Case report

Neonatal Behçet's syndrome in an infant of a mother with the disease

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SUMMARY Behçet's disease is reported in a newborn infant of a mother with the disease. The mother had recurrent orogenital ulcers, pustulonecrotic skin lesions, arthritis, thrombophlebitis, and colonic ulcers. Shortly after birth the infant presented with transient orogenital ulcerations and pustular cutaneous lesions. On healing, depressed scars developed which were very similar to those of the mother. The finding of circulating immune complexes in the mother's serum gives some support to the hypothesis that the infant's transient illness was caused by transplacental passage of maternal antibodies.

Behçet's disease is a multisystem disorder characterised by aphthous stomatitis, genital ulcers, uveitis, cutaneous vasculitis, and arthritis.^{1–3} Additional findings may include vascular, neurological, gastrointestinal, pulmonary, and renal manifestations.^{1–3} Its aetiology is unknown, although genetic, viral, and immunological mechanisms have been implicated.^{2,3} Epidemiological studies suggest important geographical differences, and a familial occurrence has been reported.^{1,2,4–11}

This report describes Behçet's disease in a mother and her newborn infant. The infant presented shortly after birth with extensive orogenital ulcerations and pustular cutaneous lesions. The acute lesions resolved spontaneously in 6 weeks, leaving depressed scars over face, tongue, and palate. Cryoglobulins and circulating immune complexes were demonstrated in the mother's serum at the time of study. Possible pathogenetic implications are discussed.

Case history

A 37-year-old woman with Behçet's disease had aphthous stomatitis and recurrent oropharyngeal

ulcers since 1960. She had had recurrent vaginal and vulvar ulcerations since 1969. Beginning in 1971, recurring acneiform pustules and papulonecrotic lesions developed; some were ulcerated and a few were triggered by trauma. Other manifestations included an episode of depression in 1973; attacks of inflammatory arthritis of elbows, knees, and/or ankles since 1974; superficial thrombophlebitis in 1975 and 1978; and 2 diarrhoeal episodes in 1978 and 1979, one of which was associated with rectal bleeding and colonic ulcers demonstrated by colonoscopy. At the time of the study in December 1979 her symptoms included ulcerations of the oropharynx, gums, lips, and genitalia, associated with arthralgia, fever, and ulcerated lesions over back and one finger. Several puckered scars from previous skin lesions were present over the shoulders, back, and thighs (Fig. 1A).

Results of laboratory evaluation included a haemoglobin (Hb) of 12.5 g/dl, white blood cell count (WBC) of $8.6 \times 10^9/l$ with a normal differential, and ESR (Westergren) of 35 mm/hour. The absolute lymphocyte count was $2.479 \times 10^9/l$ with a normal percentage of T cells (E rosette) and B cells (EAC rosette). Leucocyte function tests revealed normal bactericidal and candidacidal activities, and nitroblue tetrazolium (NBT) test. Leucocyte mobility and chemotactic responses, as measured by the skin window technique, were normal. The platelet count

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Fig. 1A Acute pustulonecrotic lesions and an old depressed scar (arrow) on mother's back. B: Puckered scar on son's cheek.

was $310 \times 10^9/l$, and the platelet survival time was within normal limits. Platelet satellitism¹² (rosettes of platelets around granulocytes) was repeatedly demonstrated during exacerbations. A bone marrow examination was normal. Urine analysis, electrolytes, calcium, phosphorus, alkaline phosphatase, blood urea nitrogen, creatinine, SGOT, and lactic dehydrogenase were normal. Protein electrophoresis pattern was normal with a total of 7 g/dl (70 g/l) and albumin 4 g/dl (40 g/l). Quantitative immunoglobulins showed IgG 1250 mg/dl (normal 800–1800 mg/dl), IgA 330 mg/dl (normal 90–450 mg/dl), and

IgM 250 mg/dl (normal 60–280 mg/dl) (SI conversion: g/l = mg/dl $\times$ 0.01). Rheumatoid factor, antinuclear antibody, anti-DNA antibody, Coombs's test, VDRL, and HBsAg were negative. At the time of study total haemolytic complement (CH50) and the third and fourth components of complement were within normal limits. Trace amounts of cryoglobulins were detected after 4 days at 4°C. The thrice-washed cryoprecipitate was quantitated spectrophotometrically by measuring ultraviolet absorption at 280 nm of acetic-acid-dissolved aliquot of the cryoprecipitate.¹³ It measured

57 µg/ml. Double immunodiffusion analysis in agar with monospecific antisera against IgG, IgM, IgA, C1q, C3, C4, and human serum albumin revealed a mixed polyclonal IgM-IgG cryoglobulin.

Rheumatoid factor activity was demonstrated in the cryoglobulin by the latex fixation test (Hyland). Cryoglobulins were transient on repeat testing. Circulating immune complexes were also detected with a liquid-phase radiolabelled C1q binding assay.¹⁴ Quantitation was performed with a standard binding curve constructed with varying concentrations of heat-aggregated human gamma globulin (HAGG). The concentration of immune complex was 0.15 mg/ml equivalent HAGG (normal: less than 0.1 mg/ml equivalent HAGG). (SI conversion: g/l = mg/ml × 1.)

Delayed hypersensitivity skin test battery gave positive responses to candida, streptokinase-streptodornase, histoplasmin, and mumps antigens. Negative responses were obtained to trichophyton, purified protein derivative and control saline. Biopsy of a skin lesion showed oedema, dense perivascular lymphocytic and neutrophilic infiltration associated with necrosis, and ulceration of epidermis. Assorted therapies including corticosteroids, ACTH, azathioprine, methotrexate, levamisole, and colchicine have not altered the course of the disease.

She has 2 children, a normal daughter born in 1962, and the affected son born in 1968 after an uneventful pregnancy. During both pregnancies the mother experienced recurrent oropharyngeal ulcerations as the sole disease manifestation. Shortly after birth the newborn infant son developed fever, severe stomatitis with oropharyngeal ulcers, and several crusted, ulcerated pustular lesions over the face, scalp, penis, and buttocks. Laboratory tests showed Hb 14.0 g/dl, WBC $32 \times 10^9/l$ with 56% neutrophils, 15% lymphocytes, and 26% monocytes. The platelet count, urine analysis, and serum protein electrophoresis were normal. Cultures of blood, stools, and oral and skin lesions were sterile. Neonatal herpes simplex infection was suspected but was not confirmed. The mucocutaneous lesions resolved within 6 weeks leaving depressed scars over tongue, palate, and cheeks. The child has remained healthy since, and the mucocutaneous lesions did not recur. He was 11 years old at the time of study in December 1979. Several puckered scars were still present over his cheeks (Fig. 1B), tongue, and palate. There were no active lesions and he appeared otherwise normal. Results of laboratory studies were unremarkable. On HLA antigen testing the mother's haplotypes were AW30, BW40, and A1, BW17. The 2 offspring were HLA-identical for A and B loci with haplotypes AW30, BW40, and A9, B7.

Discussion

The clinical features of the mother were characteristic of Behçet's disease in that she had 3 of 4 major criteria, and 3 minor criteria for the diagnosis of the disease.^{1 3 15} The infant had stomatitis, genital ulcers, and skin lesions, thus fulfilling 3 of the 4 major criteria. Although the relationship of the infant's illness to the mother's disease was not fully appreciated at the time of birth, there is indirect evidence that it was due to congenitally acquired Behçet's disease. The orogenital ulcers and pustular skin lesions were quite characteristic, and other infections, such as neonatal herpes simplex or impetigo, neither of which cause scarring, were excluded. Another diagnostic clue was provided by the striking similarity between the mother's and the son's scars as observed at the time of study 11 years later (Fig. 1A and B).

The possibility that genetic factors are involved in the pathogenesis of Behçet's disease is supported by a number of observations. A familial occurrence has been well documented.^{1 2 4-11} An autosomal dominant inheritance with variable expressivity has been suggested.¹¹ A raised frequency of HLA B5 antigen has been noted in some studies but not in others.^{16 17} In the present study, although the 2 offspring were HLA-identical for A and B loci, only the son developed the disease. Furthermore, the transient nature of the illness makes a direct genetic transmission unlikely. It is more probable that the infant's disease was due to a transplacentally acquired maternal factor. However, no specific infectious agent was identified in the mother or infant.

Alternatively, the transient Behçet's manifestations in the newborn infant could have been due to transplacental passage of maternal antibodies. Several lines of evidence indicate that alterations in humoral immunity are important in the pathogenesis of the disease.³ Antihuman oral mucous membrane antibodies,¹⁸ demyelinating antibodies,¹⁹ cryoglobulins,²⁰ and circulating immune complexes²¹ have been demonstrated in sera from some patients with Behçet's disease. In the present study, however, autoantibodies or immune complexes were not sought in the mother or the infant at the time of delivery; hence placental transfer of antibodies was not verified. Nonetheless the mother's serum contained immune complexes and traces of cryoglobulins at the time of the study 11 years later. The fact that the infant has remained healthy with no further mucocutaneous lesions since the age of 6 weeks further supports the hypothesis that the transient Behçet's manifestations were caused by antibodies transferred from the mother. A similar mechanism is known to operate in neonatal systemic

lupus erythematosus,²² idiopathic thrombocytopenic purpura,²³ and myasthenia gravis.²⁴ Few if any of these infants developed true disease.

The effects of pregnancy on the course of Behçet's disease are largely unknown.²⁵ Remissions,² exacerbations,¹¹ or no change, as with our patient, have all been described.

In conclusion, infants born to mothers with Behçet's disease may develop transient mucocutaneous lesions in the newborn period, presumably mediated by transplacental factors. It is hoped that this report will stimulate closer observation of these infants and a chance to verify transplacental passage of maternal antibodies.

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References

- Mason R M, Barnes C G. Behçet's syndrome with arthritis. *Ann Rheum Dis* 1969; **28**: 95-103.
- Chajek T, Fainaru M. Behçet's disease. Report of 41 cases and a review of the literature. *Medicine* 1975; **54**: 179-96.
- Shimizu T, Ehrlich G E, Inaba G, Hayashi K. Behçet's disease (Behçet syndrome). *Semin Arthritis Rheum* 1979; **8**: 223-60.
- Sezer N. Further investigations on the virus of Behçet's disease. *Am J Ophthalmol* 1956; **41**: 41-55.
- Fenech F F, Soler N G. Behçet's syndrome with neurological manifestations in two sisters. *Br Med J* 1968; **ii**: 473.
- Berlin C. Behçet's disease as multiple symptom complex: report of 10 cases. *Arch Derm Syph* 1960; **82**: 73-9.
- Fadli M E, Youssef M. Neuro-Behçet's syndrome in the United Arab Republic. *Europ Neurol* 1973; **9**: 76-89.
- Goolamali S K, Comaish J S, Hassanyeh F, Stephens A. Familial Behçet's syndrome. *Br J Dermatol* 1976; **95**: 637-42.
- Abdel-Aziz A M, Fairburn E A. Familial Behçet's syndrome. *Cutis* 1978; **21**: 649-52.
- Madkour M, Kudwah A. Behçet's disease. *Br Med J* 1978; **ii**: 1786.
- Berman L, Trappler B, Jenkins T. Behçet's syndrome: a family study and the elucidation of a genetic role. *Ann Rheum Dis* 1979; **38**: 118-21.
- Prchal J T, Blakely J. Granulocyte platelet rosettes. *N Engl J Med* 1973; **289**: 1146.
- Brouet J C, Clauvel J P, Danon F, Klein M, Seligmann M. Biologic and clinical significance of cryoglobulins, a report of 86 cases. *Am J Med* 1974; **57**: 775-88.
- Nydegger U E, Lambert P H, Gerber H, Miescher P A. Circulating immune complexes in the serum in systemic lupus erythematosus and in carriers of hepatitis B antigen, quantitation by binding to radiolabeled C1q. *J Clin Invest* 1974; **54**: 297-309.
- O'Duffy J D. Behçet's syndrome. *Bull Rheum Dis* 1978-1979 series; **29**: 72-9.
- Ohno S, Nakayama E, Suguiwa S, Itakura K, Aoki K, Aizawa M. Specific histocompatibility antigens associated with Behçet's disease. *Am J Ophthalmol* 1975; **80**: 636-41.
- Ersay F, Berkel A I, Firat T, Kazokoglu H. HLA antigens associated with Behçet's disease. In: *HLA and Disease*. Paris: Inserm, 1976; **58**: 100 (abstract).
- Oshima Y, Shimizu T, Yokohari R, et al. Clinical studies on Behçet's syndrome. *Ann Rheum Dis* 1963; **22**: 36-45.
- Inaba G, Aoyama J, Shimizu T. Clinical and immunological studies on neuro-Behçet's syndrome. *Clin Neurol* 1975; **15**: 1040-5.
- Scarlett J A, Kistner M L, Yang L C. Behçet's syndrome, report of a case with pericardial effusion and cryoglobulinemia treated with Indomethacin. *Am J Med* 1979; **66**: 146-8.
- Gamble C N, Wiesner K B, Shapiro R F, Boyer W. The immune complex pathogenesis of glomerulonephritis and pulmonary vasculitis in Behçet's disease. *Am J Med* 1979; **66**: 1031-9.
- Jackson R. Discoid lupus in a newborn infant of a mother with lupus erythematosus. *Pediatrics* 1964; **33**: 425-30.
- Pearson H A. In: Vaughn V C III, McKay R J, Behrman R E, eds. *Nelson's Textbook of Pediatrics*. 11th ed. Philadelphia: W. B. Saunders, 1979: 1418.
- Keesey J, Linstrom J, Cokely H. Anti-acetylcholine receptor antibody in neonatal myasthenia gravis. *N Engl J Med* 1977; **296**: 55.
- Hurt W G, Cooke C L, Jordan W P, Bullock J P, Rodriguez G E. Behçet's syndrome associated with pregnancy. *Obstet Gynecol* 1979; **53**: (3 suppl): 31s-33s.