Case Report

Rheumatoid Arthritis and Hereditary Angioedema

IAIN J.S. DUNCAN, KATHLEEN E. TYMMS, and GAVIN CARNEY

Abstract. **We describe a case in which rheumatoid arthritis (RA) developed in a patient with hereditary angioedema. Hereditary angioedema, one of the inherited complement deficiencies, has been reported in association with a number of autoimmune disorders, but there has been only 1 report of an association between RA and hereditary angioedema. (*J Rheumatol 1988;*15:700–702)**

Key Indexing Terms:
HEREDITARY ANGIOEDEMA RHEUMATOID ARTHRITIS
C1 ESTERASE INHIBITOR DEFICIENCY

Heredity is an uncommon cause of angioedema and is characterized by recurrent episodes of angioedema involving face, extremities, upper airways and gastrointestinal tract. It results from C1 esterase inhibitor (C1 INH) deficiency. Complement deficiencies have been associated with a number of autoimmune diseases, particularly systemic lupus erythematosus (SLE), and 12% of patients with C1 INH deficiency were found to have some form of autoimmune disease[1]. There is only 1 previous case of hereditary angioedema with rheumatoid arthritis (RA)[1], and in that case only the American Rheumatism Association (ARA) criteria for probable RA were fulfilled. We report a case of hereditary angioedema due to C1 INH deficiency in which definite RA (ARA criteria) developed.

CASE REPORT

A 60-year-old man presented in July, 1983 with acute upper airway obstruction due to angioedema. This settled with intravenous hydrocortisone and subcutaneous adrenaline. He had had an almost identical episode 12 years previously. There was a lifelong history of intermittent episodes of acute colicky abdominal pains lasting 24–36 h for which no cause had been found, and acute soft tissue swelling of both hands without apparent precipitant. There was no history of similar episodes in his family (and subsequently his 3 children were found to have normal C1 INH levels).

Investigations revealed a markedly reduced C1 esterase inhibitor 0.02 (normal 0.15–0.35 g/l), reduced C4 0.04 (normal 0.15–0.40 g/l), and normal C3 1.10 (normal 0.8–1.2 g/l). Tests for fluorescent antinuclear antibodies (FANA) and rheumatoid factor (RF) (latex and Rose-Waalar) were negative. The diagnosis of hereditary angioedema due to C1 esterase inhibitor (C1 INH) deficiency was made. He started prophylactic treatment with danocrine (danazol) 200 mg BD and had no further episodes of peripheral or upper airway angioedema, and no further attacks of abdominal pain. C1 INH and C4 levels returned to normal. Subsequent assays of C1q 0.22 (normal 0.15–0.23 g/dl), Clr 90% (normal 80–120%), and Cls 100% (normal 75–125%) excluded the acquired form of C1 INH deficiency. HLA-DR typing showed HLA-DR1 and DRw9.

Twelve months later he presented with polyarticular pain and swelling. There was mild synovitis in the proximal interphalangeal (PIP), metacarpophalangeal (MCP), wrist, and metatarsophalangeal (MTP) joints. Full blood count, biochemistry, serum electrophoresis and immunoglobulins were all normal. RF and VDRL were negative. FANA titer of 1:40 (speckled pattern) with DNA antibody binding of 4% and negative antibodies to SSA, SSB, RNP, or Sm antigens. Radiographs of hands and feet were normal. He was treated with indomethacin and danocrine therapy was ceased. However abdominal symptoms returned and complement levels fell without remission of arthritis. Danocrine was subsequently reintroduced with no effect on arthritis. One year later (June, 1985) hydroxychloroquine 200 mg daily was added because of persisting polyarthritis. This was stopped on Day 4 after the development of a severe desquamating rash.

In late 1986 his inflammatory polyarthritis became more severe, widespread, and debilitating. Raynaud's phenomenon was now also present, but no other connective tissue disease symptoms. Examination showed ulnar deviation of MCP joints and moderate synovitis of PIP, MCP, and wrist joints. There was a finger flexor tenosynovitis with poor grip strength, bilateral olecranon bursitis, a nodule on the extensor surface of his left elbow, bilateral irritable shoulders, and synovitis in his MTP joints, right ankle, and knees. Investigations revealed a mild normochromic, normocytic anemia (Hb 12.6 g/dl), ESR 37 mm/h, FANA negative, and RF titer 1:16 (Rose-Waalar). There were no crystals seen on examination of synovial fluid. Radiographs showed bilateral erosive changes in the hands (Figure 1) and several metatarsal heads of feet. D-penicillamine 250 mg daily was added to therapy with indomethacin and danocrine, and 4 months later his polyarthritis had markedly improved.

DISCUSSION

Angioedema is a nonpitting, nonpruritic subcutaneous or mucosal swelling resulting from increased vascular permeability. Heredity angioedema is an uncommon cause of angioedema and is characterized by recurrent episodes of angioedema involving face, extremities, upper airways and gastrointestinal tract. Hereditary angioedema results from C1 INH deficiency, and is inherited as an autosomal dominant with incomplete penetrance[2], and there is good evidence that it is not associated with HLA genes[1,3], although in one family this was not so[4]. Diagnosis is based on finding a low

From Woden Valley Hospital and Royal Canberra Hospital, Canberra, Australia.

I.J.S. Duncan, MB, BS, Rheumatology Registrar; K.E. Tymms, MB, BS, FRACP, Rheumatologist, Woden Valley Hospital; G. Carney, MB, BS, FRACP, Renal Physician, Royal Canberra Hospital.

Address requests for reprints to Dr. I. Duncan, P.O. Box 79, Garran, A.C.T. 2605, Australia.

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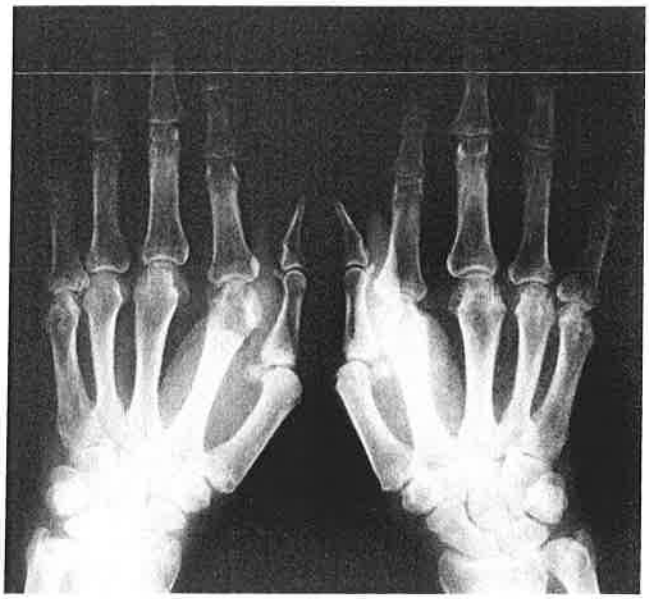

Fig. 1. Radiograph of the hands showing erosive changes, most prominent in both ulnar styloids, right 2nd and left 3rd PIP joints, and bilateral 5th MCP joints.

titer of C1 INH. There is an acquired form of C1 INH deficiency which is very rare, and this can be differentiated by C1 assays. C1q, C1r, C1s are normal or slightly low in hereditary angioedema (as in our patient), but are markedly reduced in acquired C1 INH deficiency (the latter is thought to be due to consumption of complement components). Danocrine (danazol) has been used highly successfully in the therapy of hereditary angioedema[5-11] with subsequent return to normal of C1 INH[7,9,12-14] and C4 levels[11].

Complement deficiencies have been associated with a number of autoimmune diseases particularly systemic lupus erythematosus (SLE). Brickman, *et al*[1] in a series of 157 patients with C1 INH deficiency, found autoimmune disease in 12%. In their series, glomerulonephritis, Sjögren's syndrome, inflammatory bowel disease, thyroiditis, and SLE each occurred in 2 or more cases.

The association of C1 INH deficiency and autoimmune disorders may be mediated through abnormal activation of classical complement pathway or through other mediator pathways (fibrinolytic, bradykinin, and clotting systems).

SLE-like syndrome occurs in about 2% of patients with hereditary angioedema[15,16] compared with 0.1–0.01% normals. This is similar to the lupus-like disease associated with other complement abnormalities. The SLE associated with complement abnormalities has several notable differences from classical SLE. There is more skin involvement (particularly erythema multiforme), less renal involvement, weak or absent double stranded DNA antibodies, and absent immunoglobulin or complement on skin biopsy. Antibodies to single stranded DNA are usually present.

Only 1 case of adult onset RA and 1 case of juvenile RA have been reported in association with C1 INH deficiency[1].

The adult case reported fulfilled the ARA criteria for probable RA with nonerosive, seropositive disease and secondary Sjögren's syndrome. In Brickmann's series[1] patients with hereditary angioedema tended to develop the autoimmune disorder associated with their HLA haplotype. This trend suggests that in RA occurring with hereditary angioedema, HLA-DR4 would be the expected haplotype. However, our case does not support this trend (HLA-DR1 and DRw9 in our patient).

In our case there was no substantial evidence that the polyarthritis was part of a lupus-like syndrome. There were no typical skin manifestations of SLE. The only rash was after hydroxychloroquine administration and occurred in absence of significant sun exposure (winter). Raynaud's phenomenon was the only other connective tissue disease feature. FANA, DNA binding and ENA were repeatedly negative. Danocrine therapy was also considered as a possible cause of the arthritis, but there was no change in the illness after stopping and later restarting danocrine therapy. The clinical history is consistent with RA and the subsequent development of nodules and typical erosions on radiography confirms the diagnosis. The weak positive RF supports this diagnosis.

Thus, in our patient, RA was seen in association with hereditary angioedema, and although there is only one previous case reported, it seems possible that the association is real.

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