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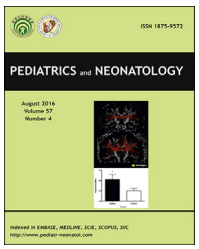

Short Communication

Association of dystrophic epidermolysis bullosa and neuroblastoma in a newborn

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1. Introduction

The term epidermolysis bullosa (EB) comprises a number of rare and genetically heterogenous disorders characterized by structural skin fragility that results in recurrent blister formation.[1] Dystrophic epidermolysis bullosa (DEB) is a subtype of EB that is caused by mutations in the COLA1 gene encoding type VII collagen; it is characterized by blister formation in the dermis, directly beneath the epidermis, and sometimes in the mucous membranes.[2] The reported incidence of DEB is 26.4 new cases per 1,000,000 live births.[3] Neonatal tumors are also very rare, with a reported incidence of 15.8—36.5 per 1,000,000 live births. Neuroblastoma (NBL) is an embryonal tumor arising from the sympathetic nervous system, representing the most common tumor in the neonatal age group.[4] As the occurrence of NBL is strongly age dependent, environmental factors are unlikely to play an important role in its pathogenesis. To the best of our knowledge, no reports regarding the association of DEB and NBL have been published to date.[5]

We report the case of a male term Caucasian infant in whom both DEB and NBL were suspected in the first days of life and then confirmed.

2. Case report

A male newborn infant was delivered at our hospital at 38 weeks of gestation. He was the first child born after an *in vitro* fertilization-assisted pregnancy in a Caucasian couple. There was no familiar history of interest except consanguinity of paternal grandparents, who were first-degree cousins. Pregnancy was uneventful, and antenatal obstetric scans revealed no abnormalities; no drugs were taken by the mother during gestation.

The weight, length, and cranial circumference at birth were adequate for gestational age. During the first neonatal physical examination, large patches of missing skin (i.e., aplasia cutis congenita; ACC) on both legs in the pretibial and perimalleoar region, extending to the plantar region of the right foot, were observed (Fig. S1). With the exception of ACC, the patient was in good clinical condition. In the following days, small, blistering lesions on the thorax and knees along with vesicles on the digits and tiny mucosal erosions of the lower lip and oral mucosa appeared.

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Incidentally, abdominal ultrasound (US) performed on the fifth day of life to exclude other congenital malformations showed a homogeneous, rounded mass in the lumbar prevertebral region. Magnetic resonance imaging confirmed the US data showing a heterogeneous and hyperintense mass lesion in T2 weighted image, with a 22-mm transversal diameter and a 34-mm longitudinal diameter, extending between the lumbar column and the abdominal aorta, suggestive of NBL (Fig. S1). On an iodine-123-meta-iodobenzylguanidine scan, the primitive mass gave a positive result, and no skeletal lesions were detected; posterior iliac crest marrow aspirates excluded bone marrow involvement. Urinary catecholamine determination strengthened the suspicion of neuroblastoma (homovanillic acid to urinary creatinine ratio: 138.4; vanillylmandelic acid to creatinine ratio: 334.8).

Taking into account the young age of the patient and the absence of life-threatening symptoms, the early oncologic postnatal strategy involved careful clinical and radiologic follow-up with US and concomitant medical examinations by the dermatologist. Due to a progressive slight enlargement of the retroperitoneal mass, complete microscopic surgical removal of the tumor was performed at 3 months of age. A polycyclic capsuled mass of 55 $\times$ 40 $\times$ 25 mm, partially hemorrhagic at the cut surface, was excised. Microscopic analysis showed a poorly differentiated neuroblastoma with a low mitosis—karyorrhexis index (MKI) (Fig. S2). Cytogenetic analysis with fluorescence *in situ* hybridization revealed the absence of N-myc amplification and 1p36 and 11q deletion along with presence of 17q addition. A diagnosis of stage L1 (localized tumor not involving vital structures and confined to one body compartment) NBL according to the International Neuroblastoma Risk Group Staging System was established.

During the same surgical session, a skin biopsy was performed. Based on both ultrastructural and immunofluorescence findings, a diagnosis of DEB was established. Electron microscopy examination demonstrated a cleavage at the ultrastructural level of the sub-lamina densa; immunofluorescence antigen mapping revealed a reduced intensity of labeling for collagen VII compared with that of control skin. DNA sequencing of the COL7A1 gene is scheduled. Based on the favorable NBL prognostic indicators (i.e., age $<$ 18 months, lack of N-myc amplification, and low MKI index), an oncologic strategy involving clinical and radiological follow-up visits every 3 months has been established and is ongoing.

At present, the patient is 12 months old and in good clinical condition. Aplasia cutis on the lower legs has healed with atrophic scarring (Fig. S1). Occasionally, new blisters on the extremities, tiny mucosal erosions, and minimal subungual hemorrhages of the fingernails develop.

3. Discussion

Even though the possibility of coincidental findings cannot be ruled out, the association of DEB and NBL arouse the intriguing possibility of a common pathogenetic pathway between these two rare conditions, both infrequently observed in the neonatal age group.

More than 50% of patients affected by recessive DEB die from squamous cell carcinoma (SCC) by the age of 40 years.[6] The etiology of skin cancer in EB patients remains unclear; however, the increased risk of developing SCC starts during adolescence, suggesting an oncogenic role of repetitive blistering and healing.[6] Only few cases of extracutaneous malignancies have been reported in DEB patients so far: the unique report of a malignancy in a pediatric DEB patient described an osteogenic sarcoma of the tibia in an 8-year-old boy.[7]

Ongoing research in DEB cell biology will hopefully lead to the discovery of new biological markers of the disease, and DNA sequencing of COL7A1 gene as well as genome-wide association studies may clarify some of the aspects seen in the present case.

Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

Dr. Parodi drafted the initial manuscript, Dr. Coppo, Dr. Tirtei, Dr. Bianchi, Dr. Morra and Dr. Frigerio reviewed and revised the manuscript.

All authors contributed to acquisition of case details and the analysis and interpretation of them.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pedneo.2019.11.001.

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