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Risk of malignancy in histiocytoid Sweet syndrome: A systematic review and reappraisal

To the Editor: Histiocytoid Sweet syndrome (HSS) is a distinct variant of Sweet syndrome (SS) where a predominance of histiocytoid mononuclear immature myeloid cells in the infiltrate is seen on histology, as opposed to the classical neutrophilic infiltrate of SS (NSS).[1,2] Compared with NSS, distinctive demographic, clinical and prognostic features have been suggested in HSS, and a higher risk of association with hematologic malignancies have been proposed by some authors[3] and refuted by others.[4] Our goal is to determine whether HSS is more frequently associated with malignancies than NSS.

Table I. Associated diseases and medications in patients with histiocytoid Sweet syndrome

Disease/medication	No. (%) (N = 218)
Idiopathic	108 (49.5)
Inflammatory disorders	9 (4.1)
Crohn's disease	3 (1.3)
Relapsing polychondritis	1 (0.4)
Uveitis	1 (0.4)
Rheumatoid arthritis	2 (0.9)
Familial Mediterranean fever	1 (0.4)
Polyarteritis nodosa	1 (0.4)
Upper respiratory tract infections	6 (2.7)
Drugs	7 (3.2)
Bortezomib	3 (1.3)
Trimethoprim/sulfamethoxazole	1 (0.4)
Azacitidine	1 (0.4)
Piperacillin tazobactam	2 (0.9)
Postvaccination	1 (0.4)
Malignancies	87 (40)
Myelodysplastic syndrome	40 (18)
Hematologic malignancies	37 (17)
Lymphoma	4 (1.8)
Lung cancer	1 (0.4)
Renal cancer	1 (0.4)
Bladder cancer	1 (0.4)
Endometrial cancer	1 (0.4)
Breast cancer	2 (0.9)

A systematic literature review was performed in PubMed/MEDLINE, Embase, and Cochrane Collaboration databases, searching for all articles on HSS with no limits on publication date, participant age, sex, or nationality. Papers published in English or French were included in this study. Supplemental Table I (available via Mendeley at https://doi.org/10.17632/tcmmmpwv6m.1) shows the stepwise approach for study selection.

Included were 43 articles: 31 case reports, 8 case series, and 4 retrospective studies (Supplemental Material 2). There were 218 patients total, with a mean age at presentation of 52 years (range, 0.4-93 years). The female predominance seen in NSS (female-to-male ratio, 4:1)[2] does not appear to apply to HSS (1.11:1). Extracutaneous involvement in HSS is extremely rare. All cases of HSS were confirmed by histology. Compared with NSS,[2,4] 11 patients (5%) had only subcutis involvement, which emphasizes the importance of a specimen from a deep skin biopsy for the diagnosis of HSS. Table I summarizes all reported associated conditions with HSS.

Approximately 40% of patients newly diagnosed with HSS were subsequently diagnosed or already diagnosed with a hematologic or solid cancer vs 21% in NSS.[2,5] HSS was more commonly associated with

Table II. Distinctive features between histiocytoid Sweet syndrome (*HSS*) associated and not associated with malignancy

Variable*	HSS associated with malignancy	HSS not associated with malignancy	*P* value†
Patients, No.	87	131	
Age at onset, median y	58	48	.00001
Prior urticaria	0 (0)	6 (4.58)	.10
Recurrence‡	11 (12.64)	1 (0.76)	.0001
Fever	69 (79.31)	27 (20.61)	<.00001
Musculoskeletal involvement	69 (79.31)	68 (51.90)	.00004
Ocular involvement	5 (5.70)	3 (2.29)	.18
Neutrophilia	1 (1.14)	2 (1.52)	.81
Increased C-reactive protein	0 (0)	3 (2.29)	.35
Increased ESR	1 (1.14)	3 (2.29)	.53
Anemia	2 (2.29)	1 (0.76)	.34
Thrombocytopenia	0 (0)	1 (0.76)	.77

ESR, Erythrocyte sedimentation rate.
*Data are presented as the number (%) unless indicated otherwise.
†The *P* value is considered significant if <.05.
‡Recurrence of HSS is defined by the original authors as the clinical reoccurrence of HSS after remission.

myelodysplastic syndrome (46% vs 2.5% in NSS) and hematologic malignancies (42.5% vs 25% in NSS), and unlike NSS, could be associated with lymphoid malignancies. Sixty percent of the malignancies were discovered before and 40% occurred after HSS onset.

As mentioned in Table II, patients with HSS associated with malignancy had an older age of onset and a higher risk of systemic symptoms than those with HSS not associated with malignancy. Tender erythematous plaques/nodules were the most frequent clinical presentation in both malignancy- and nonmalignancy-associated HSS, in contrast to the bullous/ulcerative forms more commonly observed in NSS associated with malignancy. Thrombocytopenia was not associated with higher risk of malignancy-associated HSS, as was reported with NSS.[2] The development of HSS does not appear to have prognostic implications in patients with an associated hematologic malignancy, as does leukemia cutis.[4] Screening for malignancy should begin with age-appropriate cancer screening guidelines and be based on the most commonly associated malignancies. Continued complete blood count monitoring is, however, needed because, as mentioned before, HSS may precede the diagnosis of malignancy.

In conclusion, HSS is related to a higher risk of underlying malignancy, particularly of the hematologic type. Future molecular techniques will possibly be helpful in truly defining those patients with HSS who are at genuine risk for the development of hematologic and visceral malignancies.

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Primary imputation methods impact efficacy results in hidradenitis suppurativa clinical trials

To the Editor: Missing data is a common issue in clinical trials. Analytic management of missing data involves including participants who drop out of a study in an intention-to-treat (ITT) analysis.[1] Analyzing only participants who complete a trial (per protocol [PP]) can eliminate missing data but at the expense of statistical power and external validity.[1] If the participant and disease-associated characteristics of those who completed the trial are representative of the ITT population, then PP can be valid. This is particularly important in placebo-controlled trials, where using PP may decrease the ability to detect a difference between groups (because only participants receiving placebo with a positive response tend to stay in the trial).[1]

In ITT, management of missing data involves primary imputation of missing values (Table I).[1] Multiple imputation involves complex statistical modeling and is beyond the scope of this discussion; the reader is directed to the statistical literature (Supplemental Materials; available via Mendeley at https://doi.org/10.17632/h8734gr7bc.1).[1] Primary imputation involves allocating participants a response based on the reasons/assumptions for missing data. Data can be classified as *missing not at random* (due to treatment-related factors, eg, lack of efficacy), *missing at random* (due to other documented factors such as age/sex that can be taken into account in multiple imputation), or *missing completely at random* (due to other undocumented variables not related to disease/treatment).[1] A sensitivity analysis (comparison of multiple primary imputation methods) is required to determine the effect of different analyses on the outcome(s) of interest.[1] This is especially pertinent given that clinical trial populations are not directly reflective of the general population.[1]

In the setting of hidradenitis suppurativa (HS), the high burden of disease and moderate therapeutic response rates may contribute to the high clinical trial dropout rates. The statistical methods used in these trials (Table II) vary, making comparisons complex. The PIONEER 1 and 2 studies were the only studies to conduct a sensitivity analysis,[2] conservatively presenting results of nonresponder imputation analysis. In contrast, the PIONEER Open Label Extension study[3] presented only PP data from a subset of participants, with last observation carried forward (LOCF) beyond week 96. This raises concerns regarding data validity, given that LOCF inflates response rates in long-term studies and is not recommended.[1] The use of ITT/nonresponder imputation in a randomized controlled trial of anakinra[4] in HS resulted in a loss of statistical significance. No dropout was seen in a phase 2a trial of IFX-1,[5] with differential attrition seen between arms of a phase 2 trial of bermekimab.[6] This may explain the apparent contradictory findings of an increased response rate in participants for whom anti−tumor necrosis factor (TNF) therapy failed (63%) when compared with anti-TNF−naive participants[6] (61%). Given that all participants who dropped out in the anti-TNF−failed arm achieved hidradenitis suppurativa clinical response, this may erroneously conflate the true efficacy of the drug in this population. In a cohort study of secukinumab,[7] 71% of the participants who dropped out did not achieve HiSCR, suggesting that LOCF presents a more conservative estimate of response compared with PP analysis, although the characteristics of the participants who

Table I. Definitions of primary imputation terms

Primary imputation term	Description
Missing equals success (MES)	Individuals with missing data are presumed to have achieved the endpoint of interest
Missing equals failure (MEF)	Individuals with missing data are presumed to have not achieved the endpoint of interest (equivalent to NRI)
Nonresponder imputation (NRI)	Individuals with missing data are presumed to have not achieved the endpoint of interest (equivalent to MEF)
Last observation carried forward (LOCF)	Individuals with missing data are presumed to have maintained the last observation, extrapolated forward to all future timepoints including endpoints of interest