Neonatal erythematous lupus

Case report

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SUMMARY

An infant with annular erythemas, which appeared soon after birth, is presented. The laboratory tests revealed mild anaemia and high values for anti-Ro/SS-A, and anti-La/SS-B antibodies. Routine histology and direct immunofluorescence microscopy examination confirmed the diagnosis of neonatal lupus erythematosus (NLE). The skin lesions resolved completely in the first six months of life. No cardiac abnormalities were detected during the follow-up and no systemic therapy was necesary. Sun protection was recommended. The baby's mother was asymptomatic during pregnancy and also for some months after it. One year later she developed sicca symptoms (mb Sjögren).

KEY WORDS

neonatal lupus erythematosus, infant, anto-RO, anti-LA antibodies

Introduction

Neonatal lupus erythematosus (NLE) is a rare syndrome and may occur in an infant whose mother has auto-antibodies to extractable nuclear antigens (ENA) in her serum (1). These antibodies of maternal origin are transferred across the placenta and react with fetal skin and cardiac muscle (1, 2). The antibodies in the infant's serum are transient and are not detectable 6-9 months later (2, 3, 4, 5).

The skin lesions are annular or circinate erythematous patches, most often on the face and trunk (1). The lesions are present at birth or appear soon after (6, 7, 8). The skin changes resolve spontaneously, usually in the first months. The heart is usually affected. The extent and severity of the heart block determines the further course of the disease (1, 2). A few infants with NLE also had anemia, thrombocytopenia and/or impairment of the liver (3).

Mothers may be clinically asymptomatic at the moment when their child presents symptoms of NLE (9, 10, 11). Only about 5% of the children born to these women develop NLE, although there is a risk of recurrence (25 %) (6, 12). The mother may display symptoms of SLE (systemic lupus erythematosus) , SCLE (sub-

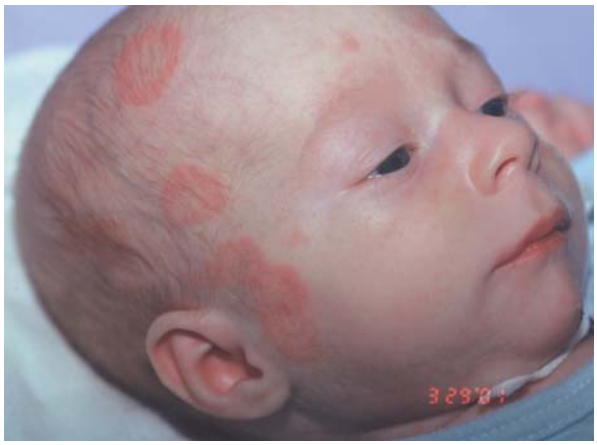

Figure 1. Neonatal erythematous lupus, skin lesions at the admission (at six weeks): erythematous plaques plaques in the occipital, temporal and preauricular areas.

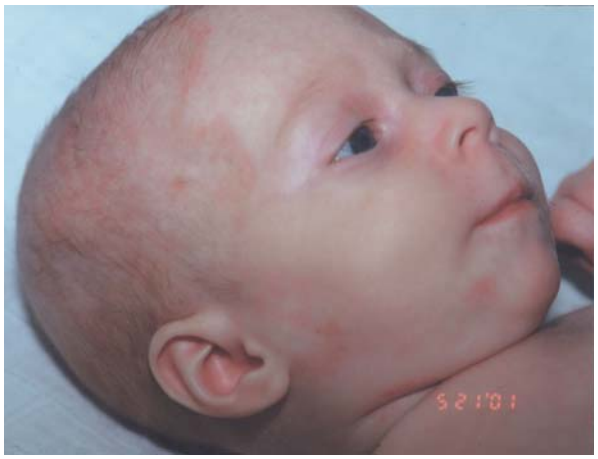

Figure 2. Regression of lesions at three months

acute cutaneous lupus erythemosus) or Sjögren's syndrome (2).

Case report

A 6-week old male infant was admitted to the Department of Dermatology (Ljubljana). He was the first child. His mother was treated because of endometriosis and became pregnant with in vitro fertilization (IVF) assistance. During the pregnancy the mother had hyperthyreosis, but did not require any therapy. The pregnancy was normal and the baby was born by cesarean section. In the second week of his life red papules in the right preaulicular region of the face became evident. In the next few days similar lesions appeared on the left temporal region and small erosions on the lower lip and in perianal region became evident. The red papules on the head spread peripherally to form annular erythematosus patches with sharp, slightly hyperkeratotic borders and central clearing. Figure 1. At the time when the infant was admitted to our department, we noticed some new red papules on the back and pectoral region. All the lesions had a tendency to spread peripherally. Blood tests were normal, and the test for occult bleeding was negative. Mycological examination of the annular patches were negative. A skin biopsy of an annular patch on the back was performed and routine histology and direct immunofluorescence examinations were done. Formalin-fixed and paraplast-embedded skin specimens were stained with hematoxylin-eosin for standard light microscopy examination. Frozen skin samples for immunofluorescence were cut in a cryostat and incubated with fluorescein isothiocyanate labelled antisera to human IgA, IgG, IgM, complement components C3 and

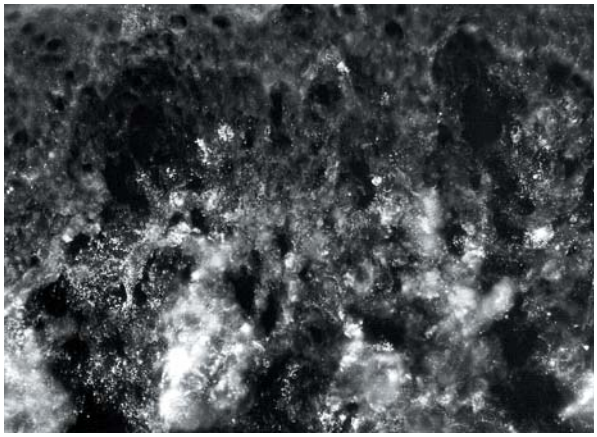

Figure 3. C1q fine speckled cellular cytoplasmic and nuclear staining in dermis as well as scanty granular deposits at dermo-epidermal junction. Direct immunofluorescence, original magnification x 130.

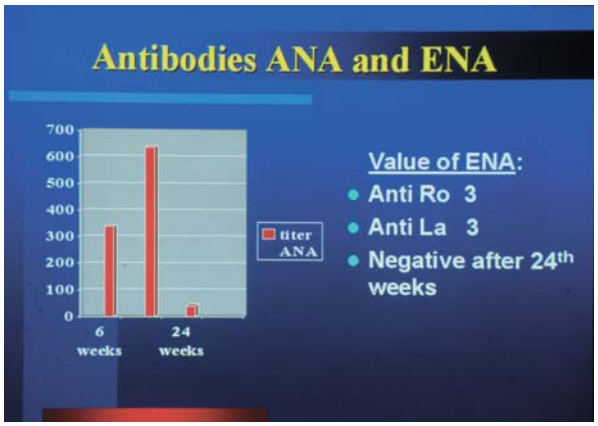

Figure 4. Results of the laboratory tests. Dynamics of ANA titers and ENA values.

C1q, and fibrin/fibrinogen (Dako, Denmark).

Histopathology revealed a mild vacuolar degeneration of basal cells in a few areas. In the papillary dermis there was an interstitial perivascular lymphocytic infiltrate. Histopathology was interpreted as compatible with the diagnosis of neonatal erythematous lupus.

Direct immunofluorescence revealed fine speckled IgG and C1q cellular cytoplasmic and nuclear staining in the dermis, the majority of positive cells being most probably inflammatory cells. In addition, scanty granular deposits of C1q were found on the dermoepidermal junction. Figure 3.

Serum from both the infant and mother was assayed for ANA, and specifically for anti-Ro/SS-A, anti-La/SS-B and anti-U1RNP antibodies. High tiers of ANA with specificity for anti-Ro/SS-A and anti-La/SS-B antibodies in high titres were found in both the infant's and mother's sera. Mother: ANA 1:640, anti-Ro/SS-A 3, anti-La/SS-B 3. Infant: ANA 1:320, anti-Ro/SS-A 3, anti-La/SS-B 3. Blood tests, liver function tests, a platelet count, Coomb's test, cardiac examination, electrocardiogram and ultra sound of the abdomen and of the head were all normal. The infant was regularly examined in the outpatient clinic. At twelve weeks the blood function test revealed mild anemia, anti Ro/SS-A, anti-La/SS-B antibodies were positive and titers for ANA reached a peak (1:640); the results of all the other tests were normal. Figure 4.

The skin lesions spread peripherally. Once they had reached approximately the size of a coin they became circinate and tended to regress spontaneously. Figure 2. Up to the age of 2 years, our patient had no cardiac abnormalities and all skin lesions disappeared without residual changes. The infant needed no systemic therapy, but sun protection was recommended. We advised the mother to stop breast feeding.

Discussion

NLE is provoked in the fetus or newborn infant by maternal IgG auto-antibodies that have crossed the placenta (9, 13). In 95% of cases, the antibodies are of IgG1 class and are directed against the Ro ribonucleoprotein antigen (14, 15). Serum from both the infant and mother should be tested for ANA, and specifically for anti-Ro/SS-A, anti-La/SS-b and anti-U1 ribonucleprotein (RNP) antibodies. In nearly all the infants with NLE anti Ro/SS-A and sometimes anti-La/SS-B antibodies are detected, the same profile is to be found in their mothers. A few NLE patients have been reported to have anti-U1RNP antibodies in the absence of anti-Ro/SS-A or anti-La/SS-B antibodies (10, 16, 17, 18). The Ro antigen has been shown to be present in fetal skin and heart (19), and most probably in the immune complexes. An accurate diagnosis of NLE in our patient was possible through detection of anti-Ro/SS-A and anti-La/SS-B auto-antibodies in both infant and mother.

Up to 60 % of infants' mothers with NLE may be clinically asymptomatic when their child develops NLE (9, 10, 11). There is however a substantial risk of subsequent development of autoimmune connective tissue diseases (6). Some of them will develop SCLE, SLE or symptoms of Sjögren's syndrome (3, 7, 20, 21). More recently, it has been recognized that about 5 % of women in child-bearing age who present leokocytoclastic vasculitis will have anti-Ro antibodies and it is probable that about 5 % of babies with NLE have mothers with leukocytoclastic vasculitis (6, 22).

The mother of our patient was asymptomatic during pregnancy and for some months after it. Later on she developed sicca symptoms (Sjögren syndrome).

In addition to the serum tests for ANA and ENA, a physical examination should be performed, including cardiac examination, echocardiogram and electrocardiogram, liver function tests and a platelet count. Further tests or procedures may be done, if indicated by physical findings (16).

Most infants with NLE have either skin lesions or cardiac lesions; approximately 10 % have both (6, 23, 24). The skin lesions of NLE take the form of well-defined areas of macular or slightly elevated erythematous lesions, frequently annular, occuring predominantly on the face, particularly on the forehead, temples and the upper part of the cheeks, and on the scalp and neck. The chest, back or limbs may also be affected. The skin lesions spread peripherally and have a scaly border (1, 2, 16). They are present at birth in about two-thirds of infants who develop cutaneous lesions (7, 8) or may appear in the next few months (6). The skin lesions resolve spontaneously, usually during the first year. In some cases residual atrophy and telangiectasia may be more persistent (25, 26). Sometimes NLE presents itself as extensive reticulate erythema with atrophy, closely resembling cutis marmorata telangiectatica (27).

In our patient the skin lesions resolved completely in the first six months of life.

The other organ that is regularly affected is the heart. Fibrosis of the bundle of His commonly results in congenital heart block. Antigens of the conducting fibres in the heart may also bind the anti-Ro antibodies during mid or late fetal development. This leads to altered membrane repolarization and selective damage to the atrioventricular (AV) node (28). About 60 - 75% of patients with NLE develop congenital atrioventricular heart block (29). The heart block is generally permanent and may require a pacemaker. About 10 % of infants with NLE and heart disease will die from cardiac complications (6, 30, 31). Our patient had no cardiac symptoms up to the age of two years.

A smaller proportion of infants with NLE also have autoimmune haemolytic anaemia and/or thrombocytopenia (3) and/or hepatomegaly, splenomegaly, lymphadenopathy, which are generally mild and fairly transient (1, 16).

Except for mild anaemia and the values for anti-Ro/SS-A and anti-La/SS-B antibodies, all the other laboratory tests were normal in our patient. The mild anaemia was transient and was probably the consequence of the reaction between auto-antibodies and infant's red blood cells.

A skin biopsy for routine histology and direct immunofluorescence microscopy examination is also recommended for an accurate diagnosis. In our patient, the histology examination showed interface dermatitis, which is compatible with annular erythemas in infants, and which also includes NLE. The reported direct immunofluorescence findings in NLE include granular deposits of immunoglobulins and complements at the dermo-epidermal junction and particulate cytoplasmic and nuclear deposition of IgG in the keratinocytes in a similar way to SCLE (32, 33). In our patient we found a characteristic scanty granular deposit of C1q on the dermo-epidermal junction and fine particulate nuclear and cytoplasmic staining for IgG and C1q not in the epidermis but rather unsually in the dermis. The dermal positive cell reaction most probably reflects local binding of anti-Ro and anti-La antibodies to their antigens and may contribute to the pathogenesis of lupus skin lesions. In conclusion, histopathology and immunofluorescence confirmed the diagnosis of NLE in our patient.

The diagnosis was confirmed by satisfying the two major criteria of NLE as established by the American College of Rheumatology: a characteristic skin rash in neonate and maternal antibodies to the 52-kd SSA/Ro, 60-kd SSB/La ribonucleoproteins (heart block and U1RNP were negative in our case) (34). Infants with skin lesions alone, or with skin lesions and systemic features other than heart block, usually show only feeble signs after the age of one year. We believe our young patient has a good prognosis, but still should undergo regular check-ups in view of the possible development of connective tissue diseases (35-38).

REFERENCES

1. Atherton DJ. The Neonate. In: Champion RH, Burton JL, eds. Textbook of Dermatology, Oxford: Blackwell Science Ltd, 1998.

2. Braun-Falco O, Plewig G, Wolff HH, Burgdorf WH. Disease of Connective Tissue. In: Braun-Falco O, Plewig G, eds. Dermatology, Berlin: Springer-Verlag, 1996.

3. Franco HL, Weston WL, Peebles C et al. Antibodies directed against sicca syndrome antigens in the neonatal lupus syndrome. J Am Acad Dermatol 1981; 4: 67-72.

4. Waston RM, Lane AT, Barnett NK et al. Neonatal lupus erythematosus: a clinical, serological and immunogenetic study with review of the literature. Medicine 1984; 63: 362-78.

5. Miyagawa S, Kitamura W, Yoshioka J et al. Placental transfer of anticytoplasmic antibodies in annular erythema of newborns. Arch Dermatol 1981; 117: 569-72.

6. Weston WL, Harmon C, Peebles C et al. A serological marker for neonatal lupus erythematosus. Br J Dermatol 1982; 107: 377-82.

7. Neidenbach PJ, Sahn EE. La(SSB)-positive neonatal lupus erythematosus: report of a case with unusual features. J Am Acad Dermatol 1993; 29: 848-52.

8. Lee LA, Weston WL. New findings in neonatal lupus syndrome. Am J Dis Child 1984; 138: 233-6.

9. McCune AB, Weston WL, Lee LA. Maternal and fetal outcome in neonatal lupus syndrome. Ann Int Med 1987; 106: 518-23.

10. Lee LA, Lillis PJ, Fritz KA et al. Neonatal lupus syndrome pregnancies. J Am Acad Dermatol 1983; 9: 401-6.

11. Drazin TH, Esterly NB, Furey NL et al. Neonatal lupus erythematosus. J Am Acad Dermatol 1979; 1: 437-42.

12. Soltani K, Pacernik LJ, Lorincz AL. Lupus erythematosus-like lesions in newborn infants. Arch Dermatol 1974; 110: 435-7.

13. Provost TT. Commentary: neonatal lupus erythematosus. Arch Dermatol 1983; 119: 619-22.

14. Bennion SD, Ferris C, Lieu T-S et al. IgG subclasses in the serum and skin in subacute cutaneous lupus erythematosus and neonatal lupus erythematosus. Arch Dermatol 1990; 95: 643-6.

15. Sontheimer RD, McCauliffe DP. Pathogenesis of anti-Ro/SS-A autoantibody-associated cutaneous lupus erythematosus. Dermatol Clin 1990; 8: 751-8.

16. David-Bajar KM. Collagen Vascular Disease. In: Fitzpatrick JE, Aeling JL. Dermatology Secrets. Philadelphia: Hanley & Belfus, Inc., 1996.

17. Dugan EM, Tunnessen WW, Honig PJ, Watson RM. U_1RNP antibody-positive neonatal lupus. Arch Dermatol 1992; 128: 1490-4.

18. Provost TT, Watson RM, Gammon WR. The neonatal lupus syndrome associated with U_1RNP (nRNP) antibodies. N Engl J Med 1987; 316: 1135-8.

19. Lee LA, Harmon CE, Huff JC et al. The demonstration of SS-A/Ro antigen in human fetal tissues and in neonatal and adult skin. J Invest Dermatol 1985; 85: 143-6.

20. Korkij W, Soltani K. Neonatal lupus erythematosus: a review. Pediatr Dermatol 1984; 1: 189-95.

21. Rendal JRS, Wilkinson JD. Neonatal lupus erythematosus. Clin Exp Dermatol 1978; 3: 69-76.

22. Borrego L, Rodrigues J, Soler E et al. Neonatal lupus erythematosus related to maternal leukocytoclastic vasculitis. Pediatr Dermatol 1997; 14: 221-5.

23. Lee LA, Norris DA, Weston WL et al. Neonatal lupus and pathogenesis of cutaneous lupus. Pediatr Dermatol 1986; 3: 491-2.

24. Lee LA. Neonatal lupus erythematosus. J Invest Dermatol 1993; 100: 9S-13S.

25. Bourquelique C, Debillon T, Mesnard B et al. Neonatal lupus presenting as telangiectasic and atrophic lesions. Pediatrie 1990; 45: 251-4.

26. Thornton C, Eichenfield L, Shinall E et al. Cutaneous telangiectases in neonatal lupus erythematosus. J Am Acad Dermatol 1995; 33: 19-25.

27. Carrascosa JM, Ribera M, Bielsa I et al. Cutis marmorata telangiectactica congenital or neonatal lupus. Pediatr Dermatol 1996; 13: 230-2.

28. Alexander E, Buyon JP, Provost TT, Guarieri T. Anti Ro/RR-A antibodies in the pathophysiology of congenital heart block in neonatal lupus syndrome: and experimental model. Arthritis Rheum 1992; 35: 176-89.

29. Petri M, Watson R, Hochberg MC. Anti-Ro antibodies and neonatal lupus. Rheum Dis N Am 1989; 15: 335-60.

30. Esscher E, Scott JS. Congenital heart block and maternal systemic lupus erythematosus. Br Med J 1979; 1: 1235-8.

31. Waltuck J, Buyon JP. Autoantibody-associated congenital heart block: outcome in mothers and children. Ann Intern Med 1994; 120: 544-51.

32. Lee LA, David KM. Cutaneous lupus erythematosus. Curr Probl Dermatol 1989; 1: 1-30.

33. David-Bajar KM, Davis BM. Pathology, immunopathology, and immunohistochemistry in cutaneous lupus erythematosus. Lupus 1997; 6: 145-57.

34. Neiman AR, Lee LA, Weston EL, Bayon JP. Cutaneous manifestation of neonatal lupus without heart block: characteristics of mother and children enrolled in a national registry. J Pediatr 2000; 137: 674-80.

35. McCue CM, Mantakas ME, Tingelstad JB et al. Congenital heart block in newborn of mother with connective tissue disease. Circulation 1977; 56: 82-90.

36. Fox RJ, McCuiston CH, Schoch EP. Systemic lupus erythematosus: association with previous neonatal lupus erythematosus. Arch Dermatol 1979; 115: 340.

37. Jackson R, Gulliver M. Neonatal lupus erythematosus: a 15 year follow-up. Br J Dermatol 1979; 101: 81-6.

38. Lanham JG, Walport MJ, Hughes GR. Congenital heart block and familial connective tissue disease. J Rheumatol 1983; 10: 823-5.

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