Coeliac disease and rheumatoid arthritis

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SUMMARY Three cases are reported of adult coeliac disease associated with rheumatoid arthritis.

Coeliac disease is associated with many disorders, such as dermatitis herpetiformis,1 2 hypopplenism,3 4 and many autoimmune diseases.6 Lancaster-Smith et al.6 found that 19% of their patients with coeliac disease gave a history of an associated autoimmune disorder, but only one of their patients studied had rheumatoid arthritis. We have recently had the opportunity of studying 3 patients with adult coeliac disease and rheumatoid arthritis. Two of these patients also had dermatitis herpetiformis, and one in addition had cutaneous vasculitis with biopsy-proven Sjögren’s syndrome.

Case histories

Case 1 Mrs A, aged 35, has suffered constant ill health for most of her life. She was weaned at the age of 5 months, then failed to thrive, with persistent diarrhoea and vomiting. Throughout her childhood she developed numerous episodes of pneumonia, and at the age of 4 she developed asthma. This was associated with the development of a rash, which was described as being vesicular, and disappeared some time during childhood. At the age of 16 she developed arthritis. This became an erosive, symmetrical polyarthritis, involving large and small joints. She also developed nodules, and later cutaneous vasculitis. She was found to have a positive rheumatoid factor of 1:320 and a weakly positive antinuclear antibody; DNA binding was normal, and she was diagnosed as having rheumatoid arthritis. Throughout the next 10 years the arthritis continued, poorly modified by gold, penicillamine, and even low-dose prednisone. At the age of 26 she became unwell with an obvious anaemia, vesicular rash, and a malabsorption syndrome. Investigations revealed a low serum folate and a 24-hour faecal fat excretion of 16 g. Small bowel biopsy showed flattening of jejunal villae. She was treated with a gluten-free diet, with dramatic improvement. Biopsy of the skin lesions confirmed dermatitis herpetiformis, and this also improved on her gluten-free diet, though she had been initially treated with dapsone. Despite improvement of her coeliac disease and dermatitis herpetiformis on the gluten-free diet her arthritis and vasculitis continued to be a problem.

In recent years, however, the patient has managed herself on an exclusion diet, eliminating dairy produce, alcohol, and red meat as well as gluten from her diet. On this diet she feels better, and clinically she has fewer complaints. There has been no further deterioration or new erosions, and recently she has discontinued all treatment. Her erythrocyte sedimentation rate (ESR) is now 23 h, haemoglobin 11 g/dl, and she remains seropositive at a titre of 1:80.

Case 2 Mrs B, aged 71, enjoyed good health until the age of 31, when she developed a herpes zoster infection. After that she developed a rash, which was subsequently diagnosed as being dermatitis herpetiformis, and responded to dapsone and sulphapyridine. Some 12 years later she developed infective endocarditis, and she subsequently required a mitral valve replacement at the age of 63. Since then she has been anticoagulated with warfarin. At the age of 64 she was found to have malabsorption. A jejunal biopsy showed flattened jejunal villae, suggesting the diagnosis of coeliac disease. This has subsequently responded to a gluten-free diet.

One year prior to this diagnosis she developed joint pain, and she subsequently developed an erosive symmetrical polyarthritis involving large and small joints. She had a positive rheumatoid factor titre of 1:320 and a weakly positive antinuclear antibody. Complement levels were repeatedly normal, and circulating immune complexes were not detected.
at this time. The pattern of erosive change that developed was somewhat atypical for rheumatoid arthritis, with predominant involvement of carpus and sparing of the metacarpophalangeal (MCP) joints, a pattern more typical of Still's disease. Initial management for the arthritis was a major problem, as she readily developed gastrointestinal bleeding on any nonsteroidal agent, a factor now compounded by her anticoagulant therapy. She is now on penicillamine 375 mg a day and low-dose prednisone 5 mg per day. Her haemoglobin is 13.4 g/dl with a mean corpuscular volume (MCV) of 85 μm² and a mean corpuscular haemoglobin of 30 μg. The rheumatoid latex test is positive at a titre of 1:40 and no other antibodies have been found.

CASE 3
Mrs C is now 57 years old. She complains of being unwell since early childhood, with explosive diarrhoea up to 4 or 5 times per day and recurrent chest infections. She subsequently developed bronchiectasis, and one of her sisters (one of a twin pair) died of bronchiectasis at the age of 16 years.

At the age of 24 she developed joint pain, and then joint swelling. Although initially she complained of a flitting arthritis, she subsequently developed erosive changes. Rheumatoid factor was positive, but no other autoantibodies were detected. She was diagnosed as having rheumatoid arthritis and managed with aspirin and low-dose corticosteroids. She was not treated at any time with second-line therapy.

In 1976 a small-bowel biopsy showed subtotal villous atrophy, consistent with the diagnosis of coeliac disease, and she was subsequently treated with a gluten-free diet. Since that time she has improved considerably. Her gastrointestinal complaints have responded well to the diet. Her arthritis also responded dramatically to the diet, and at present she is not receiving any therapy apart from the occasional analgesic. Her ESR is normal, and she is symptom-free.

Lip biopsies were performed on each of these patients and confirmed the diagnosis of Sjögren’s syndrome in case 1 only. All 3 patients were tissue typed and all found to be of the haplotype A1, B8, DRW3. This is found in approximately 80% of coeliac patients.⁷

Discussion

Recent evidence has implicated the gastrointestinal tract as a source of antigenic exposure in various conditions, including certain rheumatic disorders.⁸⁻¹² The normal adult human gastrointestinal tract is permeable to macromolecules, and in some instances these macromolecules have been shown to be antigenic.¹³ We have recently measured gut permeability in patients with rheumatoid arthritis, Sjögren’s syndrome, untreated coeliac disease, and the 3 patients described above, using polyethylene glycol polymers with high-performance liquid chromatographic analysis being performed on a 6-hour urine excretion profile. With this method we have found gut permeability to be normal in the patients except the untreated coeliac patients.¹⁴

Brinch et al.¹⁵ have suggested that the activation of complement by immune complexes may be important in the pathogenesis of adult coeliac disease. Scott and Losowsky¹⁶ suggested that circulating immune complexes found in patients with coeliac disease may be responsible for lesions not only in the small bowel but at distant sites, a possible explanation for the association with dermatitis herpetiformis. Several cases have been described where the skin lesions of dermatitis herpetiformis¹⁷,¹⁸ and cutaneous vasculitis¹⁹ have been improved by a gluten-free diet. Mohammed et al.²⁰ using 4 different methods to measure circulating immune complexes, have found them to be present in 100% of patients with coeliac disease and patients with dermatitis herpetiformis. However they did not find the circulating complexes to be associated with clinical complaints. All 3 of our patients had circulating immune complexes on more than one occasion, detected by Clq binding and rheumatoid factor binding assays. The presence of circulating immune complexes was not associated with rheumatoid disease activity, a finding confirmed by Green and Carty.²¹

The evidence for a direct relationship between dietary antigens and the development of autoimmune disorders, especially in human studies, remains controversial to say the least.

We have reported a female patient with rheumatoid arthritis who gave positive responses to RAST tests to milk and cheese antigens after challenge with these proteins. This condition was accompanied by clinical deterioration in her rheumatoid arthritis and a change in the clearance of heat-damaged red cells, suggesting impairment of reticuloendothelial function.²² In animal studies erosive changes have been produced in old English rabbits by feeding them cows’ milk,²³ and Mansson et al. produced polyarthritis and nodules in pigs fed fish meal diets.²⁴ They subsequently showed that the arthritis was related to a change in gut flora, considered to be secondary to dietary changes.

It is known that changes in the gut flora in humans may be associated with the development of reactive arthritis as shown by postdysenteric Reiter’s syndrome, and it has also been reported that there is an increased faecal carriage rate of certain Klebsiella
species that correlates with disease activity in patients with ankylosing spondylitis.  

Patients with coeliac disease develop antibodies to many dietary constituents, but the relevance of these antibodies and of circulating immune complexes to the pathogenesis of lesions in and outside the gastrointestinal tract is unknown. Only occasional reports of coeliac disease and rheumatoid arthritis occurring in the same patient have appeared.  

Our 3 patients all from the same unit would suggest that perhaps this association is more frequent than previously reported.

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