Received: 23 August 2022 | Accepted: 21 November 2022

DOI: 10.1111/jdv.18771

LETTER TO THE EDITOR

Systemic inflammatory trunk recurrent acute macular eruption (SITRAME): A new auto-inflammatory syndrome in adult?

Dear Editor,

Undifferentiated systemic autoinflammatory disorders (SAIDs) are disorders linked to innate immunity not fitting with any known autoinflammatory disease and without confirmed molecular diagnosis[1,2]: they are also called syndrome of undifferentiated recurrent fever (SURF) in children.[3–5] They are characterized by recurrent, generalized inflammation with neither infection nor autoimmune disease, and most patients display skin manifestation as a primary clinical feature. Recent evidence suggests in a relevant percentage of patients, a complete or at least partial response to colchicine.[6]

We report here a series of 16 adult patients (Table 1), equally male and female (50%), with recurrent non-pruriginous stereotyped macular, and sometimes papular, eruption involving always the trunk, sparing some part of the skin with sharp demarcation associated in 100% of cases with systemic inflammation. The median age at the diagnosis was 53 years-old [range 28–68]. All cases were sporadic and occurred among adults from cosmopolitan origin. The first attacks of the disease occurred on a mean age of 35 years [range 18–52], never during childhood.

In 13 patients (81%), the eruption extended to other parts of the body in addition to the trunk. The recurrence usually affected the exact same skin areas for each patient, and no desquamation after eruption resolution was observed (Figure 1 and Table 1). Five patients were addressed for suspicion of drug allergy.

Eruption median duration was 3 days [range 2–7]. Seven out of the 16 patients (43.75%) experienced over 20 similar episodes, occurring over decades. The median number of attacks was 20 [ranging from five to >100]. Fever was reported in nine patients (56%) and 14 (87.5%) experienced other symptoms (i.e. headache, abdominal pain, muscle pain, pharyngeal pain and FLU-like syndrome) concomitant with skin eruption (Table 1). Skin biopsy performed in eight cases during a flare, showed minimal spongiosis (6/8) and lymphocyte exocytosis (8/8) without parakeratosis or vesicle.

Eight patients (50%) reported concomitant drug intake ($n = 5$) and/or viral or bacterial infection ($n = 5$), exercise-induced trigger, stress or mRNA COVID19-vaccine ($n = 2$). C-reactive protein levels were elevated in crisis for all patients with median level of 32.5 mg/L [ranging from 10 to 152], (Table 1) whereas its baselines levels were normal in all the 16 patients. All other blood tests performed were normal during flare and basal state (i.e. complete blood count, serum protein electrophoresis, antinuclear antibodies), polymerase chain reaction for detection of some Herpes viruses were negative during flare ($n = 5$), and allergological explorations were negative ($n = 5$). Only one patient had positive antinuclear antibodies without specificity. Concerning genetic analysis, 10 patients underwent next generation sequencing (variant allele frequency detected from 2%) with panels of SAID for 62 genes ($n = 5$), 114 genes ($n = 1$) or Sanger screening for the four historical monogenic SAID ($n = 4$). No specific mutation in previously known systemic autoinflammatory disorders gene was identified.

Colchicine introduced for six patients and/or with additional oral steroid during flare in two cases, allowing a shortening of the duration of symptoms and a longer time interval between the episodes in six of them.

The high number of recurrences and the negativity of some Herpes viruses and/or the allergological explorations in our series were against a viral or a drug hypothesis. The absence of family history excludes hereditary factors as causative factors.

In conclusion, we report here a new clinical entity, with systemic inflammatory and a stereotyped trunk macular recurrent eruption occurring with exact similar topography that displays criteria of an undetermined SAID; we propose the acronym "**SITRAME**" for systemic inflammatory trunk recurrent acute macular eruption. Iterative photographs are a helpful tool. Further studies are needed to determine its aetiology and pathophysiology and thus define the best treatment.

ACKNOWLEDGEMENTS

We acknowledge Irina Giurgea from Sorbonne Université, laboratoire de Génétique, Hôpital Armand Trousseau, AP-HP, Paris, France for help with the genetic analysis.

FUNDING INFORMATION

No funding.

CONFLICT OF INTEREST

Any potential conflicts of interest involving the work under consideration for publication: none.

TABLE 1 Clinical, biological and genetic features of the 16 patients

N°	Sex/age	Rash				Fever	Concomitant extra-cutaneous manifestations	Patient-reported triggers/ exploration of triggers	Genetic tests	Skin histology	CRP level (flare/ baseline) mg/L	Therapeutic
		Number of flare	Duration (days)	Characteristics	Distribution							
1	M/56	>100	7	Macular and papular	**Trunk**, arms	+	Headache, pharyngeal pain, abdominal pain, myalgia, arthralgia	Drugs/negative allergological and viral[a] explorations	Negative (NGS)	Yes	100/<5	AH1: not effective colchicine: effective
2	F/68	50	5	Macular and papular	**Trunk**, arms	+	Pharyngeal pain, cervical lymph nodes, myalgia	None	Negative (NSG) with IL10N variant	Yes	50 to 80/<5	AH1: not effective colchicine: effective
3	M/56	10	4	Macular and papular	**Trunk**, neck, arms, inguinal folds	–	Shivers and myalgia	None	Not done	No	152/<5	None
4	F/62	20	3	Macular and papular	**Trunk**, arms, inguinal folds	+	Myalgia, shortness of breath	Drugs/negative allergological and viral[a] explorations	Not done	Yes	21.7/<5	None
5	F/41	10	2	Macular and papular	**Trunk**, arms, axillary and inguinal folds	–	None	Drugs, infections, mRNA COVID vaccine or none/ negative allergological and viral[a] explorations	Not done	Yes	16/<5	None
6	F/60	15	2	Macular	**Trunk**	+	Headache, shiver, abdominal pain, diarrhoea	Drugs/negative allergological exploration	Not done	No	13.7/<5	None
7	M/57	10	2	Macular and papular	**Trunk**, inguinal folds	+	Pharyngeal pain	Infections or none	Negative (NGS)	Yes	10/<5	AH1: not effective colchicine: effective
8	M/53	10	4	Macular and papular	**Trunk**, arms, legs	+	None	Physical activity	Negative (NGS) with variant Ser749Cys in MEFV	No	88/<5	AH1: not effective colchicine: effective + during flare: prednisolone: effective
9	F/51	20	2	Macular	**Trunk**, axillary folds, arms, sometimes face	–	Myalgia	Infections/negative viral[a] exploration	Not done	No	40/<5	None
10	F/61	5	5	Macular and papular	**Trunk**, arms	–	Myalgia, nausea, cervical lymph nodes	Stress, infections	Negative (NGS)	Yes	22/<5	AH1: not effective, prednisone during flare: effective
11	M/48	60	2	Macular	**Trunk**	+	Headache, asthenia, shivers	None	Negative (Sanger)	No	10/<5	AH1: not effective colchicine: effective
12	F/29	50	2	Macular	**Trunk**, sometimes face	–	FLU-like syndrome	None	Negative (NGS) variant VOUS in CADR9	No	30/<5	AH1: not effective colchicine: effective
13	F/55	50	3	Macular	**Trunk**, sometimes face	+	Myalgia, FLU-like syndrome	None	Negative (NGS)	Yes	35/<5	None
14	M/49	50	3	Macular and papular	**Trunk**	–	Asthenia, paresthesia	None	Negative (NGS)	No	39/<5	None

TABLE 1 (Continued)

N°	Sex/age	Rash				Fever	Concomitant extra-cutaneous manifestations	Patient-reported triggers/exploration of triggers	Genetic tests	Skin histology	CRP level (flare/baseline) mg/L	Therapeutic
		Number of flare	Duration (days)	Characteristics	Distribution							
15	M/28	50	3	Macular	**Trunk**, arms	–	FLU-like syndrome	Drugs, infections, mRNA COVID vaccine or none/negative allergological and viral[a] explorations	Not done	No	19/<5	None
16	M/44	10	5	Macular and papular	**Trunk**, inguinal folds	+	Asthenia, abdominal pain with pyrosis, myalgia	None	Negative (NGS)	Yes	45/<5	None

Abbreviations: AH1, antihistamines anti-H1; CRP, C-reactive Protein; NGS, next generation sequencing; M, male; F, female; +, fever ≥38.5°C; –, no fever.
[a]Viral exploration correspond to Herpes-viruses polymerase chain reaction with Epstein–Barr virus, Human Herpes 6 and Cytomegalovirus during flares.

Any relevant financial activities outside the submitted work (during the 3 years prior to submission): Pr Soria received personal fees from Sanofi-Genzyme and Novartis, Abbvie, Lilly, Leo Pharma and Pfizer for counselling or speaker without link to this publication. Dr Amsler received personal fees from Sanofi-Genzyme, Abbvie and Novartis without link to this publication. Pr Georgin-Lavialle received personal fees from SOBI and Novartis for counselling or speaker without link to this publication. Pr Grateau received personal fees from SOBI and Novartis for counselling or speaker without link to this publication.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding authors upon reasonable request. All authors participated in the writing of this manuscript. AS recruited patients, collected data, wrote the manuscript and conceived the study. EA recruited patients, approved the manuscript and participated in the editing of the manuscript. BG participated in the collection of data and the writing of the manuscript. PM performed the histopathological analysis of skin biopsies and approved the manuscript. NT, FC, IG, AM and GG recruited patients and approved the manuscript. GB performed most of the genetic analysis and edited the manuscript. SGL recruited patients, participated in the conception of the study, and wrote and edited the manuscript.

IRB APPROVAL STATUS

Reviewed and approved by CNIL for the JIR Cohort, a registry for autoinflammatory diseases; approval #914677.

ETHICS STATEMENT

Consent for the publication of recognizable patient photographs or other identifiable material was obtained by the authors and included at the time of article submission to the journal stating that all patients gave consent with the understanding that this information may be publicly available.

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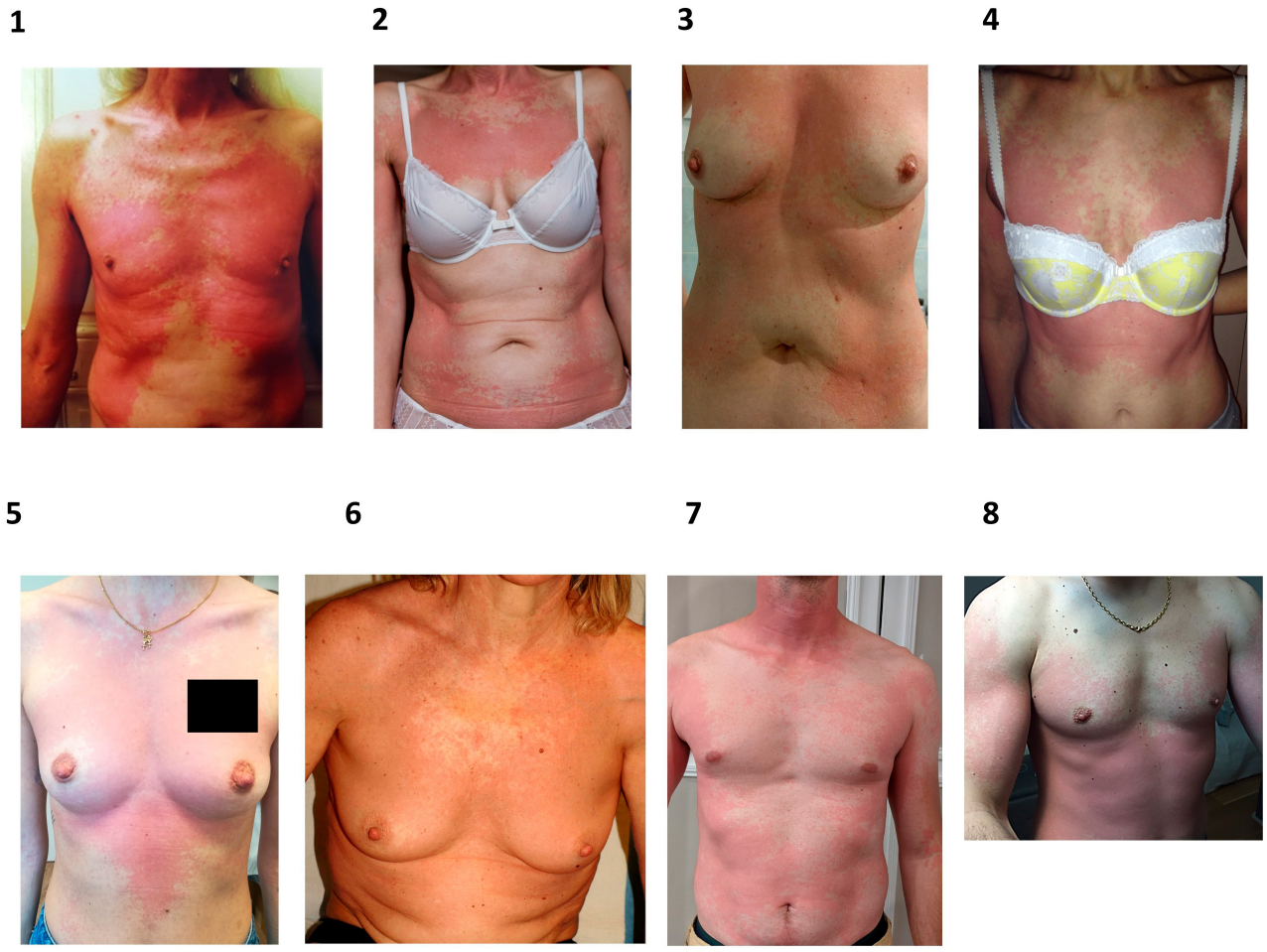

FIGURE 1 Pictures of the recurrent macular trunk eruption. Flares of the trunk, the eruption affected only some skin area of the trunk with sharp demarcation. In all patients presented here, the skin eruption does not involved the periumbilical area. 1: Patient 1, 2: Patient 5, 3: Patient 6, 4: Patient 10, 5: Patient 12, 6: Patient 13, 7: Patient 15, 8: Patient 16.

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