Drug Rash with Eosinophilia and Systemic Symptoms

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Overview

- Drug rash with eosinophilia and systemic symptoms (DRESS) is a systemic drug hypersensitivity reaction ranging in clinical presentation from more mild (rash, transient eosinophilia, lymphadenopathy) to severe (multi-organ dysfunction)
  - Encompassing term including: Anti-convulsant hypersensitivity syndrome, drug-induced hypersensitivity syndrome, drug-induced delayed multiorgan hypersensitivity syndrome
- Mortality rate is 10%, with most patients dying from fulminant liver failure or cardiac complications
- Most common offending agents: Antiepileptic drugs (carbamazepine, phenytoin, lamotrigine), Sulfa-based antimicrobials (trimethoprim/sulfamethoxazole, sulfasalazine), NSAIDs, minocycline, allopurinol, abacavir, and nevirapine
- Latency period: 2–6 weeks from drug exposure to disease onset
- Symptoms may persist for weeks following discontinuation of the inciting medication
- The exact mechanism of pathogenesis is unknown but leading theories include:
  - Drug-induced transient host lymphocyte suppression, allowing latent virus reactivation
  - EBV, CMV, HHV7, and particularly HHV6 reactivation can be seen in as many as 75% of cases
  - Another possible contributor to disease is a deficiency in detoxifying enzymes (such as epoxide hydrolase) which prevents proper clearing of drug metabolites with their accumulation resulting in an immunologic response

Clinical Presentation

- Extensive deep red-erythematous morbilliform eruption involving the face with facial and sometimes acral swelling (Fig. 6.1)
  - The facial edema is a prominent and an essential diagnostic feature as most morbilliform drug eruptions spare the face
  - There is typically periorbital sparing (relative pallor), and occasionally impetigo-like crusting around the chin

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- Rarely there is isolated mucous membrane inflammation, and vesicles/bullae, pustules, target lesions, and purpura have been reported
- There are no validated, internationally agreed upon diagnostic criteria, but suggested criteria include:
  - Drug rash
  - Fever >38 °C
  - Lymphadenopathy
  - Peripheral eosinophilia (>1000–1500 absolute eosinophilia), or atypical lymphocytosis
  - Internal organ involvement (liver, kidneys, lungs, heart)
  - HHV6 PCR may be elevated but testing is not widely available
- Despite its name, eosinophilia is not always present and is not a requirement for diagnosis
  - 90% of DRESS cases will have associated eosinophilia
  - Atypical lymphocytosis may be seen as in a viral syndrome

Histopathology

- Histology for DRESS is nonspecific and can include the following (Fig. 6.2):
  - Lymphocytic infiltrate of the papillary dermis may be band-like or perivesicular and may contain eosinophils
  - Dyskeratotic keratinocytes, vacuolar change in basilar keratinocytes, "activated" lymphocytes, and eosinophils may be seen at the dermal/epidermal junction and around follicles
  - May see papillary dermal edema and epidermal spongiosis with subcorneal pustules
  - Variable parakeratosis

Differential Diagnosis

- Morbilliform drug eruption: spares the face, less deep-red, no systemic inflammation
- Viral exanthem: varied depending on the virus, but facial involvement is less common
- Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN): DRESS-SJS overlap can occur; in SJS, mucositis is prominent, and cutaneous lesions have dusky targetoid macules
- Acute generalized exanthematous pustulosis (AGEP): DRESS-AGEP overlap can occur; in AGEP, fine pustules are present
- Staphylococcal scalded skin syndrome: diffuse and flexural superficial desquamation
- Kawasaki disease: red tongue, acral and intertriginous peeling, conjunctivitis
- Graft-versus-host disease: bilirubinemia and diarrhea can help distinguish; cutaneous GVHD often displays a fine scale and may be folliculocentric, often involves the ears

Work-Up

- Complete blood cell count with differential, liver function tests, serum creatinine level, urinalysis to evaluate for extracutaneous involvement
- Organ specific indications depending on symptomatology and presentation:
  - Low threshold to consider cardiac evaluation (EKG, echocardiogram) and pulmonary imaging
  - Small case series suggest specific drugs may be more likely to lead to specific organ dysfunction (allopurinol-renal, minocycline-pulmonary, etc.)
- Patients are at risk for delayed autoimmunity, including thyroid disease and diabetes, and should have thyroid function and glucose testing regularly for 3–6 months post-DRESS onset

Management

- Removal of offending agent and labeling patients allergic; re-exposure may be fatal
  - DRESS may have a genetic component, and ideally patients' first degree relatives will avoid similar agents
  - Avoid cross-reacting drugs, which is a particular issue with anti-epileptic agents
- Systemic corticosteroids at moderately high to high doses (e.g. prednisone 1-2mg/kg per day)
  - Median duration of systemic corticosteroids is 50 days
  - Patients often require close follow-up for delayed autoimmunity, flares of DRESS with steroid taper, and steroid-related adverse effects
- Supportive care

Suggested Readings

1. Cacoub P, Musette P, Descamps V, et al. The DRESS syndrome: a literature review. Am J Med. 2011;124(7):588–97.
2. Walsh SA, Creamer D. Drug reaction with eosinophilia and systemic symptoms (DRESS): a clinical update and review of current thinking. Clin Exp Dermatol. 2011;36(1):6–11.

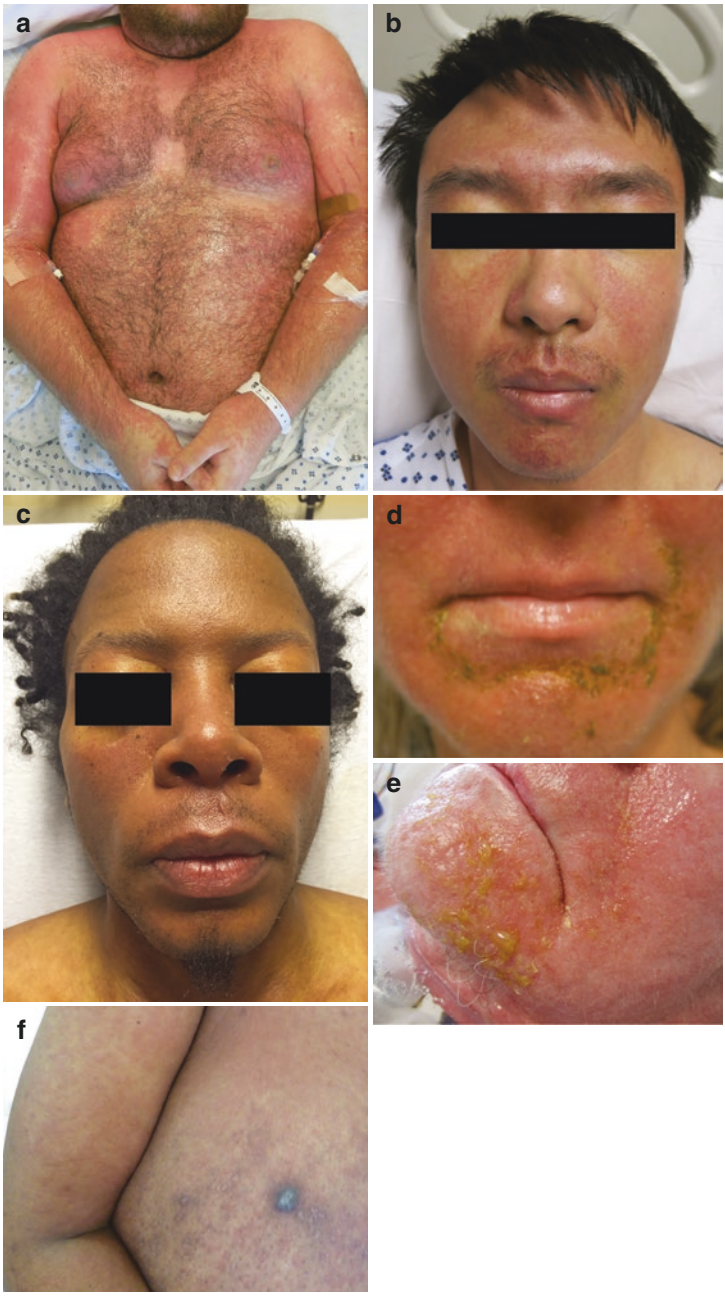

Fig. 6.1 Drug reaction with eosinophilia and systemic symptoms (DRESS): (**a**) A full-body morbilliform eruption, often deeply erythematous, is typical of DRESS syndrome. (**b**, **c**) Erythema and swelling of the face are typical findings in DRESS but may be subtle in those with darker skin (**c**). (**d**) Patients may develop impetigo-like crusting, as is seen here on the chin of a patient with DRESS syndrome. (**e**) This patient with DRESS from phenytoin exhibits extensive impetigo-like crusting of the chin. (**f**) Erythematous macules and papules coalescing into larger patches and plaques can occur in DRESS.

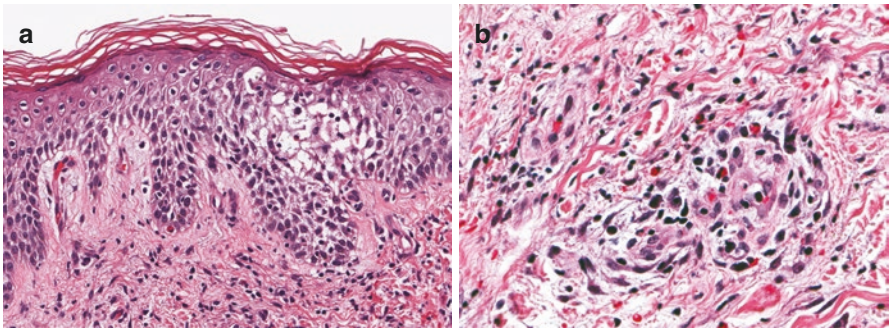

Fig. 6.2 Drug reaction with eosinophilia and systemic symptoms (DRESS) (*20*×, *40*×; *H&E*): (**a**) The histologic presentation of DRESS is variable. Features can include epidermal spongiosis, interface dermatitis with vacuolar change, perivascular lymphocytic infiltration, and eosinophils. (**b**) The perivascular lymphocytes may appear large and atypical.