Acta Derm Venereol (Stockh) 1992; 72: 211–213

Significance of Tubuloreticular Structures in Infants with Neonatal Lupus Erythematosus and Their Mothers with Sjögren's Syndrome

YUKIKO NITTA[1], TOSHIHIKO IKEYA[1] and MASARU OHASHI[2]

Departments of Dermatology, [1]Aichi Medical University, Aichi and [2]Nagoya University School of Medicine, Nagoya, Japan

Four infants with neonatal lupus erythematosus who had annular erythema on the trunk and face reacted positively to tests for anti-Ro(SS-A)/La(SS-B) antibodies. Electron microscopic examination of vascular endothelial cells in the annular erythema revealed the presence of tubuloreticular structures. Once anti-Ro(SS-A)/La(SS-B) antibodies had turned negative, these tubuloreticular structures were no longer evident in the vascular endothelial cells in the same area where annular erythema had been present. Mothers of these 4 infants reacted positively to anti-Ro(SS-A)/La(SS-B) antibodies, but had no sicca syndrome. A biopsy taken from the minor salivary gland of the lip of each mother revealed marked periductal mononuclear cell infiltration. Primary subclinical Sjögren's syndrome was confirmed. Tubuloreticular structures were also observed in the vascular endothelial cells in the region of the minor salivary gland. These findings suggest that the presence of tubuloreticular structures may be related to anti-Ro(SS-A)/La (SS-B) antibodies. ***Key words: Tubuloreticular structures in NLE and SjS***

(Accepted October 28, 1991.)

Acta Derm Venereol (Stockh) 1992; 72: 211–213.

Y. Nitta, Aichi Medical University Department of Dermatology, 21 Karimata, Nagakute-cho, Aichi-gun, Aichi-ken 480-11, Japan.

Neonatal lupus erythematosus (NLE) is a transient collagen syndrome seen within the first few weeks after birth in infants affected by annular erythema, hepatosplenomegaly, anemia, leukopenia, congenital heart block who also test positive for anti-Ro(SS-A)/La(SS-B) antibodies (1). Mothers of such NLE infants are usually found to be suffering from collagen vascular disease and react positively to anti-Ro(SS-A)/La(SS-B) antibodies. These same autoantibodies are found to turn negative in infants following spontaneous disappearance of lesions (1). It has been postulated by Franco et al. (2) and Miyagawa et al. (3) that transplacental passage of autoantibodies exists in association with NLE.

In 1969, Györkey et al. (4) were the first to find tubuloreticular structures (TRS) by electron microsopy in the endothelial cells of the renal glomerulus of patients with systemic lupus erythematosus (SLE). Subsequently, TRS was reportedly found in skin lesions of patients with SLE, Sjögren's syndrome (SjS) and dermatomyositis (5). Rich et al. (6) reported that α- and β-interferon in sera of SLE patients induced the formation of TRS.

We examined TRS in skin lesions of 4 infants with NLE. TRS were also examined in the minor salivary gland of the infants' mothers, who were all suffering from primary subclinical SjS. Based on the findings, we studied the significance of TRS in relation to anti-Ro(SS-A)/La(SS-B) antibodies.

MATERIAL AND METHODS

Patients

Cases 1 and 2 were NLE infants born to Case 1' mother, Case 3 was the firstborn child of Case 3' mother and Case 4 was a second child of Case 4' mother who had another child free from NLE. The 4 infants involved, Cases 1, 2, 3 and 4, were found to have annular erythema with no congenital heart block (Fig. 1). Case 2 had a ventricular septal defect which closed spontaneously one month after birth. In Cases 1, 2, 3 and 4, antinuclear, anti-Ro(SS-A)/La(SS-B) antibodies were all positive, while anti-DNA (both ds and ss), anti-Sm and anti-RNP antibodies were all negative. Neither α- nor β-interferon could be detected in the serum of Cases 1, 2, 3, or 4 as performed by ^{3}H-Uridinic radiochemical immunoassay (7) (Table I). Blood counts and hepatic function were within normal ranges in all 4 infants. Biopsy specimens taken from the annular erythema lesions of these infants revealed no abnormalities in the epidermis; however, there was marked edema in the upper dermis and mild perivascular infiltration

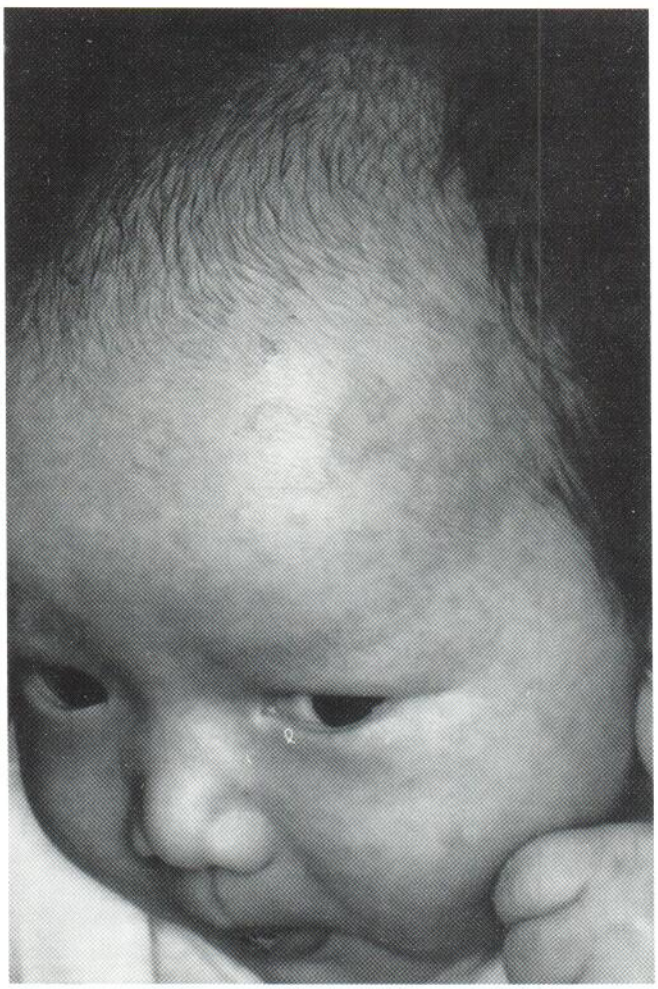

Fig. 1. Annular erythema on the face of a 6-week-old male infant (Case 4).

Table I. *Examination results for all subjects (3 mothers, 4 infants).*

	Case no.	Age (yrs)	Sex	Rheum. Factor	Anti-					Interferon	
					DNA antibody	SS A	SS B	Sm	RNP	α	β
Infants with NLE	1	4	F	–	–	4	8	–	–	–	–
	2	1	M	–	–	16	8	–	–	–	–
	3	2	F	–	–	4	2	–	–	–	–
	4	1	M	–	–	1	32	–	–	–	–
Mothers with SjS	1'	33	F	+	–	16	8	–	–	–	–
	3'	30	F	+	–	16	8	–	–	2	–
	4'	30	F	+	–	1	32	–	–	–	–

Cases 1 and 2 infants were born to Case 1' mother.
Case 3 infant was born to Case 3' mother.
Case 4 infant was born to Case 4' mother.

of the lymphoid cells. Once the annular erythema had disappeared, anti-Ro(SS-A)/La(SS-B) antibodies were no longer evident.

The three mothers involved, Cases 1', 3' and 4', each had 2 children of which either one or both had NLE. None of these mothers had any symptoms of sicca or any skin lesions, but all reacted positively to the rheumatoid factor and anti-nuclear, anti-Ro(SS-A)/La(SS-B) antibodies, and were negative for anti-DNA (both ds and ss), anti-Sm and anti-RNP antibodies. Levels of α- and β-interferon were found to be low or negative. Primary subclinical SjS was confirmed in all 3 women through biopsy of the minor salivary gland of the lip, which also revealed marked infiltration of periductal mononuclear cells (Fig. 2). Hepatic function and blood counts were normal in all mothers.

Methods for observing TRS by electron microscopy

Skin biopsies of annular erythema and skin biopsies of the lesions where annular erythema had disappeared in the infants (Cases 1, 2, 3 and 4) were taken. Biopsies of the minor salivary gland of the lip in the mothers (Cases 1', 3' and 4') were also obtained. These specimens were fixed in 3% glutaraldehyde, post-fixed in osmium tetroxide, dehydrated in graded ethanol and embedded in Quetol. Ten thin sections (0.5 μm) were prepared with an ultramicrotome from three blocks for one specimen, were stained with uranyl acetate and then with lead citrate for examination by electron microscope.

RESULTS

Electron microscopic observation of the annular erythema from the infants (Cases 1, 2, 3 and 4) revealed TRS in the keratinocytes, vascular endothelial cells, fibroblasts and lymphoid cells in the upper dermis (Figs. 3, 4). After 6 or 7 months, when titres of anti-Ro(SS-A)/La(SS-B) antibodies were found to have become negative, electron microscopic examination of keratinocytes, fibroblasts and endothelial cells of 10 capillaries in the area where annular erythema had disappeared showed no evidence of TRS in any of these infants.

In the mothers, TRS was always present in the vascular endothelial cells in repeat biopsies taken from the region of the minor salivary gland (Fig. 5).

DISCUSSION

NLE is seen in infants born to mothers with collagen vascular disorders, and is evidenced by skin lesions of annular scaly erythema and congenital heart block with positive anti-Ro

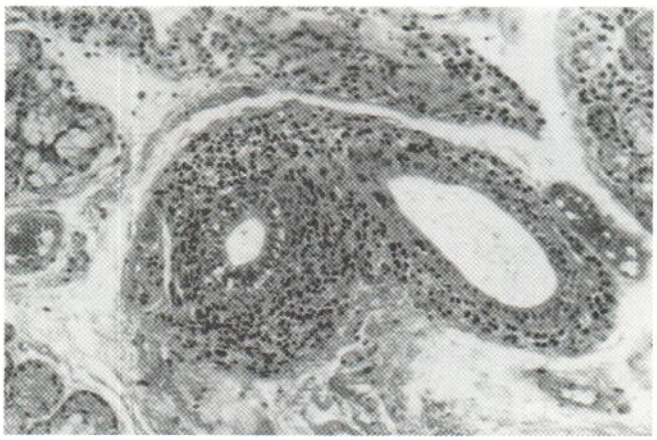

Fig. 2. Histology of minor salivary gland, from Case 1' mother. Marked mononuclear cell infiltration can be seen around the duct. HE, (×200).

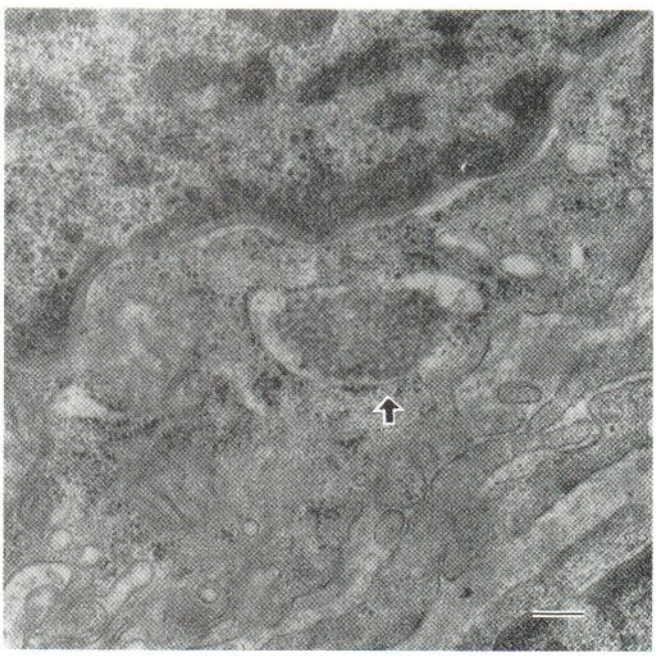

Fig. 3. Tubuloreticular structures (*arrows*) observed in an endothelial cell in the annular erythema of Case 2 infant. TRS are of high electron density, measuring 200–230 Å in diameter. Bar = 0.25 μm (×40,000).

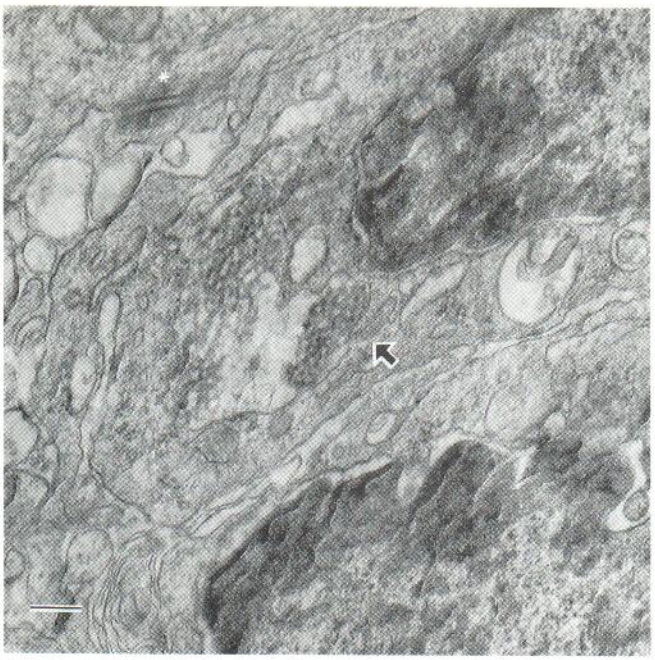

Fig. 4. TRS in a keratinocyte in the annular erythema of Case 2 infant. *Desmosome in the keratinocyte. Bar = 0.25 μm (×40,000).

(SS-A) antibody passed from the mother to the infant via the placenta (1, 2, 3).

TRS can be observed by electron microscopy in the cytoplasm of endothelial cells of skin lesions in cases of SLE (5). In 1974, Klippel et al. (8) noted that TRS was present in the

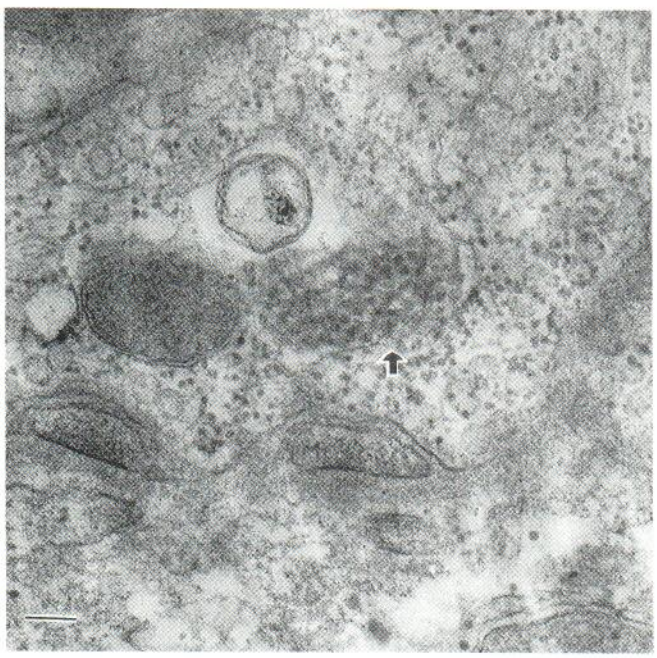

Fig. 5. Tubuloreticular structures (*arrows*) detected in vascular endothelial cells in minor salivary gland of Case 1' mother. Bar = 0.156 μm (×64,000).

umbilical cord lymphocytes in two healthy newborns whose mothers had SLE.

Levy et al. (9) reported that TRS were evident in the keratinocytes, endothelial cells and fibroblasts of a skin lesion of an infant with NLE, although the mother was healthy, with no anomalies except for positive rheumatoid factor. A skin biopsy from an unaffected region of that mother examined by electron microscope showed no evidence of TRS. There were no skin lesions in any of the mothers in our cases either. We, therefore, examined vascular endothelial cells from the minor salivary gland for any evidence of TRS.

Rich et al. (6) recently reported that high levels of endogenous α-interferon can induce TRS in affected regions of SLE patients with a high titre of the anti-DNA antibody.

In our experience, neither α- nor β-interferon could be detected in any of the sera from the 4 affected infants or their 3 mothers; however, TRS were detected in the area of annular erythema in the infants with NLE who were positive for anti-Ro(SS-A)/La(SS-B) but negative for anti-DNA antibody. After 6 or 7 months, annular erythema disappeared, and anti-Ro (SS-A)/La(SS-B) antibodies were found to have turned negative. By his time, TRS could no longer be found in the previously affected lesion areas either. TRS were present, however, in each of these mothers who was positive for anti-Ro(SS-A)/La(SS-B) antibodies, but negative for α- and β-interferon and anti-DNA antibody.

Our findings suggest that anti-Ro(SS-A)/La(SS-B) antibodies may be an indicator of the development of NLE and may also be a factor related to the formation of TRS in newborn infants.

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