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Neonatal Lupus Erythematosus: New Serologic Findings

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A child with neonatal lupus was evaluated and found to possess serum anti Ro(SSA) antibodies. The cutaneous lesions and anti Ro(SSA) antibodies disappeared during the next 5 mo.

The infant's mother was asymptomatic but possessed anti Ro(SSA) and anti La(SSB) antibodies.

Neonatal lupus erythematosus is a rare, transient, inflammatory syndrome characterized by annular skin lesions clinically and histopathologically typical of lupus erythematosus [1–10]. Systemic manifestations including cardiac conduction defects and organomegly also have been reported in some cases [11–17].

Despite the clinical features of lupus erythematosus, these infants often fail to demonstrate the serological abnormalities classically associated with systemic lupus erythematosus. For example, in a recent report summarizing the laboratory data of 23 neonatal lupus patients, only 9 infants demonstrated a positive antinuclear antibody (ANA) test or a lupus erythematosus (LE) cell preparation [1].

Thus, these infants resemble a group of adult patients with clinical manifestations of systemic lupus erythematosus, including prominent cutaneous features, who frequently fail to demonstrate a positive ANA especially when mouse liver is employed as a substrate. These patients, however, possess anti Ro(SSA) and La(SSB) antibodies [18–22].

We report here an ANA negative infant with typical neonatal lupus who possessed the Ro(SSA) antibody system. The child's ANA negative, asymptomatic mother demonstrated anti Ro(SSA) and La(SSB) antibodies.

CASE REPORT

A black female, the product of an uncomplicated full-term pregnancy, labor, and delivery, was noted to have mottled periorbital hypopigmentation at 10 days of age. Subsequently, the family also noted the appearance of widespread discrete, annular, erythematous, cutaneous lesions. Despite apparent good health and maintenance of growth at the 25th percentile level, the child continued to develop large annular erythematous skin lesions during the first 2 mo of life. 1% hydrocortisone cream was applied to the lesions without significant improvement. At 3½ mo of age, the patient was first seen by a dermatologist who noted multiple erythematous, minimally elevated, annular lesions with central hypopigmentation and a peripheral scale (Fig 1) distributed over the scalp, face, ears, trunk, and extremities. The remainder of the physical examination was unremarkable. Specifically, no organomegly was detected.

A skin biopsy was taken from a lesion on the thigh. Histological findings included mild hyperkeratosis, dilatation and plugging of hair follicles, marked epidermal atrophy, and necrosis (dyskeratosis) of individual keratinocytes (Fig 2). Basal vacuolization was prominent; in areas the vacuoles coalesced to form subepidermal clefts. The basement membrane was not thickened. The edematous papillary dermis contained large dilated blood vessels and a diffuse mononuclear infiltrate admixed with extravasated erythrocytes. A moderately dense lymphohistiocytic infiltrate surrounded the vessels and appendages of the reticular dermis. The colloidal iron stain demonstrated increased deposition of mucin between the collagen fibers in the upper and mid-reticular dermis.

Direct immunofluorescence of normal extensor forearm skin and a lesion on the left thigh were both negative for immunoglobulin (IgG, IgA, IgM) and complement (C3) deposition [23].

LABORATORY STUDIES

Abnormal laboratory studies included a white blood cell count of 11,400 per mm^3 with 8% neutrophils, 82% lymphocytes, 1% monocytes and 9% atypical lymphocytes; serum glutamic oxaloacetic transaminase (SGOT) 96 IU/L (normal 37–43 IU/L); serum glutamic pyruvic transaminase (SGPT) 64 IU/L (normal 0–54 IU/L). The following laboratory tests were either normal or negative: urinalysis, platelet count, erythrocyte sedimentation rate, blood urea nitrogen, serum creatinine, total serum protein, quantitative serum immunoglobulins, complement (C3) determination, rheumatoid factor, and syphilis serology. Hepatitis B surface antigen and antibody were not detected. A chest x-ray and electrocardiogram were normal.

A test for antinuclear antibody using mouse liver substrate was negative. Single-stranded DNA employing Farr assay utilizing I_{125} DNA was 19.2% (normal <25%). Anti-native DNA determination employing immunofluorescent techniques and Crithidea luciliae were negative [24]. Precipitin antibodies utilizing calf thymic and human spleen extracts revealed a precipitin line against human spleen extract. This precipitin line gave a line of immunologic identity in gel double diffusion with a reference serum containing antibodies against the macromolecule Ro(SSA) [25,26]. (Fig 3). No anti La(SSB), nRNP or Sm antibodies could be detected [27,28].

TREATMENT AND COURSE

The topical hydrocortisone cream therapy was continued and over a period of 6 weeks the inflammatory lesions gradually faded, leaving residual hypopigmentation and hyperpigmentation. The child has continued to do well and growth markers have increased to the 50th percentile level.

Repeat laboratory tests obtained at age 8 mo revealed the SGPT and SGOT to be within normal limits. The antinuclear antibody determination remained negative and the Ro(SSA) precipitin antibody was no longer detected in the infant's serum.

The infant's mother is 27 yr old and has been in good health. She gave a history of a prior single spontaneous abortion at 3 mo. No examination, however, was performed on the fetus. History and physical examination of the mother was completely unremarkable. Specifically she denied fever, chills, chest pains, arthralgias, arthritis, and dryness of her eyes and mouth. Laboratory investigations which were negative or normal included: complete blood count (CBC) and differential, urinalysis, rheumatoid factor, antinuclear antibody (mouse liver substrate), anti-native DNA and anti-single-stranded DNA studies. The mother did, however, demonstrate anti Ro(SSA) and La(SSB) antibodies on gel double diffusion (Fig 3). Direct immunofluorescence studies on a biopsy of the normal extensor forearm skin was negative for IgG, IgA, IgM, or C3 deposition. Repeat studies 5 mo later demonstrated persistence of anti Ro(SSA) and La(SSB) antibodies. As a control, the sera of 20 healthy pregnant women were studied for precipitins; all were negative.

DISCUSSION

Clark, Reichlin, and Tomasi in 1969 first described a precipitin antibody system Ro, which was reactive against a human spleen extract; they further characterized the antigen as a nonnucleic acid macromolecule [25]. This reference serum was

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Abbreviations:
ANA: antinuclear antibody
LE: Lupus erythematosus

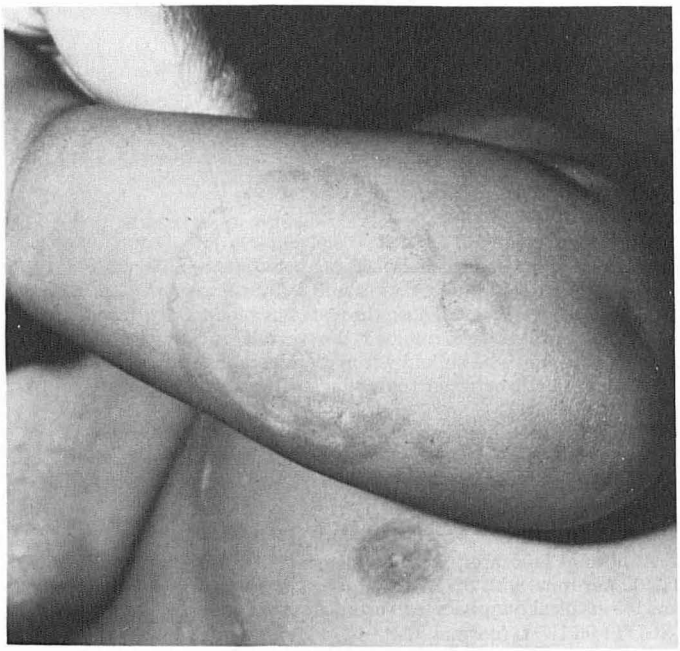

FIG 1. Circinate lesion on left forearm with minimally elevated border and irregular pigmentation.

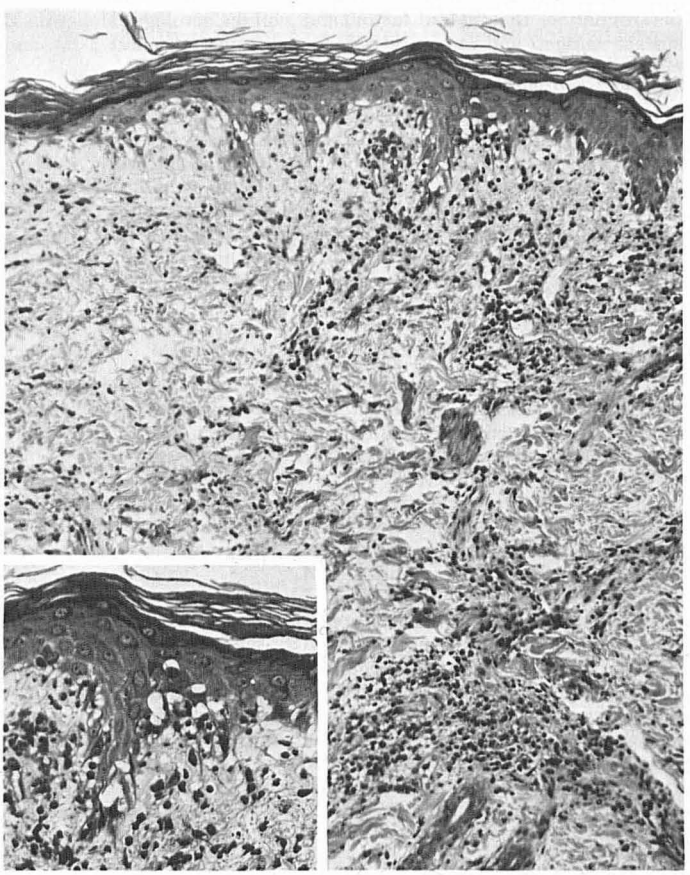

FIG 2. Lesion from the thigh showing hyperkeratosis, epidermal atrophy, basal vacuolization, dermal edema, superficial and deep perivascular mononuclear cell infiltrate (hematoxylin-eosin, × 20) *Inset.* Higher magnification of epidermis and dermal-epidermal junction. (× 200).

derived from a patient with an unusual lupus-like syndrome. Subsequent experience has shown that the precipitin Ro occurs almost exclusively in patients with collagen vascular diseases. The prevalence of Ro in clinically normal members of a recent survey population was only 0.1% [29].

Though less well studied, the precipitin La(SSB) described by Mattioli and Reichlin [26], also appears to be quite specific for a collagen vascular disease [28,30–34].

Development of a coherent global perspective on the exact significance of Ro and La in the diagnosis and assessment of autoimmune diseases has been hampered somewhat by several methodological difficulties. Firstly, only highly selected groups of patients have been studied. Secondly, (particularly with regard to Ro), several antigen substrates have been employed, and these may vary in sensitivity [25,32]. Such variations in methods may be responsible for some of the discordant findings published to date [28]. Nevertheless, a number of important associations are emerging:

1. Anti Ro antibodies are found in approximately 25% of ANA positive SLE patients [29–31], particularly in those patients with prominent cutaneous features [18,20–22]. Some of these latter patients have been termed subacute cutaneous lupus erythematosus [20,21]. A large group of Ro positive, ANA negative (mouse liver) lupus patients have now been described [22]. Skin findings are prominent in this latter group as well, particularly a photo-sensitivity-type malar rash. Save for the absence of ANA, many of these patients satisfy the ARA criteria for the diagnosis of SLE. In particular, some have had significant renal disease.

2. Forty to forty-five percent of patients with Sjögren's syndrome demonstrate Ro [29,31–34]. Some of this work was reported as demonstrative of the precipitin SSA; recent work has shown that reference sera for Ro and SSA give a reaction of identity [28]. (Neither mother nor infant described in this report had symptoms or physical findings of the sicca complex.)

3. The antibody system La is found in approximately 10% of SLE patients and in a variable percentage of patients with Sjögren's syndrome [31,27]. The precipitin antibody SSB described by Alspaugh and Tan has been shown to have immunologic identity with La [28].

4. Ro (SSA) antibodies appear to have a strong association with neonatal lupus erythematosus. Weston et al have recently presented data on 3 neonatal lupus patients [35,36]. These patients are quite similar in many respects to the child presented here. As in our patient, the annular inflammatory skin lesions cleared within 6 mo, and the anti Ro and/or anti La antibodies disappeared. This suggests that the autoantibodies

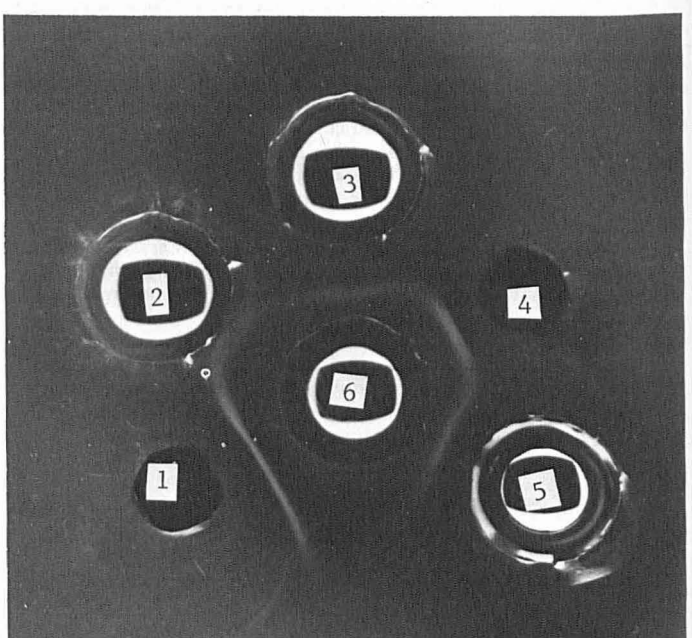

FIG 3. Gel double diffusion. Well *#1* Ro positive control; *#2* Mother's serum; *#3* Baby's serum; *#4* Ro positive control; *#5* Mother's serum; *#6* human spleen extract. Note lines of immunologic identity between the baby's, the mother's and the Ro positive control sera.

in the babies' sera were of maternal origin. Also, as in the current case, Weston's experience demonstrates that the mothers of the affected infants may be asymptomatic—2 out of 3 in his series [35].

In addition, we have had the opportunity to evaluate the serum and amniotic fluid obtained from a 20 week abortus (terminated for anencephaly and complete heart block). The mother, a known systemic lupus patient, demonstrated serum anti Ro (SSA) and anti La (SSB) antibodies. The amniotic fluid, but not the baby's serum, also contained these antibodies. (Note that the majority of maternal antibodies cross the placenta in the 3rd trimester of pregnancy. Our failure to detect the Ro antibody in a 20-week-old fetus may reflect insensitivity of the testing procedure.)

The current case is the first to document Ro as the sole evident immunologic marker for neonatal lupus. Usually either ANA or RF or both have also been present [1,35,36].

This last observation further supports Weston's proposal that the anti Ro (SSA) antibody is a marker for the neonatal lupus syndrome [35]. The anti Ro antibodies provide a serologic link between these unusual neonatal lupus patients and the more typical SLE patients. Finally, this case report and the experience of Weston et al raises the possibility that autoantibodies may be causally related to the cutaneous lesions seen in this syndrome [35].

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