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CASE REPORT

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Pemphigus herpetiformis in a 4-year-old child: Case report and review of the literature

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Abstract

Pemphigus herpetiformis (PH) is a rare form of pemphigus, especially when occurring in childhood. Misdiagnosis is common in this age group. The disease exhibits diverse clinical and histological aspects. Further immunological investigations should be performed in order to make the right diagnosis with a correct management strategy.

KEYWORDS

herpetiform blisters, pediatric auto-immune bullous disease, pediatric pemphigus, pemphigus herpetiformis

1 | INTRODUCTION

Pemphigus herpetiformis (PH), first described in 1975 by Jablonska et al,[1] is a rare form of pemphigus combining clinical herpetiform pattern and immunologic features of pemphigus. The underlying pathogenesis of the disease remains unclear with autoantibodies triggering mainly desmoglein 1 (Dsg1) and an intense underlying inflammatory reaction.[2] Presentation in children is overlapping with herpetiform dermatitis or linear IgA dermatitis, leading to misdiagnose this condition.[3] Findings in this acquired auto-immune bullous disease are polymorphic combining features of pemphigus and eosinophilic spongiosis.[4] Therefore, diagnosis is mainly based on compatible direct immunofluorescence (DIF) and immunologic findings.[2] In children, treatment of PH is challenging. Literature data are based only on case reports of pediatric PH, whereas series of patients are lacking. The purpose of this article was to describe a new case of PH of childhood with a comprehensive summary of the main characteristics of the disease.

2 | CASE REPORT

A previously healthy 4-year-old boy with no familial history of auto-immune bullous diseases presented with pruritic blistering eruption on trunk and lower limbs which appeared 2 weeks earlier. Upon admission, physical examination found annular erythematous plaques involving the chest and thighs (Figure 1).

Hyperpigmented patches and crusted erosions on the scapular area (Figure 2). Multiple blisters with

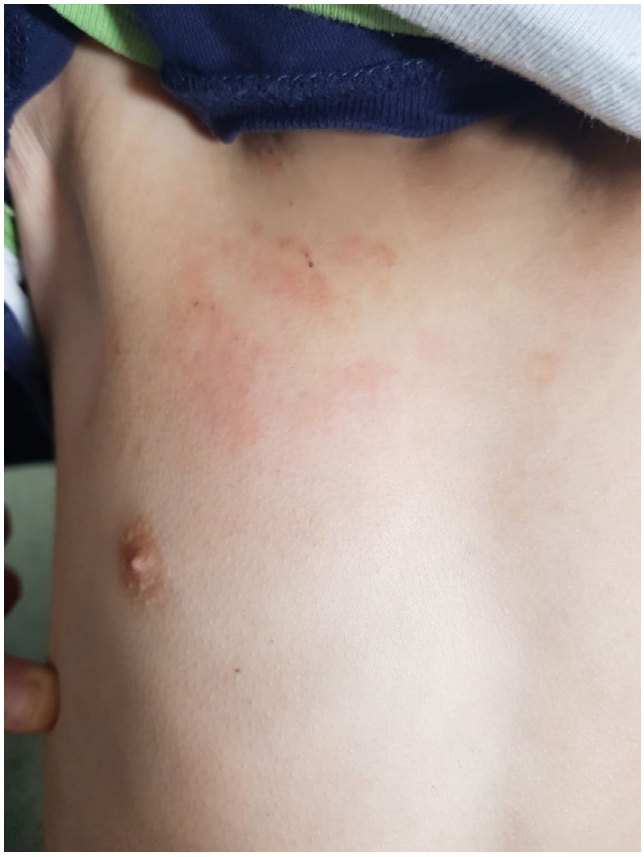

FIGURE 1 Annular erythematous plaque over the chest

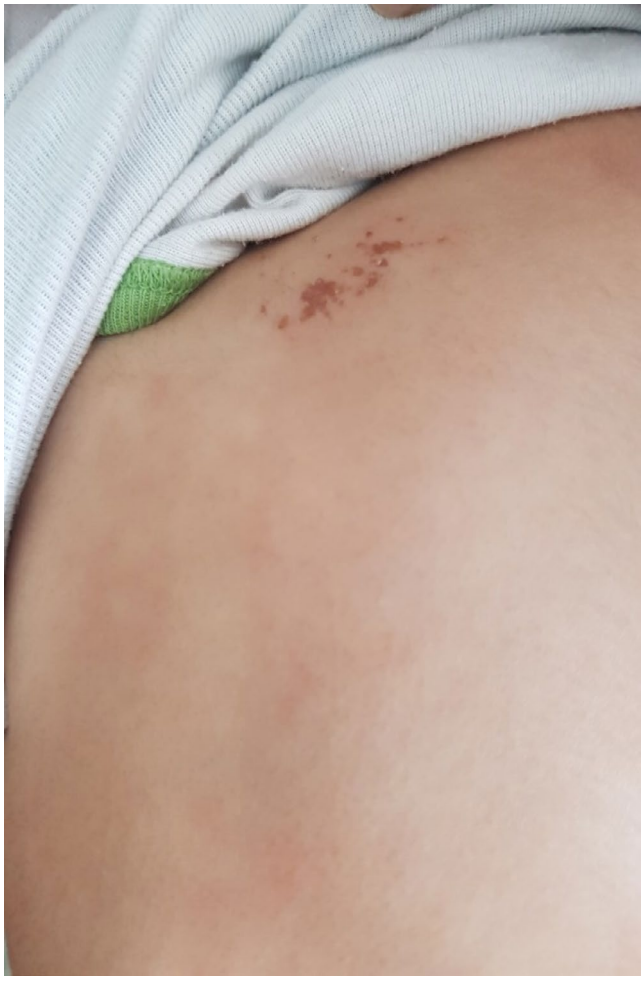

FIGURE 2 Crusted erosions over the back

erythematous background were found on his left leg (Figure 3). Herpetiform pattern was evident (Figure 4). Small tense vesicles associated with arciform erythema were found on both soles. The face and upper limbs were spared. Nikolsky sign was negative. There was no nail nor mucosal involvement. Physical examination was otherwise unremarkable. Laboratory examinations showed hyperleukocytosis (12080/μL) with eosinophilia (590/μL), hypochromic and microcytic anemia (HB 11.3g/dl, MCV 70.7 FL, reticulocytes 40.2 103/μL) with low ferritin (2.62 ng/ml). Antiendomysial and antigliadin antibodies serum titers were negative. A skin biopsy of one intact bulla revealed intraepidermal cleft in the basal and suprabasal layers making a "tomb-stone" appearance (Figure 5). Mixed type inflammatory infiltrate made of neutrophil and eosinophil cells was seen in the epidermis. Edema of the dermis with mixed spongiosis along with perivascular deposition of multiple lymphocytes was seen (Figure 6). Direct immunofluorescence of the peribullous skin showed "chicken-wire" pattern with intercellular deposits of complement C3 and IgG within the entire epidermis. Enzyme-linked immunosorbent assay (Elisa) was positive for Dsg1 (135 UI/ml) and negative for desmoglein 3 (Dsg3). The histological and immunological features along with the clinical herpetifrom pattern were consistent with PH. Giving the limited area of active cutaneous lesions, one month-course of topical betamethasone dipropionate 0.05% was started and led to marked improvement. The child relapsed after 3 months, and multiple bulla appeared on his lower limbs. The decision was to start the treatment with dapsone as an oral corticosteroid sparing agent. Laboratory monitoring including dosing of methomglobinemia and glucose-6-phosphate dehydrogenase (G6PD) activity was made. The drug was introduced at a dose of 1 mg/kg/daily than increased to 2 mg/kg/daily. A remarkable clinical improvement with regression of bullae and erythema was seen after 1 week. Dapsone treatment has been effective in maintaining clinical remission after 2 months of therapy.

3 | DISCUSSION

The underlying immunopathogenic nature of PH is still not clear combining severe inflammation with variable auto-immune reaction.[2] In adults, this subtype is considered as particular variant of pemphigus foliaceus

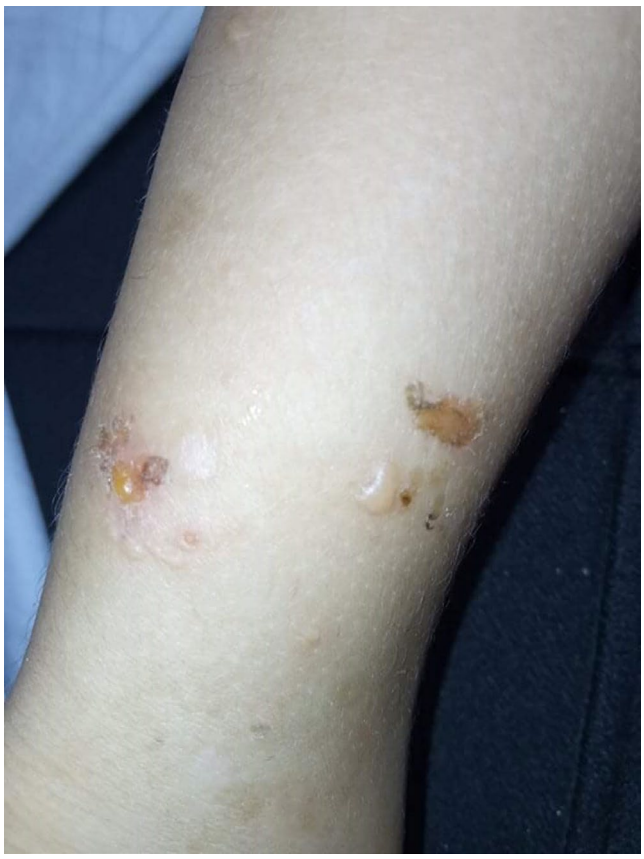

FIGURE 3 Multiple vesicles and bullae with erythematous background on the lower limb

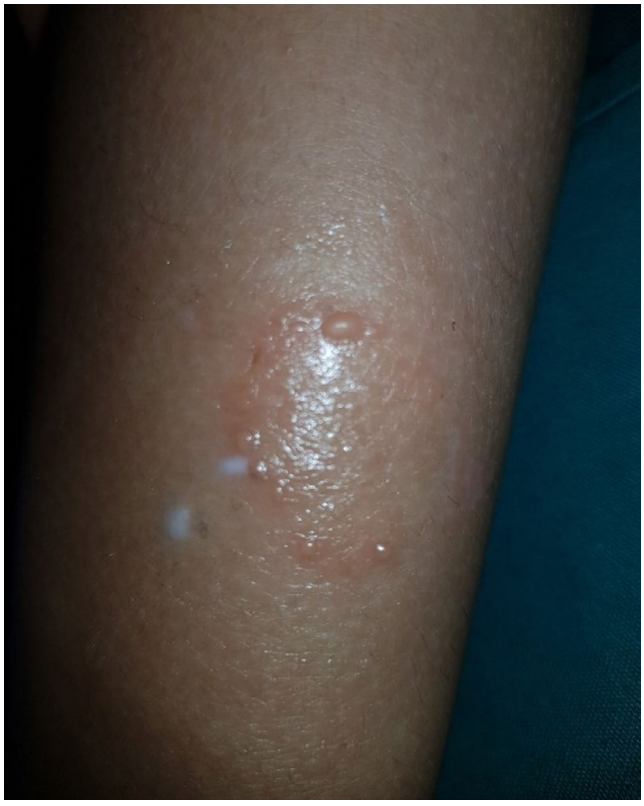

FIGURE 4 Herpetiform pattern of blisters over the left leg

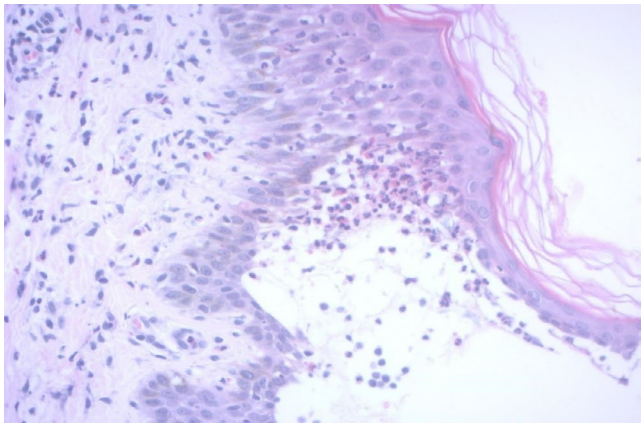

FIGURE 5 Basal and suprabasal intra-epidermal cleft with eosinophils and neutrophils infiltrate (HEX200)

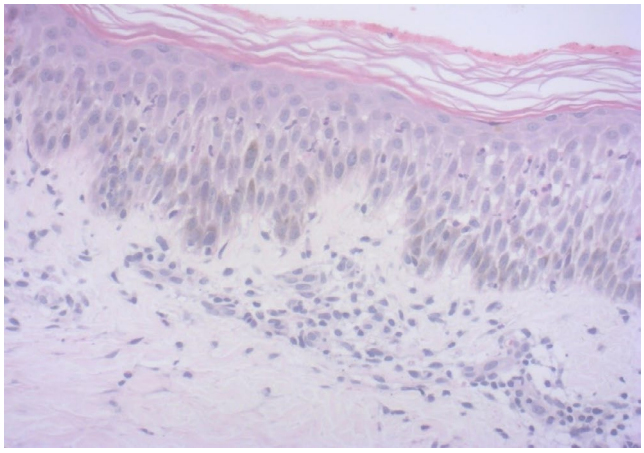

FIGURE 6 Neutrophilic and eosinophilic spongiosis with perivascular deposition of lymphocytic infiltrate in the dermis (HEX200)

with immunoreactivity triggering mainly dsg1 and predominant skin involvement.[2,5] This theory is supported by our review since even in rare cases, where mucosal involvement is seen, absence of autoantibodies against Dsg3 is constant.[6] Of note, rare cases of PH associated with reactivity to Dsg3 were reported.[2] Additive pathogenic factor of medication was suggested in a case of PH occurring in a child who received a mucolytic agent with thiol compound.[7] PH still presents challenges in diagnosis since it combines the clinical aspects of dermatitis herpetiformis and immunopathology features of pemphigus.[4] Kasperkiewicz et al[2] proposed diagnostic criteria for PH in 2014 based on the immunopathology giving the clinical and histopathologic diversity of the disease. PH is considered as a rare variant with more than 100 reported cases and only few case series.[8] In Tunisia, PH seems to be occurring in young women from rural origins with an incidence of 0.9 new cases per year.[5] Herpetiform pattern in infants can lead to clinical misdiagnosis since linear IgA

TABLE 1 Clinical characteristics of pediatric pediatric Pemphigus herpetiformis

Author	Country	Age (years)	Gender	Pruritus	Affected areas onset	Type of lesions	Nikolsky sign	Oral mucosa involved	Genitalia involved
Current study	Tunisia	4	Male	Yes	Trunk, thighs and lower limbs	Annular erythematous plaques Crusted erosions Herpetiform bulla	Negative	No	No
Huhn et al[12]	Canada	14	Female	Yes	Abdomen, back, wrists and forearms	Erythematous macules with pink papules Clear and cloudy vesicles Irregular ulcerated and crusted lesions with herpetiform configuration	NA	No	No
Duarte et al[11]	Brazil	5	Female	Yes	Face, trunk, upper and lower limbs, buttocks	Annular erythema Grouped vesicles and blisters	NA	No	Yes
Hocar et al[13]	Morocco	12	Male	Yes	Back, buttocks, chest, abdomen, legs, and arms	Vesicular and bullous lesions Erosive arciform plaques and crusted lesions	Negative	No	No
Moutran et al[14]	Lebanon	6	Female	Yes	Trunk, face and extremities	Vesicules and bullae Annular, polycyclic, and erythematous plaques	NA	No	NA
Leithauser et[15]	Ohio, United states	9	Male	Yes	Legs, arms, back, chest, and abdomen	Annular erythematous and edematous plaque, Crusted erosions Round vesicles	NA	NA	NA
Schoch et al[9]	Minnesota, United states	Neonate	Male	NA	Hands and feet	Crateriform erosions Vesiculobullous lesions	NA	No	No
Akoglu et al[7]	Turkey	9	Male	Yes	Trunk, extremities and sclap	Herpetiform vesicles and bulla Erythematous plaques	Negative	No	NA
Peterman et al[6]	Massachusetts, United States	2	Female	Yes	Face (periocular and perioral), upper and lower limbs, trunk	Eczematous and blisters Tense vesicles Hemorrhagic crusts Desquamation	NA	No	Yes Erosion of the labia minora

†NA, not available

TABLE 2 Paraclinic features of pemphigus herpetiformis in children

Laboratory abnormalities	Histology	Direct immunofluorescence	Indirect immunofluorescence	Desmoglein1	Desmoglein3
Hyperleukocytosis, anemia, eosinophilia, thrombocytosis and low ferritin	Intraepidermal cleft with a "*tomb-stone*" appearance Eosinophilic and neutrophilic exocytosis Edema of the dermis with perivascular deposits of lymphocytes	*Positive* *Intercellular deposits of IgG and C3 (Entire epidermis)*	NA	Positive *135 UI/ml*	Negative
No	On repeat biopsy: Mid-epidermal and upper-epidermal cavities with numerous acantholytic cells and neutropbils	*Positive on repeat biopsy:* Intercellular intraepidermal C3 and IgG deposits	Negative	NA	NA
Anemia, eosinophilia, thrombocytosis and low ferritin	Subcorneous blisters Rare acantholytic cells Spongiosis Eosinophilic exocytosis	Positive Intercellular deposits of IgG and C3	NA	NA	NA
No	Intraepidermal bulla containing rare acantholytic cells with eosinophil and neurophil cells Eosinophilic spongiosis and focal acanthosis (lower epidermis) Inflammatory infiltrate (superticial and reticular dermis)	Positive Intercellular intraepidermal C3 and IgG deposits	Positive 1/200 UI/l	NA	NA
NA	Acantholysis (middle and superficial layers of the epidermis) Neutrophilic infiltration	Positive Intercellular IgG and C3 deposits (Epidermis and dermo-epidermal junction)	NA	NA	NA
NA	Intraepidermal vesicle Neutrophilic and eosinophilic spongiosis Mixed type infiltrate within the superficial dermis	Positive Moderate IgG and intense C3 deposits along the surface of epidermal cells	Negative	NA	NA
No	Focal intraepidermal acantholysis Eosinophilic and neutrophilic exocytosis	Positive Intercellular C3 deposits (Lower half of the epidermis)	NA	NA	NA
No	Intraepidermal cleft Acantholytic cells Spongiosis Edema and mixed type inflammatory infiltration	Positive Intercellular intraepidermal C3 and IgG deposits	NA	Positive	Negative
No	Intraepidermal vesicle with neutrophils Acantholytic cells in subgranular epidermis **Suprabasal acantholysis** Eosinophilic infiltrate (epidermis and dermis)	Positive (on repeat biopsy) Intercellular intraepidermal IgG and C3 deposits	Indeterminate, mostly negative	Positive	Negative

†NA, not available.

TABLE 3 First and second-line treatments in pediatric pemphigus herpetiformis

First-line Treatment and period	Effect	Second-line treatment and period	Effect	Follow-up(months)
Topical Betamethasone Dipropionate 0.05% for 1 month	Rapid and marked improvement fallowed by a relapse after 3 months	Dapsone: started at a dose of 1mg/kg/daily, increased to 2mg/kg/daily: ongoing	Clinical improvement with regression of bullae and erythema with complete remission	2 months after starting dapsone
Oral penicillin with topical corticosteroids	No improvement	Oral prednisone with low dose of maintenance (Indeterminate period)	Clinical remission	NA
Prednisone 40 mg/daily with tapering by10mg /15 days (Indeterminate duration)	Clearance of 95% of skin lesions Relapse after discontinuing treatment			
Dapsone 50 mg/day for 10 days	No clinical improvement: Exfoliative dermatitis	Dapsone with Immunosuppressive doses (20 mg/day) of systemic corticosteroids for 3 weeks	Complete remission	
		Dapsone with steroid treatment taper	Relapse	
		Azathioprine (50 mg/day) with increased doses of prednisone (Indeterminate period)	Complete remission	NA
Dapsone 2 mg/kg/day (Indeteminate period)	Total clinical remission fallowed by a relapse after 2 months	Oral prednisone: 2 mg/kg daily for 4 weeks	Complete remissio	
		Progressive taper of steroids to low maintenance dose of 10mg daily: Ongoing	No relapse	12 months after onset of the disease
Oral prednisone at a dose of 10 mg/day: 0.3 mg/kg/day (Inderteminate period)	Partial clinical improvement	Prednisone with dapsone: 2 mg/kg/day	Marked clinical improvement	
	Relapse after reduction of steroids	Discontinuation of steroid treatment after 3 months of gradual taper, dapsone at the same dose: Ongoing	Complete remission	24 months after the initial diagnosis
Dapsone up to 50 mg/day, Mycophenolate mofetil up to 750 mg twice daily Azathioprine up to 175 mg daily	No significant improvement	Prednisone up to 25 mg daily (Indeterminate period)	Control of disease flares	

TABLE 3 (Continued)

First-line Treatment and period	Effect	Second-line treatment and period	Effect	Follow-up(months)
Rituximab 375 mg/m2 weekly for 5 weeks Doxycycline 50 mg and nicotinamide 250 mg twice daily Erythromycin 333 mg twice daily (Indeterminate period)		Prednisione with oral methotrexate up to 15 mg weekly for 21 months	Complete remission	
		Discontinuing methotrexate and prednisone	Disease free	22 months after discontinuing methotrexate and prednisone
None	Spontaneous improvement after 3 days Breastfed for a week: Relapse	None Mother was started on chemotherapy, dexamethasone, oral prednisone and doxycycline for 3 months with complete remission at the 9-month follow-up Breastfeeding suspended upon initiation of chemotherapy	Complete remission at 3 weeks of age with milia	
			Normal growth and development	3 months after the initial diagnosis
Methylprednisolone 1 mg/kg/day, cetirizine suspension 5 mg/ml/day and topical 0.05% betamethasone cream twice a day for 2 months Avoiding drugs and food which may induce or trigger pemphigus	Partial clinical improvement Relapse: 2 weeks after reduction of steroids to 0.5 mg/kg/day	Methylprednisolone dosage raised to 1 mg/kg/day for 1 month	Partial clinical improvement	
		Oral methotrexate 10 mg weekly with steroid treatment at the same dose for 3 months	Improvement and lower serum anti-desmoglein 1 antibody titer (1:10)	
		Gradually reducing methylprednisolone to 0.25 mg/kg/d and discontinuing methotrexate, lost for follow up (2months)	Relapse after 1 month of discontinuing steroids	
		Methylprednisolone 1.5 mg/kg/day with slow taper for 6 months	Complete remission	8 months after discontinuing methylprednisolone

(Continues)

TABLE 3 (Continued)

First-line Treatment and period	Effect	Second-line treatment and period	Effect	Follow-up(months)
Prednisone 1 mg/kg/day for 12 days Prednisone 1.5 mg/kg/day with a slow taper over 4 weeks	No improvement	Clobetasol ointment with two 10-days courses of cephalexin 125 mg three times/day	Only partial improvement with no control of disease flares	
Topical steroids (fluocinonide 0.05%, triamcinolone 0.1%, desonide 0.05%) and emollients	Significant improvement Relapse after treatment cessation			
	Initial improvement fallowed by extension of lesions	Dapsone 1 mg/kg/day (Indeterminate duration	Significant improvement with minor intermittent flares	
		Increasing doses of dapsone to 1.5 mg/kg/day: Ongoing	Complete remission	NA

†NA, not available.

bullous dermatitis is more frequent in this age group.[3] In our review of the literature, only 8 cases of PH occurring in children were identified. A summary of clinical characteristics from the reported cases is shown in Table 1. Age of onset of the disease ranges from birth to 12 years with an average of 6.7 years. Schoch et al[9] described a case of transplacental transmission of PH in a neonate whom mother was diagnosed with paraneoplastic PH in the setting of non-Hodgkin lymphoma. A slight male predominance was noted in our review (sex ratio: 5/4). All infants displayed severe pruritus. The main clinical lesion type seen was the combination of erythematous plaques with herpetiform vesiculobullous lesions (75%). The deposition of the rush showed no predilection sites. Among the cases with available data, none of the infants presented with positive Nikolsky sign. Oral mucosal involvement was absent in all reported cases whereas participation of genitalia was found in two children.[6,10] The acquired autoimmune bullous disease exhibits variable paraclinical features which are studied in Table 2. Blood eosinophilia was found in 25% of the cases. Histopathologic aspects of pemphigus including intraepidermal cleft with various acantholytic cells were seen in all infants. Exclusive eosinophlic songiosis was found in three biopsies and in conjunction to neutrophils in two. Of note, DIF was positive in 100% of the cases with intercellular IgG and C3 deposits. When ELISA is available ($n = 3$), reactivity triggering only dsg1 was seen similar to cases of pemphigus foliaceus (PF). First- and second-line therapies used in all reported cases are described in Table 3. Oral corticosteroids showed efficacy when prescribed in monotherapy ($n = 3$) and in conjunction with immunosuppressants ($n = 2$). Dapsone monotherapy as first or second-line treatment ($n = 5$) led to final clinical remission in two cases including our patient. In conjunction with oral steroids, complete remission was reached in one infant whereas flares of the disease occurred with tapering in another case. All cases showed disease control after second-line therapies. Treatment of the mother with suspension of breastfeeding helped in controlling the disease in the case of neonatal PH which is suggestive of passive transmission of autoantibodies rather than a well-established PH in the neonate.[6] No side effects of treatments were reported in the reviewed cases. The evidence base for treatment of this form of pemphigus is not clear. Oral steroids with or without dapsone should be used in first-line treatment.[10] Other options such as immunosuppressants or antibiotics with anti-inflammatory action are also considered yet with no determined role.[6,10] Topical treatments have only partial efficacy in the control of PH as seen in our case. Few cases of association to comorbidities or malignancies have been reported in adults.[2] Anemia was found in our patient and in another infant.[11] These two isolated observations may

be only a coincidence rather than a true relation-ship. Based on our case report and review, PH seems to have good prognosis in children.

4 | CONCLUSION

Clinical aspect of herpetiform blisters in conjunction with erythematous lesions should prompt consideration of diagnosis of PH in infants and lead to perform immunohistochemistry and Elisa if possible. This acquired auto-immune blistering disease seems to have different course and management strategy than in adults with good response to oral steroids and dapsone as a first-line treatment.

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CONFLICT OF INTEREST
None declared.

AUTHOR CONTRIBUTIONS
DR. Hayder Faten is the author of the article and review author and performed analysis of review data. DR. Bahloul Emna is the co-writer of the article and review author, and involved in writing quality supervisor. DR. Sellami Khadija and DR. Aounallah Amina are the co-authors of the article. DR. Jerbi Ameni, DR. Zghal Mouna, Prof. Ayedi Lobna, and DR. Masmoudi Hatem are the co-author, responsible for immunological data analysis. Prof. Turki Hamida is the co-author, review author, and supervisor of quality of writing.

ETHICAL APPROVAL
Parent/legal guardian of the patient gave written informed consent to participate in the study.

CONSENT
Written informed consent was obtained from the patient to publish this report in accordance with journal's patient consent policy.

DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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REFERENCES
1. Jablonska S, Chorzelski TP, Beutner EH, Chorzelska J. Herpetiform pemphigus, a variable pattern of pemphigus. *Int J Dermatol. Juin*. 1975;14(5):353-359.
2. Kasperkiewicz M, Kowalewski C, Jabłońska S. Pemphigus herpetiformis: from first description until now. *J Am Acad Dermatol*. 2014;70(4):780-787.
3. Lara-Corrales I, Pope E. Autoimmune blistering diseases in children. *Semin Cutan Med Surg*. 2010;29(2):85-91.
4. Costa LMC, Cappel MA, Keeling JH. Clinical, pathologic, and immunologic features of pemphigus herpetiformis: a literature review and proposed diagnostic criteria. *Int J Dermatol*. 2019;58(9):997-1007.
5. Jerbi A, Hachicha H, Feki S, et al. Pemphigus herpetiformis in South Tunisia: a clinical expression of pemphigus foliaceus? *Int J Dermatol*. 2018;57(9):1094-1101.
6. Peterman CM, Vadeboncoeur S, Schmidt BA, Gellis SE. Pediatric pemphigus herpetiformis: case report and review of the literature. *Pediatr Dermatol*. 2017;34(3):342-346.
7. Akoglu G, Yavuz SO. Pemphigus herpetiformis-type drug reaction caused by erdosteine containing mucolytic in a child. *Cutan Ocul Toxicol*. 2017;36(3):302-304.
8. Kridin K. Pemphigus group: overview, epidemiology, mortality, and comorbidities. *Immunol Res*. 2018;66(2):255-270.
9. Schoch JJ, Boull CL, Camilleri MJ, Tollefson MM, Hook KP, Polcari IC. Transplacental Transmission of Pemphigus Herpetiformis in the Setting of Maternal Lymphoma. *Pediatr Dermatol*. 2015;32(6):e234-e237.
10. Laws PM, Heelan K, Al-Mohammedi F, Walsh S, Shear NH. Pemphigus herpetiformis: a case series and review of the literature. *Int J Dermatol*. 2015;54(9):1014-1022.
11. Duarte IB, Bastazini I Jr, Barreto JA, Carvalho CV, Nunes AJF. Pemphigus herpetiformis in childhood. *Pediatr Dermatol*. 2010;27(5):488-491.
12. Huhn KM, Tron VA, Nguyen N, Trotter MJ. Neutrophilic spongiosis in pemphigus herpetiformis. *J Cutan Pathol*. 1996;23(3):264-269.
13. Hocar O, Ait Sab I, Akhdari N, Hakkou M, Amal S. A Case of pemphigus herpetiformis in a 12-year-old male. *ISRN Pediatrics*. 2011;2011:1-4.
14. Moutran R, Maatouk I, Stephan F, Halaby E, Abadjian G, Tomb R. Pemphigus herpetiformis of age of onset at 6 years. *Dermatol Online J*. 2011;17(6):10.
15. Leithauser LA, Mutasim DF. A case of pemphigus herpetiformis occurring in a 9-year-old boy. *Pediatr Dermatol*. 2013;30(6):760-762.

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