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Phototherapy-induced blistering reaction and eruptive melanocytic nevi in a child with transient neonatal porphyrinemia

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Abstract

Neonatal blue-light phototherapy induced a blistering reaction followed by eruption of melanocytic nevi on the exposed skin surface of a child with transient neonatal porphyrinemia. New nevi are still developing 4 years after the triggering event. The role of phototoxicity-induced epidermal injury, that of porphyrins and the influence of neonatal blue-light therapy, in this unique phenomenon are discussed.

KEYWORDS
blue-light phototherapy, eruptive melanocytic nevi, transient porphyrinemia

1 | INTRODUCTION

Eruptive melanocytic nevi are a rare phenomenon characterized by rapid development of numerous melanocytic proliferations in a previously unaffected skin area. It has been observed in association with blistering diseases, erosions, scaring, ultraviolet light exposure, local or systemic immunosuppression, hormonal influences, and, occasionally, without any apparent precipitating factors.

2 | CASE REPORT

A 10-month-old boy was referred for consultation because of hyperpigmented macules arranged in a rectangular shape on his chest and abdomen. Physical examination revealed a well-developed child with light hair and blue eyes. He had a sharply demarcated area on the ventral surface of the trunk with pitted scars and multiple, partially confluent brown macules, 3-5 mm in diameter (Figure 1A). There was a larger (~20 mm) brown patch with darker spots on the side of the abdomen.

He had been born in the 40th week of gestation (Apgar scores 10, A Rh positive) by caesarean section, performed because of fetal bradycardia. For 2 weeks before delivery, the mother (A Rh positive) had been treated with ampicillin for a urinary tract infection.

By 2 days of age, jaundice developed in the newborn (total bilirubin level 176.5 μmol/L, with a direct fraction of 6.8 μmol/L). Neonatal blue-light phototherapy (NBLP) (Bili-Bed, Uniwill Co., Budapest, Hungary) was initiated and continued for 12 hours. Approximately 16 hours after the start of NBLP, erythema appeared on the exposed skin of the arms, thighs, chest, and abdomen. Later, small vesicles and a few large bullae developed, mainly at the margins of the erythematous surface of the trunk. Before the onset of the skin lesions, the newborn had not received any drugs. Plasma and erythrocyte

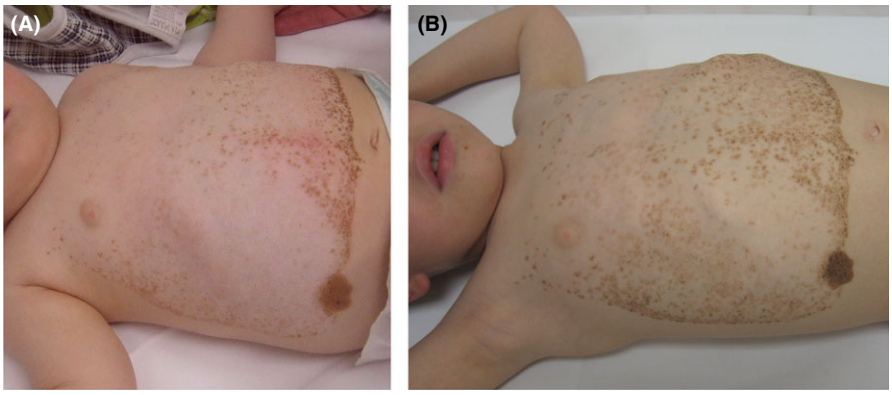

FIGURE 1 After erythema and blistering induced by a single session of blue-light phototherapy, brown macules and pitted scars developed on the exposed skin surface of the chest and abdomen of the infant boy. During follow-up, a gradual increase in number and darkness of the skin lesions was observed (the skin of the patient at 10 mo (A) and 4 y (B) of age)

TABLE 1 Porphyrin levels at 5 d and 10 mo of age

Porphyrin	5 d	10 mo	Reference value
Erythrocyte, μg/dL	107	35	<50
Plasma, μg/dL	1.7	0.2	<1.2
Urine, μg/d	1.3	8.7	<200
Stool, μg/g	10.9	-	<50

porphyrin levels were high, urine and stool porphyrin concentrations were normal (Table 1). There was no family history of porphyria, light sensitivity, pigment disorder, or melanoma. Systemic (ampicillin) and local (0.5% neomycin sulfate with 1% salicylic acid ointment) treatments were started, and the blisters resolved within 1 week. By that time, the jaundice had also subsided.

Approximately 3 months later, brown macules appeared on the previously affected skin of the trunk (Figure 1A). The skin had not been exposed to sunlight before the eruption of pigmented lesions.

At the age of 10 months, porphyrin levels in the erythrocytes, plasma, and urine were in the normal range; stool porphyrins were not determined (Table 1). The spectrum of the phototherapy lamp was checked; its emission range and irradiance provided are shown in Figure 2.

During follow-up, a gradual increase in the number and darkness of the skin lesions was observed (Figure 1B). Histology at 3 years of age revealed junctional melanocytic proliferations with nevus cell nests in the follicular epithelium (Figure 3). Clinical, laboratory, and histologic findings suggested the diagnosis of transient neonatal porphyrinemia and eruptive melanocytic nevi.

3 | DISCUSSION

Blue-light phototherapy is an effective way to reduce plasma bilirubin concentrations and is widely used to treat neonatal jaundice. Side effects of NBPL are rare, but cutaneous reactions, high transepidermal water loss, abdominal distension, mild hemolysis, and thrombocytopenia have occasionally been reported. Cutaneous side

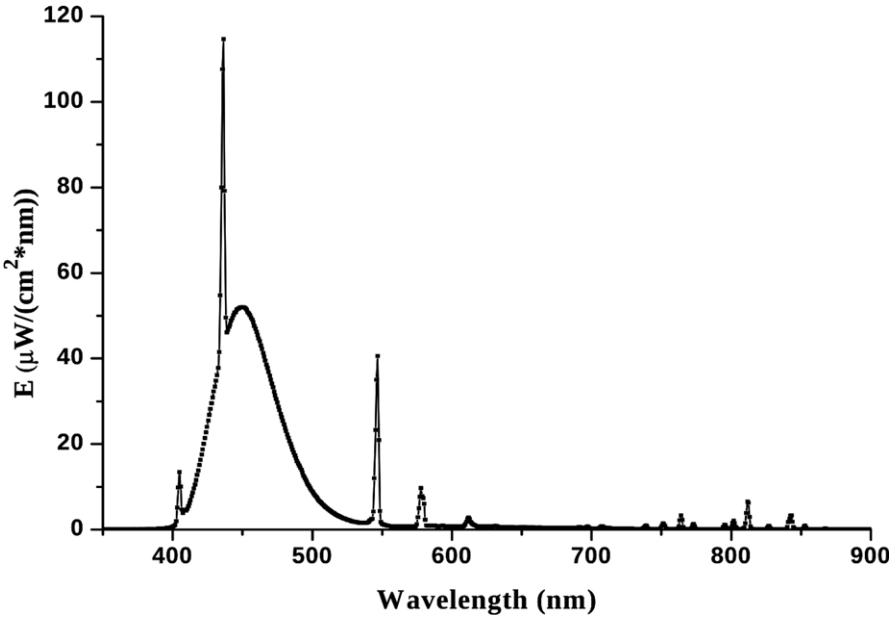

FIGURE 2 Spectrum of the blue-light phototherapy unit

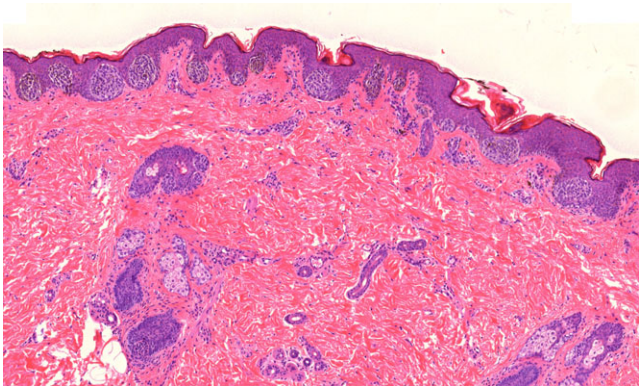

FIGURE 3 Histology revealed junctional melanocytic proliferations with nevus cell nests present also in the follicular epithelium (hematoxylin and eosin ×20)

effects include ultraviolet burns, blistering eruptions, purpuric lesions, and diffuse darkening of the skin (bronze baby syndrome). Eruption of purpura and blisters has been observed in newborns with transient or hereditary porphyrias.[1,2]

Transient porphyrinemia in newborns seems to be rare, the present being the tenth case reported.[2-6] All cases were detected because of adverse reactions to phototherapy. The etiology is unclear and may be multifactorial. The concentration of protoporphyrin within erythrocytes may rise when iron deficiency becomes manifest in disturbed heme synthesis.[7] Preterm infants have highly variable iron status, but infants born at term usually have sufficient iron stores until 4-6 months of age. Abnormal liver or renal functions may interfere with the porphyrin metabolism and excretion, and high transaminase levels, cholestasis, and mild renal dysfunction have been observed in some affected newborns,[2,4] but this does not explain the high erythrocyte porphyrin levels previously reported and seen in the present newborn. Drugs and heavy metals may likewise act as possible causal agents, but their role did not emerge in any of the cases. Porphyrin levels had returned to normal by the age of 4 to 5 months in all of the infants reported. The acute cutaneous symptoms resolved spontaneously without any permanent sequelae, or resulted in localized atrophy, scarring or milia.[2-6]

We found no clue to the etiology of transient porphyrinemia in the present patient. The acute phototoxic reaction was similar to those reported previously, but the eruption of melanocytic nevi 3 months after the blistering reaction is unique.

Rarely, blistering skin diseases may induce sudden development of multiple melanocytic nevi.[8] It has been described in patients with erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, epidermolysis bullosa, childhood vulvar pemphigoid, and bullae induced by mustard gas. Nevi appear mostly in areas of former epidermal detachment several weeks to months after epithelial regeneration. It has been presumed that specific cytokines and growth factors secreted during epidermal regeneration are the cause of melanocyte proliferation.[9]

Once they appear, eruptive nevi may remain stable for long periods (4-38 years), darken, or in contrast, fade and even regress completely. In the present case, a gradual increase in number and darkness of the melanocytic nevi has been seen up to 4 years after the initial injury. The long-lasting progression indicates that factors other than the transient dysregulation of local growth factors must be involved.

Porphyrins can generate reactive oxygen species in both the absence or presence of activating light and therefore can be potentially genotoxic.[10] They can also modulate local inflammatory reactions or directly influence the activity of immune cells.[11] Yet, in the literature, there are no observations indicating higher rates of melanocytic nevi and melanomas in patients with porphyrias.

The influence of NBPL on melanocytes is unclear. Several studies reported enhanced formation of melanocytic nevi,[12] but others found no association between the phototherapy and melanocytic nevi formation in exposed children.[13] After a meta-analysis of observational studies, Lai and Yew concluded that there was no evidence of greater risk of developing melanocytic nevi after NBPL,[14] although in their comprehensive review of experimental and epidemiological data, Oláh and colleagues emphasize that greater consideration should be given to long-term side effects when phototherapy is indicated.[15]

The role of NBLP in the acute toxic reaction observed in the present case is obvious, but its role in melanocyte proliferation is only presumed. Nevertheless, we agree with the authors of the latter two reports[14,15] that the effect of NBLP on melanocytes is an important topic that deserves further evaluation (in vitro and in vivo, as prospective cohort studies with long follow-up).

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