

Sclerema Neonatorum Treated With Intravenous Immunoglobulin: A Case Report and Review of Treatments

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Practice Points

- Sclerema neonatorum is a rare neonatal panniculitis with a high mortality rate.
- Exchange transfusion improves survival, but its use in neonates has declined.
- Intravenous immunoglobulin represents a novel treatment option that may lead to increased survival in pre-term newborns with sclerema neonatorum.

Sclerema neonatorum (SN) is a rare neonatal panniculitis that typically develops in severely ill, preterm newborns within the first week of life and often is fatal. It usually occurs in pre-term newborns with delivery complications such as respiratory distress or maternal complications such as eclampsia. Few clinical trials have been performed to address potential treatments. Successful treatment has been achieved via exchange transfusion (ET), but its use in neonates is declining. Similar to ET, intravenous immunoglobulin (IVIG) enhances both humoral and cellular immunity and thus may decrease mortality associated with SN. We report a case of SN in a term newborn who subsequently developed septicemia. Biopsy showed subcutaneous, needle-shaped clefts without associated necrosis, inflammation, or calcifications. Treatment with IVIG led to notable but short-term clinical

improvement. Sclerema neonatorum remains a poorly understood and difficult to treat neonatal disorder. Although IVIG did not prevent our patient's death, further studies are needed to determine its clinical utility in the treatment of this rare disorder.

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Sclerema neonatorum (SN) is a rare neonatal panniculitis that typically develops in severely ill, preterm newborns within the first week of life. It is characterized by rapidly progressive induration of subcutaneous fat. Treatments include supportive care, emollients, warming/maintaining core body temperature, oxygenation, antibiotics, systemic corticosteroids, and exchange transfusion (ET) with whole blood. Despite these treatment options, however, mortality is high. Exchange transfusion has been one of the most promising treatments, with reports of increased survival rates from 20% to 75%.^{1,2} Exchange transfusion may help to stabilize opsonization and complement activation by increasing immunoglobulin levels, thereby improving survival.¹⁻³ Although ET shows promising results, the overall mortality rate is 2% with this procedure (8% mortality for ill newborns), and it is associated with serious risks such as cardiovascular collapse, necrotizing enterocolitis, and bacterial sepsis.⁴ The

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use of ET in neonates has declined substantially over the last 20 years, with more newborns being treated with intravenous immunoglobulin (IVIG).⁵ Intravenous immunoglobulin is a novel treatment consideration for newborns with SN, specifically in the setting of sepsis, and may avoid some risks associated with ET while providing benefits that lead to increased survival. We report a case of SN in a newborn that was treated with IVIG.

Case Report

A female newborn delivered at 41 weeks' gestation presented with progressive hardening of the skin at 3 days of age. Prior to birth, the fetus developed a nonreassuring heart rate and was urgently delivered by cesarean birth. On delivery, meconium staining of the amniotic fluid was noted, and the newborn was cyanotic without spontaneous respirations (Apgar score of 1/6/9 at 1, 5, and 10 minutes, respectively). Despite positive pressure ventilation, metabolic and respiratory acidosis (pH 7.004) developed. Due to concomitant hypoxia, hypoglycemia, thrombocytopenia, transaminitis, hyponatremia, and possible observation of a faint consolidation in the right lung on chest radiograph, sepsis was suspected and ampicillin and gentamicin were started. Shortly after the newborn was delivered, erythematous patches were noted on her arms, legs, and abdomen, along with tender, indurated, violaceous plaques on the buttocks and back.

The patient's metabolic and respiratory status greatly improved over the first 24 hours with oxygen support. Thrombocytopenia persisted, but the patient's chest radiograph and aberrant electrolytes and glucose normalized over a few days. Blood and urine cultures were negative, and evaluation for TORCH (toxoplasmosis, other infections, rubella, cytomegalovirus infection, herpes simplex) infections was negative; a maternal drug screen also was negative. Prenatal maternal group B streptococci testing was negative and the mother reported an uncomplicated pregnancy with regular prenatal care.

Despite normalization of the electrolytes, negative infectious workup, and initial improvement of respiratory status, the patient's skin induration rapidly progressed over the next 4 days and the firm violaceous changes became circumferential around her proximal extremities and trunk, even involving her cheeks and eventually her distal extremities (Figure 1). Her movement appeared restricted and the affected areas were exquisitely tender to palpation. Calcium levels were checked due to suspected subcutaneous fat necrosis (SCFN) of the newborn but were found to be normal. Skin biopsies done on days 5 and 18 after birth showed a normal epidermis



Figure 1. Indurated violaceous plaques on the buttocks, back, and proximal extremities.

and dermis with a sparse inflammatory infiltrate and radially arranged, needle-shaped crystals in the subcutaneous fat without adipocyte necrosis, foreign body giant cells, or calcification (Figure 2), findings that are consistent with SN.

As the patient's skin became more indurated, she required ventilator support due to chest wall restriction that led to respiratory compromise. She developed multiple infections including *Serratia marcescens* and *Pseudomonas aeruginosa* infections in the urinary tract and trachea, ocular *P aeruginosa* and coagulase-negative staphylococci infections, and coagulase-negative staphylococcal bacteremia. Given the paucity of inflammation seen on biopsy and the concurrent infections, administration of high-dose corticosteroids was avoided; instead, IVIG was initiated (1 g/kg daily). The patient underwent 2 days of IVIG therapy and initially her skin slightly improved. Unfortunately, the induration subsequently worsened until it involved all skin, except for the palms and soles, and the patient developed anasarca. At 6 weeks of age, the patient's oxygen saturation was below 60% despite full respiratory support, and the family elected to withdraw ventilatory support. The patient died of respiratory failure attributed to thoracic constriction secondary to SN. Posthumous radiographs and autopsy identified no congenital anomalies.

Comment

Sclerema neonatorum, which is unusual in term newborns, typically occurs in preterm newborns with delivery complications (eg, respiratory distress, sepsis, cold exposure) or maternal complications (eg, eclampsia, placental abruption).⁶ Clinical descriptions of SN have a broad range, but all cases present

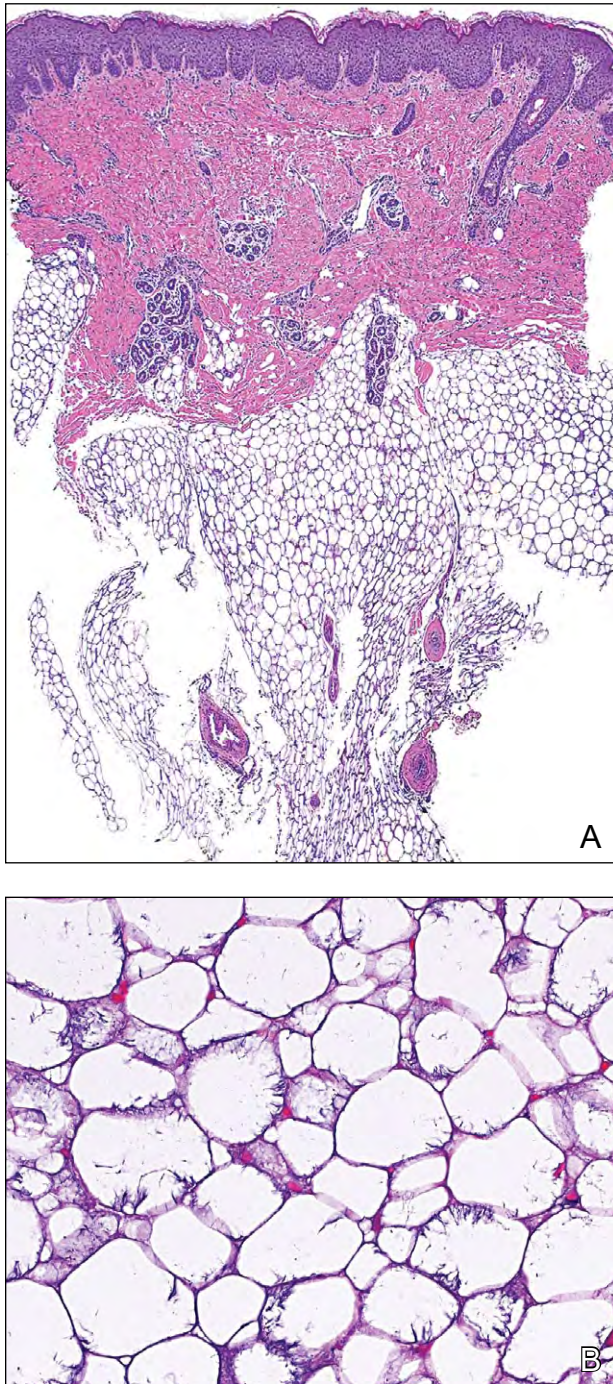


Figure 2. Sections of a punch biopsy from the buttocks showed small individual adipocytes, which is a normal finding in newborns. Inflammation was notably absent (A) (H&E, original magnification $\times 20$). Scattered adipocytes exhibited radiating, needle-shaped clefts with no inflammation and calcifications (B)(H&E, original magnification $\times 400$).

with indurated, bound down skin.^{6,9} The pathogenesis of SN is not fully understood, but several theories point to the higher ratio of saturated to unsaturated fatty acids in neonatal skin as a susceptibility

factor.^{7,10} Metabolic abnormalities and fetal distress may prevent the normal postdelivery mobilization of fatty acids from subcutaneous fat into the serum. The presence of relatively high levels of saturated fats may lead to crystallization and subsequent induration of SN.⁷ Perinatal asphyxia also may trigger a redistribution of the circulation to vital internal organs, leaving the skin in a relatively ischemic state and contributing to the crystallization of fat seen in SN.¹¹

The differential diagnosis of SN includes extensive SCFN and scleredema. In contrast to SN, SCFN typically has a later onset (ie, days to weeks after birth), usually occurs in healthy newborns, and does not tend to spread beyond the initial area(s) of involvement.⁶ Histologically, SCFN is characterized by needle-shaped clefts, necrosis, and an intense mixed inflammatory infiltrate containing foreign body giant cells in the subcutaneous fat.^{6,11} Infants with SCFN can develop hypercalcemia, which can indicate an increased risk for adverse outcomes such as cardiac arrest or infection.¹¹ In general, however, SCFN resolves spontaneously within several months.^{6,11}

Scleredema tends to occur in premature neonates during the first week of life. Clinically, it is characterized by waxlike pitting edema that more often occurs on the lower extremities. Patients tend to have congenital heart disease and may have a history of exposure to cold temperatures at birth or shortly thereafter, diarrhea, or vomiting.^{6,11} Histopathologic examination typically reveals an edematous dermis with substantial mucin deposition.^{6,11,12} Similar to SCFN, scleredema tends to heal with supportive therapy.^{6,12} Other less likely clinical considerations for the differential diagnosis of SN include restrictive dermopathy, scleroderma, steroid panniculitis, and cold panniculitis.

There is no known cure for SN. To date, treatment focuses on addressing any underlying disorders. Few clinical trials have been performed addressing the treatment and outcomes of SN (Table). Systemic corticosteroids have not shown decreased mortality but have been associated with clinical improvement of sclerema skin changes in some cases.^{8,9} Some of the most promising results have been seen with ET. Sadana et al¹ reported that ET with whole blood increases IgG, IgA, and IgM levels, and these patients have greater survival than control patients. Vain et al² reported survival of 7 of 10 (70%) infants with SN and sepsis who were treated with ET, suggesting that ET increased IgA and IgM levels, removed endotoxins, improved perfusion and tissue oxygenation, and enhanced humoral and cellular immune responses, leading to decreased mortality. In a study of 60 neonates with SN, Narayanan et al¹³ noted a

Treatment of Sclerema Neonatorum Over the Last 20 Years (Case Reports and Clinical Trials)^a

Reference (Year)	No. of Patients Treated	Treatment	Outcome
Vain et al ² (1980)	10	ET	7/10 survived (30% mortality)
Narayanan et al ¹³ (1982)	60	Supportive care only (20/60); supportive care and whole blood transfusion (20/60); ET (20/60)	2/20, 6/20, and 8/20 survived (90%, 70%, and 60% mortality, respectively)
Jardine et al ¹⁴ (1990)	1	Supportive care	Patient survived
Sadana et al ¹ (1997)	20	ET	10/20 patients survived (50% mortality)
Battin et al ¹⁵ (2002)	1	Supportive care	Patient survived
Zeb et al ¹⁶ (2009)	51	Emollients	1/51 patients survived (98% mortality)

Abbreviation: ET, exchange transfusion.

^aIn all cases, patients with concomitant sepsis were treated with antibiotics. Note that Chisti et al¹⁷ reported 30 cases of sclerema, and 21 patients survived with supportive care only; these cases were not included because the authors defined sclerema more broadly and included children beyond the neonatal period.

statistically significant decrease in mortality with ET plus dexamethasone compared to simple transfusion with whole blood plus steroids and steroids alone (mortality rate of 60%, 70%, and 90%, respectively) ($P < .05$). The main complication noted in the ET group was necrotizing enterocolitis, which was the cause of 3 of 12 deaths in that treatment group.¹³

We hypothesized that IVIG would provide several of the benefits of ET while avoiding some of the associated risks, such as necrotizing enterocolitis. Our goal was to enhance treatment of the patient's sepsis, thereby facilitating survival and subsequent improvement of her SN. Our rationale was supported by reports documenting improvement of septic neonates without SN when treated with IVIG.^{18,19} Because infants do not produce their own immunoglobulins until approximately 24 weeks of age, IVIG is administered to supply IgG for cell surface binding, opsonization, complement activation, and antibody-dependent cytotoxicity, as well as to improve neutrophilic chemoluminescence.²⁰ In our case, administration of IVIG did not prevent the patient's death, though it likely led to mild brief clinical improvement.

Conclusion

The reported benefit of IVIG in septic neonates was greater in preterm versus term neonates.¹ The lack of notable improvement with IVIG treatment in our patient may be at least partially attributed to the fact that she was a term newborn and therefore presumably had normal maternal transfer of immunoglobulins at 32 weeks' gestation and thus normal IgG levels. Because SN is a rare disorder, definitive conclusions on the best treatment of these patients remain elusive.

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