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CASE REPORT

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Presentation of ichthyosis after substrate reduction therapy in Gaucher type 1

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Abstract

We describe a case in which a type 1 Gaucher patient developed ichthyosis weeks after starting substrate reduction therapy (SRT) with eliglustat. There are no reports of ichthyosis in the literature in enzyme replacement or SRT for Gaucher disease. Ichthyosis is seen with type 2 and 3 Gaucher disease, but not type 1. This raises the question: Why would a patient develop ichthyosis after starting SRT?

KEYWORDS
case report, eliglustat, Gaucher disease, ichthyosis

1 | INTRODUCTION

Gaucher's disease (GD) is one of the most common lysosomal storage diseases that affects the recycling of cellular glycolipids into their glucose and lipid constituents. More specifically, this autosomal recessive disease arises from a deficient enzyme, glucosylceramidase, which is responsible for the degradation of glucosylceramides (Beutler & Grabowksi, 2001). A deficiency in glucosylceramidase leads to a buildup of glucosylceramides within the lysosomes of cells. This accumulation can increase glucosylceramide tissue levels 20–100 times the normal levels (Svennerholm et al., 1982).

There are numerous effects from this accumulation of glucosylceramide, and this gives rise to three different types of GD: Type 1 (GD1), type 2 (GD2), and type 3 (GD3). Each type presents with its own manifestations; however, these three types represent a continuum of the disease rather than distinct entities (Goker-Alpan et al., 2003). In all types, visceral organs, bone marrow, and bone are affected. The accumulation of lipids in visceral organs and bones is commonly observed as splenomegaly, hepatomegaly, decreased bone mineral density, and decreased bone mass density (Akiyama, 2010). GD2 and GD3, but not GD1, also impact the skin, exhibiting ichthyosis. Ichthyosis is a skin disease characterized by skin barrier dysfunction presenting with dry, polygonal scales on the skin (Charrow et al., 2000). The term ichthyosis is derived from the Greek word for "fish" which describes the fish-like polygonal scale in this family of disorders. Distinct from types 2 and 3, type 1 does not involve the central nervous system. GD2 and GD3 are distinguished from one another based on the acute or chronic nature of the disease. GD2 is characterized by severe developmental delay or regression and congenital ichthyosis whereas corneal opacity and cardiovascular calcification are rare and unique to GD3 (Amaral et al., 1993; Kaplan et al., 2006). It is important to note that while these classifications exist, there is great variability in the presentations, severity, and progression of this disease within and between each type. Furthermore, the variability of GD is demonstrated in monozygotic twins who share a genotype, as these twins can have drastically different symptoms and therapeutic responses (Lachmann et al., 2004).

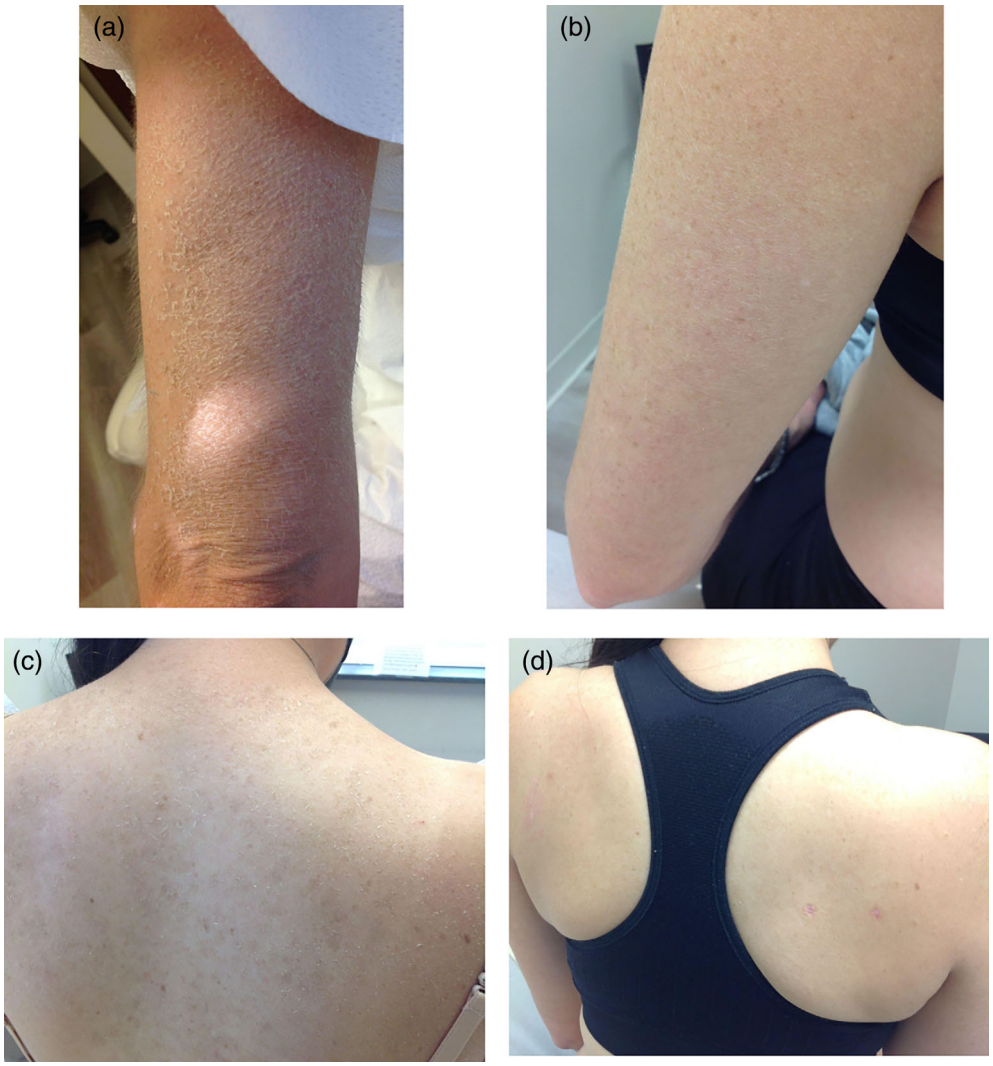

FIGURE 1 (a) Fine scale on the posterior arm while on 84 mg of eliglustat twice a day. (b) Minimal fine scale on the posterior arm at decreased dose of 84 mg once daily. (c) Fine scale on back at 84 mg eliglustat twice daily. (d) Minimal scale on back at 84 mg once daily.

The treatment options for GD1 include enzyme replacement therapy (ERT) and substrate reduction therapy (SRT). In ERT, an infusion (imiglucerase, velaglucerase alfa, or taliglucerase alfa) is administered every 2 weeks to provide functional glucosylceramidase. An initial dose can range from 15 to 60 units/kg and is based on the age of the individual and the severity of the disease (Shemesh et al., 2015).

In contrast, SRT utilizes an oral medication (eliglustat) taken daily that reduces the biosynthesis of glucosylceramides by actively inhibiting glucosylceramide synthase. The dosing of the oral medication is determined by the cytochrome P450 metabolizer status. An extensive and intermediate metabolizer may take two 84 mg tablets once daily while a poor metabolizer takes one 84 mg tablet once daily (Martins et al., 2009).

2 | CASE REPORT

A 37-year-old female patient with non-neuronopathic type 1 Gaucher disease (GD1) presented with large patches of white, polygonal, fine scale on the trunk and extensor surfaces of the extremities that started 4 months prior (Figure 1a,c). The patient was diagnosed with Gaucher's disease at age 27 but did not start treatment then due to the absence of manifestations at that time. Genetic testing showed a homozygous pathogenic variant in GBA1 (c.1226A>G, p.N409S).

The patient began SRT with eliglustat at age 36 due to changes in marrow replacement in her femurs, decreased bone mass density, mild organomegaly, and elevated glucosylsphingosine (67 ng/mL, reference interval <1 ng/mL). A blood test was conducted to determine her disease genotype and metabolizer genotype to determine her dosage. The test indicated she is a CYP2D6 genotype and a 4/41 genotype consistent with an intermediate metabolizer. With this metabolism level, she started at 84 mg of eliglustat twice daily and developed a generalized rash 2 weeks after starting.

Two punch biopsies were done for histopathologic evaluation. Top diagnoses of consideration included atopic dermatitis, drug eruption, and ichthyosis. The pathology showed mild acanthosis of the epidermis with a normal-appearing granular layer and overlying thickened compact orthokeratosis. There was no evidence of an inflammatory infiltrate, and a PAS stain was negative for fungi

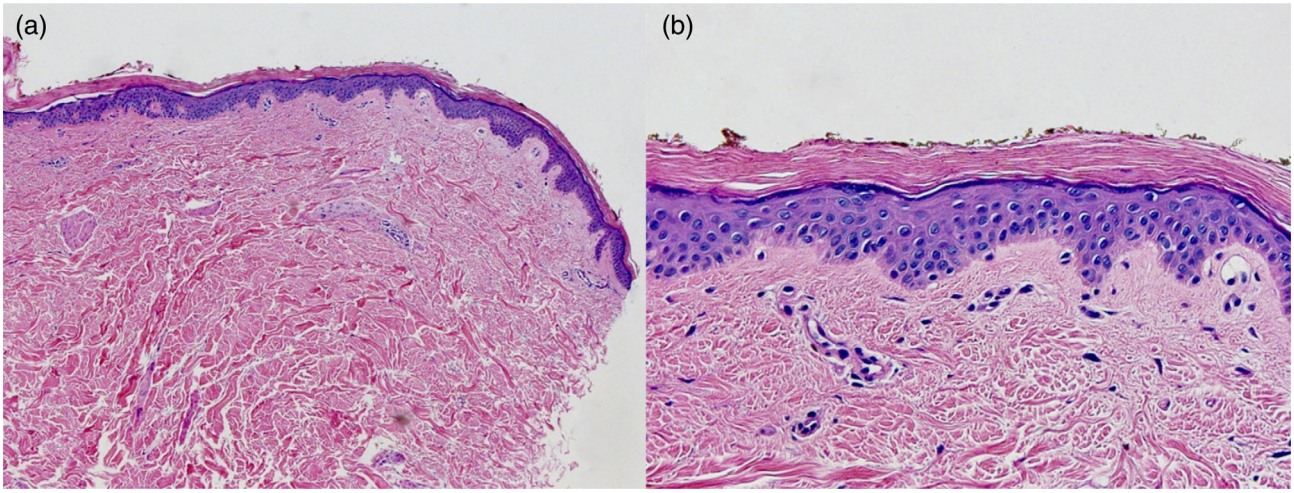

FIGURE 2 (a) Low power view of the punch biopsy shows a mostly unremarkable epidermis and dermis. There is a lack of an inflammatory infiltrate and no edema or mucin appreciated (H&E 100×). (b) Higher power examination of the epidermis reveals a normal granular cell layer with overlying thickened compact orthokeratosis. Spongiosis is not present. The PAS stain was negative for fungal organisms (H&E 400×).

(Figure 2). The clinical and pathological presentations were most consistent with ichthyosis.

The patient was prescribed urea cream to treat the dry, scaly areas on the arms and trunk, and it was recommended to moisturize frequently with an over-the-counter lotion, but she noted no improvement on her skin.

Six months after the presentation of this rash, the patient decreased the dose of eliglustat by 50 percent (84 mg once daily) given normal hematological parameters, improved organomegaly, and well controlled glucosylsphingosine levels (18 ng/mL) with the hopes of improving the ichthyosis. The patient noted significant improvement approximately 2 weeks later (Figure 1b,d).

3 | DISCUSSION

Gaucher disease presents in numerous ways, and this includes congenital ichthyosis; however, a GD1 patient who developed ichthyosis weeks after beginning SRT is distinct. There are no cases in the literature in which a GD1 patient developed ichthyosis while on eliglustat. Further, no other cases of ichthyosis have been identified with SRT in other metabolic diseases, such as Sanfilippo syndrome, Fabry disease, and Tay-Sachs disease.

There may be a relationship between the mechanism of action of eliglustat and the keratinization of the skin. More specifically, eliglustat may impact the lipid composition of the stratum corneum. As previously noted, patients with Gaucher disease have a deficiency of the enzyme glucosylceramidase and, as a result, have a buildup of glycosylceramides. Eliglustat functions by inhibiting UDP-glycosylceramide synthase, the first enzyme that catalyzes the biosynthesis of glycosphingolipids—the resultant effect is a decreased buildup of glycosylceramides in Gaucher disease. Ceramides, including glycosphingolipids, are the major lipid component of the stratum corneum of the skin. Alterations of ceramide molecular profiles have been found in several skin diseases with compromised permeability barrier functions, like atopic dermatitis. Additionally, some ichthyoses are associated with decreased levels of a unique epidermal ceramide species, omega-O-acylceramide. Thus, one may consider eliglustat indeed favorably lowered our patient's overall glycosylceramide load, but disproportionately lowered the lipid component of the stratum corneum's intercellular spaces, ultimately resulting in ichthyosis. Additional research is necessary to ascertain the pathophysiology and pathogenesis of the simultaneous presentation of GD and ichthyosis while treated with SRT.

4 | CONCLUSION

This case presents a novel finding of ichthyosis in a GD1 patient while being treated with eliglustat for SRT. Ichthyosis can be seen in GD2 but not in GD1, and there is no case in the literature noting ichthyosis while treated with SRT or ERT. In this case, 2 weeks after beginning eliglustat (84 mg twice daily), the patient developed white, polygonal, fine scales on the trunk and extensor surfaces of the extremities. The patient used urea cream and over-the-counter moisturizer regularly and had minimal improvement. Given the parameters of her GD, she was able to decrease her eliglustat dose by 50% (84 mg once daily) and she noted significant improvement 2 weeks later. This unique case calls for further research on the pathophysiology and pathogenesis of concurrent GD and ichthyosis while treated with SRT.

AUTHOR CONTRIBUTIONS

Jack Herbster: Conceptualization, investigation, writing—original draft, writing—review and editing, visualization, project administration. **Carlos E. Prada:** Investigation, resources, writing—original draft, writing—review and editing. **Carly A. Rasmussen:** Resources, writing—review and editing. **Allegra Quadri:** Resources, writing—review and editing. **Victoria Kuritza:** Conceptualization, investigation, resources, writing—original draft, writing—review and editing. **Michael Viglione:**

Investigation, resources, data curation, writing—original draft, writing—review and editing, visualization. **Sheryl Hoyer:** Conceptualization, investigation, writing—original draft, writing—review and editing, supervision.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data underlying the results are available as part of the paper and no additional source data are required. Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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REFERENCES

Akiyama, M. (2010). ABCA12 mutations and autosomal recessive congenital ichthyosis: A review of genotype/phenotype correlations and of pathogenetic concepts. *Human Mutation*, *31*(10), 1090–1096.

Amaral, O., Lacerda, L., Santos, R., Pinto, R. A., Aerts, H., & Miranda, M. C. S. (1993). Type 1 Gaucher disease: Molecular, biochemical, and clinical characterization of patients from northern Portugal. *Biochemical Medicine and Metabolic Biology*, *49*, 97–107.

Beutler, E., & Grabowksi, G. A. (2001). Gaucher disease. In C. R. Scriver, A. L. Beaudet, W. S. Sly, & D. Valle (Eds.), *Metabolic and molecular bases of inherited disease* (p. 3635). McGraw-Hill.

Charrow, J., Anderson, H. C., Kaplan, P., et al. (2000). The Gaucher registry: Demographics and disease characteristics of 1698 patients with Gaucher disease. *Archives of Internal Medicine*, *160*, 2835.

Goker-Alpan, O., Schiffman, R., Park, J. K., et al. (2003). Phenotypic continuum in neuronopathic Gaucher disease: An intermediate phenotype between type 2 and type 3. *The Journal of Pediatrics*, *143*, 273–276.

Kaplan, P., Andersson, H. C., Kacena, K. A., & Yee, J. D. (2006). The clinical and demographic characteristics of nonneuronopathic Gaucher disease in 887 children at diagnosis. *Archives of Pediatrics & Adolescent Medicine*, *160*, 603–608.

Lachmann, R. H., Grant, I. R., Halsall, D., & Cox, T. M. (2004). Twin pairs showing discordance of phenotype in adult Gaucher's disease. *QJM: An International Journal of Medicine*, *97*, 199–204.

Martins, A. M., Valadares, E. R., Porta, G., Coelho, J., Semionato Filho, J., Pianovski, M. A., Kerstenetzky, M. S., Montoril Mde, F., Aranda, P. C., Pires, R. F., Mota, R. M., Bortolheiro, T. C., & Brazilian Study Group on Gaucher Disease and other Lysosomal Storage Diseases. (2009). Recommendations on diagnosis, treatment, and monitoring for Gaucher disease. *Journal of Pediatrics*, *155*, S10–S18.

Shemesh, E., Deroma, L., Bembi, B., Deegan, P., Hollak, C., Weinreb, N. J., Cox, T. M., & Cochrane Cystic Fibrosis and Genetic Disorders Group. (2015). Enzyme replacement and substrate reduction therapy for Gaucher disease. *Cochrane Database of Systematic Reviews*, *2015*, CD010324.

Svennerholm, L., Hakansson, G., Mansso, J. E., & Nilsson, O. (1982). Chemical differentiation of the Gaucher subtypes. *Progress in Clinical and Biological Research*, *95*, 231–252.

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