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THERAPY IN PRACTICE

Morbilliform Eruptions: Differentiating Low-Risk Drug Eruptions, Severe Cutaneous Adverse Reactions, Viral Eruptions, and Acute Graft-Versus-Host Disease

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Abstract

Morbilliform eruptions, which are a clinical reaction pattern characterized by erythematous macules and papules coalescing into patches that cover most of the skin surface, are one of the most common cutaneous findings in the inpatient setting. In the hospital setting, most causes are benign and due to low-risk drug exanthems; however, morbilliform eruptions may also be a sign of high-risk diseases, including Stevens–Johnson syndrome/toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome, acute generalized exanthematous pustulosis, and graft-versus-host disease. Proper identification of the etiology and risk stratification of a morbilliform eruption is critical to ensure proper management and optimize patient outcomes. In this review, we discuss the key features that differentiate high-risk from low-risk morbilliform eruptions, as well as specific characteristics that differentiate the different high-risk eruptions. Additionally, we offer a clinical algorithm that may be applied in the management of a patient who presents with a morbilliform rash.

1 Introduction

Morbilliform eruptions are a clinical reaction pattern characterized by erythematous macules and papules that coalesce into patches and progress, typically centrifugally, generalizing over most of the skin surface. This pattern is the most common cutaneous morphology identified by dermatologists in the hospital setting [1, 2]. While most presentations are consistent with benign low-risk

Key Points

Low-risk drug exanthems are the most common causes of morbilliform eruptions in the hospital setting.

Early diagnosis of high-risk patterns, including Stevens–Johnson syndrome/toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome, acute generalized exanthematous pustulosis, and graft-versus-host disease is critical.

Features of high-risk morbilliform eruptions include facial involvement, acral involvement, mucosal involvement, and morphologic features including subtle duskiness, pustules, or vesicles/bullae.

Proper risk stratification of high-risk and low-risk morbilliform eruptions is necessary to determine the need for hospitalization and additional laboratory or skin biopsy testing.

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drug exanthems, the reaction pattern may also herald deadly diseases, including Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome (DRESS/DiHS), acute generalized exanthematous pustulosis (AGEP), and graft-versus-host disease (GVHD) [3].

Due to extensive clinical and histologic overlap, identifying the etiology of a morbilliform eruption is challenging. Early, accurate diagnosis and management are essential to reduce morbidity and mortality and differentiate patients who require admission or persistent hospitalization. Patients with severe cutaneous adverse reactions (SCARs) and GVHD must be differentiated early to risk stratify need for hospitalization and treatment. Drug eruptions in this setting are specifically associated with increased length-of-stay and deteriorated patient self-image, diet, mental health, and trust in the healthcare system [4, 5]. Costs from inappropriate diagnoses in this setting lead to inadequate treatment regimens and significantly increased healthcare costs [6].

In this review, we aim to risk stratify early morbilliform eruptions into "high-risk" morbilliform eruptions (including SCARs and GVHD) and "low-risk" eruptions (most often drug exanthems). In doing so, we offer a framework for early differentiation of etiologies of the morbilliform rash.

1.1 Epidemiology of Morbilliform Eruptions

The epidemiology of low-risk morbilliform eruptions, AGEP, and DRESS syndrome has not been well-characterized due to the lack of a single International Classification of Diseases (ICD) diagnostic code to track prevalence and mortality in large populations. An older single-center prospective cohort study of hospitalized patients identified 35 cases of drug reactions; more than half were morbilliform eruptions [7]. One single-center retrospective review of patients hospitalized for AGEP in Singapore identified 43 probable or definite cases over a 10-year period [8]. In all cases, the suspected culprit drug was promptly discontinued, and there was no attributable mortality to AGEP [8]. A single-center retrospective review of patients hospitalized for DRESS syndrome in Morocco identified 62 cases of possible, probable, or certain DRESS over a 14-year period [9]. In all cases, the suspected culprit drug was promptly discontinued; three deaths were recorded [9].

There are more robust data on SJS/TEN given its specific ICD codes. One study examining incidence and trends of SJS/TEN hospitalizations in the USA identified 51,040 (0.1%) hospitalizations for SJS, TEN, or SJS/TEN overlap syndrome over 10 years, with mortality rates of 5.4%, 14.4%, and 15.3%, respectively [10]. They further found that older age, chronic kidney disease, pneumonia, sepsis, and malignant neoplasms were associated with increased odds of mortality, and non-Hispanic white race was associated with decreased odds of mortality [10].

2 Differentiating Morbilliform Eruptions

The morbilliform reaction pattern is the most common cutaneous morphology seen in the hospital setting, encompassing 50–95% of all drug reaction types [1, 2, 7, 11, 12]. Although the majority of drug eruptions are self-limited and lack significant morbidity if the causative drug is withdrawn, a subset of cutaneous reactions can be severe and life-threatening [13]. These SCARs include AGEP, DRESS/DiHS, and SJS/TEN. While most morbilliform reactions are determined to be drug-eruption-related, it is extremely challenging to differentiate diseases such as acute graft-versus-host disease (aGVHD). For the purposes of this review, we will only consider it in the setting of patients undergoing blood or bone marrow transplantation and rarely after solid organ transplant. In the setting of the bone marrow transplant unit, it is critical to include this diagnosis, given its extremely high risk for mortality.

The risk of developing a morbilliform eruption is related to both patient and exogenous factors. Individuals at a higher risk for developing a morbilliform drug eruption include those with (1) an increased number of medical comorbidities, (2) multiple medications initiated during a hospitalization, and (3) exposure to chemotherapy [14]. Specific human leukocyte antigen (HLA) alleles have also been associated with increased risk for SCARs [15–18]. With regard to medication factors, there are several classes associated with higher rates of hypersensitivity, including antimicrobials (trimethoprim-sulfamethoxazole, penicillins, and fluoroquinolones), antiepileptics (lamotrigine, carbamazepine, phenobarbital, and phenytoin), antiretrovirals, and allopurinol [19–22].

Unlike many inflammatory dermatoses and morphologic classifications, the skin biopsy tends to have limited value in morbilliform eruptions, particularly when the clinical differential diagnosis includes a drug eruption, GVHD, and/or a viral exanthem, all of which are characterized by vacuolar interface change, dyskeratosis, and dermal infiltrate that may include eosinophils. Some studies have suggested that some histologic differences exist between morbilliform drug eruptions and other morbilliform eruptions [23, 24]. The differentiation depends on the degree of changes such as greater lymphocyte exocytosis and dermal infiltrate (which are more highly associated with drug eruptions than viral exanthems) rather than the complete presence or absence of these findings [23, 24]. These findings are difficult to categorize, and

a blinded study of two expert dermatopathologists found that skin biopsies only had a 62.9% sensitivity and 41.1% specificity for drug-induced exanthems, and no statistically significant association with specific histopathologic findings [25]. This study concluded that biopsy was only beneficial in patients with AGEP, where pustules were consistently detected between the two dermatopathologists.

While unlikely to differentiate the early diagnosis among entities characterized by vacuolar interface change, a skin biopsy can be helpful to exclude mimickers of morbilliform eruptions, such as nutritional-deficiency-associated eruptions, cutaneous T-cell lymphoma, eczematous dermatitis, and erythrodermic psoriasis. It will differentiate late stages of SJS/TEN and aGVHD both by having full-thickness epidermal necrosis and interface dermatitis. Similarly, a direct immunofluorescence test can be used to differentiate SJS/TEN from Linear IgA bullous dermatosis, both of which could occur in a patient treated with multiple antibiotics. As in all conditions, histopathology should be interpreted in tandem with appropriate clinical context, with special attention to morphology to support the diagnosis.

3 Differentiating High-Risk from Low-Risk Morbilliform Eruptions

Differentiating high-risk from low-risk morbilliform eruptions is the crucial first step in evaluation (Table 1). High-risk presentations include those indicative of early SCARs, viral eruptions, and aGVHD, which are important to differentiate, as they have confirmatory diagnostic tests and/or significant prognostic and treatment implications. Morphologic features that should increase the level of suspicion for a high-risk reaction pattern include the presence of pustules, duskiness, and vesicles or blisters. Location features that suggest high-risk drug eruptions include facial involvement, mucosal involvement, and palmar and/or plantar involvement. These features should guide the next diagnostic steps, including differential diagnosis, laboratory assessments, consideration for a skin biopsy, validated diagnostic algorithms, drug causality assessments, and follow-up (Fig. 1).

The majority of cutaneous exanthems are low-risk morbilliform reactions. The typical rash of a morbilliform drug eruption usually appears between 2 and 21 days after initiation of the culprit drug and may be accompanied by mild pruritus and a low-grade fever; symptoms are usually self-limited [26]. In the absence of high-risk features, additional workup is not necessary. However, care should be taken to identify and consider discontinuation of the most likely culprit drug(s) [26]. Diagnosis and drug causality are challenging in this setting; however, given the number of variables impacting patient hospitalization, knowledge of clinical trial data to determine overall medication-associated drug eruption rates is critical [21]. However, in this setting, it is not unreasonable to continue the putative drug if necessary. Typically, patients will be completely clear of this type of eruption in 2 weeks, and rechallenge can be considered if needed.

After identifying features indicating a high-risk subtype, including facial, palmoplantar, and oral/genital involvement, and minor morphologies including pustules, vesicles, blisters, and/or duskiness, the next step is to differentiate the SCARs while also considering viral eruptions and GVHD. The morphology of the rash itself is of significant importance, but additional clinical clues, including patient demographics, timing, and laboratory values, can all be informative. While laboratory and biopsy results should have no impact on the differentiation of high- versus low-risk eruptions, at this stage, these tests are used to confirm the subtype of high-risk eruption.

4 Differentiating the High-Risk Morbilliform Drug Eruptions

In this section, we discuss the clinical features that lead to the final diagnosis of high-risk eruptions; salient findings are summarized in Table 2.

Table 1 Features of high-risk versus low-risk morbilliform eruptions

	High-risk	Low-risk
Locations	Face and trunk	Trunk predominant
	Palmar/plantar	Sparing palmar/plantar skin
	Mucosa/genitals	Sparing mucosa/genitals
Minor morphologic features	Duskiness or purpura	Single-tone erythema
	Vesicles/bullae	No vesicles/bullae
	Pustules	No pustules
	Edema of the face, ear, and hand; “oblique earlobe crease”	No edema of the face, ear, or hand

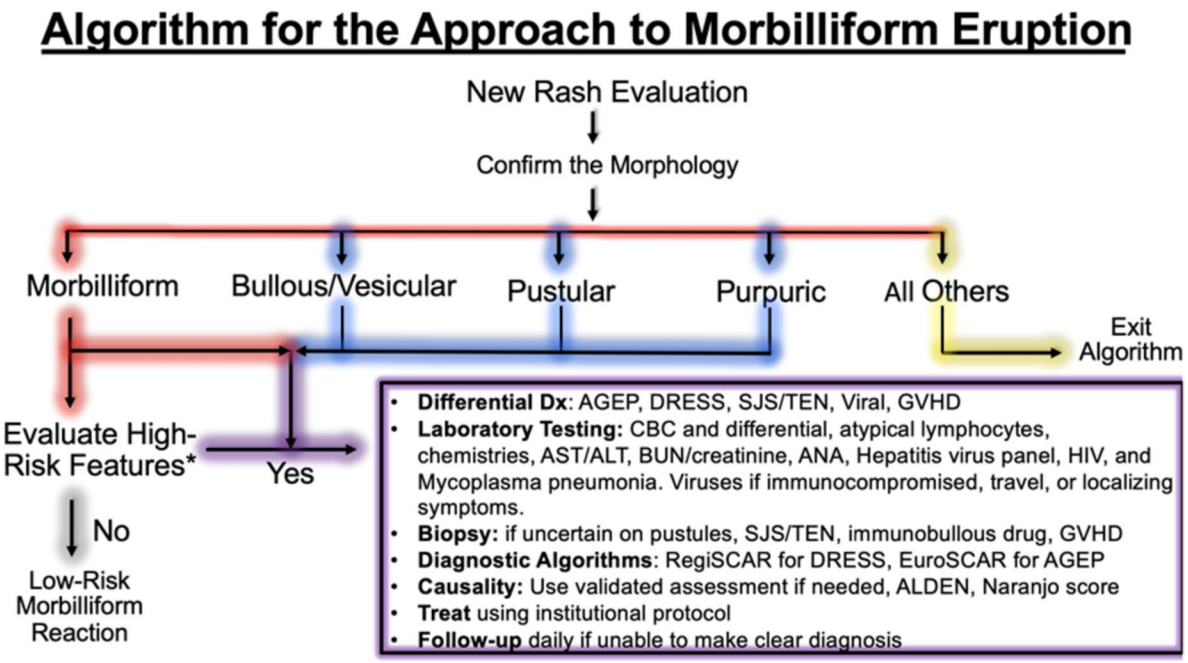

Fig. 1 Algorithm for the approach to the morbilliform eruption. Proposed clinical algorithm for the approach to the patient with a morbilliform eruption. *AGEP* acute generalized exanthematous pustulosis, *DRESS/DiHS* drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity reaction, *Dx* diagnosis, *SJS/TEN* Stevens–Johnson syndrome/toxic epidermal necrolysis, *GVHD* graft-versus-host disease, *CBC* complete blood count, *AST/ALT* aspartate transaminase/alanine transaminase, *BUN* blood urea nitrogen, *ANA* anti-nuclear antibody, *HIV* human immunodeficiency virus, *RegiSCAR* Registry of Severe Cutaneous Adverse Reactions, *EuroSCAR* European Registry of Severe Cutaneous Adverse Reactions, *ALDEN* algorithm of drug causality for epidermal necrolysis

4.1 AGEP

In the early stages of evolution, AGEP is distinguished from other morbilliform eruptions by the development of erythematous pustules that may be confused with pinpoint papules or vesicles, overlying erythematous patches. Palmar or plantar involvement is rare. Typically patients will present with high-risk involvement including the face, but pustules will first be found in the intertriginous sites including the neck, axilla, and inframammary folds (Fig. 2). Close examination within affected areas is often required to identify this hallmark feature that often appears early in the disease course. Violaceous hyperpigmentation may also be seen in more pigmented skin tones [1, 27]. Finally, as this condition resolves, collarettes of scale and extensive superficial exfoliation can be appreciated in areas where pustules were previously present.

Clinically, patients tend to present sooner after drug initiation compared with other SCARs, often within 48 h of drug initiation with constitutional symptoms, including fevers and malaise [28, 29], but generally lack features—such as mucosal involvement—which may be seen in other complex eruptions. Demographic factors can also be considered, as prior work has demonstrated that individuals who are obese and those with a history of previous drug allergy are at an elevated risk for the development of AGEP compared with other SCARs [17]. Antibiotics are the most common cause of AGEP, reflecting that this condition often develops in patients who are being treated for bacterial infections [30]. Finally, with regard to laboratory parameters, leukocytosis with neutrophilia is commonly present (often in greater than 80% of affected individuals), with concurrent eosinophilia being less commonly seen [29, 31].

For diagnostic confirmation, the European Registry of Severe Cutaneous Adverse Reactions (EuroSCAR) diagnostic criteria can be used to determine the likelihood of an AGEP diagnosis [32]. This scoring system considers morphology, clinical course, and histology, with the presence of typical pustules and erythema, fever, neutrophilia, and typical histologic findings earning greater point values [32]. This system has been shown to perform well in the differentiation of AGEP from other SCARs and low-risk drug eruptions, yet has redundancies; moreover, one model with optimized performance only relies on a morbilliform eruption with: (1) pustules, (2) acute onset, (3) lack of mucosal involvement, and (4) obesity [33, 34]. There are currently no criteria to determine drug causality specifically in AGEP. However, the lymphocyte transformation test (LTT) is an in vitro assay that can be used to identify the likely causative drug in T-cell-mediated hypersensitivity reactions more

Table 2 Differentiating high-risk eruptions

	AGEP	DRESS/DiHS	SJS/TEN
Morphology	Papules coalescing into erythematous plaques and small, non-follicular pustules progressing into a diffuse, generalized erythema with overlying pustules; intertriginous accentuation	Diffuse morbilliform eruption and facial edema and positive for oblique earlobe crease; skin lesions that are polymorphic and can be erythrodermic, eczematous, vesiculobullous, pustular, etc.	Duskiness transitioning into bullous lesions, larger bullae, and epidermal detachment; areas of denudation and sloughing; mucosal and ocular involvement common; positive Asboe–Hansen sign; positive Nikolsky sign
Timing	Usually within 2 days Can be > 2 days for beta-lactam antibiotics, hydroxychloroquine, proton-pump inhibitors, and terbinafine	Usually within 2–8 weeks Can be < 2 weeks for beta-lactam antibiotics, and radiocontrast	5–21 days
Common laboratory findings	Leukocytosis with neutrophilia	Peripheral eosinophilia, atypical lymphocytes, cytopenias, elevated transaminases, and elevated creatinine	Anemia and leukopenia
Diagnostic criteria	EuroSCAR	Bocquet et al., RegiSCAR Japanese Consensus Group, and Sontheimer and Houpt	None
Drug causality criteria	None	None	Algorithm of drug causality for epidermal necrolysis (ALDEN) [27]
Prognosis criteria	None	DRESS/DiHS Severity Score (DDS) [66]	SCORTEN [72], ABCD-10 [75], and CRISTEN [76]
Other considerations	More common in patients who are obese (versus those who have DRESS/DiHS)	Can see cytopenias in older patients	Leukopenia is associated with poorer outcomes

RegiSCAR Registry of Severe Cutaneous Adverse Reactions, *EuroSCAR* European Registry of Severe Cutaneous Adverse Reactions, *SCORTEN* Severity-of-Illness Score for toxic epidermal necrolysis, *ABCD-10* age, bicarbonate, cancer, dialysis, 10% body surface area risk model, *CRISTEN* clinical risk score for toxic epidermal necrolysis

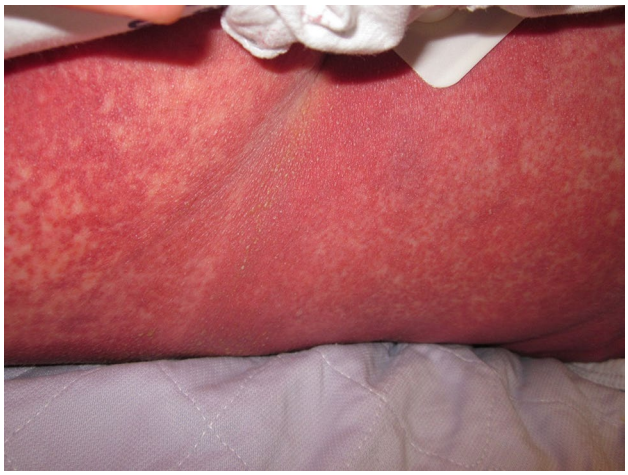

Fig. 2 Characteristic pustules of AGEP in intertriginous areas. Erythematous pustules in the inframammary fold or other intertriginous sites are characteristic of acute generalized exanthematous pustulosis (AGEP)

generally [35]. Specific, modified LTT assays that do not require the use of radiolabeled thymidine have been developed to identify the causative drug in AGEP and DRESS [36]. These tests can be considered if the causative drug is not clear from the history alone.

Of note, there are exceptions to the classic presentation of AGEP. Localized skin involvement (often with isolated involvement of the head and neck) has been described; the term "acute localized exanthematous pustulosis" ("ALEP") has been suggested to characterize these patients [37–39]. Additionally, while AGEP usually develops within 2–3 days of drug initiation, some drugs are more commonly associated with a delayed presentation, including beta-lactam antibiotics, hydroxychloroquine, proton-pump inhibitors, and terbinafine [29]. Overlap syndromes are well-described, including patients with AGEP mimicking SJS/TEN and DRESS/DiHS [40, 41].

4.2 DRESS/DiHS

DRESS/DiHS characteristically presents with a diffuse morbilliform eruption, with associated facial and ear edema. While edema in this location can be difficult to appreciate, the presence of an oblique earlobe crease shows sensitivity and specificity in differentiating DRESS/DiHS syndrome from other SCARs and low risk reactions [42] (Fig. 3). Additionally, patients with DRESS/DiHS often present with fever, malaise, and cervical lymphadenopathy, though this may be a late finding [43, 44]. Finally, lower extremity purpura is more common in patients with severe disease and may be indicative of a poorer prognosis [45].

In contrast with AGEP and SJS/TEN, DRESS/DiHS characteristically has the most delayed onset, with a mean latency period of 23.5 days and a range of 2–8 weeks [43, 44, 46]. Anticonvulsants and allopurinol appear to have longer latency periods compared with other drugs that induce DRESS/DiHS and may present 10–12 weeks following initiation [47, 48]. However, a more rapid onset of symptoms does not exclude this diagnosis, as some medication classes, including beta-lactam antibiotics and radiocontrast, may result in clinical symptoms sooner than 14 days, which also may occur in the case of medication re-exposure [49, 50]. Also of note, patients with DRESS/DiHS often show unexplained cross-reactivity to multiple drugs with different chemical structures, including those used after onset [51]. As a result, patients with DRESS/DiHS should be advised to avoid use of not only the causative drug but also other cross-sensitized drugs.

Systemic involvement is frequently observed in patients with DRESS/DiHS, with hepatic involvement being the most common [43]. While renal injury is described, care should be taken to prevent misattribution, as vancomycin and allopurinol are more likely associated with direct nephrotoxicity rather than DRESS/DiHS syndrome [48, 52]. Peripheral eosinophilia is a common laboratory abnormality seen in the majority of DRESS/DiHS patients, with incidence ranging from approximately 50% to greater than 90% of cases across international cohorts [53, 54]. Atypical lymphocytes are also a classic feature, though they are variably present. Furthermore, whether leukopenia or leukocytosis is present often depends on the timing of the blood examination. Leukopenia is often observed earlier and leukocytosis later in the disease course of DRESS/DiHS. In older patients with DRESS/DiHS, cytopenias are more common. Additionally, patients with cytopenias were found to have a higher likelihood of rehospitalization, longer hospitalization, and mortality. Therefore, close observation of hematologic labs may be indicated in older patients to monitor for adverse clinical outcomes [55]. Less commonly, pulmonary or cardiac involvement can be seen [43].

Multiple diagnostic criteria, including those set forth by Bocquet et al., the Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) study group, the Japanese Consensus Group, and Sontheimer and Houpt, can be utilized to determine the likelihood of a diagnosis of DRESS/DiHS [56–60] (Table 3). No criteria have proven superior, although there is widespread agreement that one of these systems ought to be used to confirm DRESS/DiHS diagnosis. Of note, some criteria utilize human herpes virus reactivation 2–4 weeks after rash onset to assist with the diagnosis of DRESS/DiHS syndrome [58, 61]. However, US data suggest that reactivation is uncommon at the time of diagnosis and should not be used for early diagnosis [62–64]. Currently, no criteria exist to elucidate drug causality, although a systematic approach to drug notoriety in DRESS/DiHS has been published [65]. As described above, LTT can also be considered to test for a

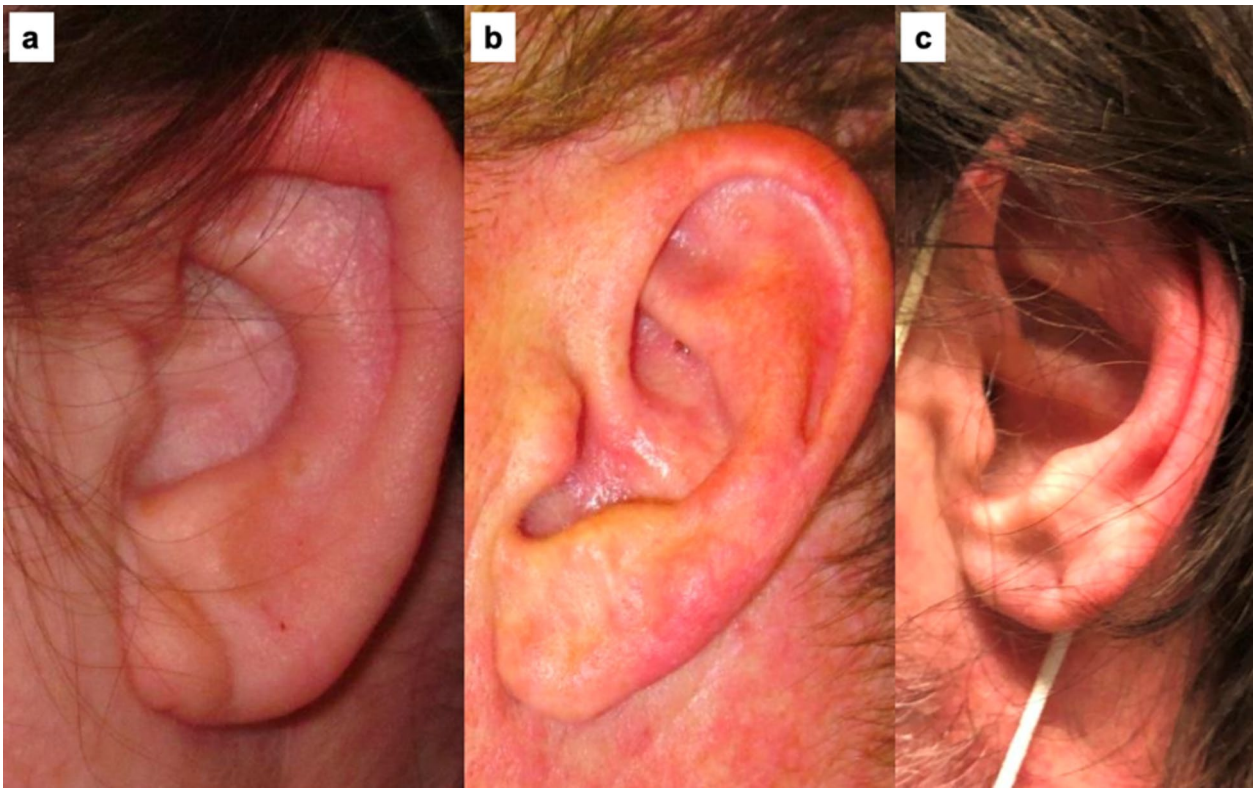

Fig. 3 Oblique earlobe crease sign. The oblique earlobe crease sign is seen in drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome (DRESS/DiHS) syndrome (A) but not in other morbilliform eruptions such as Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN; B) or low-risk morbilliform eruptions (C)

suspected causative drug [35, 36]. The DRESS-DiHS severity score (DDS) is a validated tool that can be used to assess the severity of DRESS/DiHS, predict clinical prognosis, and stratify by risk for complications [66, 67].

4.3 SJS/TEN

Locations of involvement, color, and symptoms tend to be the earliest distinguishing signs to differentiate SJS/TEN from other high-risk eruptions. The morbilliform eruption of SJS/TEN is often associated with skin pain even prior to blistering. Further, the initial erythema becomes dusky and ultimately transitions to vesiculobullous lesions; atypical targetoid lesions characterized by two or more zones of color often develop. Involvement tends to be more likely to affect the palms and, later, the soles of the feet compared with other SCARs. While facial involvement occurs as with all SCARs, genital and mucosal skin involvement is also far more likely in SJS/TEN. Early in the course of evolution, this presents as ocular, oral, and/or genital erythema and edema with associated pain and photophobia. As the disease progresses, frank desquamative mucositis with erosions is observed, and ocular pseudomembranes may develop. In later phases, larger bullae and epidermal detachment can occur, with areas of denudation and sloughing. A positive Asboe–Hansen sign, defined as the extension of a blister to adjacent unblistered skin upon application of pressure, is frequently present in later stages [68]. Associated dysfunction may persist even after the acute phase of disease has resolved, with more than 50% of patients developing long-term oral and ocular complications [69, 70].

The timeline for SJS/TEN characteristically falls in between the more rapid development of AGEP and the delayed onset of DRESS/DiHS, with a reported median duration of 12 days from exposure to onset in one large US cohort (range 5–21 days) [71]. In contrast to DRESS/DiHS, eosinophilia is relatively uncommon in SJS/TEN [72]. Instead, anemia and leukopenia are more frequently observed. Leukopenia is more commonly seen in SJS/TEN patients with greater body surface area involvement, underlying malignancy, and connective tissue disease; it is also associated with an increased risk of bacteremia, pneumonia, and prolonged length of stay [70].

There are currently no formal diagnostic criteria that can be utilized to determine the likelihood of SJS/TEN; however, highly suggestive features include a morbilliform eruption with mucosal involvement, blisters, and palm/sole involvement [73]. It is ideal to make the diagnosis before seeing blisters, as

Table 3 Comparison of different diagnostic criteria for DRESS/DiHS

Diagnostic criteria	Bocquet et al. [56]	RegiSCAR [54]	J-SCAR [58]
Skin findings and vitals	(1) Skin eruption	(1) Skin rash > 50% BSA involvement; suggestive of DRESS/DiHS (2) Rash resolution ≥ 15 days (3) Fever ≥ 38.5 °C	(1) Maculopapular rash developing > 3 weeks after starting therapy (2) Fever ≥ 38 °C
Laboratory abnormalities	(2) Blood eosinophilia (≥ 1.5 × 10^3/uL) OR presence of atypical lymphocytes	(4) Eosinophilia ≥ 0.7 × 10^9/L or ≥ 10% if WBC < 4 × 10^9/L (5) Atypical lymphocytosis	(3) Leukocytosis (≥ 10,000/mm^3) OR atypical lymphocytosis OR eosinophilia
Systemic involvement	(3) Adenopathy > 2 cm OR hepatitis OR interstitial nephritis OR interstitial pneumonia OR carditis	(6) Enlarged lymph nodes (7) Organ involvement	(4) Lymphadenopathy (5) Liver abnormalities
Other	N/A	(8) Skin biopsy suggesting DRESS/DiHS (9) Exclusion of other causes	(6) HHV-6 reactivation
Scoring	All three criteria need to be met to diagnose DRESS/DiHS.	Assignation of 1 point based on the presence of lymphadenopathy, eosinophilia, atypical lymphocytosis, skin rash > 50% of BSA, rash suggestive of DRESS/DiHS, organ involvement (1 for each organ; maximum of 2) and exclusion of other causes. Subtraction of 1 point based on the absence of fever, skin biopsy suggestive of DRESS/DiHS, or rash resolution being 15 days or greater. Definite if > 5, probable if 4–5, possible if 2–3, and not DRESS/DiHS if < 2.	Of 6 criteria, 5 need to be met to diagnose DRESS/DiHS.

BSA body surface area, *DRESS/DiHS* drug eruption with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome, *HHV-6* human herpesvirus 6, *RegiSCAR* Registry of Severe Cutaneous Adverse Reactions, *J-SCAR* Japanese Registry of Severe Cutaneous Drug Reactions

the disease is most treatable at that stage, and thus the presence of multiple hues of pigmentation (duskiness) while ensuring no pustules is a critical early clue. Fresh frozen sections can also be obtained to examine for epidermal necrosis and differentiate from mimickers lacking necrosis [74]. The algorithm of drug causality for epidermal necrolysis (ALDEN) can be used to elucidate drug causality. Additionally, multiple severity scoring systems exist for SJS/TEN, including the SCORTEN score, a TEN-specific severity-of-illness score; age, bicarbonate, cancer, dialysis, and 10% body surface area risk model (ABCD-10); and clinical risk score for TEN (CRISTEN), which can be used to predict mortality [27, 72, 75, 76]. Additionally, as described previously, LTT can also be considered to determine the causative drug [35, 36]. Unfortunately, there is a lack of validated supportive outcome measures focused on the skin that can support early diagnosis or skin severity assessment [77, 78].

4.4 Overlap Presentations

It must be noted that cases with overlap physiology exist. These include cases of SJS/TEN with pustules, targetoid lesions, and/or epidermal necrolysis that also have internal organ dysfunction and/or a delayed onset [40]. In these cases, we suggest treating for the more severe disease, i.e. if there is an overlap of SJS/TEN and AGEP, treating for SJS/TEN, or if DRESS/DiHS and AGEP overlap, treating for DRESS/DiHS syndrome.

5 Drug Causality

Determining the accurate drug causality is key in all of the SCARs. Caution must be exercised when assessing causality given that treatment interruption and labeled "allergies" may be associated with a significant impact on future treatment as well as an increase in treatment cost [6]. Utilizing a standardized tool to assign the likelihood of drug culpability, such as the Naranjo criteria,

SCAR-specific tools (such as the ALDEN score for SJS/TEN), or pharmacovigilance/drug notoriety databases, can help increase the accuracy of causality [27, 79–81].

6 Morbilliform Eruptions in Patients of Color

It is important to recognize subtle variations in diagnosing morbilliform eruptions in patients of color (POC). When evaluating POC for morbilliform eruptions, erythema may be more subtle in the early stages. Increasing ambient lighting, palpating the skin, assessing for blanching, comparing with unaffected skin, and utilizing dermoscopy are useful tools during the physical exam to assess for erythema. Additionally, patients or close family members may guide the clinician as to whether the patient has more erythema than usual. Palpating the skin may provide valuable clues that may not be visually ascertained such as textural changes, induration, increased skin temperature as well as surface discomfort/pain. Specifically in POC who develop DRESS/DiHS, duskiness and edema are more commonly seen than erythema [82]. Furthermore, focusing the high- versus low-risk morbilliform assessment on high-risk locations of involvement can be overemphasized in this population to help risk stratify. Namely, determining erythema on a relatively hypopigmented region such as the palms/soles rapidly confers necessary information of a high-risk eruption subtype. Similarly, corneal injection and/or mucosal involvement should not be affected by skin pigmentation. As erythema progresses, the contrast of duskiness or multiple hues of erythema can be more easily visualized in this population as a clue of high-risk morbilliform pattern and specifically SJS/TEN (Fig. 4).

The use of specific medications may be associated with a higher risk of drug eruptions in POC. The reasons are likely multifactorial and include genetic predisposition, structural inequities in healthcare, delays in diagnosis, and culprit drug withdrawal. Glutathione S-transferase deficiency has been suggested as an etiology for why Black patients are more likely to develop DRESS/DiHS after minocycline use [83]. Other pharmacogenomic reasons include a higher prevalence of high-risk HLA subtypes such as HLA-B*58:01 (in African and Asian ancestry), HLA-B*15:02 (in Asian ancestry), and HLA-B*13:01 (in Asian ancestry) in combination with the specific culprit drugs allopurinol, carbamazepine, and dapsone, respectively [84]. In addition, Black, Hispanic, and Native Hawaiian/Pacific Islander patients who were on Medicaid were less likely to be on newer antiepileptic medications compared with white patients [85]; POC also are more likely to develop antiepileptic-induced DRESS/DiHS [82]. Multiple studies report that the length of time to suspected causal drug withdrawal following symptom onset was longer for POC, especially for Black patients [82, 86]. In cases of delayed diagnoses in POC superficial desquamation and scale may be the predominant physical finding [86]. In both DRESS/DiHS and SJS/TEN, Black patients were reported to have higher mortality compared with white patients [10, 87].

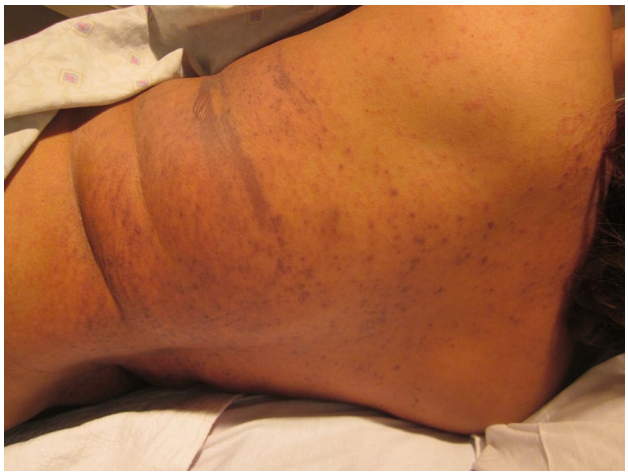

Fig. 4 Characteristic duskiness of SJS/TEN on the trunk of a patient of color. The presence of duskiness, which can be harder to appreciate in patients of color, should raise concern for high-risk morbilliform eruptions such as Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN)

7 Differentiating Acute Graft-Versus-Host Disease (GVHD) from Other Morbilliform Eruptions in Post-Stem-Cell Transplant Patients

After diagnosing high-risk morbilliform features in the setting of a recent bone marrow, peripheral blood, or even solid-organ transplant, consideration must immediately go toward excluding aGVHD. Treatment type, patient risk factors, physical exam, evidence of multiorgan involvement, and biopsy results should all be considered to help differentiate the morbilliform eruptions in this setting (Fig. 1).

aGVHD affects between 40% and 60% of allogeneic stem-cell transplant patients [88, 89]. Prompt recognition of GVHD is imperative due to its significant risk for mortality [89, 90]. aGVHD may rarely occur after transfusion of blood products, and solid organ transplantation. HLA mismatch is the strongest risk factor for aGVHD development; other risk factors include advanced age, myeloablative conditioning regimens, gender disparity between the host and donor, donor multiparity, nonconventional GVHD prophylaxis, and

use of peripheral blood stem cells as the graft source [89, 91].

The classic clinical presentation of cutaneous aGVHD includes follicular erythema and a morbilliform eruption accentuated on the face, ears, palms, and soles; in severe cases, widespread epidermolysis mimicking TEN can be seen [88]. Itching and dysesthesia are potential symptoms, but patients may be asymptomatic early [88]. Oral involvement is associated with more severe aGVHD; however, oral involvement alone is not diagnostic, as other conditions that can disproportionately impact hematopoietic stem cell transplant (HSCT) patients, such as chemotherapy-induced mucositis and flares of herpes simplex virus, can also cause oral lesions [92]. The presence of secretory diarrhea and/or hyperbilirubinemia can be helpful in distinguishing aGVHD from other morbilliform eruptions [93]. Of these features, in one study, the strongest risk association is the time from transplant, in particular a morbilliform eruption developing between days 20 and 40 after transplantation [94]. There are no diagnostic criteria to differentiate aGVHD from other morbilliform eruptions however. Skin biopsies are frequently performed; however, interpretation remains challenging [95–97]. Common histologic features of aGVHD include interface dermatitis, vacuolar degeneration of the basal layers, dyskeratosis, and superficial lymphocytic infiltrate [95]. However, these features, when subtle, are the same as those seen in drug eruptions and eruption of lymphocyte recovery, among others [98]. Histologic features more suggestive of aGVHD include follicular involvement of the interface dermatitis, as well as the exclusion of high levels of eosinophils, yet short of an extremely elevated tissue eosinophilia, no combination of histopathologic findings among dyskeratosis, basal vacuolization, satellitosis, necrotic cells in adnexa, and degree of eosinophilia were an optimal test for disease [96, 99, 100]. Utilization of fluorescent in situ hybridization (FISH) testing can confirm interface dermatitis of donor lymphocytes diagnostic of aGVHD, but is only possible in sex-mismatched transplants [101].

HSCT patients are also uniquely at risk for other morbilliform eruptions that occur in the post-transplant setting, including engraftment syndrome, eruption of lymphocyte recovery, viral exanthems, and drug eruptions. As with aGVHD, engraftment syndrome may present with non-infectious fever, morbilliform eruption, diarrhea, and hepatic dysfunction; however, engraftment syndrome can be differentiated by its timing, frequent pulmonary involvement, and often self-limited nature. This eruption tends to occur several days prior to engraftment, measured as when the absolute neutrophil count is over 500 cells/uL for 3 consecutive days, typically 1–3 weeks post-transplant [102]. Eruption of lymphocyte recovery is a similar entity with onset heralding the detection of lymphocytes in the peripheral blood, which falls under a similar 1–3 week timeframe post-transplant [98, 103]. Unlike aGVHD, eruption of lymphocyte recovery is characterized by isolated fevers and morbilliform eruption without systemic organ involvement and is self-limited, resolving over several days with desquamation and mild residual hyperpigmentation [98].

If patients are within the 100-day window since HSCT, patients with overlapping features of severe cutaneous adverse reactions and GVHD most likely have forms of aGVHD with either organ involvement (DRESS/DiHS-like presentations) and/or grade 4 aGVHD (SJS/TEN-like).

8 Differentiating Viral Eruptions

Viral morbilliform eruptions, which include eruptions secondary to measles; rubella; hand, foot, and mouth disease; exanthema subitum; scarlet fever; and infectious mononucleosis, are historically the most frequently observed diseases that should be differentiated from drug-induced morbilliform eruptions. While usually low-risk in nature, most viral eruptions tend to mimic the high-risk morbilliform morphologies. Many location and morphologic clues, such as oral involvement, are similar between high-risk eruptions and viral disease. The most important aspect is recognizing the overlap and, if clinical features of high-risk morbilliform eruptions are identified, then using laboratory and drug-history information to identify the etiology. Typically in this setting, if a patient is on a high-risk drug with recent onset, we do not evaluate further for viral eruptions. Conversely, if a patient is showing high-risk features without supportive drug history, then we consider the potential benefits of viral testing with the patient.

Viral exanthems typically involve similar locations to high-risk drug eruptions, including involvement of the hands, feet, face, and buttocks. Features, including brighter erythema and less pruritus, are typically associated with viral eruptions but can be difficult to quantify [3, 104, 105]. The primary differentiator of viral and drug eruptions is typically location, with acral, facial, and gluteal involvement all associated with viral eruptions [3, 104]. Seasonality should also be considered; viral eruptions more commonly occur in the spring and summer. Finally, systemic symptoms such as conjunctivitis, cough, headache, irritability, and vomiting are more frequently seen in viral eruptions, but can precede the rash by weeks.

Once a high-risk identification has been made and after evaluating for potential SCARs, evaluation of viral causes should be considered. Additional workup should be tailored on the basis of clinical suspicion [3]. For instance, a respiratory panel should be ordered if upper respiratory tract infection symptoms are present [3]. Symptoms of infectious mononucleosis warrant specific testing for cytomegalovirus,

Epstein–Barr virus, and human immunodeficiency virus (HIV) [3]. Arthralgias should prompt workup for parvovirus B19 and, in patients with the appropriate travel history, Dengue virus, Zika virus, and Chikungunya virus [3]. Acral and oral involvement should raise suspicion for enterovirus, coxsackievirus, and echovirus [3]. Finally, those who are underimmunized or unimmunized should be tested for measles and rubella viruses [3]. Viral testing is of particular importance if the virus in question, such as HIV, affects patient outcomes [106]. Other laboratory values, such as skin or serum cytokines, are not clinically useful to differentiate viral from other causes of drug eruptions at this time. Because the histopathology of viral eruptions can be nonspecific, skin biopsy is unlikely to be beneficial [106].

9 Immunotherapy-Induced Morbilliform Eruptions

Immune checkpoint inhibitors (ICIs) are used to treat a variety of malignancies. Blockade of CTLA-4-CD80/86 and PD1-PDL-1 are key mechanisms through which ICIs allow for increased immunologic activation that can target and destroy cancer cells. However, nonspecific T-cell activation can also damage normal tissue, resulting in myriad different immune-related adverse events (irAE). Cutaneous involvement is often the presenting irAE in patients and occurs in more than one-third of patients [107–111]. The clinical presentation of irAEs are widely variable, but morbilliform eruptions are the most common, with studies showing that 20–30% of patients on CTLA-4 inhibitors or PD-1 inhibitors are affected [112]. Using the same groundwork outlined above should evaluate these morphologies for categorization into high risk or low risk. Most of the reported morbilliform eruptions are low risk and can be rechallenged after following National Comprehensive Cancer Network guidelines [113, 114].

Immunotherapy-induced DRESS/DiHS presents similarly to classical DRESS/DiHS [115]. It is critical to differentiate whether the patient is reacting to a small molecule stimulated by immunotherapy versus immunotherapy alone. SCARs in this setting typically are a two-hit reaction, with immune checkpoint inhibition stimulating a delayed-type hypersensitivity reaction to a small molecule hapten such as concurrent trimethoprim/sulfamethoxazole. Drug attribution in this setting is critical to maintain as many lines of therapy as possible for cancer patients. Of note, if patients on a PD-1 inhibitor develop DRESS/DiHS, they may still be able to tolerate a new PD-1 inhibitor along with low-dose steroids, with one study reporting an 80% success rate with this medication change [115]. It is not recommended for patients with SJS/TEN in this setting to undergo rechallenge [116]. Despite not rechallenging patients, it is critical to ensure that patients with SJS/TEN are properly diagnosed as SJS/TEN, as Rowell's syndrome/subacute cutaneous lupus erythematosus will occur in this setting and be difficult to differentiate but should be differentiated by SSA antibody positivity and/or direct immunofluorescence testing. Progressive immunotherapy-related mucocutaneous eruption (PIRME) has been named a distinct severe reaction by some authors [117], yet it is unclear whether it is *en suis generis.* PIRME is, however, likely unique from SJS/TEN by multiple features. For example, patients with PIRME have successfully undergone rechallenge [117].

10 Conclusions

Morbilliform reactions are the most common cutaneous reaction pattern seen in hospitalized patients. Utilizing a framework for early diagnosis and risk stratification is critical. We suggest differentiating high-risk, immediately visible features from the initial evaluation, including facial involvement, palm/sole involvement, mucosal involvement, and morphologic clues such as subtle duskiness, pustules, or vesicles/bullae. This risk stratification can be used to determine the need for hospitalization and additional laboratory or skin biopsy testing. Utilization of subsequent tests then separates the high-risk eruptions into specific diagnoses, including AGEP, aGVHD, DRESS/DiHS, or SJS/TEN.

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