CASE REPORT

Expanding the spectrum of epidermolysis bullosa simplex: Syndromic epidermolysis bullosa simplex with nephropathy and epilepsy secondary to CD151 tetraspanin defect—a case report and review of the literature

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INTRODUCTION

Heritable forms of epidermolysis bullosa (EB) are considered the prototype of genetic skin fragility disorders. Classically, EB is divided into 4 types on the basis of the location of the dermoepidermal junction in relation to the basement membrane zone: EB simplex (EBS), junctional EB, dystrophic EB, and Kindler EB. Recently, these subtypes have been further divided into “syndromic” and “nonsyndromic” variants on the basis of the presence or absence of monogenic multisystem involvement.

Syndromic forms of EB are rare but carry important considerations for screening, prognosis, multidisciplinary involvement, and therapeutic targets. We present the case of a 24-year-old patient with a diagnosis of syndromic EBS with associated nephropathy, “atypical” cystic fibrosis (CF), and epilepsy secondary to a defect in CD151 tetraspanin. This is the fifth recorded case of EBS with nephropathy in relation to CD151 defects and, to our knowledge, the first case to be reported with neurologic and chloride transport complications.

CASE REPORT

A 24-year-old adopted woman with consanguineous parents presented to the dermatology clinic with concerns of blistering. She was reportedly born at term via uncomplicated spontaneous vaginal delivery without prenatal, perinatal, or postnatal complications. Her past medical history was notable for complex partial epilepsy refractory to multiple therapeutics requiring a vagal nerve stimulator, diplegic cerebral palsy, chronic kidney disease secondary to nephrotic syndrome from focal segmental glomerular sclerosis, and “atypical” CF diagnosed in infancy with positive sweat chloride testing and suggestive phenotype defined primarily by pancreatic insufficiency but no causative mutations identified on expanded CF genetic sequencing studies. Her epilepsy and cerebral palsy manifested in early childhood and are currently considered idiopathic by her neurology team with notably normal workup to date, including imaging evaluation and epilepsy-targeted genetic studies revealing no disease-associated mutations. She also has a history of sensorineural hearing loss and is followed by a gastrointestinal specialist for dysphagia with small esophageal strictures. Her guardians reported that,
3 years previously, she had developed waxing and waning blisters along the distal extensor aspects of her extremities. Biopsy results at that time were reportedly consistent with bullous pemphigoid. She had trialed topical corticosteroids, minocycline, nicotinamide, mycophenolate mofetil, methotrexate, and protracted courses of systemic corticosteroids with negligible therapeutic benefit prior to this visit. On examination, she demonstrated linear pretibial and upper extremity extensor bullae on minimally erythematous bases noted along the lateral aspect of the patient’s thigh.

**Table I.** Classification of heritable forms of epidermolysis bullosa. Recent consensus classification schemes indicate a total of 35 distinct subtypes of epidermolysis bullosa delineated by a combination of the cutaneous layer in which the separation occurs, clinical presentation, pattern of genetic inheritance, genetic abnormality, and protein involved.

| EB type          | Mutated gene       | Encoded protein                  | Inheritance pattern | Syndromic vs nonsyndromic | Syndromic associations                                      |
|------------------|--------------------|----------------------------------|---------------------|---------------------------|-------------------------------------------------------------|
| Simplex          | KRT5, KRT14        | Keratin 5, Keratin 14            | AD (>AR)            | NS                        | -                                                           |
|                  | PLEC               | Plectin                          | AR (>AR)            | S                         | Muscular dystrophy, pyloric atresia, dilated cardiomyopathy |
|                  | KLHL24             | Kelch-like member 24             | AD (>AR)            | S                         | Dilated cardiomyopathy                                      |
|                  | DST                | Bullous pemphigoid antigen       | AR                  | NS                        | -                                                           |
|                  | EXPH5              | Exophilin 5                      | AR                  | NS                        | Nephropathy with or without epilepsy, thalassemia, pancreatic insufficiency, KS-like cutaneous features |
|                  | CD151              | CD151 tetratraspanin             | AR                  | S                         | -                                                           |
| Junctional       | LAMA3              | Laminin α3                       | AR                  | NS                        | -                                                           |
|                  | LAMB3              | Laminin β3                       | AR                  | NS                        | -                                                           |
|                  | LAMC2              | Laminin γ2                       | AR                  | NS                        | -                                                           |
|                  | COL17A1            | Type XVII Collagen               | AR                  | NS                        | -                                                           |
|                  | ITGA6              | Integrin α6                      | AR                  | S                         | Pyloric atresia                                             |
|                  | ITGB4              | Integrin β4                      | AR (>AD)            | S                         | Pyloric atresia                                             |
|                  | ITGA3              | Integrin α3                      | AR                  | S                         | Interstitial lung disease and congenital nephrotic syndrome |
| Dystrophic       | COL7A1             | Type VII collagen                | AD and AR           | NS                        | -                                                           |
| Kindler          | FERMT1             | Fermitin family homolog          | AR                  | NS                        | -                                                           |

AD, Autosomal dominant; AR, autosomal recessive; EB, epidermolysis bullosa; KS, Kindler Syndrome; NS, nonsyndromic; S, syndromic.
erythematous bases (Fig 1). Onychodystrophy and dental enamel hypoplasia as well as scattered poikiloderma and patchy alopecia were also diagnosed. No mucosal ulcerations or erosions were noted. Further examination of her medical history revealed that the patient had developed small transient blisters along her extremities with minimal trauma when she was a toddler. It was not until these blisters became persistent and severe that requests for medical evaluation were prompted. Biopsies specimens were collected, which showed a subepidermal separation with negative direct immunofluorescence staining. Neither immunofluorescence mapping nor transmission electron microscopy were readily available. Suspicion of a heritable form of skin fragility prompted an EB-specific next-generation sequencing evaluation, which revealed that the patient was homozygous for an autosomal recessive c.406 C>T mutation in exon 6 of the CD151 gene, resulting in the replacement of the glutamine at codon 136 with a premature stop codon, synonymous with 2 reported cases in the literature and identified as a disease-associated variant. This finding, combined with her clinical presentation, supported a diagnosis of CD151-associated syndromic EBS with nephropathy. She was tapered off of all forms of immunosuppressants, with a care plan that was shifted to careful skin care, nutrition, and ocular health. The blisters substantially improved with this regimen, and she was referred to a multidisciplinary EB clinic for further evaluation and treatment.

DISCUSSION

EB is a complex condition defined by skin fragility with a significant degree of phenotypic heterogeneity and variable severity. Approximately 21 genes with more than 1000 separate mutations have been identified in the 35 known subtypes of heritable EB (Table 1). Diagnosis has traditionally relied on the ultrastructural evaluation of tissue with immunofluorescence mapping or transmission electron microscopy. The development of EB-specific genetic sequencing studies has substantially improved this diagnostic evaluation—especially in cases with characteristic clinical features where IFM or TEM may not be readily available. NGS, when combined with clinical phenotype, played a particularly critical role in the evaluation and ultimate diagnosis of our patient.
syndromic EBS subtypes involves an autosomal recessive mutation in tetraspanin CD151, which, in a single proband, resulted in a Kindler-like EB presentation with pretibial blistering and multisystemic manifestations, including nephropathy, poikiloderma, nail dystrophy, loss of teeth, alopecia, and esophageal strictures. Ultrastructural evaluation of this patient’s skin revealed the absence of CD151 within the basement membrane and similarities to patients with EXPH5 gene mutations (a nonsyndromic form of EBS), prompting its classification as an EBS subtype. This presentation aligned with 3 similar cases from 2 families discovered to have homozygous frame-shift mutations in CD151 and a similar pretibial blistering pattern with nephritis, sensorineural deafness, and anemia secondary to β-thalassemia.

Tetraspanin CD151 is a transmembrane protein, now known to be essential to the development of hemidesmosomes through stabilization of laminin-integrin binding. It is highly expressed in the cells of the vascular, renal, and nervous systems as well as the basal epithelia of the skin. Some studies have also shown high levels of tetraspanin CD151 expression in normal human bronchial epithelial cells, where the CF transmembrane conductance regulator plays a critical role in chloride transport. In the cutaneous basement membrane, CD151 tetraspanin binds with α6β4 integrin and stabilizes its interaction with laminin-332, playing a critical role in the formation of the hemidesmosomal complex. A similar stabilization effect occurs within both the renal tubules and keratinocyte focal adhesion units when CD151 binds to α3β1 integrin. In mice, CD151 deficiency has been shown to result in kidney failure secondary to focal and segmental glomerular sclerosis with tubular dilation. The presence of tetraspanin CD151 in the central/peripheral nervous system as well as in epithelial cells containing high concentrations of CF transmembrane conductance regulator proteins suggests that CD151 dysfunction could lead to abnormalities in chloride transport and nerve conduction. This, along with the notable absence of historical, structural, imaging-based, and laboratory-based evidence suggesting alternative etiologies underlying our patient’s epilepsy and CF, supports the notion of a unified pathologic process.

Treatment recommendations for all forms of EB are largely supportive and hinged upon careful management of blistering and systemic complications. Prognosis varies depending on the severity and type of EB, with syndromic forms typically associated with more significant morbidity and mortality. Early intervention and multidisciplinary care are crucial for optimal outcomes.
attention to wound care, blister prevention, nutrition, ocular health, and oral hygiene. In syndromic EB, screening for multisystem involvement may be prudent with the appropriate genetic findings. In the case of CD151 defects, urinalysis, renal ultrasound, and complete blood count should be considered, as well as referrals to nephrology, hematology, and audiology specialists. On the basis of our case, a reasonable argument could be made to include electroencephalography, sweat chloride testing, and detailed neurologic assessment in the screening of patients discovered to have this defect (Table II). This case also outlines the importance of considering CD151-associated EBS in patients with pediatric nephropathy and concomitant or subsequent blistering, even if the blistering is mild or delayed.

CONCLUSION
To our knowledge, this case represents the fifth report of a CD151 tetraspanin mutation resulting in EBS with nephropathy2,5 and adds to the literature by being the first reported case associated with epilepsy and CF. More reports are needed to further elucidate the full phenotypic spectrum of this rare clinical entity.

Conflicts of interest
None disclosed.

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Table II. Recommended diagnostic evaluation of patients discovered to have defects in CD151 tetraspanin

| Organ system    | Associated abnormalities                                      | Suggested workup                              |
|-----------------|-------------------------------------------------------------|-----------------------------------------------|
| Renal           | Nephrotic syndrome (focal segmental glomerular sclerosis)   | Urinalysis                                   |
| Hematologic     | β-thalassemia                                               | Renal ultrasound, Referral to nephrologist   |
| Gastrointestinal| Pancreatic insufficiency (secondary to cystic fibrosis)     | Complete blood count, Referral to hematologist|
| Neurologic      | Sensorineural hearing loss                                   | Referral to gastrointestinal specialist      |
| Other           | Cystic fibrosis                                             | Neurologic examination, Electroencephalogram |

Table II.