Milder forms of hypophosphatasia may cause calcific periarthritis due to apatite deposition, in association with axial and peripheral ossifying enthesopathy. Hyperparathyroidism (primary, but particularly secondary or tertiary in patients with renal failure) may also cause this. With renal failure crystal deposits may be massive ("tumoral calcinosis") and both form and resolve with treatment over short periods of time. By far the more common consequence of renal failure, however, is urate crystal deposition. This may result in chronic tophaceous gout and acute attacks. Treatment may prove difficult but allopurinol remains the principal agent. Oxalate crystals can deposit in many tissues, including muscles and joints, and possibly cause myalgia and acute inflammatory episodes in chronic dialysis patients.

REFERENCE

- 1 Jones A, *et al.* Diseases associated with CPPD deposition disease. *Semin Arthritis Rheum* 1992;**22**:188–202

Targets for treatment – Saturday 16 June, 12.00-13.30/South Hall

SP0116 ANGIOGENIC MEDIATORS IN RHEUMATOID ARTHRITIS

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Angiogenesis is important in a variety of fibroproliferative diseases including rheumatoid arthritis (RA). There are a number of angiogenic mediators which may play a role in RA including cytokines and growth factors like transforming growth factor-beta and hepatocyte growth factor. Other angiogenic factors include the fibroblast growth factors (bFGF), vascular endothelial growth factor (VEGF), tumour necrosis factor-alpha, and angiopoietin-1.

VEGF has been characterised over the last few years as an endothelial-selective growth factor. In arthritis models, angiogenesis inhibitors have resulted in decreased severity of arthritis and serum VEGF production. In another model, the soluble VEGF receptor flt-1 resulted in reduction of arthritis. These results indicate that modulation of angiogenesis may modulate arthritis, at least in animal models. In human RA, several groups have found VEGF in the joints. Recent interest has focused on VEGF production by RA fibroblasts. In RA patients treated with anti-TNF-alpha, vascular deactivation occurs so that serum levels of VEGF fall along with clinical improvement. Hence, VEGF is likely an important mediator of angiogenesis in the RA joint.

What is the mechanism of action of angiogenic mediators like VEGF and bFGF? Particularly important in mediating angiogenesis are the alpha v beta 3 and alpha v beta 5 integrins. It appears that cytokines like TNF-alpha or bFGF act via alpha v beta 3 integrin while VEGF acts via alpha v beta 5 integrin. In an animal model, inhibition of alpha v beta 3 integrin resulted in amelioration of a model of lapine arthritis.

We have recently examined the role of interleukin (IL)-18 as an angiogenic mediator in RA. We have shown its role in angiogenesis using a number of experimental models. IL-18 mediated endothelial chemotaxis in a modified Boyden chamber assay. IL-18 induced endothelial tube formation on the matrix protein Matrigel. Moreover, IL-18 was angiogenic *in vivo* in rodent Matrigel plug and sponge granuloma assays. IL-18 accounted for a large portion of the chemotactic activity for endothelial cells

found in RA synovial fluids. IL-18 appears to induce angiogenesis via the alpha v beta 3 integrin.

Angiogenic mediators can be broadly divided into two groups, stimulators or proangiogenic factors, and inhibitors or angiostatic factors. The regulation of angiogenesis is likely to result from a delicate balance of angiogenesis inducers and inhibitors.

Some of these inhibitors include interferons alpha, beta, and gamma and interleukin-12, and interleukin-4. Other inhibitors include placental ribonuclease inhibitor, protamine, retinoic acid and tissue inhibitor of metalloproteinase.

We have shown that another cytokine, IL-4, is a potent anti-angiogenic factor. Moreover, when an adenoviral vector bearing the IL-4 gene was given to rats prior to development of adjuvant-induced arthritis, these animals showed less severe arthritis and their joints exhibited decreased inflammatory infiltrate and decreased angiogenesis compared to controls.

Another emerging paradigm is that angiogenesis inhibitors often reside within other proteins. The idea that endothelium is quiescent for long periods of time and yet can be induced to sprout new capillaries in a matter of hours in response to an angiogenic stimulus, suggested that angiogenesis regulators might be stored for expedient use. Examples of this include angiostatin and endostatin.

It is likely that inhibitors of angiogenesis are present in the RA synovium, but are outweighed in effect by angiogenesis inducers.

Can angiogenesis regulation help us in the therapy of patients with RA? There are a number of endogenous and exogenous inhibitors of angiogenesis which have been identified to date. These include a cartilage-derived factor, troponin, angiostatic corticosteroids, minocycline, fumigillin, chloroquine, sulfapyridine, methotrexate, penicillamine and thiol containing compounds such as gold compounds.

Can we use angiogenic markers to help guide our therapy in diseases like RA? Some preliminary data from several centres indicate that VEGF and bFGF are increased in RA vs. normal serum, especially in early erosive RA and in patients who are anti-Sa and anti-native collagen positive. Serum VEGF is increased in early RA. Early RA synovial fluid VEGF and MMP-9 correlate with each other and with arthroscopic synovitis and vascularity scores. Evidence is mounting that markers of angiogenesis may help us in early RA.

Can we use angiogenic markers to predict RA disease outcome? One study presented in abstract form indicated that serum vascular markers predicted disability and radiological changes in RA. Serum VEGF was associated with greater disease activity and soluble selectins were associated with increased disability. Hence, it is tempting to speculate that angiogenic markers may help guide us in RA therapy in the future.

Review session N° 1 – Wednesday 13 June, 14.00-16.00/South Hall

SP0011 OSTEOARTICULAR DISORDERS OF RENAL ORIGIN

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Renal failure is a source of musculoskeletal features, especially in patients treated by maintenance haemodialysis. In these, bone

and joint involvement has become an important limitation of long term prognosis.

Severe secondary hyperparathyroidism can cause osteoarticular pain and an erosive enthesopathy which carries a risk of tendinous rupture.

Urate gout is a classical feature of terminal renal failure which usually does not persist after the onset of haemodialysis, as efficient uric acid clearance is achieved during dialysis sessions.

Periarticular calcifications are usually composed of calcium phosphate crystals and are favoured by hyperphosphataemia and other poorly known factors. Deposits are frequently asymptomatic but can grow into tumoral masses or cause acute articular or periarticular flares. Bone erosions, in the vicinity of deposits can be observed. In dialysis patients, secondary oxalosis usually follows vitamin C supplementation of the diet and may be responsible for soft tissue calcification, articular effusion, chondrocalcinosis and a disabling finger flexor contracture.

The incidence of bone and joint infection in haemodialysis patients is 10 to 100 fold the one in the population at large, and this must remain a permanent concern as prompt diagnosis and treatment are required to improve a gloomy prognosis. The leading causative organisms are *Staphylococcus* species, the usual portal of entry being the arteriovenous fistula. In kidney transplant patients, very unusual pathogens can be identified.

Beta 2-microglobulin amyloidosis has been documented in a few long-standing terminal renal failure patients before the start of dialysis, but most usually develops in long term dialysis patients. Up to 65 p.cent of individuals who have received ten or more years of maintenance haemodialysis using standard cuprophane membranes are affected. Ageing is also an important risk factor. Carpal tunnel syndrome is a prominent feature, although oedema, uremic neuropathy and crystal deposition may play a role in some carpal tunnel syndromes of dialysis patients. A chronic amyloid arthropathy is also frequently observed. Features include chronic arthralgias, particularly of the shoulders, chronic joint swelling, finger tendon synovitis, large subchondral bone erosions which may lead to femoral neck fracture, and destructive arthropathy. Synovial fluid is noninflammatory and may contain numerous blood cells. Destructive spondylarthropathy predominantly affects the cervical spine and can lead to spinal cord and/or nerve root compression, usually through spine instability. Shoulder pain may be related to amyloid synovium involvement and/or amyloid thickening of the cuff tendons and subacromial bursa. Systemic deposits are rare. They can be responsible for intestinal haemorrhage or cardiac dysfunction. Lack of β 2-microglobulin catabolism by the deficient kidney and unsatisfactory elimination through the dialysis membrane are important in the pathogenesis of the disorders. The use of permeable and biocompatible membranes appears to delay the onset of the disease, but has been thus far unable to totally prevent its development.

SP0012 MALIGNANCIES IN RHEUMATIC DISEASES

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Patients with rheumatic diseases have an increased risk overall for cancer compared to the normal population. This is most pronounced for patients with SLE, but patients with rheumatoid arthritis have also a significantly increased risk. Unpublished data

from Sweden also indicate that such an association exist for patients with Morbus Bechterew as well as patients with psoriatic arthritis.

However, the increased cancer risks are not general phenomenon for cancer as such. There are distinct differences in the patterns of cancer occurrence compared to the general population. Smoking related cancers, especially lung cancer, occur in excess for both rheumatoid arthritis and SLE patients as opposed to cancers of the gastrointestinal tract (especially colorectal cancer) which are inversely associated with all four disease entities mentioned above, possibly due to the pharmacotherapy these patients are exposed to.

Hematopoietic cancers (lymphomas and leukemias) also occur more than that expected in patients with rheumatic diseases. In the case of SLE and rheumatoid arthritis these excess risks are especially prominent for lymphomas, but there is also a somewhat less pronounced increased risk for leukemias. This increased risk can probably, to some extent, be explained by immunosuppressive therapy. However, the increased risk for lymphomas in a Swedish setting was already present in these patient groups before the introduction of such therapies during the 1970's. Moreover, the risk estimates for lymphomas have not been altered after the introduction of such therapies. The absence of an impact of immunosuppressives can, perhaps, to some extent be due to a substantially increased absolute risk of lymphomas in the general population, which means that the cumulative incidence of lymphomas among patients with rheumatic disease is presently higher than it was 20 years ago.

High disease activity in patients with rheumatic arthritis seems to be associated with an even more pronounced risk for lymphomas. There are indications that anti-inflammatory therapy have a protective effect, although better data is needed before such an association can be firmly established.

In conclusion, rheumatic diseases are associated with increased risk for cancer. Hematopoietic cancers are, however, the only malignancy where a causal association has been established.

SP0013 STRESS SYSTEM RESPONSE IN RHEUMATIC DISEASES

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The role of stress is emerging among the factors involved in the pathophysiology of rheumatic diseases including genetic predisposition, infections and gender. A stressor is any stimulus that disturbs or threatens to disturb homeostasis. Stressors can be exogenous or endogenous and metabolic, physiologic, infectious, inflammatory, or emotional in nature. The stress system response (SSR) is the array of physiological and behavioural adaptation to restore homeostasis and is mediated through activation of the hypothalamic-pituitary-adrenal axis (HPA) and the sympathetic nervous system (SNS). Activation of HPA axis induces synthesis and release of corticotropin-releasing hormone (CRH), adrenocorticotrophic hormone (ACTH and finally glucocorticoids (GC) such as cortisol. GC act in a permissive way to increase readily available energy resources to brain and heart during stress and terminate defense mechanisms to stress to prevent these responses to become destructive themselves. SNS activation leads to release of norepinephrine (NE) and the sympathetic division