Congenital Skin Lesions Caused by Intrauterine Infection with Coxsackievirus B3

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Summary

Background: Serious neonatal coxsackievirus infections transplacentally acquired in late pregnancy involve primarily the central nervous system, heart, liver and rarely the skin.

Patients and Methods: A boy born with a disseminated papulovesicular, nodular, bullous and necrotic ulcerated rash at 39 weeks gestational age developed pneumonia, carditis and hepatitis during the first days after birth. Molecular biological and serological methods were used for virological diagnosis.

Results: Coxsackievirus B3 (CVB3) was found in throat swabs and/or feces of the neonate and his mother. In addition, there was serological evidence of intrauterine infection.

Conclusion: Intrauterine transmission of CVB3 during late pregnancy may lead to varicella-like congenital skin lesions.

Key words

Coxsackievirus B3 · Intrauterine infection · Neonatal disease · Congenital skin lesions · Virological diagnosis

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Introduction

Coxsackieviruses and echoviruses are responsible for a wide range of diseases. Infections in adults or children are mostly mild or asymptomatic. During the neonatal period, fulminant infections with significant mortality have been described [1, 2]. They are usually the consequence of perinatal or postnatal infections.

In the last weeks of pregnancy, maternal enteroviral infections with viremia may lead to transmission of the virus to the fetus via the transplacental route. Life-threatening neonatal infections are expected when the onset of illness occurs at the time of birth or within the first few days after delivery. These usually lead to sepsis, meningoencephalitis, myocarditis or hepatitis [3]. Cutaneous manifestations have rarely been described [4, 5]. We report a case of intrauterine coxsackievirus B3 (CVB3) infection resulting in a congenital bullous-necrotic exanthema associated with pneumonia, carditis and cholestatic hepatitis.

Patients and Methods

A male infant was born at 39 weeks gestation by normal spontaneous vaginal delivery to a 25-year-old gravida one para (one female). Two weeks prior to delivery, the infant's mother, father and grandparents had been ill with mild signs of respiratory infections. The 5-year-old sister had suffered from fever, fatigue, nausea, diarrhea and a transient maculopapulous exanthema.

The infant was born with a papulovesicular, nodular, bullous and ulcerative rash covering the face, scalp, trunk, extremities, palms and soles (Figure 1). Papulovesicules at different stages of development resolved within a few weeks without scars. Ulcerations healed with varicella-like scar formations months later. On the third day after birth, the infant developed bilateral pneumonia and carditis. Hypertrophy of the adrenal glands was noted. Cholestatic hepatitis became apparent in the second week. During the following weeks, the infant suffered from repeated bacterial chest infections with *Streptococcus mitis*, *Streptococcus faecalis* and *Pseudomonas aeruginosa* resulting in bronchopulmonal dysplasia with ventricular hypertrophy.

The boy was hospitalized for 3 months and treated with penicillin, cephalosporin, aminoglycoside and glycopeptide antibiotics, aciclovir as well as supplemental oxygen. He required intubation and ventilation for 3 weeks. At 6 months of age, the child had developed atopic dermatitis with *Candida* infection and had bronchopulmonal dysplasia, impaired central coordination and disseminated varicella-like scars.

Swabs from throat, feces and vesicles were obtained from mother and neonate immediately after delivery and examined virologically. After extraction of total RNA by the acid guanidinium

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thiocyanate-phenol-chlorophorm method [6], one step reverse transcriptase PCR (Hoffmann-LaRoche, Germany) was performed with oligonucleotide primers selected from highly conserved sequences of the 5'-nontranslated regions of enteroviruses (5'-CGGTACCTTTGTAGCGCTTGTTTTA-3', 5'-CGGACACCCAAAGTAGTCGGTTCC-3', amplified product 496 bp). Internal oligonucleotides were used as primers for nested PCR (5'-CCCCGGACTGAGTATCAATA-3', 5'-CAGTTAGGATTAGCGGCATTC-3', amplified product 300 bp). DNA fragments were detected by Southern blotting and analyzed by automatic DNA sequencing (AmpliTaq®, FS Dye Terminator sequencing kit; ABI PRISM™ 310 Genetic Analyser, Perkin Elmer, Germany).

Serum samples from mother and newborn were tested for coxsackieviral serotype B3-specific IgM and IgG class antibodies using the indirect immunofluorescence assay with CVB3-infected A549 cells prepared on microscopic glass slides.

Results

Following nested PCR, DNA amplicons of 300 bp were demonstated in specimens obtained from both throat and feces of the newborn and from the mother's throat immediatelly after delivery (Figure 2). CVB3 was identified as the etiological agent by DNA sequencing. Virus shedding into the oropharynx was demonstrated in the infant during the first 6 months of life.

IgM and IgG class antibodies specific for CVB3 could be detected by indirect immunofluorescence in serum samples of the boy and his mother taken at the time of delivery. Serotype CVB3-specific IgM was positive for 4 weeks and IgG was still present in the boy's serum at the age of 1 year.

Discussion

Intrauterine enteroviral infections in late pregnancy are rarely documented because transplacental infections are difficult to confirm. The clinical picture seen in neonates ranges from inapparent infections to severe and even fatal disease including aseptic meningitis, meningoencephalitis, myocarditis and/or hepatitis [3, 7, 8]. This paper reports a case of intrauterine CVB3 infection in a male neonate born with a remarkable bullous-necrotic rash. The diagnosis was confirmed using molecular biological and serological methods.

Coxsackievirus and echovirus infections are quite frequently associated with maculopapular or rubelliform rashes which have also been described in combination with neonatal aseptic meningitis [9]. Other cutaneous findings have rarely been reported, especially in neonates. *Bowden* et al. [5] observed a case of dermal hematopoiesis caused by congenital coxsackievirus B2 infection. Necrotic skin lesions of the upper extremities were described by *Arnon* et al. [4] in a neonate with fatal echovirus 19 infection. In our case, congenital skin lesions at different stages of development were found. Immediately after birth, the rash suggested neonatal varicella infection. However, the mother was positive for varicella-zoster virus-specific IgG class antibodies and the extension of the rash to palms and soles was not typical for chicken pox. CVB3 could be identified as the etiological agent in both the neonate and his mother by molecular biological methods. In addition, there was serological evidence of intrauterine infection most likely due to maternal viremia. Mild respiratory symptoms as described by the pregnant woman and the members of her family 2 weeks before delivery are characteristic of coxsackievirus infections in adults. Fever, fatigue, nausea, diarrhea and exanthema as observed in the sister are common symptoms in children. The infections occurred during the summer, a typical period for the seasonal spread of enteroviruses in temperate climates.

Late gestation enteroviral infection is presumed if the disease occurs in the newborn at birth or within the first 2 days after delivery. Infants with an onset of disease between 3 and 10 days of age are likely to have acquired the infection perinatally [8]. *Modlin* [3] postulated that the timing of maternal infection in relation to delivery is an important determinant for the prognosis of neonatal disease.

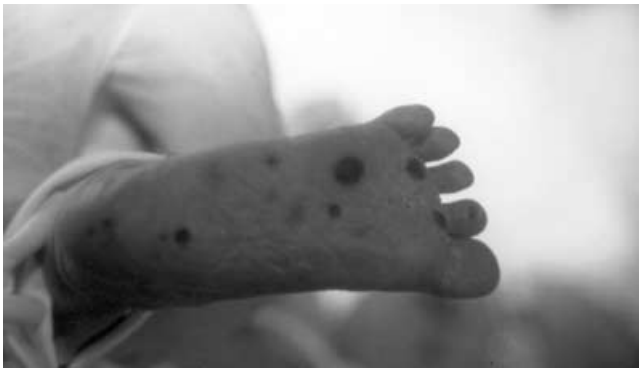

Figure 1
Papulovesicular, nodular and bullous rash on the sole of the right foot of a neonate with congenital coxsackievirus B3 infection.

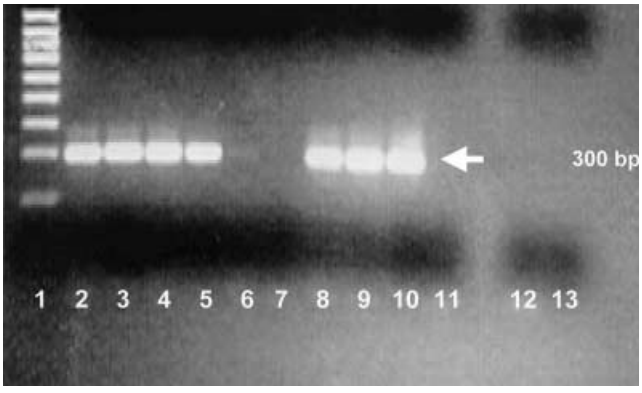

Figure 2
Detection of transcribed enteroviral DNA in clinical specimens of a neonate with congenital coxsackievirus B3 infection and his mother by nested PCR. Lane 1: molecular weight standard 100 bp, 2-5: positive controls, 6 and 7: vesicle specimens, newborn, 8: throat swab, newborn, 9: feces, newborn, 10: throat swab, mother, 11: feces, mother, 12 and 13: negative controls.

If maternal infection occurs more than 5 to 7 days before delivery, the fetus has likely acquired IgG antibodies protecting against serious sequelae. However, as our case of maternal infection 2 weeks before delivery illustrates, other risk factors may influence the severity of intrauterine transmitted neonatal enteroviral diseases, including the serotype of the virus [10], prematurity and/or gender [7].

Virus isolation in cell culture is regarded as the "gold standard" for diagnosing enteroviral infections in neonates [11]. However, in this case, virus cultures in human embryonic lung fibroblasts and human amnion cells were not successful. Reasons may be a low yield of infectious virus, restricted susceptibility of cell cultures used, or loss of infectivity since the samples were not obtained from fresh vesicles. To achieve an early as well as an accurate diagnosis, PCR technology is increasingly becoming the standard method in medical virology. PCR detection of virus in CSF, blood, vesicles or tissue can be considered as etiological evidence. In our case, investigation of swabs from vesicles did not produce unequivocally positive PCR results, however the detection of CVB3-specific IgM most convincingly confirmed acute infection. The indirect immunofluorescence assay, used in this case, has not yet been established as a routine method. This test is recommended for rapid identification of enterovirus serotypes [12] as well as for the detection of enteroviral serotype-specific antibodies [13]. In comparison, the neutralization assay, considered the "gold standard" for serological diagnosis of enteroviral infections, is time-consuming and expensive.

To date, neither causal therapy nor specific prophylaxis for coxsackievirus and echovirus infections are available. Some authors recommend empirically the treatment of affected infants with a combined therapy of intravenous gamma or hyperimmune globulin and leukocyte interferon [10, 14] or the transfusion of maternal plasma [15]. However, there is no evidence that such treatments prevent the fatal outcome of disease. At present, intensive supportive care, isolation of the infected infant and strict hygiene are the most important measures.

References

1. Jenista JA, Powell KR, Menegus, MA: Epidemiology of neonatal enterovirus infection. J Pediatr 1984; 104: 685–690.
2. Sauerbrei A, Frenzel J, Wutzler P, Sprößig M, Raabe G: Infektionen durch ECHO-Virus Typ 11 bei Neugeborenen. Dt Gesundh-Wesen 1983; 38: 501–507.
3. Modlin JF: Perinatal echovirus and group B coxsackievirus infections. Clin Perinatol 1988; 15: 233–246.
4. Arnon R, Naor N, Davidson S, Katz K, Mor C: Fatal outcome of neonatal echovirus 19 infection. Pediatr Infect Dis J 1991; 10: 788–789.
5. Bowden JB, Hebert AA, Rapini RP: Dermal hematopoiesis in neonates: report of five cases. J Am Acad Dermatol 1989; 20: 1104–1110.
6. Comczynski P, Sacchi N: Single step method of RNA isolation by guanidium thiocyanate-phenol-chlorophorm extraction. Anal Biochem 1987; 162: 156–159.
7. Chiou CC, Liu WT, Chen SJ, Soong WJ, Wu KG, Tang RB, Hwang B: Coxsackievirus B1 infection in infants less than 2 months of age. Am J Perinatol 1998; 15: 155–159.
8. Chou LL, Chang CP, Wu LC: Neonatal coxsackievirus B1 infection associated with severe hepatitis: report of three cases. Acta Paed Sin 1995; 36: 296–299.
9. Cramblert HG, Hcynes RE, Azimi PH, Hilty MD, Wilder MH: Nosocomial infection with echovirus type 11 in handicapped and premature infants. Pediatrics 1973; 51: 603–607.
10. Isacsohn M, Eidelman AI, Kaplan M, Goren A, Rudensky B, Handsher R, Barak Y: Neonatal coxsackievirus group B infections: experience of a single department of neonatology. Isr J Med Sci 1994; 30: 371–374.
11. Haddad J, Gut JP, Wendling MJ, Astruc D, Jernite M, Obert G, Messer J: Enterovirus infections in neonates: a retrospective study of 21 cases. Eur J Med 1993; 2: 209–214.
12. Rigonan AS, Mann L, Chonmaitree T. Use of monoclonal antibodies to identify serotypes of enterovirus isolates. J Clin Microbiol 1998; 36:1877–1881.
13. Zhang H, Morgan-Capner P, Latif N, Ponolfino YA, Fan W, Dunn MJ, Archard LC. Coxsackievirus B3-induced myocarditis. Characterization of the stable attenuated variants that protect against infection with the cardiovirulent wild-type strain. Am J Pathol 1997; 150: 2197–2207.
14. Abzug MJ, Keyserling HL, Lee ML, Levin MJ, Rotbart HA: Neonatal enterovirus infection: virology, serology, and effects of intravenous immune globulin. Clin Infect Dis 1995; 20: 1201–1206.
15. Jantausch BA, Luban NLC, Duffy L, Rodriguez WJ: Maternal plasma transfusion in the treatment of disseminated neonatal echovirus 11 infection. Pediatr Infect Dis J 1995; 14: 154–155.