were abdominal pain (12%) or jaundice (6%), while 65% of patients had an eosinophilia. The panniculitis is believed to result from destruction of fat cells by bloodborne lipase, and elevated serum concentrations of lipase have been reported in patients with pancreatic carcinoma and panniculitis[32].

Systemic lupus erythematosus (SLE)

Typical SLE may be seen in patients with thymoma[34]. It is possible, in view of the important role played by the thymus in lymphocyte maturation, that the thymic tumour gives rise to SLE, but equally the disordered immunoregulation seen in patients with SLE might induce uncontrolled proliferation of thymocytes. A lupus-like syndrome has been described in patients with other malignancies[35]. On theoretical grounds malignant transformation of cells could render DNA immunogenic or lead to reduced supressor cell activity and so permit expression of latent SLE. Fortunately SLE is only rarely the presenting feature of malignancy, but in such patients it may be difficult to decide whether clinical features such as pleurisy or leukopenia are due to a recurrence of tumour or to the lupus[34].

Scleroderma and carcinoid arthropathy

Patients with scleroderma appear to be particularly susceptible to carcinoma of the lung[36], but since the tumours are usually seen in patients with established pulmonary fibrosis the scleroderma is not a presenting feature of the tumour. However, skin changes resembling scleroderma have been the presenting feature of carcinoma of the stomach[37] and metastatic melanoma[38]. Scleroderma has also been reported in association with carcinoid tumours, and in a study of 5 consecutive patients by Plonk and Feldman, 3 had pain and stiffness of their fingers[39]. Hand radiographs in these 3 showed periarticular osteoporosis and in two cases cystic changes in phalanges and erosions of interphalangeal joints. In one patient treated for 6 days with an inhibitor of serotonin synthesis, there was dramatic resolution of articular symptoms[39]. Further study of this syndrome and of concentrations of circulating serotonin and other biogenic amines might throw some light on the pathogenesis of scleroderma.

Hypertrophic osteoarthropathy

Hypertrophic oesteoarthropathy (HOA) is a well recognized complication of malignancy. It consists of clubbing, periostitis, and an arthropathy which can vary from mild arthralgia to a diffuse polyarthritis which may mimic rheumatoid arthritis[40]. The arthritis is usually associated with considerable tenderness over adjacent long bones. Most often knees, ankles, wrists and metacarpophalangeal joints are involved, but elbows and shoulders may also be affected. An isotope bone scan may reveal increased uptake along the shafts of affected bones before periosteal new bone formation is apparent on plain X-ray, and so permit an early diagnosis. Synovial fluid from affected patients is typically non-inflammatory, although the synovial membrane usually shows vascular congestion and slight lymphocytic infiltration; basement membrane abnormalities and electron-dense deposits in venules have been reported[41].

The pathogenesis of HOA is uncertain, but possible mechanisms have been discussed by Schneerson[42]. Neural involvement is suggested by the rapid response to vagotomy[43] and atropine[44], while immune complexes, a circulating vasodilator, growth hormone and oestrogens have also been regarded as potential mediators of the syndrome. The possibility that the lesion results from vascular anastomoses formed in response to tissue ischaemia is supported by the observation that HOA in children with cyanotic congenital heart disease is largely confined to those cases with severe right to left shunts and reduced arterial oxygen saturation[45]. Further studies of synovial membrane and fluid are warranted, but it seems likely that clarification of the pathogenesis of this syndrome will depend upon a better understanding of the microvasculature and its innervation in bone and articular tissue.

Reflex dystrophy syndrome

The initial phase of this condition is characterized by non-segmental pain and diffuse swelling of an extremity with increased vascularity, the skin being cool, cyanotic and moist. Subsequently the limb becomes cold and shiny, the skin and muscle atrophic, and flexion contractures may develop. In early disease bone scans reveal increased distal osseous uptake, especially in juxta-articular regions; later patchy osteoporosis develops in the affected extremity[46]. Synovial biopsy shows hyperplasia of lining layer cells as well as an increase in numbers of capillaries and amount of fibrous tissue in the subsynovial layer[46]. Reflex dystrophy has been associ-

ated with a variety of tumours[47], as well as with trauma, immobilization, diabetes mellitus, cervical spondylosis and intrinsic abnormalities of the shoulder. Medsger *et al.*[48] described 6 women aged 50–65 who developed the syndrome in the two years preceding a diagnosis of adenocarcinoma of the ovary, and recommended a careful pelvic examination be performed in any woman who developed reflex dystrophy. The pathogenesis of this syndrome is uncertain, but there is some recent evidence to support the long-held view that it results from abnormal activity of the sympathetic nervous system[49]. As with hypertrophic osteoarthropathy, it seems likely that further study of the neuronal regulation of blood flow might illuminate the pathogenesis of this puzzling disorder.

Comment

Patients with cancer may develop a wide variety of disorders of the musculoskeletal system. While some such as dermatomyositis and hypertrophic osteoarthropathy are well known, other less well recognized syndromes may also be the presenting feature of an underlying neoplasm. We believe that several of these disorders could serve as useful models and have suggested some experimental studies which might illuminate the pathogenesis of idiopathic rheumatic diseases.

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