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Early onset granulomatous arthritis, uveitis and skin rash : characterisation of skin involvement in Blau syndrome

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Abstract

Background. Blau syndrome (BS) is a rare monogenic autoinflammatory disease caused by *NOD2* mutations. BS classically presents in early childhood as a triad of granulomatous polyarthritis, uveitis and skin involvement. Joint and ocular involvement have been characterized by several cohort studies but only very little data is available on skin lesions.

Objectives. We aimed to provide a detailed clinical and microscopic analysis of skin manifestations and to study whether they may contribute to an early diagnosis.

Methods. We conducted a retrospective multicentre study in a French cohort of 21 patients diagnosed with genetically confirmed BS.

Results. Skin involvement was the first clinical manifestation of BS in 15/16 patients with dermatological manifestations. Presence of skin lesions was associated to significant shorter age at diagnosis (p=0.03) and diagnostic delay (p=0.04). Dermatological assessment allowed an earlier diagnosis (p=0.003) and reduces the diagnostic delay (p=0.048). Early skin lesions had a homogeneous, stereotypical clinical presentation, namely non-confluent erythematous or pigmented millimetric papules in 13/14(93%) patients. In contrast, skin lesions occurring during later disease stages had a more heterogeneous clinical presentation, including ichthyosiform dermatosis, panniculitis, livedoid lesions and vasculitis. Whatever their time of occurrence and the clinical aspect, all biopsied showed histologically presence of granuloma.

Conclusion. Skin involvement in BS is the earliest clinical manifestation of the BS in the large majority of patients. The recognition of dermatological manifestations as granulomatous skin lesions and early dermatological expertise are the key to an early diagnosis of BS. In view of our results it seems reasonable to propose a simplified view of skin lesions of BS in which the granuloma is the keystructure.

Introduction

Blau syndrome (BS) is a rare monogenic autoinflammatory disease resulting from mutations of the NOD2/CARD15 gene on chromosome 16.[1,2] BS classically presents in early childhood as a triad of granulomatous polyarthritis, uveitis and skin involvement.[3–5] In some patients however the clinical triad remains incomplete or appears progressively over time.[4,6] Approximately half of patients also present manifestations beyond the classical triad, including vascular and/or visceral organ involvement.[4] Joint and ocular involvements have been well characterized by several cohort studies.[4] Skin involvement is considered as an early manifestation of the BS triad and a better knowledge of dermatological manifestation may thus contribute to an earlier recognition and diagnosis.[4,7] However, surprisingly little is known about dermatological manifestations of BS. Data on skin involvement is limited to case reports and case series which provide little details on clinical and histological presentation. Therefore, we conducted a retrospective, multicentre observational cohort study to describe clinical and microscopic features of skin lesions of BS.

Materials and Methods

Study design and patient selection. We conducted a retrospective multicentre French cohort study on patients with BS. Patients were identified through a call to the French Society for Rheumatology and Inflammatory Diseases (SOFREMIP) and the Research Group of Pediatric Dermatology French Society (GRSFDP). Patients with a diagnosis of BS with at least one symptom of the triad confirmed by presence of specific mutation of *NOD2* (or a variant of sure/probable pathogenicity) or a granulomatous involvement and a proven Blau mutation in related were eligible for the study. All patients were informed about the study and gave consent. The study was declared to French regulatory authorities (CNILno.2210327).

Data analysis. Using a survey and analyses of medical records, we collected the following data: date of diagnosis, data on disease onset, genetic findings, demographic and clinical data with focus on dermatological features (clinical records, photographs, biopsies).Skin lesions present at

onset of disease, before the age of 5 years, were designated as "early lesions". We used the term "late lesions" for skin lesions that appeared after the age of 5 years and skin lesions that changed their aspect during the disease evolution. Evolution of skin lesions before treatment was designated as follows: at least 2 independent recurrences of skin lesions were called disease "flares". Persistence of lesions" corresponded to permanently present skin lesions and the term "disappearance" was defined by definitive resolution of skin involvement. All available biopsy material and/or histological reports, together with clinical information (basic lesion, topography) were reviewed, analysed and classified by a dermatopathologist.

Statistical analysis. Statistical analysis was performed using Wilcoxon-Mann-Whitney test with GraphPad prismR and Studio (Version 1.1.447) software. Test was statistically significant when $p<0.05$.

Results

Patients. We included 21 patients from 13 families (14 patients from 6 families and 7 sporadic cases), 7 children and 14 adults, followed in 9 French tertiary hospitals. Sex ratio M/F was 0.75. Demographic characteristics are described in **Table 1**. Median age at diagnosis of BS was 4.2 (0.25-54) years.

(Insert Table1)

Incidence and chronology. We compared the incidence and the chronology of onset of clinical triad symptoms. Skin involvement was present in 16/21 (76.2%) patients. An early dermatological assessment had been performed in 10/16 (62.5%) cases. Joint involvement was observed in 19/21 (90.5%) patients and uveitis in 13/21 (62%) patients. Skin lesions were the earliest manifestation with a median age of onset at 2.25 years (range 3 months to 20 years), followed by joint involvement (4 years; range 6 months to 20 years) and uveitis (9.5 years; range 3.1 to 25 years) (**Fig.1a and 1b**). Skin lesions were present at disease onset of BS in 15/16 (93.8%). Distribution was limbs, trunk, face, and back or bottom in 8/16 (50%),6/16 (37.5%), 4/16 (25%), 2/16 (12.5%) patients, respectively. Skin lesions were initially or secondarily widespread on several body regions in 6/16 patients (37.5%). We studied evolution of skin lesions without treatment. The mean follow-up before initiating treatment was 15.5 years (range 0.5-52). Skin

involvement disappeared spontaneously and definitely within 5 years without treatment in 3/15 (20%) patients (1missing data) (**Supplementary material 1**). 7/15 (47%) patients had a persistent evolution including one patient with cutaneous flares occurring simultaneously with extra cutaneous disease manifestations. In 5/15 (33%) patients, skin lesions progressed in flares occurring after complete remission for periods of variable lengths. Medical records mentioned disease flares occurred concomitantly with delivery in 1 patient and within 6 months after BCG vaccination in 2 patients; Medical records of patient 13 mentioned 5 BCG vaccinations that were retrospectively considered as the trigger of 5 episodes of papular skin rashes (without providing more details about the exact delay). We concluded that skin lesions are the earliest clinical manifestation of BS.

(Insert Figure1)

Clinical aspect of skin lesions. We analysed clinical aspect of skin lesions. Detailed data of early skin lesions (<5 years) were available in 14 patients (**Table 1** and **Fig.2 a-k**). Early lesions were millimetric papules in 13/14 (93%) patients, characterized by millimetric erythematous, flesh-colored or pigmented papular elementary lesions (**Table 1** and **Fig.2a-e and g-k**). These papules were most often non-confluent. They were grouped in plaque-like lesions in patients 7 (**Fig.2 e**) and 12 and formed an annular plaque-like lesion suggestive of granuloma annulare in patient 20 (**Table 1**and **Fig.2f**).

(Insert Figure 2)

Detailed data of late lesions (> 5 years) were available in 12 patients (**Table 1**and **Fig.3 a-d**). Late lesions corresponded to the late onset of skin involvement in 2 patients and the clinical course of early lesions in10 patients. Late onset skin involvements were nodules with a livedoid disposition (**Fig.3d**) and, in one patient, lesions were described as a livedo (without dermatological assessment or photographs). Evolution of early lesions consisted in persistence of lesions without changes of the macroscopic aspect over time in 6 patients, changes in macroscopic aspect in 4 patients: millimetric papules became papules (size change) (n=1/10 patients, #13; **Fig.3a**), millimetric papules flattened and clumped together into ichthyosiform lesions (n=2/10 patients, #7 #12 **Fig.3c**), or lesions had a livedoid disposition (3/10 patients, #12 #13#14 **Fig.3a**).Coexistence of different macroscopic aspects of lesions was observed in two patients. In terms of functional impact,3 patients complained of cutaneous pain. No itching was reported.

From these data, we concluded that early skin lesions have a homogeneous, stereotypical clinical presentation and that late skin lesions have a more heterogeneous clinical presentation.

(Insert Figure 3)

Microscopic aspect of skin lesions. Records of 11 skin biopsies, taken from 11 different patients were available (**Table 1**). 8 biopsies concerned early lesions and 3 concerned late lesions. Skin biopsies were performed in early lesions presenting as millimetric papules and later on lesions described as a livedo, a nodule and millimetric papules with livedoid disposition. All skin biopsies of early and late lesions, regardless the clinical aspect, showed granuloma. Six skin biopsies were available for a centralized analysis by a dermatopathologist (**Fig.2 l-q and Fig.3 e-h**). Four biopsies were from millimetric papules, (**Fig.2 l-q**) including one with a livedoid disposition. One biopsy was from the livedo (**Fig.3 e and f**) and one from a nodule with livedoid disposition (**Fig.3. g and h**). Biopsies showed a "naked" sarcoidal granuloma « typical » of sarcoidosis in 4/6 (66.7%) cases (**Fig.2 l-q**). "Naked" granuloma was associated to a granulomatous vasculitis (**Fig.3 e and f**) in the biopsy from the livedo. Histology from the nodule with livedoid disposition showed a granulomatous interstitial dermatitis (**Fig.3 g and h**), in favor of granuloma annulare. All skin biopsies were granulomatous and all were suggestive of the diagnosis of sarcoidosis or BS. We did not observe emperipolesis or coma-shaped bodies in granuloma. We concluded that all skin lesions of BS are granulomatous.

Contribution of skin involvement to BS diagnosis. Diagnostic delay was shorter in patients with skin involvement than in patients without (mean 6.73 y vs 19y; p=0.04) (**Fig.1d**). When patients were initially referred to a dermatologist, diagnostic delay and age at diagnosis were shorter (respectively 0.9 y vs 16.5 y; p=0.048 and 2.1y vs 21.9 y; p=0.003; **Fig.1e and 1f**). In patients with early skin involvement explored by a biopsy (n=8), the age at diagnosis was shorter than in patients (n=8) who had skin lesions without biopsy (mean 2 years vs 17 years, p=0.02).

For all patients with a skin biopsy, the histological analysis allowed diagnosis of BS. In the absence of dermatological assessment and/or biopsy of the early skin, misdiagnosis (rheumatoid arthritis, Still's disease) was substantial in 3/8 patients. Overall, diagnosis of BS was made by histological analysis of early skin lesions in 8 patients, by dermatologic clinical semiology in combination with a familial context of BS in 3 patients, and by genetic analysis in 10 cases. We concluded that skin involvement and specific dermatological expertise contributed to early diagnosis of BS.

Discussion

Our study provides a detailed description of the clinical and histological presentation of the skin involvement in 21 BS patients. BS is an orphan disease andits diagnosis is challenging. In our study, skin involvement was observed in 16/21 (76.2%) patients. Similarly, an international retrospective BS cohort study included 18 children and 13 adults found cutaneous involvement in 25/31 (80.6%) patients.[4] Together these findings indicate that skin involvement is a frequent feature of BS.

In our cohort, almost a half of patient did not exhibit the complete classical clinical triad symptoms (granulomatous uveitis, granulomatous skin involvement or joint involvement). These observations are in line with data from the literature suggesting that BS patients do not necessarily exhibit complete clinical triad.[6] Clinical symptoms of the triad can appear progressively over time, especially in pediatric populations.[4] Therefore, in pediatric patients the diagnosis of BS should be considered (and confirmed by genetic analysis) in patients with at least one triad, especially in patients with a positive family history.

Consistently with data from the literature[6–9], skin manifestations first occurred in early childhood, at a median age of 2.25 years. In our study, skin involvement was the first manifestation of the classical BS triad. Its median occurrence preceded onset of joint involvement by 1.75 years and onset of uveitis by 7.25 years. The international BS cohort study also reported median age of skin involvement (1.1 years), articular symptoms (2years) appearing before ophthalmological involvement (4.4 years).[4] Thus, for the physician skin involvement is often the first opportunity to establish the diagnosis of BS. Pivotal role of skin involvement for diagnosis is underlined by the finding that patients with skin involvement had an earlier diagnosis than patients without skin disease. Implication of a dermatologist further shortened diagnostic delay. Together these finding show that a good knowledge and exploration of skin lesions using dermatological expertise and histological analysis may allow an early diagnosis of this orphan disease.

A link between BCG and skin involvement in BS has been suggested previously[9–12] and *Mycobacterium avium paratuberculosis* ADN and Heat Shock Protein (HSP) have been found in BS skin biopsies.[13]In some patients of our cohort, data suggested a possible temporary association between skin flares and BCG vaccination. However, medical records did not allow us to precisely

trace delays between these vaccinations and cutaneous disease flares. The investigationof a putative link between BCG vaccination and disease flares of BS will require additional studies.

In our study, all skin lesions corresponded histologically to a granuloma, regardless the time of occurrence after disease onset and their clinical aspect and were mainly a “naked” granuloma, which is a characteristic histological feature of adult sarcoidosis.[14].We did not observe coma shape bodies or emperipolesis that have been suggested as specific features of BS.[15,16]Granulomatous skin involvement is known to mean a smooth palpable lesion. Depending on their diameter, these lesions are called millimetric papules (millimetric), papules (less than 1cm) or nodules (larger than 1cm). They can also be confluent forming "plaques" or localized in the subcutaneous fat (panniculitis). In our cohort, skin lesions occurring before the age of 5 years (early lesions), were non-confluent millimetric papules in 93% of cases, whereas later skin lesions had a more heterogeneous clinical presentation. Late lesions could present as millimetric papules, papules or nodules but also as livedoid lesions, ichthyosiform lesions or as panniculitis.

In several patients, early skin lesions changed their clinical aspect over time. In half of the patients with late skin lesions, we observed a livedoid disposition of elementary lesions (millimetric papules, papules, nodules), which were histologically characterized by the presence of granuloma, without vasculitis, that we called “livedo-like” lesions. In only one patient, lesions were described as an authentic livedo, with a histological analysis showing granulomatous vasculitis and perivascular granuloma. To the best of our knowledge this is the first report of small vessels granulomatous vasculitis. Rare cases of granulomatous vasculitis have also been reported in classical sarcoidosis.[17] Presence of vasculitis in BS has been suggested in some case reports clinically mimicking Takayasu[10] or skin lesions such as a palpable purpura[18],papules with urticaria[19]anda livedo.[20] However, only one of these reports (presenting as urticaria) was documented histologically and showed a leukocytoclasicvasculitis.[19] Thus, the presence of an authentic, histologically confirmed, vasculitis in BS seems to be possible but rare. In contrast, a livedoid disposition of granulomatouslesions may be a relatively common feature of BS skin involvement during later disease stages.

Two patients of our cohort had late ichthyosiform (ichthyosis-like) lesions. An ichthyosiform evolution of skin lesions from the early papular rash corresponds to papules flattening (causing a loss of relief perception), an increase of pigmentation (probably post-inflammatory) and a cross-linked disposition that can resemble ichthyosis (ichthyosiform). In contrast, authentic ichthyosis, which has been proposed to be associated to BS[4,21], is clinically

characterized by hyperkeratosis, scaling or both and histologically by epidermal hyperplasia and varying degrees of hyperkeratosis, corresponding to an exclusive and non-granulomatous damage of epidermis. Ichthyosiform, eczematiform and scaly lesions in BS patients have also been reported by others.[11,18,22] These reports do not mention whether the lesions occurred during early or late disease stages and do not provide microscopic data. In our cohort, ichthyosiform lesions were found only in a minority of late lesions and never in early lesions. We did not observe scaly or eczematiform lesions. Taking into account all clinical and microscopic data of the ichthyosiform lesions of our study and published data, we suggest that signs of epidermal involvement in BS lesions, which can lead to slight hyperkeratosis, or scaling[6,22], are epidermal consequences of granulomatous dermal inflammation during the long-term disease evolution.

When skin lesions involve the subcutaneous fat, dermatologists diagnose panniculitis. In our study, one patient had nodular lesions on arms and legs. Initially, the physician considered these lesions as being erythema nodosum (EN). However, dermatological assessment and granulomatous histology rectified the diagnosis to granulomatous panniculitis. Subcutaneous nodules have also been described in the literature.[23,24] The term EN, which is often used in the BS literature to describe these lesions[4,11,20,25,26], corresponds histologically to septal panniculitis which, per definition, must not be granulomatous. To our knowledge, available data on erythema nodosum observed in BS patients in the literature were never confirmed histologically. No EN was observed in our cohort. Together, these data suggest that the EN described in the literature may in reality correspond to granulomatous panniculitis, which should be classified as part of the BS triad symptom "skin manifestations" because of its granulomatous histology.

Ulcerated lesions in lower limbs or poikilodermic lesions (which associate atrophy, telangiectasias and pigmentation disorders) were described in at least 3 cases in the literature[20,27,28], but not in our cohort. In 2 of these cases skin biopsies showed a granulomatous histology. Given the provided macroscopic and microscopic data on these lesions, we propose that the trophic disorders, ulceration and atrophy, should be considered as consequences of chronic and severe dermal and hypodermal granulomatous inflammation, which can lead to necrosis and secondary fibrosis.

In view of our observations and data from published cases, it seems reasonable to propose a simplified view of skin lesions of BS in which the granuloma is the key structure. Indeed, all cutaneous manifestations observed in our study and in published reports can be considered as variations of primary granulomatous skin lesions. According to their age, size, distribution and

confluence, they may cause a large variety of macroscopic presentations (millimetric papules, papules, nodules, plaques, scaling, ichthyosiform, livedoid and ulcerative lesions), but they all correspond histologically to primary granulomatous skin lesions.

Our study had several limitations. Patients were identified by a call for inclusions, using mailing lists of medical societies and a selection bias may not be rules out, which might be responsible for an overestimation of skin involvement frequency. The retrospective nature of our study and data acquisition by multiple physicians in charge of the patients may have induced some information bias.

In conclusion, early BS skin lesions have a homogeneous, stereotypical clinical presentation, namelynon-confluent erythematous or pigmented millimetric papules, whereas late BS skin lesions have a more heterogeneous clinical presentation. Early skin lesion can change over time. They canbecome more confluent papules leading to ichthyosiform dermatosis, become larger leading to nodules with livedoid aspect or become deeper extending to subcutaneous fat, which is called panniculitis. Vasculitis may occur in some rare cases. Nevertheless, whatever the clinical aspect is, these lesions are always granulomatous. Skin involvement in BS is specific, frequent and most often the earliest clinical manifestation of the BS triad. The recognition of dermatological manifestations as a granulomatous skin lesions and early dermatological expertise are the key to an early diagnosis of BS.

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Figure legends

Figure 1. Skin lesions contribute to diagnosis of BS. a-b Age at onset of triad symptoms.**a**Median age of cutaneous onset was early at 2.25 years (n=16) (versus joint median 4 (n=17; 2MD), eye median 9.5 (n=13). **b**Mean age at skin onset was earlier than ocular onset (3.9 years (n=16) vs 10.2 years (n=14); p=0.0006), whereas no difference was observed with regard to onset ofjointsymptoms (6.2 years; p=0.06). **c-d** Skin involvement.Skin lesions were associated to shorter age at diagnosis (**c**) (Mean 9.5 years (n=16) vs 25.6 years (n=5);p=0.03) and diagnostic delay **(d)** (Mean 6.73 years (n=16) vs 19 years (n=4);p=0.04).**e-f** Dermatological assessment. Dermatological assessment allowed (**e**) an earlier diagnosis (Mean 2.1 years (n=10) vs 21.9 years (n=6); p=0.003) and (**f**) reduced the diagnostic delay (Mean 0.9 years (n=10) vs 16.5 years (n=6); p=0.048). (*p<0.05; **p<0.01 ; ***p<0.001)

Figure 2. Clinical and histological presentation of early onset skin involvement. a-k Photographs of early onset skin lesions<5 years. Early onset skin lesions have a stereotypical clinical presentation. **a-e and g-k** Millimetric papular skin lesions patients 2 (**a,b,c,d**), 7 (**e**), 8 (**g,h**) , 21 (**i,j,k**). **f** Granuloma annulare, patient 20. **l-q** Histology of early onset skin lesions. Hematoxyline and eosin stain (p: magnification x50. l, n, q: magnification x 100. m, o: magnification x 200) l-q: Sarcoidosic granuloma, patients 2(**l,m**), 8(**n,o**), 21(**p,q**).

Figure 3. Clinical and histological presentation of late skin involvement.

a-d Photographs of late skin lesions>5 years. Late lesions have a more heterogeneous clinical presentation. **a** Papules with livedoid distribution, patient 13. **b** Millimetric papules, patient 5. **c** Ichthyosiform millimetric papules, patient 7 **d** Nodules with livedoid distribution patient 18. **e-h** Histology of late skin lesions. Hematoxyline and eosin stain (e:.magnification x50. g: magnification x 100. f,h: magnification x 200). **e and f** Perivascular sarcoidosic granuloma associated with granulomatous vasculitis (**A**) patient 19. **g and h** Granulomatous interstitial dermatitis (**B**) patient 18.

Table 1. Characteristics of the study cohort.

Supplementary material 1. Evolution of skin involvement without treatment. Persistent 47% (n=7), flares 33% (n=5), disappearance 20% (n=3). Mean follow-up was 15.6 years.

Supplementary material 2. Age at diagnosis and diagnostic delay depending on symptoms showed by patient.a-b Joint involvement. No significant difference has been shown for age at diagnosis (**a**) (Mean 13.3 years (n=19) vs 13.6 years (n=2) ; p=0.60) and diagnostic delay (**b**) (Mean 9.4 years (n=18) vs 6.9 years (n=2) ; p=0.50).**c-d** Ocular involvement. No significant difference has been shown for (**c**) age at diagnosis (Mean 11.3 years (n=13) vs 11.6 years (n=8) ; p=0.51) and (**d**) diagnostic delay (Mean 8.5 years (n=13) vs 10.5 years (n=7) ; p=0.80). (*p<0.05 ; **p<0.01 ; ***p<0.001)

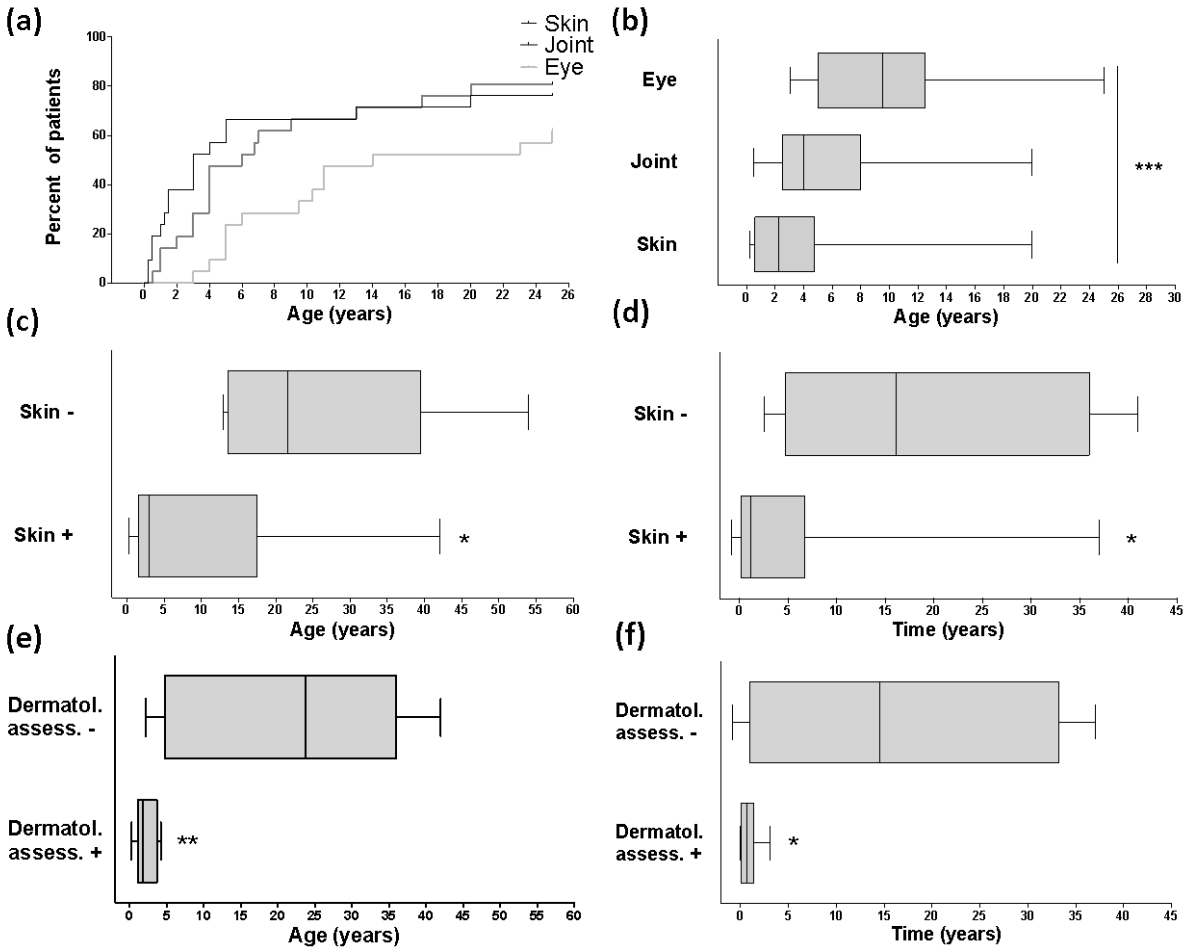
Table 1. Characteristics of the patients with BS in the cohort

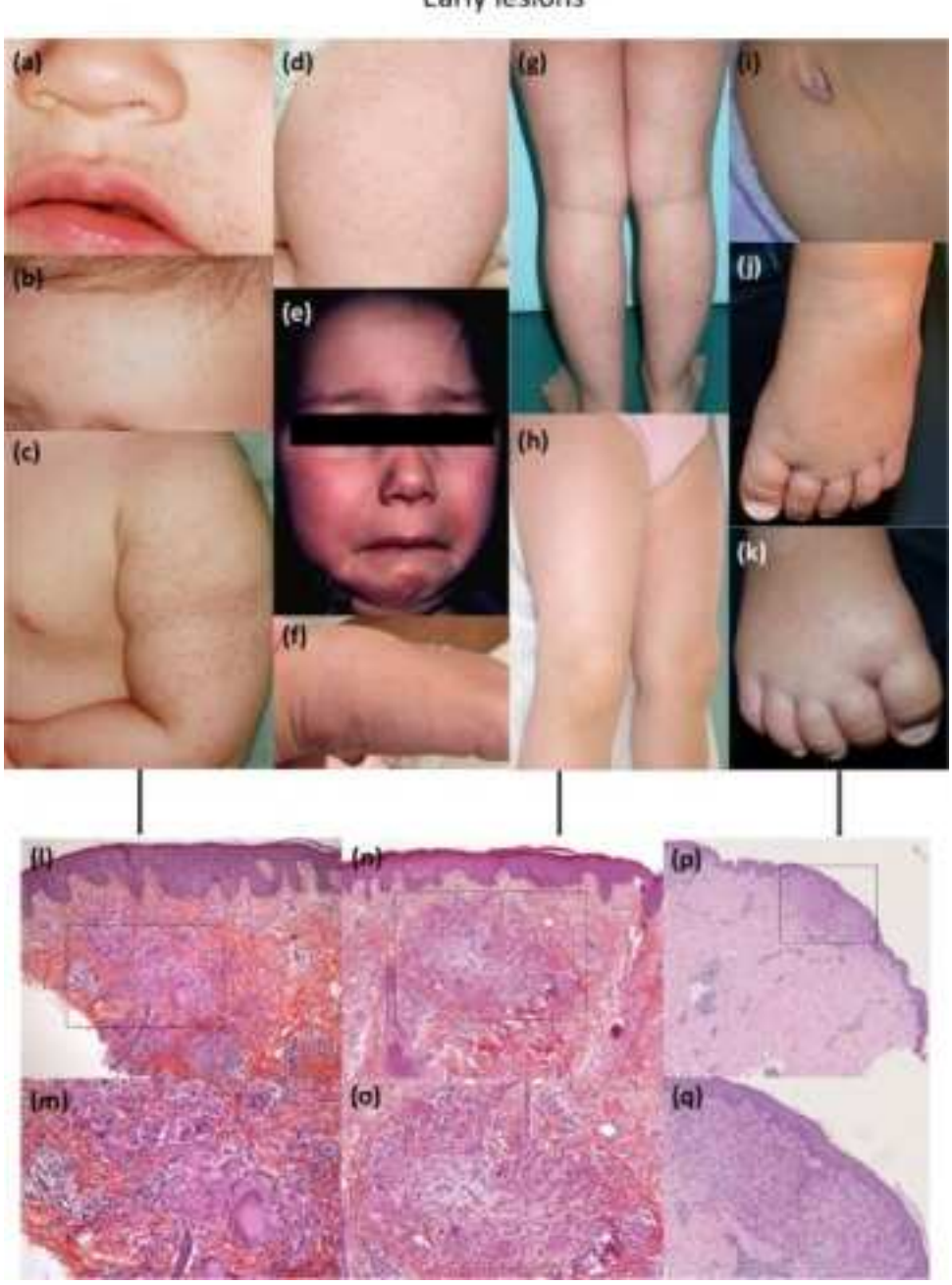
Patient number	Current age/ sex	Family	Genotype	Age at BS diagnosis (years)	Age at skin onset (years)	Age at joint onset (years)	Age at uveitis onset (years)	Age at Dermatological Assessment (years)	Early lesions <5years	Late lesions >5years	Skin biopsy	Course without treatment	Pho
1	40/M	1	R334W	1.6	1.5	3	5	1.6	Millimetric papules	-	Granuloma*	Disap.	-
2	13/F	1	R334W	0.6	0.25	4	5	0.6	Millimetric papules	Millimetric papules	Granuloma*	Persist.	2.a.b
3	29/M	2	R334Q	4.2	3	4	MD[#]	4.2	Millimetric papules	MD	Granuloma*	MD	-
4	46/M	2	R334Q	21.6	-	MD[§]	MD[#]	-	-	-	NA	NA	-
5	36/M	3	Y563S	0.25	0.25	0.5	<5	0.25	Millimetric papules	Millimetric papules	Granuloma*	Persist.	3.I
6	63/M	3	Y563S	54	-	13	-	-	-	-	NA	NA	-
7	40/F	4	R334Q	3.6	0.5	6	11	3.6	Millimetric papules Plaque-like cheeks	Millimetric papules Ichthyosiform	Granuloma*	Flares	2.e
8	15/F	4	R334Q	1.9	1.4	9	9.5	1.9	Millimetric papules	Millimetric papules	Granuloma*	Persist.	2.g
9	18/M	5	R307Q	2.1	3	4	11	-	Millimetric papules	Millimetric papules	-	Persist.	-
10	21/F	5	R307Q	5.6	4	4	4	-	Millimetric papules	Millimetric papules	-	Persist.	-
11	57/M	5	R307Q	42	<5	7	14	-	Millimetric papules	Millimetric papules	-	Disap.	-
12	30/F	6	L469F	2.5	0.83	6.8	23	2.5	Millimetric papules Plaque-like	Millimetric papules Livedoid distribution Ichthyosiform	Granuloma*	Persist.	-
13	53/F	6	L469F	26	<5	20	25	26[†]	Millimetric papules	Papules Livedoid distribution	-	Flares	3.a
14	21/F	6	L469F	1.25	1.25	MD[§]	-	5	Millimetric papules	Millimetric papules Livedoid distribution	Granuloma[††]	Flares	-
15	18/F	7	H287Y L682F	14.3	-	-	3.1	-	-	-	NA	NA	-

16	17/M	8	A725G	12.9	-	-	10.3	-	-	-	NA	NA	-
17	35/F	9	R334W	25	-	4	-	-	-	-	NA	NA	-
18	46/F	10	R333W	34	20	2	6	39[†]	-	Nodules Livedoid distribution	Granuloma[††]	Flares	3.(
19	22/M	11	K225M	21.4	13	17	-	-	-	Livedo	Granuloma +Vasculitis[††]	Flares	-
20	5/F	12	A282V	4	3	3	-	4	Granuloma annulare	-	-	Disap.	2.
21	1/F	13	R334Q	1.7	0.5	1	-	1.7	Millimetric papules	-	Granuloma*	Persist.	2.i.j

MD[#]: no data available in medical files, MD[§]: clinical feature present but age of onset not documented in medical files, NA: not applicable

Skin biopsies performed in n=11 patients *biopsy allowed diagnosis [†]late dermatological assessment [††]late biopsy. Evolution: Disap =disappearance, Persist =persistent.





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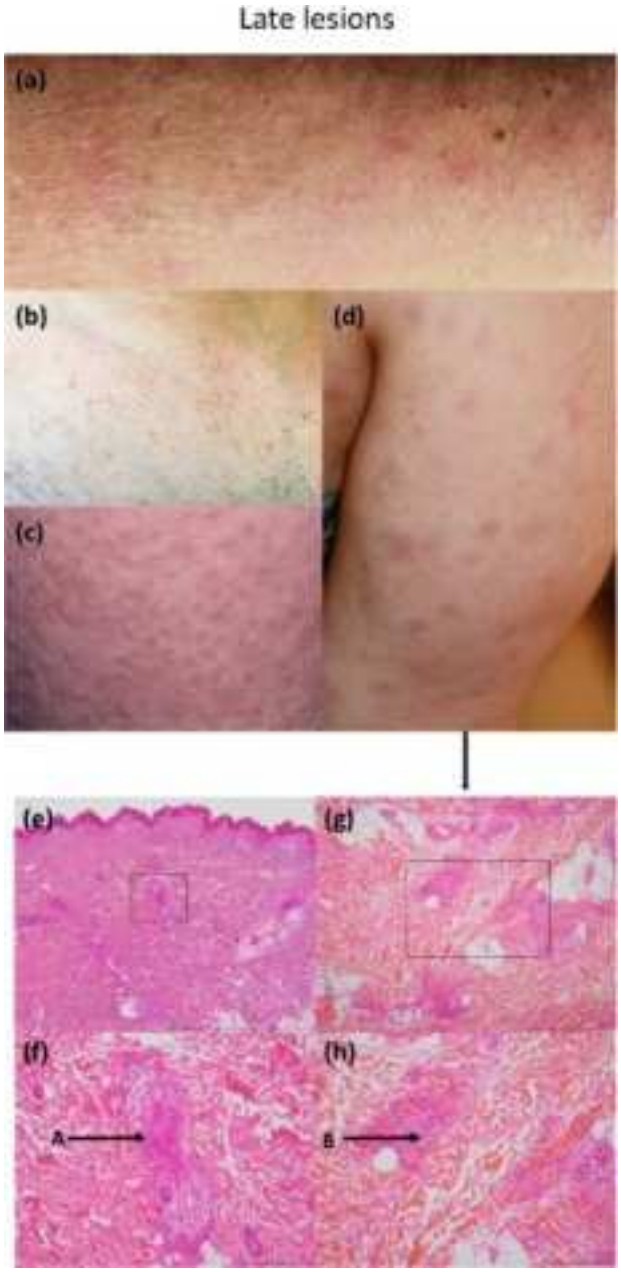

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