CHAPTER **40**

EPIDERMOLYSIS BULLOSA: Literature Review

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Inherited epidermolysis bullosa (EB) involves a number of rare and debilitating disorders that cause recurrent blister formation and fragility of the skin and other tissues. In the US alone it has a prevalence of 8 cases per million and 19 per million live births. EB appears as idiopathic blistering due to minor frictions affecting the skin. In the literature today, over 1,000 mutations that involve at least 10 different structural genes have been reported. Major types and subtypes of EB have been discovered and revised since its first classification scheme proposed by Pearson in 1962. Since then, three international consensus meetings on diagnosis and classification of epidermolyis bullosa have been held, one in 1988 in Washington DC, one in Chicago in 1999, and the third in 2007 in Vienna, Austria.

According to the third meeting about EB, and based on a combination of clinical and nonmolecular laboratory findings of the ultrastructure level within which epidermis separates from the dermis and blistering of the affected area occurs, there are 4 major types of EB. Epidermolysis bullosa simplex (EBS) is intra-epidermal, junctional epidermolysis bullosa (JEB) occurs at the intralamina lucida, dystrophic (DEB) appears as sublamina densa separation, and mixed epidermolysis bullosa involves different levels while including other genodermatoses associated with skin fragility like Kindler syndrome (KS).

EBS targets keratin5, keratin 14, plectin, a6b4 integrin, plakophilin-1, and desmoplakin. JEB targets laminin 332, a6b4 intergrin, and type XVII collagen. DEB targets type VII collagen and KS Kindlin-1. There are 6 major EB subtypes including suprabasal EBS, basal EBS, JEB-H, JEB other, dominant DEB, and recessive DEB. The life quality and expectancy of a patient with EB is directly related to the subtype of the disease. The majority of EBS and DDEB patients will have a normal life expectancy whereas those with JEB (JEB-H) are not expected to live past the first few years of life. An increased risk of muco-cutaneous squamous cell carcinoma is associated with KS patient morbidity according to Techanuku et al.

Localized blistering of the hands and feet, severe skin fragility, chronic wounds, generalized blistering of the skin, oral cavity blistering, and internal organ injury are only a few of the many clinical symptoms present in a patient with EB. Other symptoms include milia or tiny firm white papules, hypohydrosis, hyperhydrosis, esophageal stenosis, nail loss or dystrophy, dermatogenic contractures of the hands and feet, and on rare cases even widespread congenital absence of skin. The clinical presentation alone is not enough to make a diagnosis of EB and it needs to be correlated with imunofluorescent mapping and extensive patient family history.

The differential diagnosis for EB includes but is not limited to epidermolytic hyperkeratosis, peeling skin syndrome, pachyonychia congenital, ectodermal dysplasia, congenital absence of skin, EB acquisita, bullous pemphigoid, herpes simplex, staphylococcal scalded skin syndrome, and bullous impetigo. A correct clinical diagnosis is highly likely with increased level of training and experience of the physician.

Diagnosis of EB is confirmed with the help of transmission electron microscopy, immunofluorescence mapping, and mutational analysis. Electron microscopy allows successful diagnosis of EB only if performed in a highly experienced laboratory. Mutation analysis is often very costly to the patient and nonreimbursable by insurance companies. Even though immunofluorescence mapping is semi-quantitative at best and some false negatives may occur, it is recommended as the primary laboratory means of diagnosis by Fine et al. According to Najjar et al, not only is immunological mapping easy to perform and interpret but it also allows visualization of the level of the cleavage. Sub-categorization is also facilitated, which is important in determining the risk of mucosal involvement, premature death, and in providing genetic counseling.

Treatment for these patients is focused on prevention of injury by protecting susceptible tissues from trauma. Conservative treatment of the lower extremity requires shock absorbing custom molded foot orthoses to prevent future blistering. Pedors is the only company that has a line of shoes for EB patients. Silver-lined socks keep the feet cool and reduce the friction effects while providing great antibacterial benefits. In the cases of patients who are already experiencing recurrent ulcers, it has been found that water and salt baths are efficient in reducing the pain and discomfort of bathing or dressing changes. Mepilex

dressing is usually recommended and works by absorbing the exudate from the wound bed and gently adheres to the skin without causing trauma upon removal.

Early exercises and physiotherapy may help reduce the severity of contractures, which are almost inevitable. Methylprednisolone, dapsone, colchicine, and even amytriptylline are used to increase patient comfort. Surgical treatment in patients with EB is attempted to cover an ulceration or in the upper extremity where some dexterity is necessary. In the lower extremity, surgical intervention is rarely attempted and more focus is turned toward providing the patient with shoe gear that accommodates the deformity and allows for ambulation.

Intradermal injections of WT fibroblasts in patients with DEB results in new depositions of collagen VII and full function recuperation of dermal epidermal junction previously affected as presented by Fritsch et al in 2008. In another study performed by Natsuga et al, allogenic cultured dermal substitute shows promising results in the treatment of intractable skin ulcers in patients with recessive DEB. The future of the cure for epidermolysis bullosa lies in gene therapy, which is slowly becoming a reality. Michele de Luca reported the first ever successful gene therapy ex vivo in an adult patient. In this study the patient's own laminin 5-3 chain deficient epidermal stem cells (JEB) taken from palm biopsies were transfected ex vivo with a retroviral vector expressing normal laminin 5-3. The newly cultured skin was used to successfully cure areas in the thighs of the patient. Bone marrow stem cell transplantation has been also successfully used in the treatment of RDEB.

EB is a highly debilitating condition. It causes major deformities and morbidities while rendering the patient dependent. The physical, psychological, and emotional trauma caused by this group of diseases affects not only the patient but also their immediate family. In a clinical study by Tabolli et al, it was reported that the family burden increased significantly with increasing severity of disease and increasing patient's body surface involved. The emotional burden was higher in family members of RDEB children. In this study 90% of the parents reported they needed more information on the disease, and 72% were disappointed about their child's disease. Common symptoms among caregivers of patients with EB were noted: anger, difficulty to speak to the patient about the disease, guilt about child's disease or about not having enough time for other family members, depression, and anxiety. A total of 79% of the patients depend on family members to face the disease. The statistics of this study puts into perspective the fact that a health professional should facilitate and assist the caregivers while treating the patient as well.

DeBRA (dystrophic epidermolysis bullosa research association) is one of the biggest nonprofit organizations that gives the necessary information about the disease and treatment options providing support for the patients, families and primary care doctors. EBIG (epidermolysis bullosa interest group) consists of worldwide health care providers and facilitates collaboration and expert opinions about EB.

The case presentation is a 17-year-old male with severe EB of both hands and feet (Figures 1-5). The patient requested surgical options for hammertoes and bunion deformities. The patient had difficulty wearing over the counter shoes. Surgery was not recommended because the skin was so frail and thin and the deformities were rigid. Custom molded shoes were dispensed.

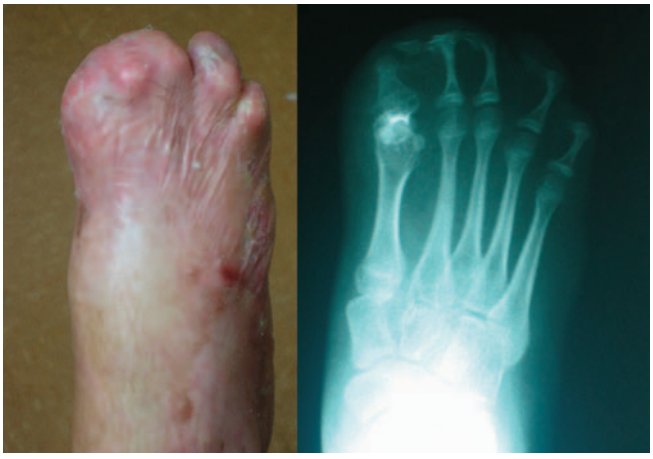

Figure 1.

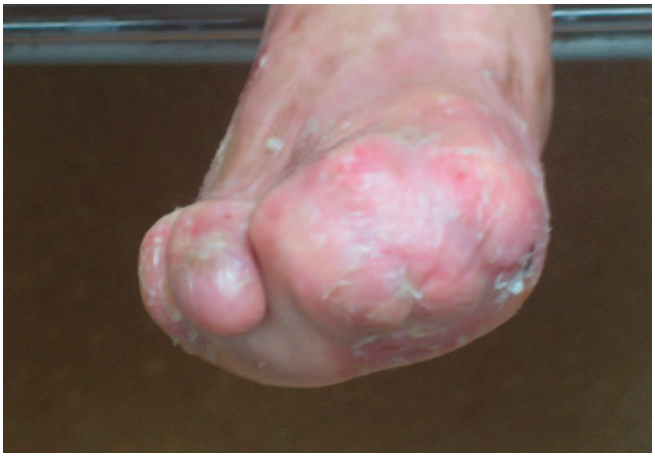

Figure 2.

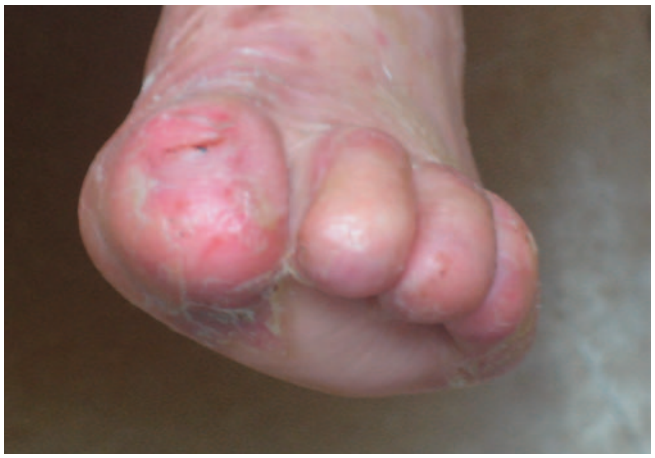

Figure 3.

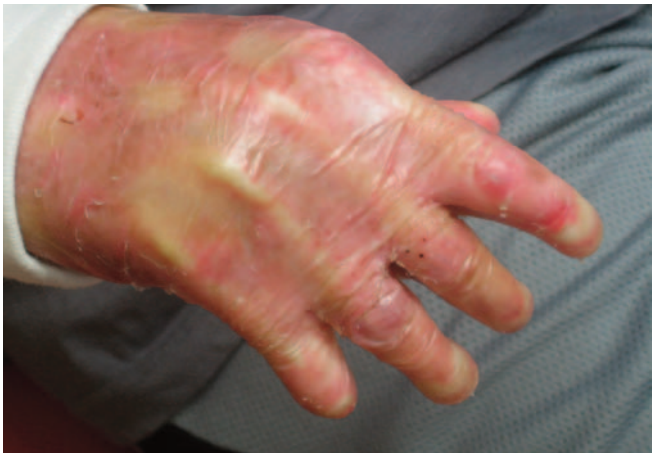

Figure 5.

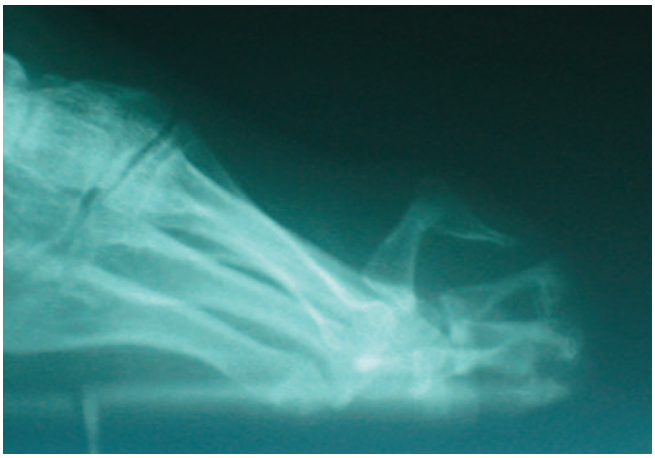

Figure 4.

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