LETTERS TO
THE EDITOR

Recurrent infections, pericarditis and renal disease in a patient with total C2 deficiency and decreased NK cell function consistent with acute rheumatic fever and systemic lupus erythematosus

Patients with C2 deficiency have an increased risk of systemic infections with encapsulated bacteria and for rheumatological disorders, particularly a lupus-like illness.1 2 Renal disease is seen infrequently in the lupus-like illness and these patients often have low or absent antinuclear antibody titres but typically have SS-A antibody.1 3 We present a patient with a history of recurrent infectious diseases and C2 deficiency who had clinical and laboratory findings consistent with acute rheumatic fever with subsequent diagnosis of classic systemic lupus erythematosus (SLE). Extensive immunodeficiency evaluation revealed only total C2 deficiency and decreased natural killer (NK) cell function.

A 29 year old white woman had an immune deficiency evaluation for a history of recurrent infections, including neonatal H influenzae meningitis and recurrent otitis media, pneumatic sepsis and meningitis. At presentation, she reported fatigue and mild morning stiffness in her hands and feet. There was no evidence of arthritis or rash. Serum IgG, IgA, IgM and IgG subclasses were unremarkable. Serum complement levels were C4 - 23 mg/dL (normal 20-50 mg/dL); alternative pathway total haemolytic complement - 38 units/mL (normal 8-51 units/mL); classic pathway total haemolytic complement (CH50) - 0 units/mL and C2 functional level - 0 units/mL. DNA analysis of the patient’s peripheral blood cells using polymerase chain reaction established type I (typical) C2 deficiency.4 5 Antinuclear antibody was detectable in a speckled pattern (greater than 1:2,560 dilution) and SS-A antibody was present.

Four months after initial evaluation she developed an acute illness characterised by fever and sore throat with a positive culture for group A beta haemolytic streptococcus. After several days of penicillin therapy, she developed pleuritic chest pain, dyspnoea and was admitted to hospital with carditis. Erythrocyte sedimentation rate (137 mm/hr) and ASO titre (>200 IU) were elevated. She fulfilled the Jones’ criteria for acute rheumatic fever. She also had lymphopenia (830 lymphocytes/mm3) and I+ proteinuria. No urinary casts were identified and a 24 urine collection had 0-6 gm protein (normal <0-15 gm/24 hours) and a normal creatinine clearance (105 mL/min). Double stranded DNA antibody was not elevated. She responded well to oral prednisone and intravenous antibiotics.

Nine weeks after admission to hospital, she had an extensive immunodeficiency investigation which showed: normal NK cell numbers with decreased NK cell function [NK cell activity was 0-04 lytic units/106 PBL with mean (SD) NK cell activity = 13-57 (0-38)]; high spontaneous lymphocyte proliferation but normal responses to recall antigens and mitogens; normal lymphocyte secretion of interleukin 2 (IL-2); and normal lymphocyte subset distribution by flow cytometry. Four weeks later she was admitted to hospital with fever, sore throat and productive cough unresponsive to oral erythromycin. Throat culture was negative and ASO titre was normal. The presence of hand, foot and knee arthralgias, lymphopenia, proteinuria, serositis and elevated antinuclear antibody were consistent with the diagnosis of SLE. The patient responded well to prednisone, but at follow up one week later had 2+ proteinuria, I+ haematuria, 3-4 red blood cells per 400× field and 3 red blood cell casts. Renal biopsy demonstrated mild mesangial proliferative glomerulonephritis (fsg) consistent with either mesangial proliferative lupus nephritis (WHO Class II) or resolving post-infectious glomerulonephritis, a lesion that has been described in patients with acute rheumatic fever.

Thus this is the third reported case of acute rheumatic fever-like illness associated with C2 deficiency.1 2 6 7 Subsequently, she developed symptoms consistent with typical classic SLE with abnormal renal findings distinct from the lupus-like illness that is seen typically in patients with C2 deficiency. Like previously reported patients with C2 deficiency, she had an elevated anti-SS-A antibody1 2 and antinuclear antibody. Her course demonstrates the potential for patients with C2 deficiency to develop: 1) recurrent infectious diseases; 2) an acute rheumatic fever-like illness; and 3) classic features of SLE with significant major organ involvement. Our patient is unlike the ‘usual’ C2 deficient patients described by Agnello as having: “(1) increased incidents of discoid lesions; (2) low incidence of renal disease; (3) low or absent titers of antinuclear antibodies and antibodies to native DNA, and (4) infrequent findings of immunoglobulin and complement in the skin lesions . . . ”

Only one of the patients in Figueroa and Jensen, and Ross and Jensen reviews1 2 had C2 deficiency associated with recurrent infectious diseases, acute rheumatic fever-like illness and classic features of SLE with significant major organ involvement.7 Neither she nor the other patients with SLE or acute rheumatic fever and C2 deficiency had been examined extensively for other immunodeficiencies.6 9 It is possible that these patients might have had other immune defects responsible for the development of SLE, recurrent infections or acute rheumatic fever. The only abnormal finding in our patient was a decrease in NK function, a finding that remains unexplained. This suggests that patients with C2 deficiency should also be tested for NK cell function, as well as for other immune functions, to see if an additional immune defect is associated with C2 deficiency. Such a defect could explain why some patients with C2 deficiency are normal and other patients develop serious, life threatening infections or connective tissue diseases.

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(Left) Renal biopsy showing diffuse mild mesangial hypercellularity (haematoxylin and eosin × 550). (Right) electron microscopy showing numerous mesangial immune complex deposits and diffuse loss of podocyte foot processes (arrows) (× 7800).
Eosinophilic fasciitis in a father and son

Eosinophilic fasciitis is a rare syndrome consisting of: (1) localised skin involvement; (2) pronounced thickening of the subcutaneous fascia; (3) absence of visceral changes and Raynaud's phenomenon; (4) peripheral blood eosinophilia, hypergammaglobulinaemia raised ESR and (5) beneficial response to steroids. Some authors believe it is a variant of scleroderma whilst others believe it to be a separate disease. 

We report two cases of eosinophilic fasciitis occurring in a father and son with clinical and laboratory evidence of the disease, presenting nineteen years apart.

Patient 1, a 19 year old man, presented in 1969 with a one year history of aching in the small joints of his hands and feet and tightness of the skin over his forearms and legs. Physical examination revealed board-like skin over the limbs, hands and trunk. His ESR was raised in the first hour and his white cell count was 25 x 10^9/dl with 80% eosinophils. The SGOT was normal and an extensive search for occult parasites was negative. He had normal chest radiograph and barium swallow.

A full thickness skin biopsy was performed and this was reported to show changes of dermatomyositis. Review of the biopsy was diagnostic of eosinophilic fasciitis. It showed broad bands of collagen extending as deep as the fascia and deep into the subcutaneous fat with numerous areas of inflammation. The infiltrates consisted of plasma cells, lymphocytes and eosinophils. Similar extensive infiltrates were found throughout the fascia.

A diagnosis of 'dermatomyositis with scleroderma' was made and the patient was started on prednisolone 45 mg daily. The skin thickening rapidly improved and the peripheral eosinophilia resolved. His prednisolone was withdrawn after three years and when seen recently his skin was normal.

Patient 1 had two sons, one of whom has colic disease (tissue type: HLA A3, A32, B8, B35, BW6, CW4, CW7). The other presented in July 1988 at the age of 14 years with a six month history of stiffness of his fingers and tightness of the skin over his arms and legs. There was no history of Raynaud's phenomenon and no problems with his swallowing, chest or digestion.

On examination he had woody, tethered oedematous skin over his arms and legs. He had flexion contractures of the MCP joints bilaterally and his elbows and wrists were immobile.

Laboratory tests showed an Hb 13 g/dl, wcc 8.7 x 10^9/dl with 16% eosinophils, ESR 16 mm%s per hour. His electrolytes, C3, C4 levels were normal. His IgG was 20.5 g/l, IgA and IgM normal. ANA and anti-Scl 70 were negative, chest and hand radiographs were normal.

A full thickness skin biopsy revealed a normal epidermis; almost all the glandular elements were tightly bound with collagen. There was loss of fat, infiltration by lymphocytes and plasma cells. The fascia was infiltrated with numerous lymphocytes and occasional plasma cells. The cells extended between the muscle fibres—all the changes suggested eosinophilic fasciitis.

He was started on prednisolone 30 mg daily and clinically he improved together with the disappearance of his eosinophilia and hypergammaglobulinaemia. He is presently on prednisolone 4 mg alternate days but his skin has not yet completely returned to normal.

HLA typing was performed on the father and son, which showed the son inherited A3, B52, CW null haplotype from his father.

The two patients described appear to be the first cases of eosinophilic fasciitis involving a father and son. Both had the characteristic features and responded to corticosteroids. The father initially cluded diagnosis as the disease had not yet been described by Shulman.2

The only other familial cases of eosinophilic fasciitis is the report of siblings with identical HLA genes.3 Our patients, however, had completely different haplotypes from those described.

We feel eosinophilic-fasciitis probably has a multifactorial aetiology with a combination of genetic and environmental factors playing a role.

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Massive eosinophilic synovitis and reactive arthritis associated with filarial infection

Eosinophils are infrequently recovered from either the synovial fluid or the synovial membrane.1 We report a case of reactive arthritis and massive synovial fluid eosinophilia associated with filarial infection.

A 26 year old African-American woman was admitted to hospital with acute left ankle arthritis. She had resided in the United States for four years. Eight months before she was seen, however, she had returned to Nigeria for four weeks. Three months before admission she experienced right wrist swelling that resolved spontaneously within three days. Similarly, transient right ankle swelling occurred one month before presentation.

On admission, the patient denied any history of constitutional, gastrointestinal or other nonarticular symptoms. Physical examination was normal except for left ankle swelling. Complete blood count revealed 9200 WBC/mm³ with a differential of 20% neutrophils, 30% lymphocytes, and 47% eosinophils. The erythrocyte sedimentation rate (ESR) was 72 mm/h. Serological studies, including ANA, RF, VDRL, hepatitis B surface antigen, and serum concentrations of complement proteins C3 and C4 were negative or normal.

Analysis of synovial fluid aspirated from the left ankle revealed 56 000 WBC/mm³, with a differential of 8% neutrophils, 4% lymphocytes, 15% monocytes and 73% eosinophils (absolute eosinophil count 40 880/mm³). A radiograph of the left ankle was normal. Cultures of synovial fluid, blood, urine, pharynx, rectum and cervix were negative. Stool specimens showed Entamoeba histolytica, Trichuris trichiura, and the non-pathogenic pathogen Trichomonas vaginalis. Histological and pathological analysis of a synovial biopsy specimen revealed granulomatous tissue with numerous eosinophils within the synovial tissue. Parasitic organisms could neither be seen nor cultured.

The patient was treated with doxycycline, azithromycin, mebendazole and ivermectin. Despite the completion of appropriate courses of antibiotics and the elimination of pathogens from stool cultures, left ankle swelling persisted. Subsequently, a panel of parasitic serologies was obtained, and revealed very high serum titres of antifilarial antibodies (1>1:2048), with insignificant titres to other invasive parasitic agents including Entamoeba histolytica. Four months after her initial presentation her ankle arthritis persisted. Treatment was initiated in hospital with diethylcarbamazine. On her last clinic visit before being lost to follow-up, the patient no longer had joint swelling.

Reactive arthritis (ReA) has been associated with a variety of infectious agents. In the West, the most common organisms are Chlamydia trachomatis or facultative bacteria such as Chlamydia trachomatis.2 ReA associated with parasitic infection has been reported, but is rare. Filarisis is the most commonly implicated aetiological agent.2 Infections with filarial parasites are believed to be associated with ReA in up to 10% of patients with filariasis.4

Approximately two thirds of the patients develop a monarticular arthritis affecting the
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