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