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Juvenile generalized pustular psoriasis is a chronic recalcitrant disease: an analysis of 27 patients seen in a tertiary hospital in Johor, Malaysia

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ABSTRACT

Background

Limited information exists regarding juvenile generalized pustular psoriasis (GPP). We aim to determine the clinical profile and outcome of Malaysians with juvenile GPP.

Methods

Review of hospital case notes on patients with juvenile GPP

Results

Twenty-seven patients with juvenile GPP were identified. Female: male =1.4:1. The median age at onset of GPP was 6.5 years. Ten patients had prior psoriasis with a median pre-pustular duration of 2.7 years. Onset of GPP was earlier in patients without prior psoriasis (5.1 years versus 12.0 years, p=0.002). Precipitating factors identified included stress, upper respiratory tract infection, systemic steroid use, vaccination and pregnancy. A positive family history of psoriasis and GPP was present in 6 and 1 patient(s) respectively.

Twenty-one patients had acute, 5 annular and 1 localized variant of GPP. Arthritis was present in 22.2%. Fever, leukocytosis and transaminitis were mainly seen in patients with acute GPP at 80.9%, 72.2% and 11.1% respectively. Among 20 patients screened, 8 carry IL36RN variants and 1 has CARD14 mutation. IL36RN-positive patients have more severe disease characterized by early onset, low prevalence of prior PV, high prevalence of systemic inflammation and need for continuous long-term systemic therapy. Acitretin and cyclosporine were effective in aborting acute GPP in 100% of 16 and 66.7% of 6 patients treated respectively. However, relapses were common. Only 3 out of the 17

patients whose initial acute GPP were controlled with systemic agents, were successfully weaned off treatment.

Conclusions

Juvenile GPP is a chronic recalcitrant disease. IL36RN-positive patients have more severe disease.

INTRODUCTION

Psoriasis is a chronic inflammatory disease that affects about 2% of adults and 0.6% to 1.4% of children.[1-2] Onset during childhood was reported in 20-30% of affected adults.[1-2] Chronic plaque psoriasis (PV) is the most common phenotype of juvenile psoriasis whereas generalized pustular psoriasis (GPP) is most rare in children.[2-6] Pustular psoriasis accounted for only 0.6- 6.7% of all childhood psoriasis.[2-4] The first detailed clinical review of 104 GPP cases by Baker and Ryan, which included only 5 children, classified GPP into 4 clinical variants: acute GPP of von Zumbusch, sub-acute annular pustular psoriasis (APP), exanthematic and localized variant of GPP.[5] Although there were many subsequent case reports/series, few had more than 10 children with pustular psoriasis.[6-9]

In a review of 13 children with GPP, Zelickson and Muller categorized juvenile and infantile pustular psoriasis into acute GPP, APP and a mixed acute GPP/APP variant.[6] A more recent study of 18 childhood pustular psoriasis defined 4 variants; acute GPP, psoriasis vulgaris with pustulosis, APP and erythrodermic pustular psoriasis.[7] Although distinct phenotypes of GPP were well documented[5-8] there is little agreement on the classification of these clinical variants. The clinical course of these variants is largely unknown although pustular psoriasis may change from one clinical variant to another over time in the same patient.[6-9] There is also limited information on the outcome of juvenile GPP especially in Asians although it is believed to be more benign than adult-onset GPP. The objective of this study is to determine the clinical profile including demography, clinical variants, clinical course, treatment and long-term outcome of

juvenile GPP in our population. We also described a few patients in detail to highlight the sequential existence of different GPP variants in a patient and the challenges of treating recalcitrant juvenile GPP.

MATERIALS AND METHODS

Study design and population

This study was done by reviewing the medical records of dermatologist-confirmed GPP that developed before the age of 18 years. Only cases with clear documentation of at least one episode of widespread macroscopic sterile pustulosis that lasted more than 2 weeks were included. Data collection was done from November 2015 and updated till April 2016. Data collected includes demographic characteristics (age, gender and ethnicity), personal and family history of psoriasis, clinical patterns of pustular psoriasis, precipitating factors, laboratory findings, biopsy results, genetic status, treatment and outcome of treatment. The genetic analysis of our patients with GPP had been previously described and reported.[10-12] This study was approved by the Malaysian Ministry of Health Institutional Review Board and Medical Research Ethics Committee.

Statistical analysis

Descriptive statistics are presented as counts and percentages for categorical variables. Mean with standard deviation (SD) was used for normally distributed data while median with interquartile range (IQR) was used for data which were not normally distributed. Mann-Whitney U test was used for univariate analysis. Chi-square and Fisher's Exact test were used where appropriate to investigate the association between 2 categorical

variables. Statistical significance was set at $p<0.05$. SPSS version 17.0 was used for data analysis.

RESULTS

A total of 27 patients with juvenile GPP were identified. The median duration of follow-up after onset of GPP was 8.8 years (IQR: 4.3, 22.8 years). The median age of patients was 16.3 years (IQR: 11.5, 24.9). Female to male ratio was 1.4: 1. Seventy-four percent of our patients were Malay, 22.2% Chinese and 3.7% Indian. The median age at onset of GPP was 6.5 years (IQR: 2.0, 11.5). Ten patients had prior PV with a median pre-pustular duration of 2.7 years (IQR: 1.0, 3.6)**.** A positive family history of psoriasis was present in 7 (25.9%) patients. Among them, one patient had a maternal aunt with acute GPP. Table 1 summarizes the clinical characteristics and laboratory results of the different clinical variants of GPP seen. Males appeared to have an earlier onset of pustular psoriasis at a median age of 5.5 years (IQR: 2.0, 7.5) compared to 8.2 years (IQR: 3.6, 14.0) in females but the difference observed was not statistically significant (p= 0.084). Onset of GPP was significantly earlier in patients without prior PV at a median age of 5.1 years (IQR: 1.4, 7.5) versus 12.0 years (IQR: 6.8, 15.2), (p=0.002).

All 21 patients with acute GPP had widespread erythematous plaques with pustules and lakes of pus (Fig.1a). The majority of acute GPP were provoked. Triggers identified in 16 patients (76.1%) included stress (7 patients), upper respiratory tract infection (URTI, 7 patients), systemic steroid withdrawal (3 patients), pregnancy (3 patients) and vaccination (2 patients). Leukocytosis of $\geq$12 X10^9/L was documented in 72.2% of 18 patients with available results. All 5 patients with APP had characteristic annular/serpiginous lesions with erythematous scaly or pustular margins (Fig.2) without fever. However, one patient

with extensive APP had leucocytosis (16 $X10^9$/L). Stress, URTI and menstruation were identified aggravating factors. The only patient with localized variant of GPP had extensive well-defined psoriatic plaques overlying flat pustules (Figs. 3a & b). Staphylococcus aureus was cultured from a pustule. She was otherwise well and responded to a course of cloxacillin and 6 months of acitretin. Table 2 summarizes the clinical course, treatment and outcome of all patients with PP. Sixteen patients with acute GPP were admitted for a mean duration of 15.5 days (range 1-38 days). Two among them developed severe septicaemia but there was no fatality in this study.

Biopsies performed in 19 patients showed characteristics features of pustular psoriasis namely spongiform microabscesses of Munro and Kogoj, superficial perivascular infiltrate of lymphocytes and some neutrophils, and dilated, tortuous blood vessels in the papillary dermis. Typical epidermal changes of psoriasis namely parakeratosis, regular acanthosis, hypogranulosis and suprapapillary plate thinning were prominent only in APP and L-PPP. Eight out of 20 patients screened have IL36RN mutations; 5 homozygous (115+6T>C/ c.115+6T>C), 1 compound heterozygous (c.115+6T>C/p.Ser113Leu) and 2 heterozygous (c.115+6T>C/negative). One patient without IL36RN variant has CARD14 mutation (p.Asp176His substitution).

SELECTED CASE REPORTS

Patient 1 is a 14-year-old Malay boy who developed pustular lesions at 3-month-old after his 1st Diphtheria-Tetanus-Pertussis vaccination. He was hospitalized and treated as infected eczema. The 2nd vaccination with only Diphtheria-Tetanus, 2 months later, precipitated a severe, biopsy-confirmed GPP requiring hospitalization and oral acitretin. Hence, the 3rd dose of vaccination was omitted. His pustules settled after 2 weeks of acitretin which was stopped 1 month later when his skin normalized. His skin remained clear for 4 years before he was readmitted for another unprovoked GPP which also responded to acitretin 1mg/kg body weight (b.w). He was dependent on acitretin and relapsed promptly on withdrawal of treatment.

While on maintenance with acitretin 0.5mg/kg b.w, he still had pustular flares every few months which were controlled by dose escalation of acitretin. Flares started with fiery red erythematous plaques on abdomen, scrotum and right scapular region which became pustular (Figs.4a &b) within a day but further spread was halted with increased dose of acitretin. Geographic tongue (Fig. 4c) appeared and disappeared with the flares. Most flares were spontaneous but possible triggers included URTI, excessive sun exposure, post-varicella and emotional stress namely family disharmony and parental separation. Highest leukocytosis documented was 50.4 $X10^9$/L (neutrophil, 43.3 X 10^9/L), CRP was 107.4 mg/L and ESR was 50mm/hr. Other biochemical tests were normal. ASOT was positive (400-800 units/mL, normal range: <200 units/mL) during several flares but suggestion for tonsillectomy was rejected. Blood cultures during multiple admissions

were negative and skin swabs occasionally grew staphylococcus aureus, staphylococcus epidermidis or mixed growths of staphylococcus and acinetobacter baumanii.

His skin was clear in between attacks until PV appeared when he was 8- year-old (Fig. 4d). His PV progressed slowly into localized variant of GPP (Fig. 4e) by 15 months. During these 15 months, he had 4 episodes of acute GPP which was controlled by dose escalation of acitretin but his localized variant of GPP responded poorly to acitretin. The consequent erythrodermic psoriasis with recurrent pustulosis was inadequately controlled with methotrexate 10 mg weekly (0.37mg/kg b.w) and subsequent cyclosporine (5mg/kg b.w). Addition of a short course of prednisolone was also not beneficial. Repeated offers of biologics were rejected by parents. During the last follow-up in March 2015, patient was still erythrodermic (Fig. 4f) with pustules on both legs. He has no family history of psoriasis and does not carry IL36RN variant.

Patient 6 is a 12-year-old Malay boy who was admitted for severe acute GPP (Fig.1a) 4 years ago. He had scalp and groin lesions 1 year before GPP supervened. On admission, he was moribund with a temperature of 39.8^0C. He was tachycardic (pulse rate: 134/minute), tachypnoeic (respiratory rate: 30/minute) with a blood pressure of 107/40 (normal range: 90-130/60-90). Intravenous meropenem and amikacin were started by the pediatric team. Chest radiography revealed perihilar haziness but sputum culture was negative. Laboratory tests showed neutrophilia, elevated ASOT (400 units/mL), raised ESR and CRP. However, skin and blood cultures were negative. GPP was confirmed by skin biopsy. Acitretin was started on day 6 and patient recovered after 38 days in the

ward. He had another pustular flare 1 year later when he defaulted follow-up. He endured multiple flares triggered by URTIs while on acitretin and only reverted to PV (Fig.1b) 4 years later. At the time of writing, he was re-admitted for another severe flare (Fig. 1c & d) after his GPP slowly deteriorated over the past 4 months in spite of dose escalation of acitretin to 1.5mg/kg b.w. His GPP, fever (38.8^0C), leukocytosis (29.6 $X10^9$/L with neutrophil, 23.9 X 10^9/L), elevated CRP (84.3 mg/L) and ESR 28mm/hour normalized after 2 days of cyclosporine (5mg/kg bw) and azithromycin. Other biochemical tests were normal. Skin and blood culture were negative. He has compound heterozygous Il36RN mutation (c.115+6T>C/p.Ser113Leu).

Patient 14 is a 38-year-old Malay lady with PV since 9-year-old. Pregnancy induced GPP at the age of 13.5 years. She had suboptimal response to prednisolone but managed to deliver a healthy son. For the last 25 years, she is dependent on retinoid (initially etretinate, currently acitretin) to control her GPP. No classic PV was noted ever since and ill-defined plaques with pustules appeared promptly when acitretin was reduced to below 0.5mg/kg b.w. Attempts to switch to methotrexate and cyclosporine failed. She wore intrauterine contraceptive device for 5 years and used oral contraception in between this period. She was not compliant with oral contraception and underwent two induced abortions when she got pregnant while on oral retinoids. One failed induced abortion fortunately resulted in a healthy daughter. Another unplanned pregnancy at the age 26 precipitated severe GPP. Poor response to cyclosporine prompted therapeutic abortion together with bilateral tubal ligation. She does not carry IL36RN variant.

Patient 18 is a 30-year-old Chinese lady who had abnormal pustular nail lesions since 3-year-old. She received multiple courses of systemic antifungals before psoriasis was diagnosed 3 years later. At age 17 years, she developed acute GPP which settled with acitretin but promptly relapsed with dose reduction. Attempt to switch to methotrexate failed. Even when her disease was quiescent for >6 months while on acitretin, omission of therapy triggers pustular flares within 2 weeks. She is depressed by this dependency on acitretin which disrupted her plan to start a family. She is also disturbed by the side-effects of acitretin namely cheilitis and palmoplantar desquamation. She inherited CARD14 variant (pAsp176His) from her maternal aunt who also had recurrent GPP. She also feared suffering the same fate as her aunt who had severe pregnancy-induced acute GPP with consequent cesarean section and bilateral tubal ligation.

DISCUSSION

Juvenile GPP is rare, with few studies that included more than 10 cases.[6-9] Contradictory gender preponderance and variable onset-age were documented in these small case series (Table 3).[6-9] However, female preponderance seen in this study was also observed in our patients with adult-onset GPP.[13] Disease onset is significantly earlier in our patients without prior PV, confirming the results of a Japanese study.[14] Consistent with previous studies, the majority of our juvenile GPP (66.6%) were provoked (Table 3) and precipitating factors identified were also similar, namely URTI, stress, systemic steroid withdrawal, vaccination and pregnancy.[6-9] URTI is a major trigger for juvenile GPP whereas systemic steroid withdrawal is commonly implicated in adult GPP.[5] Systemic steroid was the most common trigger in our adult-onset GPP, accounting for 44.1% of 102 patients seen in our institution, followed by pregnancy (16.6%) and URTI (15.7%).[7] In contrast, juvenile acute GPP in our population was mainly triggered by URTI (33.3%) and stress (33.3%), with only 3 cases (14.2%) attributable to systemic steroid. This may be because children are less likely to be prescribed systemic steroid and are more vulnerable to URTI.

Like what we observed in our previous study on adult GPP, once GPP is initiated by whatever trigger, psoriasis remains unstable and pustular flares frequently recur on exposure to classic triggers and also for unknown reasons.[13] Only 7 patients had a single episode of severe GPP (BSA>30%) and even then, 2 among them are still on acitretin because of prompt relapses on dose reduction (Table 2). Topical treatment was effective

in only 4 patients with GPP. Acitretin at 1 mg/kg b.w is our treatment of choice for acute GPP and it was effective in controlling acute flares in all 16 patients treated. However, at the time of writing, 13 patients were still on acitretin (Table 2). We did not observe any significant skeletal toxicity or growth retardation in our patients on long-term acitretin.

Cyclosporine, our treatment of choice for pregnancy-induced GPP, was effective in patient 17 who had 2 episodes of pregnancy-induced GPP. Cyclosporine also rapidly cooled down the inflammation in 3 other patients (Patient 6, 15 and 21) with severe flares while on acitretin. However, it was not effective in patient 14 and 20. We did not use methotrexate as first-line therapy but attempts to switch therapy of 3 patients of child-bearing age (Patient 14, 18 and 20) from acitretin to oral methotrexate failed. Prednisolone was used for pregnancy-induced GPP in Patient 14 before cyclosporine was available but response was inadequate. Although biologics were reported to be useful in juvenile GPP,[15-17] we have no experience in using them because biologics are not registered for the treatment of pediatric psoriasis in Malaysia. Recently, we successfully induced remission of a severe protracted flare in Patient 20 with a single dose of infliximab 5mg/kg b.w after failing to control her GPP with dose escalation of acitretin and cyclosporine.

Consistent with previous studies,[6-9] our patient with localized variant of GPP reverted readily to mild PV while patients with APP continued to have recurrent annular lesions. However, one patient with extensive APP and associated leukocytosis, finally converted to stable PV with adalimumab after failing phototherapy, methotrexate and cyclosporine.

APP is known to be a more benign variant of GPP that responds to topical agents[5,7,13,18] but severe juvenile APP that failed conventional systemic therapy and conversion into acute GPP had been documented.[7,18]

Juvenile GPP are repeatedly reported to be more benign than adult-onset GPP[6-9,15] but in our experience, juvenile GPP, particularly the acute von Zumbusch variant, is as recalcitrant as adult-onset GPP. Although acitretin and cyclosporine were effective in controlling acute flares, relapses were common and occurred promptly on withdrawing effective systemic therapy or on exposure to classic triggers such as URTI or stress as illustrated with our case reports. **The majority of our patients with acute GPP (66.6% of 21 cases) had multiple pustular flares and admissions. Unlike previous studies whereby the majority of juvenile acute GPP either developed stable PV or entered long-term remission without further systemic therapy,[7-8] the majority of our patients required continuous systemic treatment to prevent recurrences (Table 2). After a mean follow-up duration of 14.8 years (range: 0.5 to 45 years), only 7 patients reverted/converted to PV while 8 persons continue to have recurrent pustular flares, three have persistent acropustulosis (Fig. 5), two were lost to follow-up and one developed erythroderma with pustulosis. Only 3 out of the 17 patients whose initial acute GPP were controlled with systemic agents, were successfully weaned off treatment. We found that extensive APP can also be very recalcitrant after managing Patient 26 whose severe APP and subsequent arthritis 10 years later, finally improved with adalimumab.**

About 20% of GPP patients carry recessive mutations of IL36RN, the gene encoding the IL-36 receptor antagonist.[10] This antagonist counteracts the pro-inflammatory effects of IL36-α, β and γ, a group member of IL-1 family cytokines, and prevent the downstream activation of NF-κB signaling. Reports of successful treatment of recalcitrant GPP with anakinra, an IL-1-receptor antagonist, supports the importance of IL-1 signaling in the pathogenesis of GPP.[19-21] A systematic review of 233 patients with GPP which included 6 of our IL36RN-positive and 11 of our IL36RN-negative patients in this study, showed that homozygous IL36RN mutations define a more severe phenotype characterized by i) early onset, ii) low prevalence of PV and iii) high-risk of systemic inflammation (defined as fever >38^{0}C and leukocytosis >12 X 10^9/L).[10] This review also found that heterozygous IL36RN mutations increase disease risk. Although disease onset was significantly delayed in heterozygous patients, high prevalence of systemic inflammation was seen in both groups.

Within this small subset of 20 patients who were screened for IL36RN mutations, we observed similar characteristics; i) disease onset was earlier in homozygous patients (median age at onset: 3.5 years versus 11.5 years, p=0.031) ii) prior PV was uncommon in IL36RN-positive patients (12.5% versus 66.6%,p=0.028), and iii) 85.7% of patients with one or two disease alleles had systemic inflammation compared to 27.3% of IL36RN-negative patients (p=0.050). Additionally, our study showed that IL36RN-positive patients required long-term systemic maintenance therapy. All eight IL36RN-positive patients, with a mean follow-up duration of 23.5 years (range 3.3 to 45 years),

are still dependent on systemic agents to prevent frequent relapses compared to 50% of IL36RN-negative patients(p=0.042).

CONCLUSIONS

Juvenile GPP is a chronic recalcitrant disease. Conventional systemic agents namely acitretin and cyclosporine are effective in controlling acute flares but relapses are common. IL36RN-positive patients have more severe disease.

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TABLES

Table 1. Characteristics of 27 Malaysians with juvenile generalized pustular psoriasis

Clinical variants	Acute GPP (n=21)	Sub-acute APP (n=5)	L-GPP (n=1)
Gender (female/male)	12/9	3 /2	1 female
Onset age in years (median, IQR)	7.5 (3.5,14.7)	11.5 (6.5,14.0)	5.0
Fever	17 (80.9%)	0	0
Geographic tongue	13 (61.9%)	0	0
Nail involvement	10 (47.6%)	3 (60.0%)	1 (100%)
Associated arthritis	5 (23.8%)	1 (20.0%)	0
Leukocytosis	13 (72.2%) of 18 available)	1 (20.0%)	0
Elevated AST/ALT	2 (11.1% of 18 available)	0	0
ASOT	7 (63.6% of 11 tested)	1 (20%)	0
IL36RN variants	7 (43.7% of 16 tested)	1 (33% of 3 tested)	0
Biopsy performed	14 (66.6%)	4 (80%)	1 (100%)

GPP: generalized pustular psoriasis of von Zumbusch; APP: annular pustular psoriasis; L-GPP: localized variant of GPP

Table 2. Clinical course, treatment and outcome of 27 patients with juvenile generalized pustular psoriasis

Patient number	Current age (years)	GPP variant	Incident psoriasis	Age at GPP onset (years)	No. of pustular episode(s)	Treatment of pustular flares	Current psoriasis	Status on last follow up	Post-PP Follow-up (years)
1	14.5	Z	Z	0.3	>20	Acitretin	Erythroderma	Severe on acitretin	14.3
2	4.5	Z	Z	0.8	1	Acitretin	LTF	Clear	0.7
3	30.0	Z	Z	5.2	>20	Etretinate, Acitretin, doxycycline	ACH	Mild on acitretin	24.8
4	15.3	Z	Z	6.5	2	Acitretin	Z	Clear on topical	8.8
5	13.1	Z	PV	7.0	1	Topical	PV	Mild on topical	6.1
6	12.6	Z	PV	8.5	5	Acitretin CyA	Z	Moderate on CyA	4.1
7	24.8	Z	PV	11.5	5	Acitretin	Z	Mild on episodic acitretin	13.3
8	24.8	Z	ACH	17.0	1	Acitretin	ACH	Moderate on acitretin	22.8
9	3.0	Z	Z	0.4	1	Topical	LTF	Clear on topical	0.5
10	10.0	Z	Z	0.5	1	Topical	PV	Mild on topical	9.5
11	7.5	Z	Z	6.5	1	Acitretin	Z	Mild on episodic acitretin	1.5
12	11.5	Z	PV	6.5	1	Topical	PV	Mild on topical	5.0
13	10.8	Z	Z	7.5	5	Acitretin	Z	Mild on acitretin	3.3
14	37.8	Z	PV	12.5	10	Etretinate, acitretin, MTX, CyA, prednisolone	Z	Mild on acitretin	25.3
15	24.3	Z	PV	15.0	12	Acitretin, CyA	PV	Moderate on acitretin	9.3
16	24.5	Z	PV	14.5	2	Acitretin	PV	Mild on acitretin	10.0
17	19.2	Z	PV	16.0	2	CyA	PV	Mild on topical	3.2

18	30.0	Z	ACH	17.0	3	Acitretin, MTX	Z	Moderate on acitretin	27.0
19	47.5	Z	ACH	31.0	4	Etretinate Acitretin	ACH	Moderate on acitretin	45.0
20	41.9	Z	Z	9.0	7	Acitretin, CyA, MTX, infliximab	Z	Moderate on acitretin	32.9
21	44.5	Z	Z	2.0	5	Acitretin CyA,	PV	Mild on acitretin	42.6
22	11.8	APP	APP	7.5	1	Acitretin	APP	Mild on topical	4.3
23	13.0	APP	APP	5.5	1	Topical	APP	Mild on topical	7.5
24	16.3	APP	APP	11.5	1	Topical	APP	Mild on topical	4.8
25	24.3	APP	PV	16.0	1	Doxycycline	APP	Mild on topical	8.3
26	24.9	APP	APP	12.0	1	MTX, CyA, phototherapy, adalimumab	PV	Moderate on adalimumab	12.5
27	11.5	L	PV	5.6	1	Acitretin	PV	Mild on topical	6.0

PV: psoriasis vulgaris, GPP: generalized pustular psoriasis; Z: acute GPP of von Zumbusch; APP: Annular GPP; L: Localized variant of GPP; ACH: Acrodermatitis continua of Hallopeau, LTF: lost to follow-up
MTX: methotrexate; CyA: cyclosporin**e**
Mild: lesion affects < 10% BSA; Moderate: lesion affects 10-30%, Severe: lesion affects > 30%

Table 3. Comparison of clinical studies on juvenile pustular psoriasis

	This study (Malaysia) n = 27	Popadic (Serbia) n = 18	Oliveira (Brazil) n = 7	Zelickson (USA) n = 13	Juanqin (China) n = 30
Male : female	0.68	1.25	0.75	0.86	2.33
Mean onset-age (year, range)	7.2 (3.6 months – 16 years)	6.4 (1.5 months –16 years)	6.0 (1 month – 11 years)	5.2 (1week – 17 years)	7.0 (2 – 12 years)
Prior psoriasis vulgaris	37.0%	38.9%	33.3%	NA	30.0%
Associated arthritis	22.2%	0	28.5%	NA	6.6%
Triggers identified	66.6%	NA	80%	92%	66%
Family history	28.5%	5.5%	14.2%	30.7%	NA
Mortality	0	0	1	0	0

NA: not available

LEGENDS

1. Figure 1 Patient 6 with compound heterozygous IL36RN mutations (a) Extensive erythema studded with pustules and lakes of pus in 2011 (b) Classic psoriasis vulgaris in 2015 (c) Numerous sterile pustules on erythematous base and (d) geographic tongue seen in spontaneous relapse in 2016 while on acitretin
2. Figure 2 Multiple annular and polycyclic erythematous plaques with pustular and/or scaly margins characteristic of annular pustular psoriasis
3. Figure 3. (a)Extensive psoriasis with some glazed deep red non-scaly plaques and (b) flat pustule below scaly plaque characteristic of localized variant of generalized pustular psoriasis
4. Figure 4 Shows sequential clinical variants of psoriasis in Patient 1 (a) generalized pustular psoriasis characterized by erythematous plaques with sterile pustules, (b) geographic tongue, (c) discrete pustules on scrotal skin, (d) classic plaque psoriasis (e) localized variant of GPP with pustules within psoriatic plaques and (f) erythrodermic psoriasis with pustulosis
5. Figure 5. Shows persistent acropustulosis inadequately controlled by acitretin in Patient 8