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Systematic Review: Sweet Syndrome Associated with Inflammatory Bowel Disease

Joseph Sleiman,[a] Asif A. Hitawala,[a] Benjamin Cohen,[b] Katie Falloon,[b] Marian Simonson,[c] Benjamin Click,[b] Urmi Khanna,[d] Anthony P. Fernandez,[e] Florian Rieder[b]

[a]Department of Internal Medicine, Cleveland Clinic, Cleveland, OH, USA [b]Department of Gastroenterology, Hepatology and Nutrition, Digestive Diseases and Surgery Institute, Cleveland Clinic, Cleveland, OH, USA [c]Floyd D. Loop Alumni Library, Cleveland Clinic, Cleveland, OH, USA [d]Department of Dermatology, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY, USA [e]Departments of Dermatology and Pathology, Cleveland Clinic, Cleveland, OH, USA

Corresponding author: Florian Rieder, MD, Department of Inflammation and Immunity, and Department of Gastroenterology, Hepatology & Nutrition, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, USA. Tel: (216) 445-4916; Fax: (216) 636-0104; Email: riederf@ccf.org

Abstract

Background and Aims. Sweet syndrome [SS] is a dermatological condition associated with both inflammatory bowel disease [IBD] and azathioprine use. We performed a systematic review to better delineate clinical characteristics and outcomes of SS in IBD patients.

Methods. Peer-reviewed, full-text journal publications from inception to April 2020 in English language and adult subjects with IBD were included. Skin biopsy was required as SS gold-standard diagnosis. Azathioprine-associated SS required recent azathioprine introduction or recurrence of SS after azathioprine re-challenge.

Results. We included 89 publications with 95 patients [mean age of SS diagnosis: 44 years; 59% female; 20 with azathioprine-associated SS and 75 without]. SS was diagnosed prior to IBD in 5.3%, at time of IBD diagnosis in 29.5% and after diagnosis in 64.2%. In total, 91% of patients with SS had known colonic involvement and the majority [76%] had active IBD at diagnosis; 22% had additional extra-intestinal manifestations. Successful therapies for SS included corticosteroids [90.5%], anti-tumour necrosis factor [TNF]-α inhibitor therapy [14.8%] and azathioprine [11.6%]. Azathioprine-associated SS was distinct, with 85% male patients, mean age of SS diagnosis of 50 years and a lower likelihood to be prescribed corticosteroids for treatment [75% vs 94.7% of non-azathioprine-associated SS, $p = 0.008$]. All patients with azathioprine-associated SS improved with medication cessation and developed recurrence after re-challenge.

Conclusions. SS may precede or occur with IBD diagnosis in almost one-third of cases. Azathioprine and IBD-associated SS present and behave distinctly, especially with regard to gender, age at diagnosis and recurrence risk. Corticosteroids and TNF-α inhibitors have demonstrated efficacy in treating SS in IBD.

Key Words: Sweet syndrome; inflammatory bowel disease; azathioprine; skin; extraintestinal manifestation

1. Introduction

Patients with inflammatory bowel disease [IBD] may develop various chronic inflammatory conditions in organs outside of the gastrointestinal tract. These so-called extra-intestinal manifestations [EIMs] have been reported to occur in between 6% and 47% in both Crohn's disease [CD] and ulcerative colitis [UC] patients and most frequently involve the eyes, skin and joints.[1–8] Among cutaneous EIMs, pyoderma gangrenosum and erythema nodosum are the most common.[9]

Sweet syndrome [SS], or acute febrile neutrophilic dermatosis, is one of the less common skin manifestations of IBD, and as such has not been included in the large IBD studies focusing on EIM phenotypes and outcomes.[1,2,7–11] It presents as an abrupt onset of painful erythematous plaques or nodules, often with fever and elevated inflammatory markers, with histopathological evidence of neutrophil-rich infiltrates without vasculitis.[12,13] SS is diagnosed at a rate of three per 10 000 dermatological visits in the general population.[14] Within IBD cohorts, its occurrence may range between 0.07% and 0.21%.[15,16] IBD-associated SS is seen as a sub-group of classical-type SS, and SS cohorts have historically included patients with IBD as rates ranging from 0% to 20% [Supplementary Table 1].[13–47] Non-classical SS types otherwise include those related to malignancy or induction by certain drug exposures.[48] Curiously, while being used as an IBD therapy itself, azathioprine [AZA] is one of the most commonly reported inciting agents in patients with drug-induced SS.[49–53]

Only a limited number of papers describing the pattern of SS in IBD patients have been published. It is, however, clinically useful to understand if different demographics, clinical characteristics and treatment responses exist among SS populations with CD or UC, as well as among IBD patients with AZA-associated and non-AZA-associated SS. Here we aimed to describe the demographic, clinical features and treatment outcomes in IBD-related SS using a systematic review approach.

2. Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[54]

2.1. Information sources and search strategy

A literature search was performed on Ovid MEDLINE, Cochrane Central Register of Controlled Trials [CENTRAL], EMBASE and Web of Science from inception to April 2020. A combination of Medical Subject Headings [MeSH], other controlled vocabulary and keywords were used to search for 'Sweet syndrome', 'acute neutrophilic dermatosis', 'inflammatory bowel disease', 'ulcerative colitis' and 'Crohn disease'. In addition, reference lists of relevant articles from title/abstract screening were manually searched for citations not identified by the electronic searches. A detailed description of each search strategy is provided in the Supplementary Material.

After removing duplicate citations, titles and abstracts of articles were independently screened by two reviewers [J.S. and A.A.H.]. The full texts of relevant articles were obtained and analysed independently by J.S. and A.A.H according to predefined inclusion/exclusion criteria. Disagreements were resolved by mutual discussion between J.S. and A.A.H. and if necessary arbitrated by a third author, F.R.

2.2. Eligibility criteria

Inclusion criteria consisted of original articles on SS in adults with IBD, a confirmed diagnosis by biopsy, cases of neutrophilic dermatosis of the dorsal hands [NDDH] and SS in patients with IBD linked to AZA drug exposure. AZA exposure was defined as AZA newly introduced within 1 month prior to SS development or in cases when skin lesions disappeared upon AZA interruption and recurred with re-challenge by AZA. Three patients had long-term exposure to AZA prior to developing SS that was managed without mentioning the possibility of AZA-induced SS; those were included in the non-AZA group. Because of the limited number of larger studies, case series, case reports, case illustrations, vignettes, letters to editors, correspondences and brief communications were included, if it was possible to obtain enough information to perform a risk-factor analysis. Patients less than 18 years of age, diagnosis of SS made without a skin biopsy, articles describing a case with unclear diagnosis and articles reporting AZA hypersensitivity rather than AZA-associated SS, international publications with non-English content, meeting abstracts, animal studies and review articles were excluded.

2.3. Data collection process

Data from eligible studies were independently extracted by two reviewers [J.S. and A.A.H.]. Discrepancies were rectified by the arbitrator, F.R. When articles included patients from a previously published study and added additional patients, only the latter were considered for this analysis. In the case of mixed cohorts, only data regarding patients with IBD and SS were included. Attention was paid to describe subgroups based on recent AZA exposure linked to SS eruption [AZA and non-AZA groups], as well as to the type of IBD linked to SS eruption [CD or UC groups]. IBD was considered active at the time of SS diagnosis if indicated by the authors either by specifically mentioning clinical activity, by reporting active IBD flare symptoms [abdominal pain, diarrhoea and/or blood per rectum], by recent need to increase IBD medication due to uncontrolled disease or by endoscopic assessment with verified endoscopic activity. Data extracted from each primary study are shown in Supplementary Table 2.

2.4. Statistical analysis

Descriptive statistics were used. Differences between the subgroups were analysed by using the Chi-square test, Fisher's exact test or Mann–Whitney U test as appropriate. A 5% alpha level was considered significant.

2.5. Data quality metrics

Given that all retrieved articles were either case reports, illustrations, vignettes or case series, and no standardized published methods for quality assessment of such articles is available, we referred to published guidelines for writing case reports [CARE guideline] and case series and used them as a reference to create our own method for quality assessment.[55,56] We examined both CARE guidelines [28 items] and the case series checklist [20 items] and eliminated items that would not be applicable to SS particularly. Examples include question 8-B in CARE guidelines requesting identification of diagnostic challenges [financial, language] or 10-b requesting information on follow-up tests, which would not be needed in SS. For CARE guidelines specifically, the total score varied based on the type of article because letters to editors and communications, for example, did not require abstracts [items 3a-b-c] or keywords [item 2 on the

checklist] and this would lower the score due to journal format requirements. For every question in both checklists, we assigned one point, if a criterion was fulfilled, 0 points if it was absent and eliminated the criteria if it was not applicable. Study quality was considered high if it received ≥2/3 of potential total score, and low for ≤1/3 of total score. For case series, total score was 13, and quality scoring was divided into low [0–4], medium [5–9] and high [10–13]. A detailed method of quality assessment is included in Supplementary Table 3.

3. Results

3.1. Characteristics of included studies and data quality

After literature search and review of titles and abstracts, 89 articles met our pre-defined inclusion criteria and were included for analysis [Supplementary Figure 1 and Table 2].[57–145] A total of 95 individual cases were identified, with the majority of full-text articles being case reports or case series [Table 1]. The majority of cases [53/95, 55.8%] were reported within the past 10 years [Supplementary Figure 2].

Of the included articles, 71 of 89 [79.7%] were considered high quality based on CARE or case series guidelines, with the remainder being medium quality [Table 1]. Case series were most consistent in reporting the aim of the study, describing the characteristics of the patients and reporting the intervention of interest [average scores 0.92, 0.92 and 0.92 over 1 for each question], but did not score well on multicentre data collection [0.08], having homogenous cases at a similar point in the disease [0.38], and on reporting adverse events [0.23] and authors conflicts of interests [0.08]. For all other article types, the most consistently well-scored sections were case presentation details [criteria 5b and 6 = 1], reporting of diagnostic methodology [8a = 1] and types of intervention used [9a = 1]. Articles were inconsistent in reporting all important time points of cases [7 = 0.56], and in reporting changes in therapy, adverse events of therapies used [10 c/d = 0.35/0.4], and patient perspectives or informed consent processes [12/13 = 0.03/0.45] [Supplementary Table 3].

3.2. Baseline demographics of the cohort

3.2.1. Overall cohort

Table 2 summarizes demographic findings of SS in patients with IBD. In our SS-IBD cohort, 56 of 95 patients [58.9%] were female, and most with identifiable race [68/75, 90.7%] were white. Median age at SS diagnosis was 44 years (N = 95, interquartile range [IQR] 32–53 years), and at IBD diagnosis was 38 years [N = 77, IQR 29–47 years]. SS occurred at a median of 8.4 months [N = 77, IQR 0–6 years] after IBD diagnosis [Supplementary Figure 3]. Eighteen cases did not report the age of IBD diagnosis and were not accounted for in this median calculation. Overall, the majority of SS cases [61/95, 64.2%] occurred more than 3 months after IBD diagnosis. Only five [5.3%] cases occurred prior to IBD diagnosis. Interestingly, IBD and SS were diagnosed concurrently [within 3 months of each other] in 29.5% of cases [28/95], with SS being the first to occur in three of 28 of such cases [10.7%]. Overall, 48 [45.3%] patients had CD and 43 [50.5%] had UC; four [4.2%] patients had IBD undetermined. In patients whose IBD activity was known at the time of SS diagnosis, SS ensued while IBD was active in 53 of 69 cases [76.8%]. Most patients [58/95, 61.1%] were on at least one IBD therapy at the time of SS diagnosis. Medications used for IBD at the time of SS diagnosis were most commonly oral 5-aminosalicylic

Table 1. Assessment of data quality

Type of article	Article count	Case count extracted	Year of publication [median, range]	Quality metric[a]	Average total score	Low quality	Medium quality	High quality
Case Report	40	40	2009 [1983–2019]	19.15 ± 1.33	24	0	2	38
Case Series	13	20	2006 [1964–2015]	8 ± 1.63	13	0	10	3
Case Illustration	14	14	2015 [2003–2020]	13.79 ± 2.33	19.21	0	4	10
Letter to Editor	15	15	2015 [2006–2019]	15.6 ± 1.45	20.33	0	0	15
Correspondence	3	3	1996 [1995–2013]	13.33 ± 1.15	19.33	0	1	2
Clinical Vignette	2	2	2011 [2009–2013]	15.5 ± 0.43	19	0	0	2
Brief Communication	1	1	2008	19	24	0	0	1
Total	88	95	2009 [1964–2020]	NA	NA	0	17	71

[a]Case series and all others were measured differently.

Table 2. Demographics and baseline clinical features of the cohort

Factor	Overall [*N* = 95]		AZA group [*N* = 20]		Non-AZA group [*N* = 75]		*p*-value	Crohn's disease [*N* = 48]		Ulcerative colitis [*N* = 43]		*p*-value
	N	Statistics	*N*	Statistics	*N*	Statistics		*N*	Statistics	*N*	Statistics	
Sex, *n* [%]	95		20		75		***<0.00001***[a]	48		43		**0.005**[c]
Male		39 [41.1]		17 [85.0]		22 [29.3]			13 [27.1]		24 [55.8]	
Female		56 [58.9]		3 [15.0]		53 [70.7]			35 [72.9]		19 [44.2]	
Diagnosis age of SS, median [range], years	94	44 [19 - 87]	19	50 [29 - 75]	75	41 [19–87]	***0.009b***	48	41.5 [21 - 87]	42	44.5 [19 -78]	*0.90*[a]
Diagnosis age of IBD, median [range], years	77	35 [9–68]	16	43 [21–55]	61	36 [9–68]	*0.16*[b]	40	36.5 [9–63]	33	38 [10–68]	*0.60*[b]
SS occurrence in terms of IBD, *n* [%]	95		20		74		*0.24*[a]	48		42		**0.004**[a]
within 3 months of IBD diagnosis		25 [26.3]		3 [15.0]		22 [29.3]			0 [0.0]		3 [7.1]	
3 months before IBD diagnosis		3 [3.2]		0 [0.0]		3 [4.0]			18 [37.5]		5 [11.9]	
>3 months after IBD diagnosis		61 [64.2]		17 [85.0]		44 [58.7]			27 [56.3]		33 [78.6]	
>3 months before IBD diagnosis		5 [5.3]		0 [0.0]		5 [6.7]			3 [6.3]		1 [2.4]	
Race, *n* [%]	75		17		58		*0.59* [a]	34		38		**0.02**[a]
White		68 [90.7]		15 [88.2]		53 [91.4]			33 [97.1]		32 [84.2]	
Hispanic		1 [1.3]		0 [0.0]		1 [1.7]			1 [2.9]		0 [0.0]	
Asian		6 [8.0]		2 [11.8]		4 [6.9]			0 [0.0]		6 [15.8]	
Associated medical history relevant to SS, *n* [%]	95		20		75			48		43		
Active solid malignancy		1 [1.1]		0 [0.0]		1 [1.3]	*1*[a]		0 [0.0]		1 [2.3]	*0.47*[a]
Current pregnancy		3 [3.2]		0 [0.0]		3 [4.0]	*1*[a]		1 [2.1]		2 [4.7]	*0.60*[a]
New recent drug exposure within 2 weeks of SS		22 [23.2]		20 [100.0]		4 [5.3]	***<0.00001a***		11 [22.9]		10 [23.3]	*1*[a]
Recent URTI or GI infection		5 [5.3]		0 [0.0]		5 [6.7]	*0.58*[a]		3 [6.3]		2 [4.7]	*1*[a]
Other autoimmune disorder		3 [3.2]		0 [0.0]		3 [4.0]	*1*[a]		2 [4.2]		1 [2.3]	*1*[a]
Other conditions		10 [10.5]		0 [0.0]		10 [13.3]	*0.11*[a]		3 [6.3]		6 [14.0]	*0.30*[a]
IBD type, *n* [%]	95		20		75		*0.95*[a]	48		43		*NA*
Ulcerative colitis		48 [50.5]		8 [40.0]		32 [42.7]			0 [0.0]		43	
Crohn's disease		43 [45.3]		11 [55.0]		40 [53.3]			48		0 [0.0]	
Undetermined IBD		4 [4.2]		1 [5.0]		3 [4.0]			*NA*		*NA*	
IBD clinical activity at SS diagnosis, *n* [%]	69		16		53		*0.06*[a]	33		32		*0.41*[c]
Active		53 [76.8]		15 [93.8]		38 [71.7]			24 [72.7]		26 [81.3]	
Inactive		16 [23.2]		1 [6.2]		15 [28.3]			9 [27.3]		6 [18.8]	

Table 2. Continued

Factor	Overall [*N* = 95]		AZA group [*N* = 20]		Non-AZA group [*N* = 75]		*p*-value	Crohn's disease [*N* = 48]		Ulcerative colitis [*N* = 43]		*p*-value
	N	Statistics	*N*	Statistics	*N*	Statistics		*N*	Statistics	*N*	Statistics	
History of extraintestinal manifestations, *n* [%]	21		1		20		*0.06*[a]	13		8		*0.46*[a]
Peripheral arthropathy type 1		6 [28.6]		0 [0.0]		6 [30.0]	*0.33*[a]		5 [38.5]		1 [12.5]	*0.34*[a]
Peripheral arthropathy type 2		5 [23.8]		0 [0.0]		5 [25.0]	*0.58*[a]		4 [30.8]		1 [12.5]	*0.61*[a]
Spondylitis/sacroiliitis		2 [9.5]		0 [0.0]		2 [10.0]	*1*[a]		1 [7.7]		1 [12.5]	*1*[a]
Erythema Nodosum		5 [23.8]		0 [0.0]		5 [25.0]	*0.58*[a]		4 [8.3]		1 [12.5]	*0.61*[a]
Pyoderma gangrenosum		5 [23.8]		1 [100.0]		4 [20.0]	*1*[a]		0 [0.0]		5 [62.5]	***0.0028a***
Oral aphthous ulcers		4 [19.0]		0 [0.0]		4 [20.0]	*0.58*[a]		4 [30.8]		0 [0.0]	*0.13*[a]
Uveitis/episcleritis		3 [14.3]		0 [0.0]		3 [15.0]	*1*[a]		1 [7.7]		2 [25.0]	*0.53*[a]
Medications for IBD at SS diagnosis, *n* [%]	95		20		75			48		43		
5-Aminosalicylic-acid, rectal		8 [8.4]		4 [20.0]		4 [5.3]	*0.06*[a]		3 [6.3]		5 [11.6]	*0.47*[a]
5-Aminosalicylic-acid, oral		25 [26.3]		5 [25.0]		20 [26.7]	*0.88*[c]		8 [16.7]		16 [37.2]	***0.026c***
Steroid, rectal		1 [1.1]		0 [0.0]		1 [1.3]	*1*[a]		0 [0.0]		1 [2.3]	*0.47*[a]
Steroid, systematic		25 [26.3]		12 [60.0]		13 [17.3]	***0.0001c***		7 [14.6]		17 [39.5]	***0.007c***
Budesonide		2 [2.1]		0 [0.0]		2 [2.7]	*1*[a]		2 [4.2]		0 [0.0]	*0.50*[a]
Infliximab		8 [8.4]		2 [10.0]		6 [8.0]	*0.63*[a]		4 [8.3]		4 [9.3]	*1*[a]
Adalimumab		7 [7.4]		0 [0.0]		7 [9.3]	*0.34*[a]		3 [6.3]		4 [9.3]	*0.70*[a]
Mercaptopurine		1 [1.1]		0 [0.0]		1 [1.3]	*1*[a]		1 [2.1]		0 [0.0]	*1*[a]
Azathioprine		23 [24.2]		20 [100.0]		3 [4.0]	***<0.00001a***		8 [16.7]		14 [32.6]	*0.077*[c]
Methotrexate		1 [1.1]		0 [0.0]		1 [1.3]	*1*[a]		1 [2.1]		0 [0.0]	*1*[a]
None		37 [38.9]		0 [0.0]		37 [49.3]	***<0.00001a***		21 [43.8]		13 [30.2]	*0.18*[c]

Abbreviations: SS, Sweet syndrome; IBD, inflammatory bowel disease; URTI, upper respiratory tract infection; GI, gastrointestinal; AZA, azathioprine; N, number.

p-values in italic/bold are of values <0.05.

[a]Fisher's exact test.

[b]Mann–Whitney U test.

[c]Pearson's Chi-square test.

acid [5-ASA] [25/95, 26.3%], systemic steroids [25/95, 26.3%] and AZA [23/95, 24.2%]. IBD-related symptoms during SS eruption included abdominal pain [45.3%], rectal bleeding [62.3%] and loose stools [88.7%]. Twenty-one patients [22.1%] overall had additional EIMs, which involved the skin (13.7%, including five for each of pyoderma gangrenosum [PG] and erythema nodosum, and four for oral aphthous ulcers), joints [11.6%, 11 with peripheral arthropathy and two with spondylitis/sacroiliitis] and/or eyes [3.2%, three with uveitis or episcleritis].

3.2.2. Comparison of AZA vs non-AZA

Among 95 patients, 20 were noted to have AZA-associated SS and 75 had non-AZA-associated SS. Of the 20 cases of AZA-associated SS, 19 occurred within 28 days of starting AZA, and one patient was diagnosed based on recurrence of SS after AZA re-challenge. There were no racial differences among the AZA and non-AZA SS cohorts, but patients with AZA exposure were significantly older [50 vs 41 years-old, $p = 0.009$] and predominantly male [85% vs 29.3%, $p < 0.00001$] compared to those without exposure. Interestingly, although not statistically significant, secondary conditions linked to SS were exclusively described in the non-AZA cohort: 21 of 75 [28%] patients had conditions other than IBD that could be linked to SS development, including recent infection [5.3%], pregnancy [3.2%] and other autoimmune disorders [3.2%]. In contrast, none of the IBD patients diagnosed with AZA-associated SS had another condition that could be linked to SS. Patients in the AZA group were more likely to be on systemic steroids [60% vs 17.3%, $p < 0.0001$] compared to the non-AZA group. The AZA group only had one patient [1/20, 5%] with another EIM [PG], while 20 of the 75 patients [26.7%] in the non-AZA cohort had other EIMs.

3.2.3. Comparison of CD vs UC

When comparing 43 patients with CD and 48 with UC, no age difference was detected, but UC patients were more likely to be male [55.8% vs 27.1%, $p = 0.005$] and SS cases in the Asian population were strictly in the UC population [15.8% vs 0%, $p = 0.02$]. Patients with UC were less likely to have a concurrent diagnosis of IBD and SS diagnosis than CD patients [19% vs 37.5%, $p = 0.004$]. No significant differences in distribution were noted among other conditions associated with SS. Patients with UC and CD had similar rates of IBD activity at SS diagnosis, but the UC group was more likely to be on systemic steroids [39.5% vs 14.6%, $p = 0.007$] and oral 5-ASA [37.2% vs 16.7%, $p = 0.026$]. PG was exclusive to UC patients [11.6% vs 0%, $p = 0.0028$], and no difference among IBD cohorts was noted for the occurrence of other EIMs. Thirty-five of the 48 patients with CD had descriptions of their CD location available. Colonic disease location was predominant [32/35, 91.4%], with ten of those patients [31.4%] having ileocolonic disease. One had jejunal CD [1/35, 2.9%], six had perianal disease [6/35, 17.1%] and two upper gastrointestinal [GI] disease [2/35, 5.7%]. CD phenotype was described in 32 patients, of which non-stricturing, non-penetrating presentation was the most common [23/32, 71.9%], followed by internal penetrating [6/32, 18.8%] and stricturing [2/32, 6.3%] disease. Perianal disease occurred in seven patients [21.9%]. Twenty-three patients with UC had a description of the extent of their disease available, which was primarily extensive [10/23, 43.5%], followed by left-sided and sigmoid equally [6/23, 26.1% each], and rectal only in one case. Perianal disease was described in two cases [8.7%].

3.3. Clinical features of SS in the cohort

3.3.1. Overall cohort

Table 3 summarizes clinical features of SS in the IBD cohort. The vast majority of IBD patients presented with a clinical picture that is characteristic of SS in general, including fever [83%], arthralgias [43.6%], myalgias [7.4%] and headache [4.3%]. A polymorphic erythematous rash occurring as multiple lesions was found in 94.6% of cases, with most lesions being painful [59.6%] but not necessarily pruritic [only 6.4% reported pruritis]. The morphology of SS skin lesions was described as plaques [56%], maculopapular rash [46.2%] and nodules [20.9%]. Lesions occurred most commonly on the upper [67%] and lower [61.7%] limbs, followed by trunk, head and neck, oral mucosa and dorsum of the hands. The genital area was rarely involved [1.1%], but it is difficult to know if this was due to reporting bias. No description of a peri-ostomy rash was mentioned in the five patients with stomas. Elevated erythrocyte sedimentation rate [ESR] [94.9%, median 79.5 mm/h, IQR 55.5–86.5], C-reactive protein [CRP] [100%, median 16.6 mg/dL, IQR 10.6–23] and neutrophilia [94.9%, median 11.2 × 10^9 cells/L, IQR 9.36–14.58] were the most common laboratory abnormalities at presentation, followed by anaemia [58.3%] and thrombocytosis [5.9%]. Anti-nuclear antibodies [ANA] and anti-neutrophil cytoplasmic antibodies [ANCA] were evaluated in 14 and five patients, respectively, and were each positive in only one case. Biopsies were done within a median of 6 days [range: 1–1500 days] from the start of SS symptoms. Histopathology of lesional skin revealed neutrophil-rich inflammatory infiltrates [96.6%], admixed with eosinophils, histiocytes and lymphocytes in 7.5%, 9.7% and 12.9%, respectively. The most common pathological variants were classical neutrophil-rich type in 83 of 93 [89.2%, seven of which were NDDH] cases, followed by histiocytoid [5.4%], subcutaneous and bullous [both <5%].

3.3.2. Comparison of AZA vs non-AZA

Both AZA and non-AZA cohorts had similar skin findings in terms of type of skin eruption, lesion frequency and distribution, except that trunk predominance was noted in the AZA group [85% vs 50%, $p = 0.005$]. There were no different distributions of histopathology among the subgroups.

3.3.3. Comparison of CD vs UC

There were no differences in clinical SS lesion characteristics, nor laboratory or histopathology variations across the subgroups of IBD.

3.4. Treatment strategies and recurrence rate

SS was successfully controlled within a median of 7 days [range: 2–46 days] of therapy initiation. Steroids were the most commonly used therapy [86/95, 90.5%] for SS, which was systemic [oral or intravenous] in 93.7% of cases and only topical in the rest. Biologic therapy was the second most common choice [14/95, 14.8%], either combined with steroid use [7/14, 50%], after failure of steroid therapy [4/14, 29%] or individually when steroids use was not appropriate [3/14, 21%]. Biologics included infliximab in nine cases [90,105,106,111,119,121,125,130,133] an unspecified anti-tumour necrosis factor [TNF]-α in another case,[138] and one case for each of vedolizumab,[68] ustekinumab[82] and golimumab.[70] Of these 14 cases, only nine had active IBD at the time of diagnosis of SS. Other SS treatments included non-steroidal anti-inflammatory drugs [NSAIDs], dapsone, colchicine, cyclosporine and methotrexate, each used in <5% of cases. Interestingly, AZA itself was an SS treatment choice in 11 of

Table 3. Clinical features of Sweet syndrome in the cohort

Factor	Overall [*N* = 95]		AZA group [*N* = 20]		Non-AZA group [*N* = 75]		*p*-value	Cohn's disease [*N* = 48]		Ulcerative colitis [*N* = 43]		*p*-value
	N	Statistics	*N*	Statistics	*N*	Statistics		*N*	Statistics	*N*	Statistics	
Skin findings, *n* [%]	91		20		71			46		41		
Macules and papules		42 [46.2]		13 [65.0]		29 [40.8]	*0.06*[c]		21 [45.7]		18 [43.9]	*0.87*[c]
Subcutaneous EN-like		2 [2.2]		0 [0.0]		2 [2.8]	*1*[a]		2 [4.3]		0 [0.0]	*0.50*[a]
Plaques		51 [56.0]		11 [55.0]		40 [56.3]	*0.92*[c]		29 [63.0]		21 [51.2]	*0.27*[c]
Pustules		36 [39.6]		9 [45.0]		27 [38.0]	*0.57*[c]		16 [34.8]		19 [46.3]	*0.27*[c]
Pseudo-vesicular		18 [19.8]		4 [20.0]		14 [19.7]	*1*[a]		10 [21.7]		8 [19.5]	*0.80*[c]
Bullous		10 [11.0]		1 [5.0]		9 [12.7]	*0.45*[a]		3 [6.5]		6 [14.6]	*0.30*[a]
Nodular		19 [20.9]		4 [20.0]		15 [21.1]	*1*[a]		10 [21.7]		9 [22.0]	*0.98*[c]
Lesion frequency, *n* [%]	92		19		73		*0.42*[a]	46		42		*0.66* [a]
Single		5 [5.4]		0 [0.0]		5 [6.8]			2 [4.3]		3 [7.1]	
Multiple		87 [94.6]		19 [100.0]		68 [93.2]			44 [95.7]		39 [92.9]	
Lesion distribution, *n* [%]	94		20		74			47		43		
Upper limbs		63 [67.0]		12 [60.0]		51 [68.9]	*0.45*[c]		33 [70.2]		29 [67.4]	*0.78*[c]
Dorsum of hands		20 [21.3]		3 [15.0]		17 [23.0]	*0.55*[a]		9 [19.1]		11 [25.6]	*0.46*[c]
Palms		13 [13.8]		4 [20.0]		9 [12.2]	*0.46*[a]		7 [14.9]		6 [14.0]	*0.90*[c]
Lower limbs		58 [61.7]		16 [80.0]		42 [56.8]	*0.0* [a]		33 [70.2]		23 [53.5]	*0.10*[c]
HEENT		52 [55.3]		14 [70.0]		38 [51.4]	*0.14*[c]		22 [46.8]		28 [65.1]	*0.08*[c]
Trunk		54 [57.4]		17 [85.0]		37 [50.0]	***0.005a***		27 [57.4]		26 [60.5]	*0.77*[c]
Oral mucosa		24 [25.5]		5 [25.0]		19 [25.7]	*0.95*[c]		14 [29.8]		8 [18.6]	*0.22*[c]
Genital area		1 [1.1]		0 [0.0]		1 [1.4]	*1*[a]		1 [2.1]		0 [0.0]	*1*[a]
Neutrophilia, *n* [%]	75		16		59		*0.12*[a]	41		32		*1*[a]
Yes		67 [89.3]		16 [100.0]		51 [86.4]			36 [87.8]		29 [90.6]	
No		8 [10.7]		0 [0.0]		8 [13.6]			5 [12.2]		3 [9.4]	
Elevated ESR, adjusted for age, *n* [%]	39		8		31		*0.20*[a]	23		16		*1*[a]
Yes		37 [94.9]		7 [87.5]		30 [96.8]			22 [95.7]		15 [93.8]	
No		2 [5.1]		1 [12.5]		1 [3.2]			1 [4.3]		1 [6.2]	
Anaemia *n* [%]	60		12		48		*0.07*[a]	31		26		*0.39*[c]
Yes		35 [58.3]		4 [33.3]		31 [64.6]			19 [61.3]		13 [50.0]	
No		25 [41.7]		8 [66.7]		17 [35.4]			12 [38.7]		13 [50.0]	
Abnormal platelet counts, *n* [%]	51		11		40		*0.32*[a]	25		24		*0.49*[a]
Yes		3 [5.9]		1 [9.1]		2 [5.0]			2 [8.0]		0 [0.0]	
No		48 [94.1]		10 [90.9]		38 [95.0]			23 [92.0]		24 [100.]	
CRP level, median [range], mg/dL	44	16.6 [1.4–36.4]	11	16.16 [1.4–30.6]	33	16.8 [7.2–36.4]	*0.94*[b]	27	16.8 [7.2–30.6]	16	13.02 [1.4–30.9]	*0.76*[b]
Pathology variant, *n* [%]	93		20		73		*0.38*[a]	46		43		*0.25*[a]
Classical		76 [81.7]		19 [95.0]		57 [78.1]			39 [84.8]		34 [79.1]	
Histiocytoid		5 [5.4]		0 [0.0]		5 [6.8]			4 [8.7]		1 [2.3]	
Subcutaneous		2 [2.2]		0 [0.0]		2 [2.7]			1 [2.2]		1 [2.3]	
Bullous		3 [3.2]		1 [5.0]		2 [2.7]			0 [0.0]		2 [4.7]	
NDDH		7 [7.5]		0 [0.0]		7 [9.6]			2 [4.3]		5 [11.6]	
Successful treatments used, *n* [%]	95		20		75			48		43		
Steroids		86 [90.5]		15 [75.0]		71 [94.7]	***0.008c***		42 [87.5]		40 [93.02]	*0.49*[a]
Indomethacin or NSAIDs		3 [3.2]		0 [0.0]		3 [4.0]	*1*[a]		3 [6.25]		0 [0]	*0.24*[a]

Table 3. Continued

Factor	Overall [*N* = 95]		AZA group [*N* = 20]		Non-AZA group [*N* = 75]		*p*-value	Cohn's disease [*N* = 48]		Ulcerative colitis [*N* = 43]		*p*-value
	N	Statistics	*N*	Statistics	*N*	Statistics		*N*	Statistics	*N*	Statistics	
Dapsone		4 [4.2]		0 [0.0]		4 [5.3]	*0.58*[a]		2 [4.17]		2 [4.65]	*1*[a]
Colchicine		3 [3.2]		0 [0.0]		3 [4.0]	*1*[a]		2 [4.17]		1 [2.33]	*1*[a]
Infliximab		9 [9.5]		3 [15.0]		6 [8.0]	*0.39*[a]		5 [10.42]		4 [9.3]	*1*[a]
Other biologics		5 [5.3]		1 [5.0]		4 [5.3]	*1*[a]		3 [6.25]		2 [4.65]	*1*[a]
Cyclosporine		1 [1.1]		0 [0.0]		1 [1.3]	*1*[a]		0 [0]		1 [2.33]	*0.47*[a]
Methotrexate		3 [3.2]		1 [5.0]		2 [2.7]	*0.51*[a]		1 [2.08]		2 [4.65]	*0.6*[a]
Azathioprine		11 [11.6]		2 [10.0]		9 [12.0]	*1*[a]		5 [10.42]		6 [13.95]	*0.61*[c]
Antibiotics		7 [7.4]		1 [5.0]		6 [8.0]	*1*[a]		7 [14.6]		0 [0.0]	***0.013a***
Recurrence of SS, *n* [%]	95	22 [23.2]	20	4 [20.0]	75	18 [24.0]	*N/A*		12 [25]		9 [20.93]	*0.65*[c]

Abbreviations: HEENT, head eyes ears nose throat; NSAID, non-steroidal anti-inflammatory drug; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; NDDH, neutrophilic dermatosis of the dorsal hands; AZA, azathioprine; N, number.

p-values in italic/bold are of values <0.05.

[a]Fisher's exact test.

[b]Mann–Whitney U test.

[c]Pearson's Chi-square test.

95 [11.6%] cases, ten of which were in the non-AZA group, and in one case in the AZA group [dose was actually increased]. One patient received ten sessions of leukocytopheresis alongside steroids.[135] Treatment delays occurred in 22/95 cases [23.2%] due to initial misdiagnosis [mainly cellulitis] and treatment with antibiotics, antivirals or antifungals before histopathological results. In seven other cases, however, antibiotics were used after SS diagnosis alongside steroids; antibiotics included fluoroquinolone, nitroimidazole [i.e. metronidazole] and penicillin classes. Antibiotics were added to steroid therapy due to either severe illness of the patient or for complicated IBD [fistula, abscess or perianal disease]. Among subgroups, steroids were less commonly used in the AZA group compared to the non-AZA group [75% vs 94.7%, $p = 0.008$], and antibiotics were more likely to be used for patients with CD than UC [14.6% vs 0.0%, $p = 0.013$].

SS recurred in 22 patients overall [23.2%]. In the AZA group, all four cases in which AZA was discontinued and then restarted had a recurrence of SS skin eruptions. SS recurred within 90 days [range: 17–1460 days] in the general population and 30 days [3–30 days] in the AZA group. Recurrence coincided with steroid taper in six cases, with recurrence of IBD flare in nine, AZA use in four cases and another SS-associated condition in one case.

4. Discussion

SS is a cutaneous eruption that has been associated with both IBD and AZA exposure.[48,146] The present systematic review describes, to date, the largest cohort of patients with IBD and SS, and thus is able to shed light on important clinical aspects in this particular population including IBD subtype and potential inciting medications such as AZA. We found that: [1] SS occurs most commonly in middle-aged white female patients with IBD, with no specific predilection to CD or UC; [2] colonic involvement is notable in patients with IBD and SS, especially the CD population; and [3] SS may be an early EIM in the natural course of IBD, often occurring alongside IBD diagnosis and occasionally occurring in parallel with IBD disease activity.

Overall, our cohort is generally middle-aged with a female and white predominance, similar to other non-IBD SS cohorts, where the range of female patients was 40–60%.[146] However, we found a male predominance in the AZA group, as well as older age than non-AZA group, which is consistent with a previous report.[52] On the other hand, studies of IBD patients with other cutaneous EIMs show a female predominance, even in UC, whereas CD had more female predominance than UC in our study.[9] It is also worth noting that the CD and UC groups also had a difference in timing between IBD diagnosis and SS occurrence, as well as Asian race occurring solely in the UC cohort. Although reporting bias is the more likely explanation, should these findings be true, they do draw attention to potential risk factors that allow SS to occur under different circumstances in patients with different IBD subtypes.

In comparison to IBD cohorts where EIMs other than SS were studied, our cohort was slightly older at EIM diagnosis,[8,9] which may reflect the characteristic median age of SS presentation.[146] For example, studies describing patients with younger age of CD [31 years] and UC onset [36.6 years], with similar IBD phenotypes to our cohort, showed no SS cases.[11,147] A study in IBD focused on cutaneous EIMs found no SS in a cohort of 195 IBD patients with mean age of 39.5 years.[148] SS may thus be a rare cutaneous EIM mostly of concern in the older IBD population.

SS occurred at a short median duration from diagnosis of IBD [0.7 years, IQR 0–6 years], and this timeframe is shorter compared to other non-cutaneous EIM occurrences in relation to IBD.[8,9] In fact, a study of 480 patients with IBD showed that cutaneous EIMs typically occur earlier than other EIMs, the majority of them in the first 2 years of IBD diagnosis, which further supports our findings.[1] A striking characteristic is that IBD and SS were diagnosed concurrently in 28/95 [29.5%] cases. Thus, suspicion for IBD should be high when patients present [probably to non-gastroenterologists] with SS, especially if they complain of GI symptoms. Another clue is the very high percentage of colonic involvement of our CD patients[1,9,10,149] accompanied by a non-complicated [no internal penetrating disease and no strictures] phenotype: overall, more patients had non-stricturing, non-penetrating disease compared to other IBD cohorts describing EIMs.[9] This further suggests that SS, should it occur, is one of the earlier EIMs in the clinical course of IBD.

We saw an equal distribution of EIMs among CD and UC cohorts, except for PG. Although our study is too small to draw conclusions on EIMs other than SS, it is not consistent with other studies where CD is overall more associated with EIMs than UC, and where PG is more common in CD.[1,2,9] The patients in the AZA group had fewer EIMs [although not statistically significant] than non-AZA patients. SS occurrence in the non-AZA cohort is probably more closely linked to IBD as an EIM than a drug eruption, and IBD patients are more likely to develop other EIMs once they had a first EIM.[1,10] In contrast, SS in the AZA group may not predict a risk of other EIMs. This becomes important because we have seen that AZA and non-AZA groups clinically present in the same manner. Should a patient with IBD develop SS, it is important to consider AZA-induced disease as opposed to IBD-associated disease, especially if it occurred within 28 days of AZA initiation and with no other condition known to precipitate SS; otherwise, IBD activity and EIM history may assist in diagnosing the latter.

The occurrence of EIMs in relation to the activity of IBD is always a point of interest.[1,8,149] A recent review noted that SS probably parallels IBD activity,[150] and data from this systematic review strengthen that notion by three observations. First, most cases of SS occurred with underlying active IBD [76.8%], and this was higher, understandably, in the AZA cohort, as it was probably an added medication due to uncontrolled IBD. Second, multiple case reports described the SS occurrence as a heralding sign to new IBD diagnosis, as the patient was experiencing GI symptoms that later were diagnosed as a first IBD flare event.[76,97,102] There was a total of 29.5% of cases where IBD and SS diagnosis were only 3 months apart. Third, we see a significant rate of recurrence being related to either steroid tapering or recurrence of IBD flare. Further prospective, multicentre studies can help solidify this assumption of correlation between IBD activity and SS occurrence.

AZA-associated SS always presented with multiple lesions, most commonly on the trunk [$p = 0.005$], invariably had neutrophilia, and almost always presented as the classical subtype of SS on histopathology. This is in contrast with another review of AZA-associated SS where lower extremities were more commonly involved.[151] Patients in this cohort were not treated for SS with steroids as frequently as the non-ASA group; this may be due to more patients in this cohort being on steroids at SS onset for active IBD management, which aligns with other studies.[152] All four patients re-challenged with AZA developed SS recurrence, a phenomenon that supports drug-induced SS, particularly with AZA.[151] Still, an interesting finding in our data is that AZA itself could be used to treat SS in the non-AZA group, and was in fact increased in one case of AZA-associated SS with clearance of the eruptions and better control of IBD. Again, the ability to differentiate between IBD-related SS and AZA-associated SS perhaps plays the most important role in making the decision of stopping AZA or changing its dose. In the literature, AZA-associated SS is within the spectrum of AZA hypersensitivity reactions, whereby half could present without skin manifestations, the majority of which were neutrophilic dermatoses.[152] Since IBD is the most common disease state linked with AZA-associated SS,[152] this may suggest a particular tendency for AZA reactions to present as a neutrophilic dermatosis in the IBD host. Thiopurine methyltransferase [TPMT] has been assessed as a tool for differentiation of AZA-associated disease, and has not been deemed useful[152] because the AZA-associated hypersensitivity reactions are dose-independent and thus occur regardless of TPMT level.

The mechanisms underlying IBD-associated SS or AZA-associated SS are not fully known. SS is considered part of the spectrum of neutrophilic dermatoses which include PG, another condition that is associated with IBD.[153] Many immunological components suspected to play a role in SS are also involved in IBD pathogenesis.[153–157] However, AZA-associated SS may not be easily explained by these mechanisms. The variety of conditions that are associated with SS, such as IBD and medications such as AZA, have suggesting that SS is a hypersensitivity reaction to antigens from drugs, pathogens or host cells.[153] This would certainly fit well with reports describing AZA-associated SS as a spectrum of AZA hypersensitivity syndrome,[152] yet we do not have evidence showing immune-complexes, immunoglobulins or changes in complement to fully support this notion. Still, the fact that SS is treated with corticosteroids, with stopping the offending drug, or sometimes with treating underlying infections or malignancies with antibiotics or chemotherapy, adds to the theory of a hypersensitivity reaction. Our study also reinforces the idea that SS probably occurs with active IBD, as explained above, and that AZA-associated SS recurred consistently with AZA re-challenge, which fits with this theory. Some studies have involved photoinduction of SS and its association with pro-inflammatory signals that activate neutrophils in the skin, such as TNF-α and interleukin-8.[158,159] This could explain why limbs are more frequent locations for SS, but also could be interesting for future studies on the impact of these agents on SS occurrence in IBD cohorts with or without anti-TNF-α therapy.[160–163]

This study's strength lies in a clearly defined comprehensive search and case definition using precise selection and exclusion criteria, especially requiring appropriate histopathological findings for diagnosis. This may have led to reduced misclassification of cases. This review also included cases from many countries, which allowed us to explore several treatment strategies. However, our data are limited by reporting bias, owing to the articles being purely case reports or case series. For example, AZA-associated SS seems to occur without any other conditions associated with SS compared to non-AZA SS, which may be a reporting bias. We did attempt to address this issue by evaluating the quality of the case reports, and found that most reports had appropriate descriptions of case presentations, the relevant intervention and clinical response. Roughly half the cases had enough clinical information on the course of IBD itself beyond the medications the patients were on at the time of SS occurrence.

5. Conclusion

SS is an EIM that can occur in both CD and UC. Its occurrence can signal an IBD diagnosis early, with the majority of cases correlating with active yet non-advanced IBD. Evaluation for IBD is

thus recommended when SS ensues, especially with evidence of GI symptoms. Similarly, re-evaluation for disease activity in known IBD is warranted once SS occurs. In this largest and best-defined IBD-associated SS cohort to date, we found that patients with IBD who develop SS after recent exposure to AZA may behave differently than other IBD cohorts, and can rapidly respond to AZA de-escalation. Corticosteroids are the mainstay of SS treatment, but biological therapy can be equally effective for controlling SS and IBD, if both are active simultaneously. Diagnosing SS as secondary to IBD or AZA exposure is important, as the decision to continue or re-challenge AZA becomes highly relevant with high recurrence rates in the latter. We could not determine particular risk factors for need for treatment with biologics or for recurrence; larger studies are needed for such analysis to be significant.

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Conflict of Interest

F.R. is consultant to Agomab, Allergan, AbbVie, Boehringer Ingelheim, Celgene, Cowen, Falk Pharma, Genentech, Gilead, Gossamer, Guidepoint, Helmsley, Index Pharma, Jannsen, Koutif, Mestag, Metacrine, Morphic, Origo, Pfizer, Pliant, Prometheus, Receptos, RedX, Roche, Samsung, Takeda, Techlab, Theravance, Thetis, UCB and received funding from the National Institute of Health, Helmsley Charitable Trust, Crohn's and Colitis Foundation, Rainin Foundation, UCB, Boehringer-Ingelheim, Pliant, Morphic, BMS, 89Bio. B.H.C. is a consultant to Takeda, TARGET-RWE and serves on speakers bureau for Takeda. B.L.C. receives the following financial support: Advisory Boards and Consultant for Abbvie, Celgene-Bristol Myers Squibb, Pfizer, Sublimity Therapeutics, TARGET RWE; CME Companies: Cornerstones, Vindico; Speaking fees: Abbvie. A.F.P is a consultant to AbbVie, Novartis, Mallinckrodt and Alexion, serves on speaker bureau for AbbVie, Novartis and Mallinckrodt, and receives research funding from Corbus, Pfizer, AbbVie, Novartis and Mallinckrodt. J.S., A.A.H., K.F., M.S. and U.K. have no conflicts of interest to disclose.

Authors Contributions

All authors made substantial contributions to all of the following: [1] the conception and design of the study, or acquisition of data, or analysis and interpretation of data, [2] drafting the article or revising it critically for important intellectual content, [3] final approval of the version to be submitted. J.S., F.R., M.S. and A.A.H. contributed in the conception and design of the study, acquisition of data, analysis and interpretation of data, as well as drafting the article. B.C., K.F., B.C., U.K., A.F. and F.R. contributed in the conception and design of the study and interpretation of data, as well as revising the article critically for important intellectual content. The authors had no writing assistance while drafting the article. The manuscript, including related data, figures and tables has not been previously published and the manuscript is not under consideration elsewhere.

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Data Availability Statement

The data underlying this article are available in the article and in its online supplementary material.

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Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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