ONSET OF EPIDERMOLYSIS BULLOSA NEVUS AND LABIAL METAPLASIA FOLLOWING TOXIC EPIDERMAL NECROLYSIS: A CASE REPORT AND REVIEW OF THE LITERATURE

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Keywords Melanocytic nevus, metaplasia, toxic epidermal necrolysis, epidermolysis bullosa, child.

Abbreviations **EB** = epidermolysis bullosa; **TEN** = toxic epidermal necrolysis.

Case report. In January 2023, a 3-year-old female was admitted to the intensive care unit due to toxic epidermal necrolysis (TEN). A few days prior to hospitalization, the patient presented with a fever up to 40°C (104°F) of unknown origin, for which the primary care physician had prescribed acetaminophen and ibuprofen. Additionally, a few days before the onset of the fever, the patient had taken Bach flower drops (Biofloral®) recommended by a physical therapist. Two days after the onset of fever, small, pruritic, red maculopapules appeared on the trunk, face, and palms. Following a positive pharyngeal swab for Group A *Streptococcus*, therapy with amoxicillin combined with desloratadine was initiated. However, the maculopapular exanthem spread to the entire body, accompanied by the appearance of oral ulcerations and urogenital pain (Fig. 2).

Following the diagnosis of TEN, amoxicillin and ibuprofen were discontinued, and clarithromycin (140 mg three times daily) and clindamycin (100 mg twice daily) were initiated. The patient was then transferred to the burn center of our hospital. Symptomatic treatment consisted of cetirizine, dimetindene drops, and acetaminophen.

Clinical examination revealed targetoid bullous lesions on the trunk and extremities with central vesiculation. Mucosal erosions and aphthous lesions were also observed in the oral, genital, and ocular regions. Nikolsky's sign was positive on the chest. Screening for infectious triggers was negative for

Fig. 1

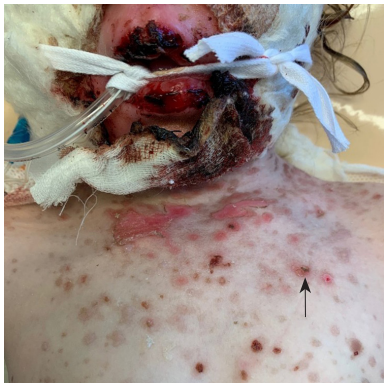

Fig. 2

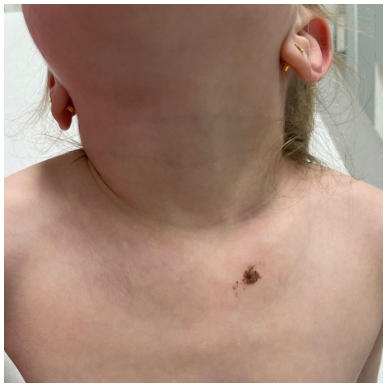

Fig. 3

Fig. 1, 2, 3: In Fig. 1, a patient before TEN with a normal vermilion border and a left subclavicular melanocytic nevus. In Fig. 2, the same nevus (arrow) on erosion during TEN. In Fig. 3, the same nevus 5 months after TEN with the appearance of an EB nevus.

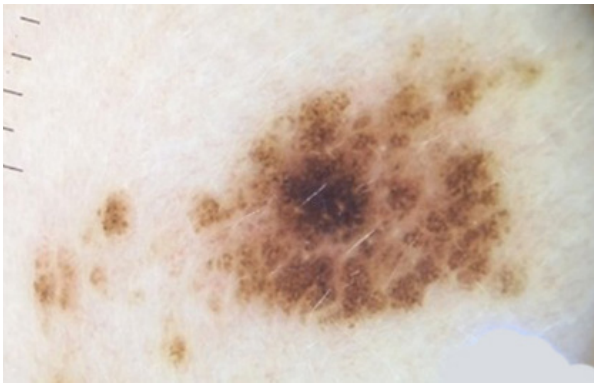

Fig. 4

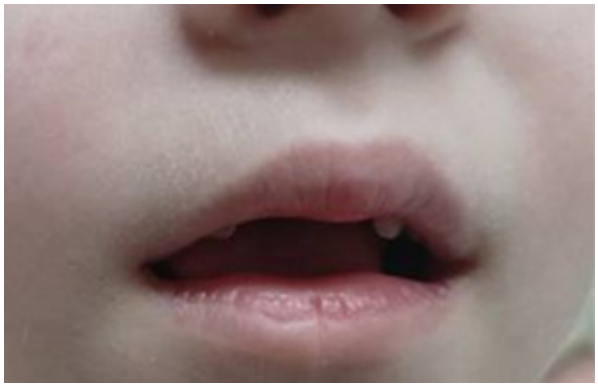

Fig. 5

Fig. 4, 5: Dermoscopic appearance of the EB nevus (Fig. 4) and vermilion border metaplasia (Fig. 5).

CMV, EBV, Parvovirus, *Mycoplasma*, and *Chlamydia* via serological testing, and for influenza and HSV via PCR assay. Frozen sections of the skin biopsy showed epidermal detachment and partial necrosis, consistent with TEN. Upon clinical assessment, we recorded a SCORTEN of 2 (affected body surface area >10% and bicarbonate <21 mmol/L) (1).

A short course of oral methylprednisolone (Solumedrol®) 40 mg four times daily) was administered for 48 hours. Supportive care consisted of analgesics (tramadol hydrochloride and acetaminophen), 5% glucose solution, and wound care using petrolatum and calcium alginate dressings (Kaltostat®). Two weeks after onset, re-epithelialization of over 80% of the body surface area occurred, although some active erosions on the arms and desquamation on the palms were still present.

At the 2-week follow-up visit, complete re-epithelialization of the skin was observed. Nine months after the TEN episode, patch tests were performed for Bach flowers, amoxicillin, ibuprofen, acetaminophen, and desloratadine. No hypersensitivity to any of these compounds was demonstrated. However, negative patch test results do not exclude these drugs as potential triggers for TEN.

Five months after the TEN episode, the parents expressed concern regarding a growing nevus on the neck (Fig. 3). The nevus was already present prior to the onset of TEN (Fig. 1), but at the follow-up visit, it showed distinct growth and a change in shape during the months following re-epithelialization. Clinical examination revealed a flat, asymmetric melanocytic macule with irregular pigmentation. Dermoscopy demonstrated a peripheral reticular pattern and a central homogeneous dark pattern. Furthermore, small surrounding satellite nevi were present, clinically suggesting a diagnosis of EB nevus (Fig. 3). Clinical and dermoscopic follow-up at 6 months and 1 year showed stable findings.

Two years later, we noted prominent keratinization of the lips. The keratosis was particularly evident on the vermilion border of the lips, in the exact location of the erosions that had developed during the acute TEN episode (Fig. 5). A diagnosis of labial metaplasia was made.

Discussion. Eruptive melanocytic nevi are classified into two groups: diffuse eruptive nevi and Köbner-type nevi (2).

Diffuse eruptive nevi present as small, asymptomatic, monomorphic macules with a benign appearance and have been associated with systemic diseases, immunosuppressive therapy, and chemotherapy (3). Conversely, Köbner-type nevi are large, atypical, irregular, and polymorphic pigmented lesions, frequently accompanied by satellite lesions. These have been described in association with

epidermolysis bullosa (EB) and non-EB-related bullous disorders, such as erythema multiforme (4), Stevens-Johnson syndrome (2, 5, 6), and toxic epidermal necrolysis – TEN – (2, 7, 8), as well as with immunosuppressive therapy (2). They typically develop at sites of prior blisters, or cutaneous injury.

When occurring in association with EB, the term "EB nevus" is also applied. The EB nevus is the most frequently described subtype in the literature and can develop in association with all EB variants. Two pathophysiological theories regarding this nevus have been proposed. One theory suggests that the continuous disruption of the basement membrane prompts nevus cell nests of melanocytes to escape senescence and trigger proliferation. The other theory suggests that melanocytes and nevus cells float freely within the EB bulla during the active phase of the disease, randomly deposit after the blister resolves (seeding in different locations), and subsequently proliferate during epidermal regeneration (9, 10).

The clinical appearance of an EB nevus is characterized by a flat, asymmetric, irregularly pigmented melanocytic lesion, often surrounded by small satellite nevi. On dermoscopy, it can exhibit features highly suggestive of melanoma, specifically a multicomponent pattern, an irregular atypical network, irregular dots and globules, milky-red areas, an atypical vascular pattern, structural asymmetry, and an abrupt border termination (10). Despite their alarming clinical presentation, no malignant transformation has been reported in EB nevi; however, regular follow-up is indicated due to these atypical clinical and dermoscopic features (3, 9, 10).

To date, six cases of eruptive nevi following TEN have been published in the literature (2, 11), with an age of onset ranging between 8 and 33 years. The longest follow-up period reported for an eruptive nevus following Stevens-Johnson syndrome in a single patient is 38 years, with no development of malignancy (6).

In addition to the EB nevus, our patient developed post-TEN labial metaplasia. Labial metaplasia is an adaptive epithelial change in which the normally non-keratinized mucosal epithelium of the lip transitions toward a keratinizing squamous phenotype. Labial metaplasia is an exceptionally rare finding. In the literature, only one retrospective review has described the presence of labial metaplasia as a long-term sequela after TEN, affecting 2 out of 6 patients, with a mean age of 37 years (12). The pathogenesis of labial metaplasia remains fully elucidated. Generally, metaplasia occurs in response to chronic irritation or injury (repeated UV exposure, mechanical trauma, tobacco use, or inflammatory conditions), which can induce epithelial stem or progenitor cells to adopt a more resilient, keratinized lineage (13). Although metaplasia is initially reversible if the noxious stimulus is removed, persistent triggers can stabilize this state of altered differentiation.

Since our case involved a single episode of mucosal damage rather than repeated injury, it is possible that labial squamous metaplasia may arise from acute damage that destroyed the sebaceous glands of the lip (Fordyce spots), thereby compromising mucosal homeostasis and reducing its lipid protection. This state of persistent fragility would then be compensated for by replacement with a more resistant, keratinized epithelium.

Conclusion. The present case of a post-TEN EB nevus is reported due to its rarity and to alert dermatologists to the existence of this clinically alarming yet essentially benign entity.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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