

# Digital necrosis in an infant with severe spinal muscular atrophy

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Spinal muscular atrophy (SMA) is the leading genetic cause of death for infants.<sup>1,2</sup> Digital necrosis is an ultra-rare manifestation of this disease, and its etiology has yet to be elucidated.<sup>4,5</sup> We present a child who was referred to genetics for extensive digital necrosis after cardiac surgery. The infant was ultimately diagnosed with SMA by single gene testing that revealed a homozygous deletion of exons 7 and 8 on the *SMN1* gene. SMA is a motor neuron disorder typically presenting with neurologic symptoms but should be considered in any infant with digital necrosis.

## Case report

The child was born uneventfully to a family with an unremarkable medical history. At age 1 month, he presented with failure to thrive. Workup revealed a large atrial septal defect and multiple ventricular septal defects. Pulmonary artery banding was performed at age 2 months. Postoperatively, he required intubation for 3 weeks. He also developed severe necrosis of all 10 toes (figure, A). A hypercoagulation panel was normal. A Doppler ultrasound revealed a left femoral clot, which was successfully treated with anticoagulation, aspirin, and nitroglycerin. However, the necroses progressed, and no cause was initially identified. Allowing autoamputation of the toes was recommended. He was discharged home at age 4 months on gastrostomy tube feeds. By then, developmental delay was noted, although he was able to roll from his stomach to his back and bring his hands to his mouth. At home, he started having respiratory problems, with oxygen saturations in the mid 80s. He intermittently developed diaphoresis and tachypnea.

He was readmitted 1.5 weeks later. His mother had additionally noticed a violaceous discoloration of his fingernails (figure, B). Despite heparin, aspirin, methylprednisolone (in case of vasculitis), and a supraclavicular nerve block with the intent of reversing any vasoconstriction, this progressed to severe necrosis. CT angiography and an echocardiogram did not reveal an embolic source. At that time, the child was also found to have clinically recognizable hypotonia, decreased right palmar grasp strength, and a tremulous tongue. On the day of readmission, he went into respiratory failure requiring intubation. A workup for rheumatologic conditions returned negative including an antiphospholipid panel, antinuclear antibodies, cryoglobulin levels, anti-neutrophil cytoplasmic antibodies for myeloperoxidase, anti-neutrophil cytoplasmic antibodies for proteinase 3, adenosine deaminase 2 deficiency, and a cytokine panel. A brain MRI returned normal. Trio whole-exome sequencing was sent, and results were nondiagnostic. An electromyogram demonstrated evidence of possible anterior horn cell dysfunction as can be seen in SMA. *SMN1* genetic testing was sent, and PCR amplification showed a homozygous deletion of exons 7 and 8, diagnostic of SMA. In addition, the *SMN2* copy number was tested revealing that the patient had only 1 copy of *SMN2*. The pediatric palliative care team helped elucidate the family's goals for the patient, facilitated a comfort care plan, which included a compassionate extubation, and continued to provide bereavement support for the family.

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(A) Left foot. (B) Right hand.

## Discussion

SMA is a result of biallelic intragenic deletions or pathogenic variants in the *SMN1* gene located on chromosome 5q13, which cause loss of function of the survival of motor neuron protein (SMN). SMN is ubiquitously expressed, and although SMA is characterized by loss of motor neurons in the ventral horn of the spinal cord, multiple organs, including cardiac, skeletal, and gastrointestinal, are negatively affected as well.<sup>2,3</sup> The severity and age at onset span a continuum. Digital necrosis is rare in SMA and has been reported in only 4 other cases, all infants with a severe form of the disease.<sup>4,5</sup> Of interest, mouse models for severe SMA given life-prolonging treatments have developed tail and ear necrosis.<sup>6</sup> The *SMN2* gene is nearly identical to the *SMN1* gene except for a single nucleotide change, which causes skipping of its exon 7, resulting in only 10% of its protein product being functional. The copy number of *SMN2* varies in the population and inversely correlates with disease severity. In our case, the patient was found to have only 1 copy of *SMN2*. The antisense oligonucleotide nusinersen was approved for treatment of certain cases of SMA. Nusinersen increases the percentage of *SMN2*'s functional protein product by including transcription of its exon 7.<sup>7</sup> This along with other interventions is expected to improve life expectancy. Our patient presented before the approval of this medication, and it is not known whether a manifestation such as a digital necrosis would respond to this new therapy. Further delineation of the phenotype of SMA will aid in uncovering etiologies of the disease's manifestations and directed therapies. This report describes the fifth case of an infant with severe SMA who developed distal digital necrosis. An examination of *SMN2* copy number in more of these cases with this unusual and dramatic complication would be useful. Our case highlights the need to consider SMA in the differential diagnosis for infantile digital necrosis.

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## Appendix Authors

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