INTRODUCTION

Pemphigus herpetiformis (PH), first described in 1975 by Jablonska et al., 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.

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
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 peribul- lous 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 herpetiform 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 methemoglobinemia 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. In adults, this subtype is considered as particular variant of pemphigus foliaceus...
with immunoreactivity triggering mainly Dsg1 and predominant skin involvement.\textsuperscript{2,3} This theory is supported by our review since even in rare cases, where mucosal involvement is seen, absence of autoantibodies against Dsg3 is constant.\textsuperscript{6} Of note, rare cases of PH associated with reactivity to Dsg3 were reported.\textsuperscript{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.\textsuperscript{7} PH still presents challenges in diagnosis since it combines the clinical aspects of dermatitis herpetiformis and immunopathology features of pemphigus.\textsuperscript{4} Kasperkiewicz et al\textsuperscript{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.\textsuperscript{8} In Tunisia, PH seems to be occurring in young women from rural origins with an incidence of 0.9 new cases per year.\textsuperscript{5} Herpetiform pattern in infants can lead to clinical misdiagnosis since linear IgA
**TABLE 1** Clinical characteristics of pediatric pemphigus herpetiformis

| Author          | Country            | Age (years) | Gender | Pruritus | Affected areas on 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 al²     | 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 al¹¹  | Brazil             | 5           | Female | Yes      | Face, trunk, upper and lower limbs, buttocks | Annular erythema Grouped vesicles and blisters                                  | NA            | No                   | Yes                |
| Hocar et al¹³   | 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 al¹⁴ | Lebanon            | 6           | Female | Yes      | Trunk, face and extremities | Vesicules and bullae Annular, polycyclic, and erythematous plaques              | NA            | No                   | NA                 |
| Leithauser et al¹⁵ | 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 al⁹   | Minnesota, United States | Neonate | Male   | NA       | Hands and feet | Crateriform erosions Vesciculobullous lesions                                   | NA            | No                   | No                 |
| Akoglu et al⁷   | Turkey             | 9           | Male   | Yes      | Trunk, extremities and scalp | Herpetiform vesicles and bulla Erythematous plaques                             | Negative      | No                   | NA                 |
| Peterman et al⁵ | 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
| Laboratory abnormalities                        | Histology                                                                 | Direct immunofluorescence                                                                 | Indirect immunofluorescence | Desmoglein1 | Desmoglein3 |
|-----------------------------------------------|---------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|-----------------------------|-------------|-------------|
| Hyperleukocytosis, anemia, eosinophilia,      | Intraepidermal cleft with a “tomb-stone” appearance                      | Positive                                                                  | NA                          | Positive    | Negative    |
| thrombocytosis and low ferritin               | Eosinophilic and neutrophilic exocytosis                                 |                                                                           |                             | 135 UI/ml   |             |
|                                               | Edema of the dermis with perivascular deposits of lymphocytes            |                                                                           |                             |             |             |
| No                                            | On repeat biopsy:                                                        | Positive on repeat biopsy:                                                   | Negative                    | NA          | NA          |
|                                               | Mid-epidermal and upper-epidermal cavities with numerous acantholytic    |                                                                           |                             |             |             |
|                                               | and neutrophils                                                           |                                                                           |                             |             |             |
| Anemia, eosinophilia, thrombocytosis and low  | Subcorneous blisters                                                    | Positive                                                                  | NA                          | NA          | NA          |
| ferritin                                       | Rare acantholytic cells Spongiosis                                        | Intercellular deposits of IgG and C3                                        |                             |             |             |
|                                               | Eosinophilic exocytosis                                                  |                                                                           |                             |             |             |
| No                                            | Intraepidermal bulla containing rare acantholytic cells with eosinophil   | Positive                                                                  | Positive on repeat biopsy:  | NA          | NA          |
|                                               | and neutrophil cells                                                     |                                                                           | Intercellular intraepidermal |             |             |
|                                               | Eosinophilic spongiosis and focal acanthosis (lower epidermis)           |                                                                           | C3 and IgG deposits         |             |             |
|                                               | Inflammatory infiltrate (superficial and reticular dermis)               |                                                                           |                             |             |             |
| NA                                            | Acantholysis (middle and superficial layers of the epidermis)            | Positive                                                                  | NA                          | NA          | NA          |
|                                               | Neutrophilic infiltration                                                | Intercellular IgG and C3 deposits                                           |                             |             |             |
|                                               |                                                                           | (Epidermis and dermo-epidermal junction)                                    |                             |             |             |
| No                                            | Intraepidermal vesicle Neutrophilic and eosinophilic spongiosis          | Positive                                                                  | Negative                    | NA          | NA          |
|                                               | Mixed type infiltrate within the superficial dermis                      | Intercellular IgG and C3 deposits                                           |                             |             |             |
|                                               |                                                                           | (Epidermis and dermo-epidermal junction)                                    |                             |             |             |
| No                                            | Focal intraepidermal acantholysis                                        | Positive                                                                  | NA                          | NA          | NA          |
|                                               | Eosinophilic and neutrophilic exocytosis                                 | Intercellular C3 deposits (Lower half of the epidermis)                     |                             |             |             |
| No                                            | Intraepidermal cleft                                                     | Positive                                                                  | NA                          | Positive    | Negative    |
|                                               | Acantholytic cells                                                        | Intercellular intraepidermal C3 and IgG deposits                             |                             |             |             |
|                                               | Spongiosis                                                                |                                                                           |                             |             |             |
|                                               | Edema and mixed type inflammatory infiltration                          |                                                                           |                             |             |             |
| No                                            | Intraepidermal vesicle with neutrophils                                 | Positive (on repeat biopsy)                                                | Indeterminate, mostly      | Positive    | Negative    |
|                                               | Acantholytic cells in subgranular epidermis                              |                                                                           | negative                    |             |             |
|                                               | **Suprabasal acantholysis**                                              |                                                                           |                             |             |             |

†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 followed 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 with Immunosuppressive doses (20 mg/day) of systemic corticosteroids for 3 weeks | Complete remission | |
| Dapsone 50 mg/day for 10 days | No clinical improvement: Exfoliative dermatitis | Dapsone with steroid treatment taper Relapse | | |
| Dapsone 2 mg/kg/day (Indeterminate period) | Total clinical remission followed by a relapse after 2 months | Oral prednisone: 2 mg/kg daily for 4 weeks | Complete remission | |
| Oral prednisone at a dose of 10 mg/day: 0.3 mg/kg/day (Indeterminate period) | Partial clinical improvement | Prednisone with dapsone: 2 mg/kg/day | Marked clinical improvement | |
| 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 | |
| First-line Treatment and period | Second-line treatment and period | Follow-up (months) | Effect |
|--------------------------------|---------------------------------|--------------------|--------|
| Rituximab 375 mg/m² weekly for 5 weeks | Prednisone with oral methotrexate up to 15 mg weekly for 21 months | Discontinuing methotrexate and prednisone | Complete remission | 22 months after discontinuing methotrexate and prednisone |
| Doxycycline 50 mg and nicotinamide 250 mg twice daily | Erythromycin 333 mg twice daily | (Indeterminate period) | Disease free | |
| Oral methotrexate 10 mg weekly with steroid treatment at the same dose for 3 months | Methylprednisolone 1 mg/kg/day, cetirizine suspension 5 mg/ml/day and topical 0.05% betamethasone cream twice a day | Partial clinical improvement | Oral methotrexate 0.25 mg/kg/day and discontinuing steroids, lost to follow up (2 months) | |
| Avoiding drugs and food which may induce or trigger pemphigus | Methylenidoxime 1.5 mg/kg/day with slow taper for 6 months | Complete remission | Relapse after 1 month of discontinuing methylenidoxime | |
bullous dermatitis is more frequent in this age group. 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 described a case of transplacental transmission of PH in a neonate whose 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. 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 include intraepidermal cleft with various acantholytic cells were seen in all infants. Exclusive eosinophilic spongiosis 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.

| First-line Treatment and period | Effect | Follow-up(months) | Second-line treatment and period | Effect | Follow-up(months) | Period | Effect | Follow-up(months) |
|-------------------------------|--------|-------------------|---------------------------------|--------|-------------------|--------|--------|-------------------|
| Prednisone 1 mg/kg/day for 12 days with a slow taper | No improvement | | | | | | | |
| Prednisone 1.5 mg/kg/day for 12 days with a slow taper | Prednisone 1.5 mg/kg/day for 12 days with a slow taper | | | | | | | |
| Topical steroids (fluocinolone 0.05%, triamcinolone 0.1%, desonide 0.05%) and emollients | Significant improvement | | | | | | | |
| Initial improvement followed by extension of treatment | Significant improvement followed by extension of treatment | | | | | | | |
| | Significant improvement followed by extension of treatment | | | | | | | |
| | Complete remission | | | | | | | |
| Prednisone 1 mg/kg/day with a slow taper | Only partial improvement with no control of disease flares | | | | | | | |
| Clobetasol ointment with two 10-days courses of cephalexin 12.5 mg three times/day | Only partial improvement with no control of disease flares | | | | | | | |
| Clobetasol ointment with two 10-days courses of cephalexin 12.5 mg three times/day | Only partial improvement with no control of disease flares | | | | | | | |
| Dapsone 1 mg/kg/day (indeterminate duration) | Only partial improvement with no control of disease flares | | | | | | | |
| Topical steroids (fluocinolone 0.05%, triamcinolone 0.1%, desonide 0.05%) and emollients | Increasing doses of dapsone to 1.5 mg/kg/day: Ongoing | | | | | | | |
| | Significant improvement with minor intermittent flares | | | | | | | |
| | Complete remission | | | | | | | |
| | Complete remission | | | | | | | |

†NA, not available.

TABLE 3 (Continued)

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. Other options such as immunosuppressants or antibiotics with anti-inflammatory action are also considered yet with no determined role. 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. Anemia was found in our patient and in another infant. These two isolated observations may
be only a coincidence rather than a true relationship. 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 autoimmune 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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