Sweet Syndrome Associated with Active Inflammatory Bowel Disease: A Case Series of a Rare Extra-intestinal Manifestation

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BACKGROUND

- Up to 20% of IBD patients have cutaneous extra-intestinal manifestations (cEIM).
- Sweet syndrome (SS) is a rare cEIM in IBD with limited case reports.
- We present the largest retrospective cohort on the occurrence and management of SS in IBD.

METHODS

- Patients age ≥ 18 years with diagnoses of IBD and SS were identified at a quaternary center from 1980 to March 2021 using ICD-10 codes.
- Subsequent manual chart review selected for all adult IBD patients with histopathology-proven SS as the gold-standard. Demographics, clinical IBD history, and SS-related clinical, laboratory, histopathological, treatment and outcome data were collected.
- Global IBD disease activity was inferred from the reported symptoms, laboratory, imaging, endoscopic and histologic data at the last pre-SS physician outpatient assessment.
- AZA-induced SS was defined as new AZA exposure within 4 weeks of SS occurrence.

CONCLUSIONS

- Contrary to previous case reports, SS was a cEIM of IBD that occurred later than 5 years after diagnosis in our cohort with occurrences paralleling global IBD disease activity.
- Although AZA-induced and IBD-associated SS were both effectively treated with corticosteroids, distinguishing them is relevant for future IBD treatment.
- Despite its low frequency, SS may indicate an unrecognized IBD flare and affect IBD therapy choices.
- Larger SS-enriched IBD cohorts needed to tease out unique clinical and histopathological patterns that could help clinicians differentiate SS/IBD subtypes, and optimize treatment approaches in IBD-SS co-occurrences.

RESULTS

Table 1: Patient demographics, clinical features, and management of sweet syndrome in inflammatorybowel disease cohort.

	Overall (N=25)		Crohn's Disease (N=16)		Ulcerative Colitis & IBD unclassified (N=9)	
FACTOR	**N**	**Statistics**	**N**	**Statistics**	**N**	**Statistics**
DEMOGRAPICS						
Female, n (%)	25	18 (72)	16	11 (69)	9	7 (78)
Age at Diagnosis SS, Median (IQR), yrs	24	47 (33-54)	16	48 (38-54)	8	43 (32-56)
Age at Diagnosis IBD, Median (IQR), yrs	25	37 (28-47)	16	40 (27-47)	9	35 (28-47)
Race: White, n (%)	25	25 (100)	16	16 (100)	9	9 (100)
IBD CLINCIAL FEATURES						
SS Occurrence in Terms of IBD, n (%)	25		16		9	
SS and IBD diagnosed at same presentation		1 (4)		1 (6)		0 (0)
>3 Months After IBD Dx		24 (96)		15 (94)		9 (100)
Global IBD Clinical Activity at SS Diagnosis, n (%)	18		13		5	
Active		15 (83)		10 (77)		5 (100)
Inactive		3 (17)		3 (23)		0 (0)
Prior IBD Surgeries, n (%)	25	14 (56)	16	11 (69)	9	3 (33)
History of Extraintestinal Manifestations, n (%)	25	15 (60)	16	8 (50)	9	7 (78)
Peripheral Arthropathy type 1		4 (16)		1 (6)		3 (33)
Peripheral Arthropathy type 2		5 (20)		3 (19)		2 (22)
Pyoderma Gangrenosum		2 (8)		1 (6)		1 (11)
Oral Aphthous Ulcers		2 (8)		0 (0)		2 (22)
Ocular (Uveitis/Iritis/Episcleritis)		3 (12)		1 (6)		2 (22)
Primary Sclerosing Cholangitis		2 (8)		2 (12)		0 (0)
Other		6 (24)		5 (31)		1(11)
SS CLINICAL FEATURES						
SS Rash Description, n (%)	24		16		8	
Maculopapular		15 (63)		11 (69)		4 (50)
Plaques		7 (29)		6 (37)		1 (12)
Pustules		8 (33)		6 (37)		2 (25)
Nodules		6 (25)		2 (12)		4 (50)
Pseudo-vesicles		4 (17)		4 (25)		0 (0)
Bullae		3 (13)		1 (6)		2 (25)
Location of SS Lesions, n (%)	24		16		8	
Upper Limbs		17 (70)		11 (69)		6 (75)
Lower Limbs		15 (63)		10 (62)		5 (62)
Torso and Back		12 (50)		9 (56)		3 (37)
Head and Neck		8 (33)		5 (31)		3 (37)
Dorsal Hands		3 (13)		2 (12)		1 (12)
Painful Lesion, n (%)	24	13 (54)	16	9 (56)	8	4 (50)
Pruritic Lesions, n (%)	24	8 (33)	16	6 (37)	8	2 (25)
SS HISTOPATHOLOGICAL FEATURES						
Time from SS Symptoms Onset to Biopsy, Median (IQR), days	24	16.5 (5.5-62.75)	16	10.5 (4-35)	8	30.5 (18-143)
Biopsy Findings, n (%)	24		15		8	
Neutrophilic Infiltrates		24 (100)		15 (100)		8 (100)
Lymphocytes		9 (38)		7 (47)		2 (25)
Eosinophils		4 (17)		2 (13)		2 (25)
Macrophages/Histiocytes		3 (13)		2 (13)		1 (12)
Type of SS on Histopathology, n (%)	24		15		9	
Classical		21 (87)		13 (87)		8 (89)
Bullous		3 (13)		2 (13)		1 (11)
SS LABORATORY FEATURES [1]						
Neutrophilia (ANC >6000), n (%)	18	12 (67)	10	6 (60)	8	6 (75)
Anemia (Hb <13 g/dL in M, <12 g/dL in F), n (%)	20	16 (80)	11	11 (100)	9	5 (55)
Abnormal Platelet (<150 OR >500 plt./μL), n (%)	19	5 (26)	11	3 (27)	8	2 (25)
ESR, Median (IQR), mm/hr	13	46 (26-81)	5	32 (29-46)	8	66 (24.5-86.7)
CRP, Median (IQR), mg/dL	10	5.6 (2.1-10.6)	3	1.9 (1-9.3)	7	8 (2.8-10.3)
ANA positive, n (%)	8	2 (25)	4	1 (25)	4	1 (25)
ANCA positive, n (%)	3	1 (33)	2	0 (0)	1	1 (100)
SS MANAGEMENT						
Hospitalized During SS Episode, n (%)	25	10 (40)	16	8 (50)	9	2 (22)
Steroid Use for Treatment of SS, n (%)	25	21 (84)	16	13 (81)	9	8 (89)
Oral Steroids	20	12 (60)	13	7 (54)	7	5 (71)
IV Steroids With Any Other Form	20	5 (25)	13	3 (23)	7	2 (29)
Topical Steroids	20	1 (5)	13	1 (8)	7	0 (0)
Oral and Topical Steroids	20	2 (10)	13	2 (15)		0 (0)
Duration of Steroid Treatment, Median (IQR), days	12	25 (16.5-39)	9	21 (15-38)	2	25 (25-104.5)
Other Non-Steroidal Therapies, n (%)	25		16		9	
Dapsone		3 (12)		0 (0)		3 (33)
NSAID		1 (4)		1 (6)		0 (0)
AZA (Concomitant IBD and SS Therapy)		2 (8)		0 (0)		2 (22)
Duration of SS Symptoms, median (IQR), days	19	45 (23.5-95)	13	27 (20-89)	6	79 (58-162.2)

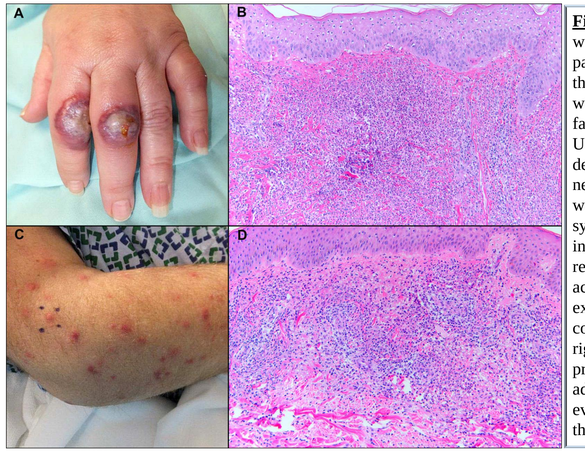

Figure 1: Examples for Sweet syndrome cases: (A) 54-year-old woman with Ulcerative colitis (UC) for 6 years developed painful, erythematous papules with bullous formation overlying the proximal interphalangeal joints of several fingers associated with edema of the involved digits. She had similar lesions on her face and arms, and this was associated with a flare of her UC. **(B)** A lesional biopsy from her left arm demonstrated a dense, dermal inflammatory infiltrate composed almost entirely of neutrophils with karyorrhectic debris (leukocytoplasia) and without evidence of vasculitis, consistent with Sweet syndrome. Additional stains were negative for the presence of infectious organisms. **(C)** 63-year-old man with Crohn's disease, relapsing polychondritis, and psoriatic arthritis hospitalized for active colitis developed erythematous papules on his trunk and extremities in association with fever within several days of a total colectomy and end ileostomy. **(D)** A lesional biopsy from his right shoulder revealed a dermal inflammatory infiltrate predominantly composed of neutrophils with karyorrhectic debris, admixed with lymphocytes and histiocytes. Vasculitis or evidence of infection was not identified with further studies, and the patient was diagnosed with Sweet syndrome.

- A total of 25 IBD patients with SS were identified including 3 patients which had AZA-induced SS.
- Majority of SS patients were female (72%).
- Sixteen patients had CD (64%), eight had UC (32%) and one had IBD unclassified (**Table 1**).
- Median age of diagnosis was 47 years (IQR 33-54 years); SS appeared at a median of 6.4 years after IBD diagnosis.
- IBD patients with SS had a high rate of complicated IBD phenotypes (75% extensive colitis in UC and 73% stricturing or penetrating disease in CD, with 100% colonic involvement).
- SS occurrence correlated with global IBD disease activity as 83% had active IBD at SS diagnosis.
- Most common SS associated symptoms: fevers (54%), arthralgia (50%), ocular symptoms (21%) and myalgias (13%) (**Figure 1**).
- Corticosteroids are an effective therapy for SS in IBD.
- Recurrence rate of SS was 36%.