VIA MEDICA

CASE REPORT

Forum Dermatologicum
2024, Vol. 10, No. 3, 97–100
DOI: 10.5603/fd.100812

ISSN 2451–1501, e-ISSN 2451–151X

A benign form of epidermolysis bullosa pruriginosa with a novel mutation in *COL7A1* gene in a Polish family: a case series and literature review

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ABSTRACT

Epidermolysis bullosa pruriginosa is an extremely rare form of dystrophic epidermolysis bullosa. Its cause is the underlying mutation, most often in the *COL7A1* gene. Based upon a specific type of mutation in a patient (missense, non-sense, frameshift, splice-site mutations), a distinct, specific phenotype can be observed. This study presents a case series of three family members from the Pomerania region in Poland, with a novel missense mutation of p.Val2402Gly/-c.7205T>G in exon 94 of the *COL7A1* gene.

Forum Derm. 2024; 10, 3: 97–100

Keywords: epidermolysis bullosa pruriginosa, dystrophic epidermolysis bullosa, genodermatoses

CASE REPORT

A 34-year-old female patient (Fig. 1), her 12-year-old daughter and her 66-year-old father (Fig. 2) presented to the Dermatological Outpatient Clinic because of chronic, relapsing skin eruptions of non-specific character. Clinical examination revealed in the 34-year-old woman and her father multiple, diffuse firm papules, plaques and nodules located on the back and extensor surfaces of the extremities. The lesions were very pruritic, and numerous excoriations and scattered scars were observed. The clinical manifestation was consistent with prurigo nodularis. The following conditions were included in differential diagnosis: pemphigoid nodularis, lichen simplex, lichen planus, nodular scabies, dermatillomania, Münchhausen syndrome by proxy, as well as epidermolysis bullosa pruriginosa (EBP). Laboratory tests did not reveal any abnormalities. Evaluation of severe pruritus causes were performed: complete blood cell count, metabolic panel, thyroid studies [free T4 (fT4) and thyroid stimulating hormone (TSH)], urinalysis, stool exam, HIV antibodies, serum IgE and chest X-ray. Laboratory tests did not reveal any abnormalities. The histopathological assessment demonstrated thickening of the epidermis, ortho-hyperkeratosis, irregular epidermal hyperplasia, and pseudoepitheliomatous hyperplasia. Moreover, focal parakeratosis with irregular acanthosis, diminished nerve fibre density and a nonspecific dermal infiltrate containing lymphocytes, macrophages, eosinophils, and neutrophils were observed (Fig. 3). Direct immunofluorescence test was negative. No circulating antibodies indicative of bullous diseases were detected.

Molecular genetic tests were performed — firstly by new generation sequencing (NGS) study that covered 33 mutations related to EB (this included: CAST, CD151, CDSN, COL17A1, COL7A1, CSTA, DSG1, DSP, DST, EXPH5, FERMT1, ITGA3, ITGA6, ITGB4, JUP, KLHL24, KRT1, KRT2, KRT5, KRT10, KRT14, KRT16, KRT17, LAMA3, LAMB3, LAMC2, PKP1, PLEC, PLOD3, SERPINB8, SPINK5, TGM5, VPS33B). A novel missense mutation of p.Val2402Gly/- c.7205T>G in exon 94 of the *COL7A1* gene was found in the patient, her daughter and her father (Tab. 1). As of the 2nd of August 2023, this mutation is not yet present in Mondo Global Medical Database (MGMD) and Clinical Variant Database (ClinVar). Based on the Genome Aggregation Database (GnomAD), the incidence of this mutation in the general population is very low — that is 0,00089%. NGS study was later confirmed with Sanger

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Received: 23.05.2024 Accepted: 1.08.2024 Early publication date: 21.08.2024

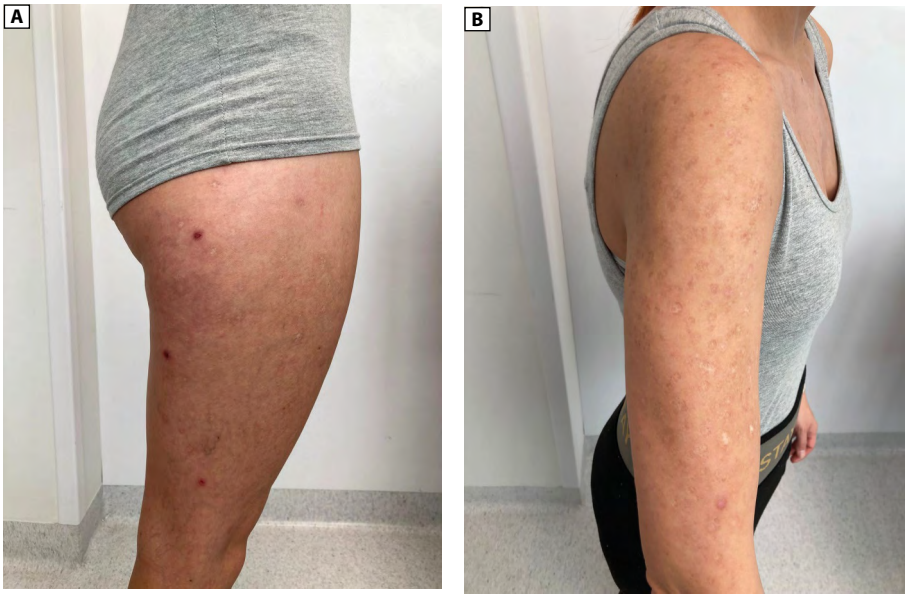

Figure 1A, B. Numerous scars and post-inflammatory hyperpigmented macules on the patient's upper extremities (a 34-year-old female) with erosions and prurigo-nodularis-like nodules on lower extremities

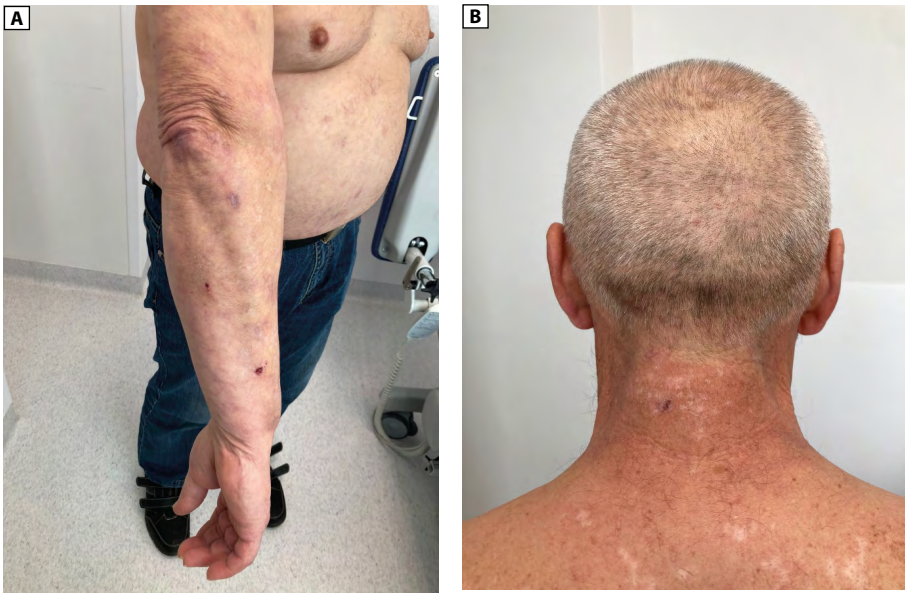

Figure 2A, B. Numerous scars, singular erosion on the patient's father (a 66-year-old male)

sequencing. Finally, the diagnosis of EBP was made based on the family history, symptoms and results of molecular genetic tests. The patient's asymptomatic 6-year-old son was also included in the study, but the result of the genetic tests was negative. Treatment was implemented: topical emollients and potent topical steroid creams that resulted in improvement in the patient's daughter and father. Due to the lack of substantial clinical benefits, the patient was given local corticosteroid injections (triamcinolone acetonide 40 mg/mL), oral antihistamines and phototherapy with ultraviolet B (UVB) 311 nm. After a 3-month treatment period, complete skin lesions and reduction of itch were achieved. The patient and their family remain in constant care and observation.

DISCUSSION

Epidermolysis bullosa pruriginosa (EBP) is an extremely rare form of dystrophic epidermolysis bullosa (DEP). Its cause is the underlying mutation, most often in the *COL7A1* gene. Based upon a specific type of mutation in a patient (missense,

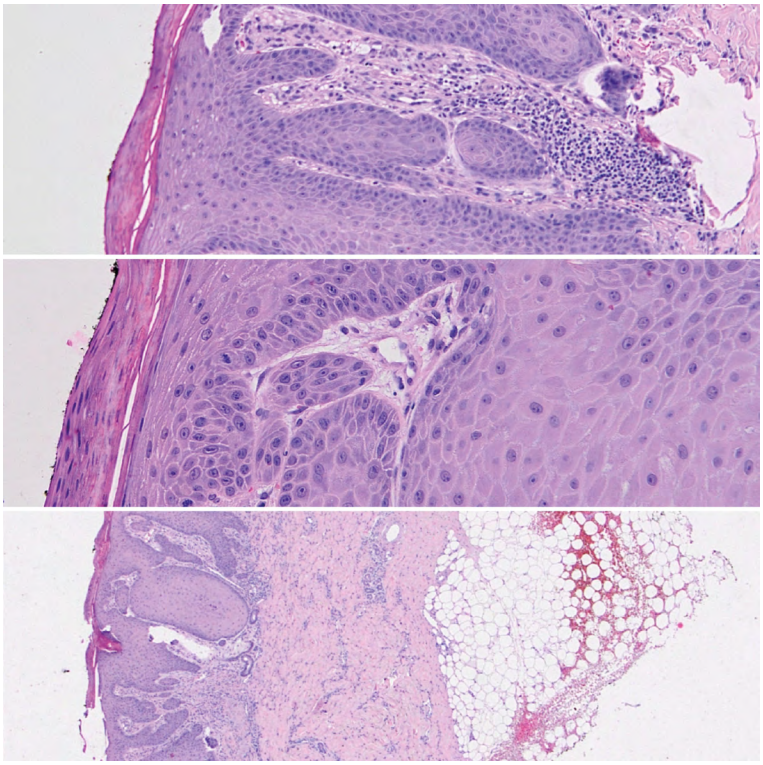

Figure 3. The result of the histological picture of the 34-year-old female patient

Table 1. The result of DNA analysis

Patient	1	2	3
Age	34	12	66
Sex	Female	Female	Male
Indication	Prurigo-like skin lesions	Prurigo-like skin lesions positive result of NGS — Col7A1 in patient 1	Prurigo-like skin lesions positive result of NGS — Col7A1 in patient
Material for laboratory testing	**DNA**	**DNA**	**DNA**
Medical procedure	Analysis of any mutation without DNA isolation (GEN23A)	Analysis of any mutation without DNA isolation (GEN23A)	Analysis of any mutation without DNA isolation (GEN23A)
Result	Col7A1:Val2402Gly/-VUS	Col7A1:Val2402Gly/-VUS	Col7A1:Val2402Gly/-VUS

NGS — next-generation sequencing; DNA — deoxyribonucleic acid; VUS — variant of uncertain significance

non-sense, frameshift, splice-site mutations), a distinct, specific phenotype can be observed [1–3]. Clinically, the mean time of symptoms onset is the age of 14. Constant, intense pruritus is present in nearly all patients. The main skin lesions found in EBP are hypertrophic prurigo-like papules and plaques nodules, and violaceous papules, often in a linear or circular configuration, often with secondary lichenification, nodule, plaque and scar tissue formation. Other skin findings are millia, nail dystrophy, albopapuloid lesions, and atrophic scars [4]. The phenotype-genotype correlation of EBP is substantially wide and is based on the mutation type. However, some family members with the same mutation can present significantly different manifestations of the condition. Thus, other environmental factors must be accounted for EBP's non-negligible heterogeneity, however, no specific factors were found in its pathogenesis. In 2015 Kim et al. [1] analysed this correlation and divided 74 patients into four mutation groups: glycine substitution (GS) — 52.7%, in-frame skipping (IFS) — 33.8%, non-glycine substitution (NGS) — 8.1%, and premature terminal codon (PTC) — 5.4%. Except for IFS carriers, EBP patients were predominantly female (66.2%). IFS patients were more prone to develop blisters and shared a more linear or circular configuration of the lesions, but had lower nail involvement, presence of milia, and atrophic scars and showed no albopapuloid lesions (which were mostly present in the PTC group). GS was also found to be a group with the most clinical features [1].

CONCLUSIONS

Epidermolysis bullosa pruriginosa is usually inherited in an autosomal dominant manner, but an autosomal recessive pattern is also present in the literature [1]. Another study points to a possible skewed T-helper type 2 (Th2)-related immunity in patients with EBP [4].

Treatment in EBP is purely symptomatic and revolves around reducing the itch. Traditionally, topical glucocorticosteroids and emollients are applied to the skin to reduce the itch. Some patients are treated with phototherapy, most commonly (narrowband ultraviolet B) NB-UVB with moderate success.

Recently, some cases of EBP treated with dupilumab were reported with positive clinical outcomes [5–8]. No causal treatment is currently available for EBP.

Article information and declarations

Acknowledgements

None.

Author contributions

Writing: original draft, data curation, conceptualization — KK; supervision — RN; writing-original draft, analysis and description of histopathological examination — EGD; data curation, table and figure preparation — AK; supervision — IB. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. All authors had full access to all of the data in this study and took complete responsibility for the integrity of the data and the accuracy of the data analysis. No medical writing or editorial assistance was received in the preparation of this manuscript.

Funding

The authors declare that no financial support was received for the research, authorship, and/or publication of this article.

Supplementary material

None.

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