REVIEWS

Mycoplasmas and arthritis

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The interest in mycoplasmas as human pathogens has increased again after the discovery of *Mycoplasma fermentans* strain *incognitus* in samples from patients with AIDS.¹⁻³ The role of mycoplasmas as causative agents in arthritis has been considered since they were found 50 years ago in rats and mice with arthritis.⁴⁻⁶ Their role in human arthritis remains unsolved, however; several workers have been unable to subcultivate primary mycoplasma isolates in cell free media.

Mycoplasma arthritis in animals

Mycoplasmas are established pathogens in animals and birds. At least 31 mycoplasma species have been implicated.⁷ Under field conditions *M synoviae* is the most common cause of mycoplasma induced joint disease in poultry, resulting in acute or chronic arthritis, tenosynovitis, and lesions in periarticular tissue. In severe cases an erosion of articular cartilage occurs. Systemic changes include anaemia, arthritis, and atrophy of the thymus.⁸

M hyorhinis is one of the aetiological agents of arthritis in pigs.⁹ The general pathological changes in mycoplasma arthritis of pigs are similar to human rheumatoid arthritis.⁷ *M agalactiae* infection in sheep and goats may be complicated by arthritis as well as *M bovis* and *M alkalescens* infection in cattle.

In addition to arthritis, *M gallisepticum* infection of poultry results in disease of many of the arteries in the periarticular soft tissues of the affected joints. These lesions are selective, occurring only in the periarticular tissues and in the neighbourhood of joints with arthritis. Both the arthritis and arteritis can be suppressed by treating the chickens with sodium aurothiomalate.¹⁰

Experimental *M arthritidis* infection in mice, rats, and rabbits by Cole and Washburn has been reviewed previously.¹¹ Deposits containing immunoglobulin and complement were found in joint tissues, suggesting that immune complexes may participate in the chronic phase of mycoplasma induced arthritis in rabbits.¹²⁻¹⁴

Transmission electron microscopy of articular cartilage in neonatal rats infected with *M pulmonis* revealed the presence of mycoplasmas within the matrix and lacunae. The mycoplasmas appeared to have a tropism for the chondrocytes and induced lysis of the chondrocytes and the cartilage matrix.¹⁵

Five different tetracyclines were highly active against *M arthritidis* and *M pulmonis* induced arthritis in rodents.¹⁶

Arthritis associated with mycoplasma infection in humans

M pneumoniae infection may cause arthralgias or less commonly a migratory polyarthropathy affecting medium sized joints. This condition may be severe, with joint swelling, morning stiffness, and considerable functional disability. It may be the dominant clinical feature outlasting all other manifestations of the disease, though remission can usually be expected within eight weeks. Rarely, a peripheral symmetrical polyarthritides indistinguishable from rheumatoid arthritis may occur.¹⁷

Isolation of *M pneumoniae* from joint fluid specimens has been reported in four patients of whom three had hypogammaglobulinaemia.¹⁸⁻²¹ *M pneumoniae* infection with joint symptoms in two children was confirmed by the determination of a specific antibody response by enzyme linked immunosorbent assay and immunoblotting. It was concluded that *M pneumoniae* infection should be considered in any patient with acute respiratory illness who subsequently develops arthropathy.²² Among 1259 patients with serologically confirmed *M pneumoniae* infection, 11 (0.9%) had arthritis in one or several large leg joints, which lasted for one to ten weeks.²³

M hominis has caused septic arthritis in association with puerperal fever, and non-Hodgkin's disease as well as traumatic joint infection and prosthetic infections.²⁴⁻³⁰ The arthritic symptoms resolved after prolonged treatment with tetracycline.³¹ *M salivarium* has been described in connection with arthritis of a patient with hypogammaglobulinaemia.³²

Ureaplasma urealyticum has also been recovered from samples of joint fluid, especially in immunocompromised hosts.³³⁻³⁸ In one instance both *M hominis* and *U urealyticum* were isolated from a joint.³⁷

Fastidious mycoplasmas and human arthritis

The positive findings in this field have been reviewed elsewhere.^{11 39} In Finnish studies mycoplasmas were isolated from several patients with arthritis.⁴⁰⁻⁴² Using the same cultivation method Markham recovered mycoplasma-like organisms in nine of 11 patients with rheumatoid arthritis.⁴³

In the 1980s we started to use the SP-4 medium developed by Tully *et al* for spiroplasma work.⁴⁴ With this substrate we studied 'blindly' 14 joint fluid specimens from patients with arthritis and eight synovial tissue specimens from traumatic joint lesions. Fastidious slow growing mycoplasmas were cultivated

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from patients with arthritis but not from the control subjects. Using a large field microscope tiny granular colonies with a diameter of 15–50 µm were seen. Except for a few instances we have been unable to subcultivate the isolates for a long time. This may depend on their partly parasitic nature. The same has happened to other workers in this field.^{45 46}

The Finnish isolates seemed to form a homogeneous group sharing antigens with *M hominis* type 2 presently named *M arthritidis*.⁴⁷ *M hominis* type 2 strain Campo was originally isolated by Dienes in 1948 when he was studying urethral specimens from patients with polyarthritis.⁴⁸ *M hominis* type 2 was also found by Bartholomew in a synovial fluid specimen⁴⁹ and by Brown *et al* in a pleural effusion from a patient with rheumatoid arthritis.⁵⁰

Our earliest isolate strain 20-P is growing well and has been studied by polyacrylamide gel electrophoresis. It showed similarities in its protein pattern with that of *M arthritidis* strain PG6 and especially strain Campo. In electron microscopic studies it showed a so-called S-layer, which may be connected with its pathogenetic properties (K Hakkarainen *et al*, unpublished data). 20-P mycoplasma was also found to form plaques on the lawns of its own as well as on the lawns of *Acholeplasma laidlawii*.⁵¹ So far we have been unable to establish the nature of this plaque forming agent.

Pathogenic mechanisms

Two major concepts of mycoplasma induced tissue damage have been presented: a cytotoxic hypersensitivity and an autoimmune reaction.⁸ Antigen complexed with antibody and deposited in synovial and cartilaginous tissues appears to provide the stimulus for chronic inflammation.

Gram positive cocci and mycoplasmas have developed an extremely potent mechanism of T cell stimulation by closely mimicking the recognition of specific antigens. The designation 'superantigens' has been suggested for these molecules.⁵² Such a superantigen MAM has been isolated from *M arthritidis* by Cole and Atkin.⁵³ They suggest that MAM not only activates T cells, with a resulting liberation of inflammatory lymphokines, but also suppresses host defences.

As a result of their limited biosynthetic capabilities, mycoplasmas require complex growth media or a close parasitic relation with animal cells.⁵³ They are extremely difficult to isolate from human synovium.⁵⁴ The surface plasma membrane of mycoplasma closely resembles the bilayer of eukaryotic cells. Once attached the mycoplasmas may adsorb complement and histocompatibility antigens onto their membranes. This phenomenon could alter the recognition of 'self' antigens by the host, leading to an autoimmune response. The close association of mycoplasmas and host cell membranes may also alter the host's immune response.⁵⁵

Future prospects

To determine the incidence of mycoplasmas in

human arthritis new direct methods such as the polymerase chain reaction and a known human mycoplasma isolate should be used. Cooperation on an international level would be valuable.

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