

# Novel cutaneous manifestations of a pediatric patient with Farber lipogranulomatosis



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**Key words:** ceramidase deficiency; diagnosis; Farber's disease; genetic syndrome; genetic testing; genodermatosis; lysosomal storage disease; pediatric dermatology; pediatrics.

## INTRODUCTION

Farber lipogranulomatosis or Farber's disease (FD), is an extremely rare, often fatal, autosomal recessive, lysosomal storage disease (LSD) that is characterized by a triad of hoarse cry, joint abnormalities, and the formation of multiple subcutaneous nodules.<sup>1,2</sup> While the presence of these nodules is well-documented, other cutaneous manifestations of FD are seldom reported.

## CASE PRESENTATION

A 19-month-old girl with global developmental delay, cardiac arrest, suspected hypoxic brain injury, seizures, spastic quadriplegia, and multiple subcutaneous nodules from 2 months of age, and a hoarse cry since birth, was referred to our dermatology clinic. She was born prematurely at 33 weeks via spontaneous vaginal delivery to consanguineous parents. She spent 14 days in the neonatal intensive care unit due to respiratory distress and required nasogastric tube feeding. The family history was unremarkable.

Upon examination, multiple erythematous, subcutaneous nodules and plaques were identified on the scalp, back, and extremities (Figs 1 to 3). A large fungating, pedunculated, bleeding tumor was also noted on the buttocks (Fig 2). This lesion was a previously existing subcutaneous nodule that grew in size and began to ulcerate. Furthermore, multiple, scattered, ill-defined, hypopigmented macules,

### Abbreviations used:

|      |                                |
|------|--------------------------------|
| EDM: | extensive dermal melanocytosis |
| FD:  | Farber's disease               |
| LSD: | lysosomal storage disease      |
| PV:  | pathogenic variant             |

patches, and atrophic plaques were noted throughout (Figs 1 to 3). Some of these lesions had a hyperpigmented rim. The patient's father denied any trauma to these areas. Lastly, multiple blue-gray to violaceous patches, clinically consistent with extensive dermal melanocytosis (EDM), were noted on the back (Fig 3).

Genetic testing identified a homozygous pathogenic variant (PV) in the N-acylsphingosine amidohydrolase gene on chromosome 8p22, confirming the diagnosis of FD. Both parents were found to carry a heterozygous PV of this gene. Additionally, a homozygous variant of uncertain significance was detected in the PCDHGC4 gene, with both parents carrying a heterozygous variant of uncertain significance. PVs in the PCDHGC4 gene are linked to an autosomal recessive neurodevelopmental disorder characterized by poor growth and skeletal anomalies.<sup>3</sup>

An echocardiogram showed mitral and tricuspid regurgitation. Brain magnetic resonance imaging (MRI) revealed mild supratentorial parenchymal atrophy, moderate ventriculomegaly, and a stable focus of susceptibility effect in the left caudothalamic

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Funding sources: None.

Patient consent: The authors obtained written consent from the patient's parents for the photographs and medical information to be published in print and online and with the understanding that this information may be publicly available. Patient consent forms were not provided to the journal but are retained by the authors.

IRB approval status: Not applicable.

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JAAD Case Reports 2024;51:45-7.

2352-5126

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<https://doi.org/10.1016/j.jidcr.2024.04.040>



**Fig 1.** Multiple erythematous, subcutaneous nodules were noted on the posterior scalp, posterior neck, and back. Additionally, there is a hypopigmented macule noted on the *upper* back.



**Fig 2.** There are multiple erythematous, subcutaneous nodules, and plaques on the back. Furthermore, multiple *blue-gray* to violaceous patches that are consistent with extensive dermal melanocytosis (EDM) are evident. Additionally, multiple hypopigmented macules and patches are visible. Lastly, the buttocks reveal a large, fungating, pedunculated, and bleeding tumor.



**Fig 3.** An erythematous to violaceous, subcutaneous nodule is noted on the palmar surface of the bilateral thumbs. There are also numerous hypopigmented macules, patches, and atrophic plaques across the chest and abdomen, some of which have a hyperpigmented rim.

groove, likely indicating previous microhemorrhage. A whole spine MRI detected a large soft tissue lesion in the atlantoaxial joint, mild foramen magnum narrowing, and mass effect on the cervicomedullary junction. There were also various subcutaneous soft tissue masses from L1-L4 and over the sacrococcygeal region. Chest x-ray showed bilateral ground-glass infiltrates. Abdominal and kidney ultrasounds were normal. X-ray of both lower limbs revealed anterior bowing of the femurs and osteopenia.

Education, reassurance, and discussion of possible treatment options were discussed with the parents including possible excision of the lesions. A conservative approach with observation was elected with regular wound care of her tumor with topical twice daily applications of 2% fucidic acid ointment and metronidazole 0.75% gel. Analgesia was deferred. The patient was referred to the pediatric hematology team for a possible hematopoietic stem cell transplant but was not a candidate due to her severe neurological insult.

Unfortunately, by the time of writing this manuscript, our patient had passed away from cardiac arrest.

## DISCUSSION

FD is due to a homozygous PV of the N-acylsphingosine amidohydrolase gene located on chromosome 8p22. This PV results in a deficiency of acid ceramidase and leads to the accumulation of ceramide in multiple cell types including histiocytes and epithelial cells, with subsequent granulomatous formation of various organs, including the brain, larynx, liver, kidney, lungs, and skin. The disease is

subclassified into 7 subtypes based on the phenotypic spectrum of severity and may be associated with the involvement of other organs including, cardiovascular, lymphatic, and neuromuscular systems. Furthermore, depending on the disease onset and severity patients may have a reduced life expectancy of 3 years.<sup>1,2,4-6</sup> Our patient's subcutaneous nodules, joint abnormalities, hoarse cry, and neurological symptoms are consistent with type-1 FD.<sup>2</sup>

Cutaneous manifestations of FD, beyond subcutaneous nodules and erythematous plaques, are rarely reported. Previous reports have indicated that patients with FD may have "stiff skin" or "scleroderma-like" lesions. Biopsies from FD patients have shown increased dermal collagen, potentially accounting for a higher susceptibility to keloid formation.<sup>1</sup> This may explain our patient's ulcerated tumor and hypopigmented lesions, possibly due to impaired wound healing or tissue remodeling. Other findings in the biopsied samples included hyperkeratosis and "Farber bodies" within foamy histiocytes.<sup>1</sup>

Based on our patient's clinical findings, we hypothesize that FD, like other LSDs, may be associated with EDM. Previous reports have shown that EDM, when combined with other LSDs, like Hunter and Hurler syndrome, can appear atypically with an anterior component and be both persistent and progressive. Hanson et al previously proposed that abnormalities in the interactions between the melanocyte's chemotropic receptor for nerve growth factor may lead to an arrested transdermal migration of melanocytes and the development of EDM.<sup>7,8</sup>

To our knowledge, this is the first reported case of EDM in a patient with FD. This may suggest a novel finding of EDM in association with FD but the data is limited and more research is needed to confirm this association. Although keloids and scarring have been previously recorded, no cases of ulceration or dyspigmentation have been reported.

Given its rarity, with an estimated prevalence of  $\leq 1/1,000,000$ . FD poses a treatment challenge, as there are no treatments currently available that are approved by the Food and Drug Administration.<sup>2</sup> Reports have shown modest improvement with hematopoietic stem cell transplant, but its usage is restricted due to an elevated risk of morbidity and mortality. Researchers conducted proof-of-concept studies on mouse models and cultured human FD fibroblasts, pointing to gene therapy and enzyme replacement therapy as viable future treatment options. However, current management emphasizes pain and inflammatory symptom control as the primary treatment.<sup>1,5,9</sup>

Diagnosing and managing FD requires a high level of clinical suspicion as it can mimic other

comparable entities such as hyaline fibromatosis syndrome and juvenile idiopathic arthritis, resulting in misdiagnosis and treatment delays.<sup>2,9,10</sup> Thus, a multidisciplinary team approach is required to ensure consistent patient outcomes.

In conclusion, consider genetic testing, a multidisciplinary approach, patient education and regular follow-up in a patient with FD that presents with a myriad of findings in association with EDM.

## DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work the author(s) used GPT4, Grammarly, and QuillBot in order to shorten the manuscript to fit the word count and improve readability, fluency and grammar. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

## Conflicts of interest

None declared.

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