Cutaneous Lupus Erythematosus in Neonates and Infants: Maternally Derived Autoimmunity and the Neonatal Lupus Syndrome

Introduction and Epidemiology

Neonates are not sufficiently immunologically competent to develop IgG autoantibody–mediated disease independently. However, IgG autoantibodies from the mother transmitted in utero can initiate disease in susceptible individuals. In a small percentage of fetuses and neonates exposed to maternal autoantibodies of the Ro/SSA family, an autoimmune disease called “neonatal lupus erythematosus (NLE)” will develop (Lee 1993, 2001). It may be argued that NLE is misnamed, as many of its clinical findings are not shared by systemic LE (SLE) of children or adults, but the name NLE remains in common use. The main features of the syndrome are cutaneous lupus lesions, cardiac disease (primarily complete congenital heart block), hepatobiliary disease, and hematologic cytopenias. Many affected individuals have only one manifestation of NLE, but any combination of these findings may occur.

NLE is an uncommon condition. Although approximately 1 in 200 pregnant women have anti-Ro/SSA autoantibodies, few have a child with NLE (Harmon et al. 1984). The incidence of NLE has been estimated as 1 in 20,000 live births (Lee and Weston 1996). Cardiac disease is reportedly the most common feature, but this may be due in part to its being more likely than the other manifestations to be detected and properly diagnosed. The sex distribution is approximately equal for children with cardiac NLE, but girls outnumber boys approximately 2:1 in cases of cutaneous NLE (Buyon et al. 1998, Neiman et al. 2000).

Cutaneous Neonatal Lupus Erythematosus

The skin lesions of NLE represent subacute cutaneous LE (SCLE), although with a distribution distinct from that of SCLE in adults. Cutaneous NLE is characterized by annular, erythematous, nonscarring, photosensitive plaques, sometimes associated with hypopigmentation (Weston et al. 1999). Occasionally, lesions reminiscent of cutis marmorata congenita occur. The onset is generally in the first few weeks of life, although lesions have been noted at birth in several cases. There is a predilection for the head, in particular the periorbital skin, but lesions may occur at any site. The
affected periorbital skin has been described as having an “owl eye,” “eye mask,” or “raccoon eye” appearance. Disease activity resolves in a few weeks or months, but dyspigmentation may persist for several months, and in some cases there are residual telangiectasias (Thornton et al. 1995).

The risk for a child with cutaneous NLE to have extracutaneous features is not precisely known. It has been estimated that approximately 10% of children with cutaneous NLE also have cardiac disease (Lee 1993). An examination of records from a national NLE registry indicates that 23% of children with cutaneous NLE without cardiac disease have hepatobiliary or hematologic findings (Neimann et al. 2000). Thus, perhaps one third of the cases of cutaneous NLE have extracutaneous manifestations.

Extracutaneous Manifestations of Neonatal Lupus Erythematosus

Cardiac NLE is the most frequently reported manifestation of NLE. Cardiac NLE has significant morbidity and mortality: approximately two thirds of the children with cardiac NLE require permanent pacemaker implantation, and there is 15%–20% mortality (Buyon et al. 1998, Eronen et al. 2000). The most commonly occurring lesion is third-degree heart block. Heart block almost always begins in utero during the second or third trimester, often presenting as a lesser degree of block that relatively quickly advances to complete heart block. Complete heart block is almost always permanent. Autopsy studies have shown replacement of the atrioventricular nodal area by fibrosis and calcification (Lee et al. 1987, Lev et al. 1971). Assuming that the pathologic findings are similar in surviving children, it is easy to understand why heart block persists despite resolution of disease activity.

In some children with complete heart block, cardiac muscle is involved as well. This is often evident shortly after birth, when correction of the low heart rate with pacemaker implantation fails to correct heart failure. However, heart failure has developed later during infancy in a few individuals, demonstrating the importance of close monitoring in children with cardiac NLE (Taylor-Albert et al. 1997).

Hepatobiliary disease of NLE apparently may assume several phenotypes. In a review of data from a national research registry, approximately 10% (19/219) of the cases in the registry had evidence of hepatobiliary disease (Lee et al. 2002). The three types of presentations noted were as follows: (a) liver failure in utero or shortly after birth, often having the phenotype of neonatal iron storage disease (also known as “neonatal hemochromatosis”); (b) transient conjugated hyperbilirubinemia occurring in the first few weeks of life; and (c) transient aminotransferase elevations, occurring at 2–3 months of age. The latter two presentations eventuate in complete resolution, with no apparent residua. It has not been shown conclusively that each of these presentations truly represents a manifestation of NLE, but based on currently available information it seems likely.

The cytopenia most commonly associated with NLE has been thrombocytopenia (Watson et al. 1988). Remarkably, 5 of 57 children with cutaneous NLE in the national registry had neutropenia (Neiman et al. 2000). The cytopenias are transient and usually not associated with morbidity. One child had a nonfatal episode of gastrointestinal bleeding attributed to thrombocytopenia (Lee et al. 1993).
Laboratory Evaluation

Skin biopsy is not always performed owing to the age of the child and the predilection of lesions for the face. Biopsy findings for histologic examination and immunofluorescence are consistent with the findings of SCLE (David-Bajar et al. 1992). Notably, there is basal cell damage and a lymphocytic inflammatory infiltrate in the upper dermis. Histologic features more closely associated with discoid lupus, such as an intense deep dermal inflammatory infiltrate, an intense periadnexal infiltrate, follicular plugging, and basement membrane thickening, are not prominent in NLE. In the author’s experience, the immunofluorescent finding characteristic of cutaneous NLE is epidermal particulate deposition of IgG. This finding can be reproduced in an animal model by infusion of anti-Ro/SSA antibodies (Lee et al. 1986, 1989).

Autoantibody testing of serum samples from the mother, the child, or both is important for diagnosis. The exact specificity or specificities responsible for NLE are debated, but there is no question that virtually all patients have autoantibodies of the Ro/SSA family. Autoantibodies reported to be associated with NLE include antibodies to 60-kDa Ro/SSA, 52-kDa Ro/SSA, La/SSB, calreticulin, alpha-fodrin, a 57-kDa protein, and a 75-kDa phosphoprotein (Buyon et al. 1994, Maddison et al. 1995, Miyagawa et al. 1998, Lee et al. 1994, Lieu et al. 1989, Wang et al. 1999, Weston et al. 1982). In a few cases of cutaneous NLE, antibodies to Ro/SSA were not detected but antibodies to U1RNP were (Provost et al. 1987). Many of the assays for autoantibodies associated with NLE are performed only in certain research laboratories. For the clinician, assays for antibodies to Ro/SSA, La/SSB, and U1RNP are commercially available and should suffice to confirm or, if negative, seriously question the diagnosis.

It is reasonable to evaluate children with cutaneous NLE for extracutaneous manifestations. Laboratory screening may include electrocardiography, liver function tests (transaminases and fractionated bilirubin), and a complete blood cell count with differential.

Pathogenesis

The available evidence points strongly to autoantibodies as the cause of NLE. Maternal autoantibodies are uniformly present in NLE, and they are of a distinct family of autoantibodies. Disease activity resolves as the maternal autoantibodies are metabolized. Antibody deposits in tissues have been shown to represent anti-Ro/SSA (Lee et al. 1989, Reichlin et al. 1994). The autoantibodies most closely linked to NLE are antibodies to 60-kDa Ro/SSA and antibodies to 52-kDa Ro/SSA (Lee et al. 1994). Several investigators have attempted to reproduce disease using infused anti-Ro/SSA. Isolated rabbit cardiac muscle has been shown to develop abnormalities of repolarization when infused with anti-Ro/SSA-containing serum (likely representing a combination of anti-60-kDa Ro/SSA and anti-52-kDa Ro/SSA) (Alexander et al. 1992). Isolated rabbit hearts and isolated rat hearts perfused with anti-Ro-containing serum and anti-52-kDa Ro/SSA developed heart block (Boutjdir et al. 1998, Garcia et al. 1994, Viana et al. 1998). Some newborn mice whose mothers received anti-Ro/SSA and/or La/SSB-containing IgG during pregnancy experienced bradycardia and prolonged PR interval (Mazel et al. 1999). An interaction of NLE maternal IgG with human fetal cardiac sarcolemma and
with human L-type calcium channel alpha (1C) protein has been demonstrated (Qu et al. 2001).

The 60- and 52-kDa Ro/SSA proteins are apparently expressed ubiquitously, and it has not been clear why the disease process in NLE is apparently limited to only a few organs. It has been proposed that tissue specificity may be conferred by cross-reactivity between 52-kDa Ro/SSA and the 5-HT4 serotonergic receptor (Eftekhari et al. 2000). Pups from mice immunized with anti-5HT4 receptor peptides developed bradycardia, incomplete atrioventricular block, prolonged QT, skin lesions, and neuromotor problems (Eftekhari et al. 2001). One group reported that NLE serum samples contain, independent of anti-Ro, autoantibodies to neonatal heart M1 muscarinic acetylcholine receptor (Borda and Sterin-Borda 2001). The finding of expression of different isoforms of 52-kDa Ro/SSA at different times during cardiac development led to a proposed link between expression of specific 52-kDa Ro/SSA isoforms and the development of congenital heart block (Buyon et al. 1997). RNAs associated with 60-kDa Ro/SSA are also expressed differentially during development (Fraire-Velquez et al. 1999).

Genetic factors that have been identified as contributors to NLE include genes of the major histocompatibility complex (MHC) and C4 (Lee et al. 1983, Miyagawa et al. 1997, 1999, Watson et al. 1992). These associations are noted in NLE mothers and may in part be related to increased risk for production of anti-Ro/SSA autoantibodies. Genetic factors that contribute to determining which babies exposed to maternal anti-Ro/SSA autoantibodies will be affected and which will not have not yet been completely established, but there is emerging evidence that tumor necrosis factor (TNF)-α and transforming growth factor (TGF)-β polymorphisms may contribute (Clancy et al. 2003).

Management

Cutaneous NLE is best managed conservatively. Low-potency topical corticosteroid therapy may aid in decreasing inflammation, and sun protection measures are advisable. Residual telangiectasia may be treated with a vascular laser such as a pulsed dye laser.

Optimal therapy for cardiac NLE has not been established. Pacemaker implantation and medications traditionally used to treat heart failure are used when indicated. Several other therapeutic interventions have been tried, including prophylactic therapy of the mother with corticosteroids during the first trimester, corticosteroid therapy during gestation for fetuses with heart block, plasma exchange for an infant with heart block and cardiomyopathy, and corticosteroid therapy for neonates and infants with progressive disease (Copel et al. 1995, Shinozaka et al. 1999, Taylor-Albert et al. 1997, Yamada et al. 1999). Larger studies are needed before particular approaches may be accepted as standard care.

Long-Term Prognosis

Clearly, children with cutaneous NLE do well in the short run. For children with cardiac NLE, there is mortality of ca. 15%–20% (Buyon et al. 1998, Eronen et al. 2000). There is little mortality data concerning hepatobiliary NLE and hematologic NLE.
The finding of 6 deaths in 19 children with hepatobiliary disease in a survey of a national registry indicates that hepatobiliary disease may have a significant mortality rate as well, but more information is needed on this point (Lee et al. 2002).

A long-term concern is the possibility of the development of autoimmune disease later in life. It is to be expected that children with NLE have a slightly increased risk of autoimmunity because by definition they have a family history of autoimmunity. It is the magnitude of the risk that is in question. In a national registry study of 57 children with cutaneous NLE, one child developed Hashimoto’s thyroiditis at age 7 years, two developed juvenile rheumatoid arthritis at ages 2 years and 5 years, one developed Raynaud’s disease during childhood, and one had a persistently positive high-titer antinuclear antibody (Neiman et al. 2000). This high frequency of autoimmunity at an early age is of concern and points to the advisability of good patient and family education and continued follow-up.

The presence of NLE in a child is an indicator of autoimmunity in the mother. Many mothers are asymptomatic when the child is found to have NLE. With time, however, most mothers develop some symptoms of autoimmunity. Studies differ about which symptoms are most common, with some series indicating Sjögren's symptoms to be most common and others emphasizing LE or undifferentiated connective tissue disease (McCune et al. 1987, Press et al. 1996, Waltuck and Buyon 1994). One group found that mothers of babies with cutaneous NLE were more likely to have symptoms of an autoimmune disorder than were mothers of babies with cardiac NLE (Lawrence et al. 2000).

Mothers who have had one child with NLE are at a relatively high risk for having an affected child in a subsequent pregnancy. Several studies have examined the risk, with results ranging from approximately 1 in 6 pregnancies to 1 in 3 pregnancies resulting in another affected baby (Buyon et al. 1998, Julkunen et al. 1993, McCune et al. 1987, Neiman et al. 2000). It is not unusual for a woman who has had a baby with cutaneous NLE to have a baby with cardiac NLE in a subsequent pregnancy.

**Cutaneous Lupus Erythematosus in Children**

**Introduction and Epidemiology**

Cutaneous LE (CLE) developing later than 1 year of age is almost certainly not NLE but rather CLE in childhood. CLE in childhood is frequently seen in the context of systemic disease. SLE is a condition that affects females much more often than males, and sex steroids play a major role in initiating the disease. Thus, CLE is much more common in adolescent girls than in either prepubertal children or adolescent boys. Unfortunately, most reports of childhood LE do not discriminate between prepubertal and postpubertal LE.

The incidence of LE in childhood has been estimated to be 0.6 in 100 000 per year (Lehman 1993). The incidence of CLE in childhood is probably lower. Girls outnumber boys among adolescents with LE, but the effect of sex is not so strong in younger children (Schaller 1982). The prevalence of lupus in black, Asian, and Hispanic children has been reported to be three times that in white children (Siegel and Lee 1973).
Cutaneous Lesions

Malar erythema has been noted in up to four fifths of children with SLE (Font et al. 1998, Lehman 1993, Schaller 1982, Wananukul et al. 1998). Discoid lesions may occur in children with SLE, sometimes as a presenting sign. In a review of 16 cases of childhood discoid LE (DLE) with onset before age 10 years (10 boys and 6 girls), progression to systemic disease was common (George and Tunnessen 1993). Of the 16 cases, 10 were followed into adulthood, and 5 of the 10 developed SLE. SCLE, LE tumidus, LE panniculitis, and bullous LE have all been noted in children (Kettler et al. 1988, Kuhn et al. 2000, Provost et al. 1983, Siamopoulou et al. 1989, Taieb et al. 1986).

Extracutaneous Disease

Childhood-onset SLE has often been described as more severe than adult-onset disease, with a relatively high likelihood of nephritis (Font et al. 1998, Vlachoyiannopoulos et al. 1993). Studies of childhood-onset SLE are frequently limited by a small number of subjects and, often, a lack of distinction between prepubertal and postpubertal SLE. Effects of the disease and its treatment on growth and on emotional and intellectual development may be especially important considerations in the child and adolescent age groups.

Laboratory Evaluation

One study reported a correlation of childhood SLE with anti-Ro/SSA autoantibodies (Lehman et al. 1989). Complement deficiencies have also been reported in association with childhood SLE and in children with SCLE and lupus panniculitis (Meyer et al. 1985, Provost et al. 1983, Taieb et al. 1986).

Pathogenesis

LE is a complex genetic disease with environmental contributions. It may be that individuals who develop disease at an early age have a stronger genetic component through inheritance of more than the usual complement of lupus susceptibility genes.

Genes associated with childhood LE include MHC and complement genes. There are case reports of DLE occurring in association with chronic granulomatous disease (Manzi et al. 1991).

Management

Management of childhood CLE is similar to management of adulthood cutaneous LE, but special consideration must be given to the effects of therapy on growth, social and intellectual functioning, later ability to conceive, and later development of malignancy. Emphasis on conservative therapies such as sun protection and local corticosteroid therapy is advisable in most cases of childhood CLE. Cosmetic camouflage should not be overlooked as an integral part of management. Antimalarial therapy may be used if local measures are insufficient or if scarring in cosmetically sensitive areas is imminent. Education about the negative effects of tobacco use on the effec-
tiveness of antimalarial drugs may be helpful (Jewell and McCauliffe 2000, Rahman et al. 1998). Systemic corticosteroids and immunosuppressive drugs are usually not indicated for cutaneous disease but may be indicated for severe systemic disease. Retinoids have been used in adults with CLE (Newton et al. 1986), but there is little information about the use of retinoids in children with CLE.

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