CASE REPORT

Could "Islets of Sparing" Be a Clue for Neutral Lipid Storage Disease with Ichthyosis in Patients with Congenital Ichthyosiform Erythroderma?

Filiz Topaloglu Demir, Baran Cayhan[1], Cagla Karaoglan[2], Zafer Turkoglu[1], Nesimi Buyukbabani[3], Mesut Ayer[4], Bugrahan Duz[5], Bulent Uyanık[6]

Abstract

The prevalent form of ichthyosis in neutral lipid storage disease (NLSDI) is nonbullous congenital ichthyosiform erythroderma (CIE) characterized by fine, whitish scales on erythematous skin over the whole body. Here, we report a late-diagnosed, 25-year-old woman with NLSDI presenting with diffuse erythema and fine whitish scales throughout the body with patches of apparently normal skin, "islets of sparing" on her lower extremities. We observed that the size of the normal skin islets changed with time, and even the entire lower extremity was covered with erythema and desquamation like the rest of the body. Frozen section histopathological examinations were made from lesional skin and normal-looking skin; no difference was observed in terms of lipid accumulation. The only noticeable difference was the thickness of the keratin layer. In CIE patients, observation of patches of apparently normal skin or "islets of sparing" might be a clue for NLSDI to be distinguished from other CIE conditions.

From the Medipol University, Faculty of Medicine, Dermatology Clinic, Istanbul, [1]Basaksehir Cam and Sakura City Hospital, Dermatology Clinic, Istanbul, [2]Bakırköy Dr. Sadi Konuk Education and Research Hospital, Pathology Clinic, Istanbul, [3]Istanbul University, Faculty of Medicine, Pathology Clinic, Istanbul, [4]Basaksehir Cam and Sakura City Hospital, Hematology Clinic, Istanbul, [5]Haseki Education and Research Hospital, Medical Genetics Clinic, Istanbul, [6]Bezmialem Vakıf University, Faculty of Medicine, Medical Genetics Clinic, Istanbul, Turkey

Address for correspondence:
Dr. Baran Cayhan, Basaksehir Cam and Sakura City Hospital, Basaksehir/Istanbul, Turkey.
E-mail: cayhanbaran@gmail.com

Key Words: *Chanarin–Dorfman syndrome, congenital ichthyosis, genodermatoses, neutral lipid storage disease with ichthyosis*

Introduction

Neutral lipid storage disease with ichthyosis (NLSDI) is a rare, nonlysosomal, autosomal recessive triglyceride storage disease associated with systemic accumulation of triacylglycerol (TG) in many tissues, especially in the skin, muscle, liver, and leukocytes.[1,2] Here, we present a late-diagnosed woman with NLSDI presenting with congenital ichthyosiform erythroderma (CIE) with transient normal-looking skin islets, sensorineural hearing loss, hepatosteatosis, and myopathy.

Case Report

A 25-year-old female patient was admitted to our clinic with a complaint of widespread scaling and dryness. The parents of the patient were second-degree consanguineous. Similar findings were found in both siblings, and all had a history of collodion membrane at birth. In the dermatological examination, widespread erythema and fine desquamation were detected in all body areas, except for apparently normal skin islets on both lower extremities [Figure 1a]. It was observed that the size of these islets on the lower extremities changed with time, and even the entire lower extremity was covered with erythema and desquamation like the rest of the body in three months [Figure 1b]. The patient had these transient lesions for 11 years, and her 19-year-old sister also had this phenomenon appearing recently in the lumbar region.

Blood tests were normal except for serum creatine phosphokinase and lactate dehydrogenase. A

Access this article online

Quick Response Code:

Website: www.e-ijd.org

DOI: 10.4103/ijd.ijd_1154_20

How to cite this article: Topaloglu Demir F, Cayhan B, Karaoglan C, Turkoglu Z, Buyukbabani N, Ayer M, *et al.* Could "islets of sparing" be a clue for neutral lipid storage disease with ichthyosis in patients with congenital ichthyosiform erythroderma? Indian J Dermatol 2022;67:579-82.

Received: December, 2020. **Accepted:** September, 2022.

second-degree hepatosteatosis on abdominal ultrasonography and mild sensorineural hearing loss, especially to high-frequency sounds, were detected. Deltoid 4/5, triceps 4/5, biceps 5/5, hand extensors 5/5, iliopsoas 3/5, quadriceps femoris 4/5, gastrocnemius 5/5, and foot extensors 5/5 detected in muscle strength examination; also, there was proximal muscle weakness in the lower extremities. Normal conduction in sensory and motor nerves and moderate myogenic involvement were stated in electromyography. Muscle biopsy was not performed. In ophthalmologic examination, blepharitis, bilateral esotropia, ectropion, and lagoftalmia were detected. Widespread vacuoles in neutrophils, eosinophils, and monocytes (Jordan's anomaly) were seen in peripheral blood smear [Figure 2]. Frozen examination of skin biopsy showed compact hyperkeratosis, mild acanthosis, and discrete vacuolization of basal keratinocytes, sweat glands, and mild superficial perivascular lymphohistiocytic infiltrate in the papillary dermis. Scharlach and Oil Red-O stains clearly and elegantly demonstrated the lipid content of these discrete vacuoles [Figure 3]. The vacuoles had a distinct distribution characteristic: their density increased towards the ends of the rete ridges. The patient was diagnosed with NLSDI based on these clinical, laboratory, and histopathological findings. Her siblings were examined after the diagnosis was finalized. CIE, grade 1 hepatosteatosis, sensorineural hearing loss, Jordan's anomaly, and lipid accumulation in frozen skin biopsy were detected in her 22-year-old sister. Furthermore, CIE, grade 2 hepatosteatosis, blepharitis, Jordan's anomaly, and lipid accumulation in frozen skin biopsy detected in her 17-year-old brother. Genetic analysis confirmed a homozygous mutation in the ABHD5 gene [ABHD5, NM_016006, c. 594dupC p.(Arg199GInfs*11) rs387906335] in all siblings. The patient was young and in fertile ages and did not accept acitretin treatment. Therefore, we recommended regular use of emollients and a diet which was low in long-chain fatty acids (minimal saturated fat) and enriched with medium-chain fatty acids.

In the sixth month of the follow-up, the majority of the lower extremities returned to normal-looking skin, although the patient had not yet begun a diet. She stated that this change occurred as the weather got warmer [Figure 1c]. The second biopsy performed from the transient, apparently intact area showed no substantial difference, except for the thinner keratin layer measured by ocular micrometry as 50 μm and 25–30 μm in the first and second biopsies, respectively [Figure 4].

Discussion

NLSDI is caused by mutations in the ABHD5 gene located in chromosome-3.[3] The ABHD5 gene produces a protein involved in fat metabolism called CGI-58. This protein helps the activity of the main enzyme, which is

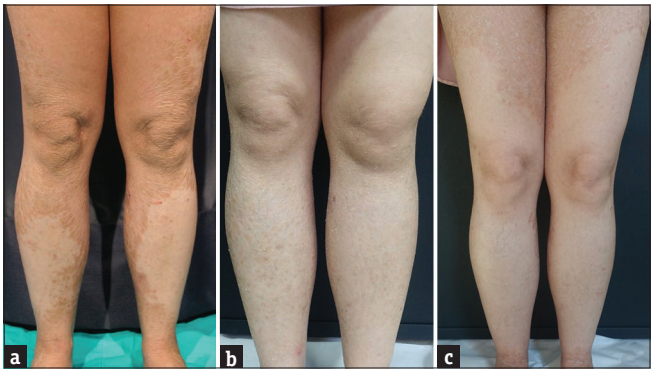

Figure 1: (a) Nonbullous congenital ichthyosiform erythroderma with patches of apparently normal skin "islets of sparing" (September 2018). (b) In the follow-up, the lower extremities were completely covered by erythema and desquamation (December 2018). (c) In the sixth month of follow-up, these almost normal-looking areas reappeared in a larger area than before on the lower extremities (March 2019)

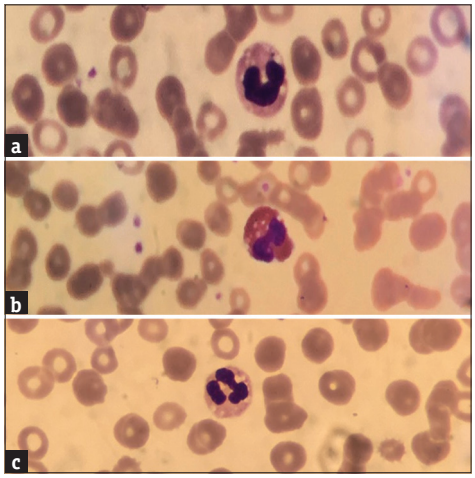

Figure 2: Widespread vacuoles in monocytes, eosinophils and neutrophils (Jordan's anomaly) (40×)

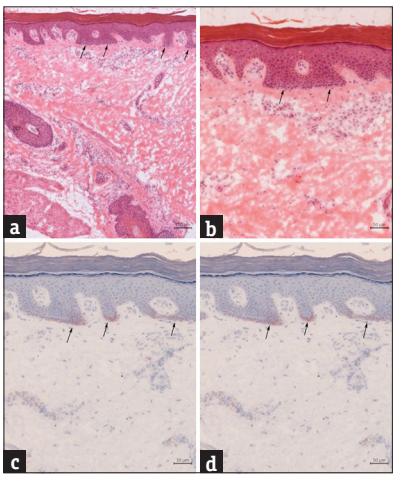

Figure 3: (a and b) Compact hyperkeratosis, mild acanthosis, and discrete vacuolization of basal keratinocytes, sweat glands, and mild superficial perivascular lymphohistiocytic infiltrate in the papillary dermis (20×). (c and d) Scharlach and Oil Red-O stains clearly and elegantly demonstrated the lipid content of these discrete vacuoles (40×)

adipose TG lipase. When the TG cannot be broken down, it accumulates in various parts of the body as lipid droplets and causes different symptoms. Accumulation of lipid is related to dry, scaly skin at birth, as well as progressive hepatosteatosis and various degrees of muscular involvement, ophthalmologic problems, hearing loss, mild intellectual disability, etc.[4]

Although nonbullous CIE is the commonly seen form of ichthyosis in NLSDI, rarely different forms of ichthyosis have been reported, such as nonspecific ichthyosiform dermatosis or even nonerythrodermic ichthyosis. In a few cases, a presentation with normal-looking skin islets in different body parts as well as widespread erythema and desquamation has also been reported.[2,5,6] This phenomenon was also described by Pujol *et al.*[2] as erythrokeratodermia variabilis-like ichthyosis and by Singh *et al.*[5] as progressive symmetric erythrokeratodermia-like features in NLSDI. In the follow-up, differently from the literature, we found that these normal-looking skin islets on the lower extremities were covered entirely with erythema and ichthyosis that fit in CIE clinic.

Since these normal-looking skin areas always appear in the same area, we initially thought that there might be a relatively high level of enzyme or helper protein activity in keratinocytes of these areas due to differences in ABHD5 mutations or additional unidentified mutations, but this hypothesis was not supported by the fact that lipid vacuoles were roughly in similar distribution and number in the second biopsy. No biopsy from normal-appearing skin was taken to compare findings with the lesional area in the other studies in the literature. We found that the keratin layer thickness was almost halved on normal-looking skin. Ujihara *et al.*[6] and Pujol *et al.*[2] reported that skin findings were aggravated with temperature elevation. Unlike these two studies, in our case, the severity of skin findings decreased with increasing temperature [Table 1]. Mieremet *et al.*[7] compared at a range of 33–37°C the epidermal maturation in full-thickness skin models in vitro. Their results showed that keratin layer thickness decreases with culture temperature rising to 37°C. This indicates that the ambient temperature plays an important role in epidermal morphogenesis. Low temperature and low humidity have also been shown to cause an overall decrease in the function of the skin barrier.[8]

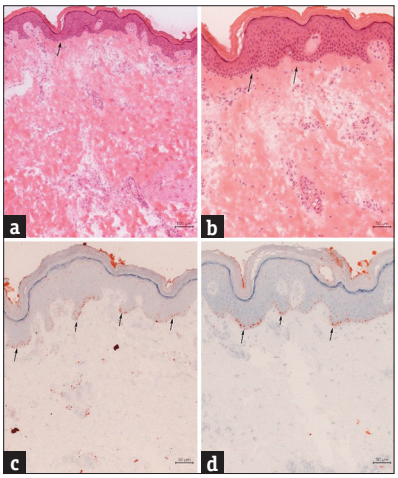

Figure 4: The second biopsy performed from the transient, apparently intact area showed no substantial difference, except for the thinner keratin layer measured by ocular micrometry as 50 µm and 25–30 µm in the first and second biopsies. 4a-b: Thinner keratin layer and similar distribution of vacuoles, compare with Fig.3a-b (H&E (20×)); 4c-d: Similar amount of intracytoplasmic lipid droplets (Scharlach and Oil Red-O) (40×), compare with fig.3c-d

Another important aspect of our case report is that frozen tissue examination played a key role in the diagnostic workup. In the routine histopathological examination of a skin biopsy in NLSDI, the lipid accumulation appears as empty vacuoles that can be easily overlooked. A PubMed search was done for "neutral lipid storage disease and biopsy" and "Chanarin–Dorfman and biopsy", and we found that frozen section examination was used in only five reports.[4-6,9,10] We recommend frozen examination instead of routine histopathological examination in order not to miss the diagnosis, in all nonbullous CIE patients, not only in NLSDI.

In conclusion, patches of normal-looking skin, "islets of sparing" may be an important clue to distinguish NLSDI from other diseases in the spectrum. We consider that this phenomenon is not associated with a different type of ichthyosis than nonbullous CIE in NLSDI, as it was limited to a particular region, disappeared completely, and was a finding that emerged years later. In order not to miss the diagnosis, we also recommend performing peripheral blood smear on all nonbullous CIE patients.

Table 1: A comparative table highlighting the findings from reports in literature

	Topaloglu Demir *et al.*	Pujol *et al.*[2]	Ujihara *et al.*[6]
Nonbullous congenital ichthyosiform erythroderma	+	+	+
Islets of sparing (normal-looking skin)	+	+	+
Recovering entirely with erythema and ichthyosis in islets of sparing	+	-	-
Relationship between the severity of skin findings and temperature	The skin findings decreased with increasing temperature	The skin findings aggravated with increasing temperature	The skin findings aggravated with increasing temperature

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given her consent for images and other clinical information to be reported in the journal. The guardian understands that her names and initials will not be published and due efforts will be made to conceal the patient's identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Eskiocak AH, Missaglia S, Moro L, Durdu M, Tavian D. A novel mutation of ABHD5 gene in a Chanarin Dorfman patient with unusual dermatological findings. Lipids Health Dis 2019;18:232.
2. Pujol RM, Gilaberte M, Toll A, Florensa L, Lloreta J, González-Enseñat MA, *et al.* Erythrokeratoderma variabilis-like ichthyosis in Chanarin-Dorfman syndrome. Br J Dermatol 2005;153:838-41.
3. Lefèvre C, Jobard F, Caux F, Bouadjar B, Karaduman A, Heilig R, *et al.* Mutations in CGI-58, the gene encoding a new protein of the esterase/lipase/thioesterase subfamily, in Chanarin-Dorfman syndrome. Am J Hum Genet 2001;69:1002-12.
4. Elias PM, Williams ML. Neutral lipid storage disease with ichthyosis. Defective lamellar body contents and intracellular dispersion. Arch Dermatol 1985;121:1000-8.
5. Singh S, Sharma S, Agarwal S, Nangia A, Chander R, Varghese B. Neutral lipid storage disease with unusual presentation: Report of three cases. Pediatr Dermatol 2011;29:341–4.
6. Ujihara M, Nakajima K, Yamamoto M, Teraishi M, Uchida Y, Akiyama M, *et al.* Epidermal triglyceride levels are correlated with severity of ichthyosis in Dorfman–Chanarin syndrome. J Dermatol Sci 2010;7:102–7.
7. Mieremet A, van Dijk R, Boiten W, Gorris G, Bouwstra JA, El Ghalbzouri A. Characterization of human skin equivalents developed at body's core and surface temperatures. J Tissue Eng Regen Med 2019;13:1122-33.
8. Engebretsen KA, Johansen JD, Kezic S, Linneberg A, Thyssen JP. The effect of environmental humidity and temperature on skin barrier function and dermatitis. J Eur Acad Dermatol Venereol 2015;30:223–49.
9. Wolf R, Zaritzky A, Pollak S. Value of looking at leukocytes in every case of ichthyosis. Dermatologica 1988;177:237-40.
10. Demerjian M, Crumrine DA, Milstone LM, Williams ML, Elias PM. Barrier dysfunction and pathogenesis of neutral lipid storage disease with ichthyosis (Chanarin–Dorfman syndrome). J Invest Dermatol 2006;126:2032–8.