Dermatopathologic Emergencies Part I

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Abstract

In dermatopathology, there are several conditions which must be addressed emergently. While some conditions necessitate emergent intervention because of the pathology of the cutaneous manifestations, others require recognition of the underlying serious systemic conditions represented by the cutaneous signs and symptoms. We describe the desquamating disorders (Staphylococcal scalded skin syndrome, Stevens–Johnson syndrome/toxic epidermal necrolysis, and edema-related desquamation), erythema multiforme, cutaneous aspergillosis, tinea/Candida overlying fractures, rickettsial infections, and eczema herpeticum as diseases which should be addressed immediately upon presentation because of the seriousness and rapidity of progression of their pathology. Moreover, porphyria cutanea tarda, Birt-Hogg-Dubé syndrome, Muir-Torre syndrome, and acquired ochronosis may exemplify conditions where the cutaneous signs serve as warnings for severe systemic disease that may not be emergencies in isolation, but can indicate rapid occult development of destructive and sometimes deadly noncutaneous pathology. The literature review was conducted using searches in Pubmed and references to textbooks on the subjects.

Keywords: Carcinoma, dermatopathologic, desquamating, emergency, erythema

INTRODUCTION

In dermatopathology, there are several conditions which must be addressed emergently. With regard to conditions that represent emergencies upon presentation of the cutaneous manifestations, desquamating disorders, including Staphylococcal scalded skin syndrome (SSSS), toxic epidermal necrolysis (TEN), and edema-related desquamation; erythema multiforme (EM); Aspergillus infection; tinea or Candida overlying fractures; and rickettsial infections require rapid identification and intervention. Conditions for which the cutaneous manifestations indicate an underlying serious systemic disease that can necessitate emergent intervention based on the patient’s clinical situation, porphyria cutanea tarda, Birt-Hogg-Dubé syndrome, Muir-Torre syndrome, and ochronosis are noteworthy. These diseases must be recognized and managed promptly to avoid disfigurement and/or death. The literature review was conducted using searches in Pubmed and references to textbooks on the subjects.

DERMATOPATHOLOGIC EMERGENCIES

Desquamating disorders
Staphylococcal scalded skin syndrome

SSSS is a bacterial skin infection caused by certain strains of Staphylococcus aureus which produce serine protease exfoliative toxins that cleave desmoglein 1 in the superficial epidermis. The toxins destroy cell–cell adhesion, causing the skin to blister, denude, and eventually desquamate.[1,2] Patients may present with generalized erythema, bullae, and desquamation of the skin. However, mucosal surfaces are usually spared. Physical examination reveals a vesiculobullous disorder with Nikolsky’s sign and a scalded skin appearance. Although SSSS may resemble other blistering disorders, such as TEN,[3] SSSS does not involve the mucous membranes and creates more superficial epidermal desquamation compared to the full-thickness denudation in TEN.[2,4]

Whereas the blood cultures are usually negative in pediatric patients,[5] adult blood cultures tend to be positive and may aid diagnosis.[2] Skin biopsy may show superficial intraepidermal cleavage beneath the stratum corneum, and the stratum corneum may only be a single epidermal cell layer thick. SSSS and TEN both exhibit minimal inflammation but SSSS

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SSSS is a very different clinical entity in a pediatric patient compared to an adult. The mortality rate of SSSS is between 3.6% and 11% in children but is between 40% and 63% in adults, though this increased rate may be due to underlying comorbidities. In contrast to pediatric patients who are usually otherwise healthy when they manifest SSSS, almost all adult SSSS patients are immunocompromised with graft versus host disease (GVHD), HIV infection, chronic renal disease, malignant neoplasms, chemotherapy, diabetes mellitus, or intravenous drug abuse. Given the alarming mortality rate in adults, rapid diagnosis of SSSS is critical, and management should be initiated swiftly.

Stevens–Johnson syndrome/toxic epidermal necrolysis

TEN may appear as violaceous or erythematous patches, atypical targetoid lesions, erosions, bullae, and ulcers. Nikolsky sign of the bullae may be present, which is slipping away of upper layers of skin from the lower layers upon light lateral pressure. Notably, a distinguishing feature of Stevens–Johnson syndrome (SJS)/TEN is mucosal involvement, with oral sites involved more commonly than genital, anal, or ocular mucosa. Preceding skin and mucous membrane findings by 1 to 3 days, patients may also have systemic symptoms such as headaches, pain of the eyes, skin, or other mucous membranes, rhinitis, sore throat, malaise, myalgias, and cough.

The mechanisms behind the pathogenesis of SJS/TEN have not been fully elaborated. A combination of host genetic factors, including immunity, T-cell clonotypes, drug metabolism, and drug structure appear to contribute to the etiology of SJS/TEN. Of particular note, the characteristic pathologic finding in SJS/TEN is full-thickness epidermal necrosis [Figure 2].

In addition, TEN may demonstrate endothelial apoptosis, subepidermal splitting, and a lymphocytic infiltrate at the dermoepidermal junction with CD8+ T-cells in the epidermis and CD4+ T cell in the dermis. Although previous studies have demonstrated a higher ratio of CD8+/CD4+ T lymphocytes in the dermis in TEN compared to skin GVHD, recent work attempted to quantify the difference in ratio as four-fold greater in TEN versus stage 4 skin GVHD.

Upon pathologic confirmation, the medical team is required to discontinue suspected drugs and immediately begin management. This is marked contrast to treatment of edema-related desquamative dermatitis (see below) and this difference is a primary reason why this entity constitutes a dermatopathologic emergency. TEN itself has a mortality rate of approximately 25%–30%. Sepsis preceding multiorgan failure is the most common reason for death, though additional mortality comes from pulmonary embolism, pulmonary edema, gastrointestinal bleeding, and myocardial infarction.

"SCORe of TEN (SCORTEN)" is a rapid seven-item assessment schema for severity of illness validated for TEN and SJS. It helps determine the prognosis of patients with TEN using clinical and laboratory values, including age, percent of body surface area (BSA) detachment, presence of tachycardia, history of malignancy, and serum glucose, urea, and bicarbonate. For example, a patient with a SCORTEN of two has a mortality rate at hospital discharge of 12%, whereas a patient with a score of four has a 58% mortality rate.

The diagnosis of SJS is made when there has been detachment of <10% of the BSA along with diffuse erythematous or purpuric macules or atypical, flat target lesions. Overlapping SJS/TEN occurs when detachment is between 10% and 30% of BSA. TEN with spots is classified as detachment of >30% of BSA; TEN without spots occurs with detachment in large epidermal sheets >10% of BSA but without target lesions or purpuric macules. A recent case report form for SJS/TEN was created from consensus of international experts to standardize the documentation of individual cases and collection of patient information.
Edema-related desquamation

Edema is defined as a clinically apparent, palpable swelling produced by an increase in the interstitial fluid volume. It may be localized or generalized and is associated with many pathologic states, including heart failure, cirrhosis, nephrotic syndrome, vasculitides, and lymphatic disease. Dermal changes include proliferation of small blood vessels in the papillary dermis, variable dermal fibrosis, perivascular lymphocytic infiltration, extravasated erythrocytes, and hemosiderin-laden macrophages."

Generalized and local edema predispose the skin to injuries from lateral shear force; the dermis or epidermis may acquire edema at a markedly different rate than the other, causing lateral shear force leading to rapid full-thickness desquamation [Figure 3]. In cases of drug-induced anasarca, this can result in desquamation of a large surface area. Of paramount importance is to distinguish this cause of desquamative dermatitis and the others previously discussed. Withholding of the offending agent are necessary to prevent further injury, but this is rarely an emergency. The epidermal change is due to the shearing force created by the increased volume between the dermis and epidermis rather than the drug itself. Obesity is another factor that predisposes the skin to shear-force related injury due to direct mechanical pull on the epidermis. Obesity also predisposes the skin to local edema, which can cause small-scale shear-force.

Generalized and local edema can also cause exfoliative dermatitis in addition to shear-force related injury. Exfoliative dermatitis can involve most of the skin and causes massive scaling. Complications can be life threatening, and hospitalization is required for treatment. Any case of desquamative dermatitis must be distinguished from TEN and adult SSSS, which have high morbidity and mortality and require rapid diagnosis, often by frozen section. Histologically, TEN shows full-thickness epidermal necrosis and a dermal–epidermal splitting as opposed to the nonspecific histopathological findings in exfoliative dermatitis.

Edema is characterized by a mild to moderate lymphocytic infiltrate with some involvement of the basal layer, which may cause distortion of the dermoeidermal interface. Large granular lymphocytes may be found within the epidermis and they are associated with prominent epidermal cell death not limited to the basal layer. The mechanism of cell death is apoptosis. There may also be some epidermal spongiosis and basal vacuolar change. Vesicles are characterized by splitting at the dermoeidermal interface and marked epidermal cell death in the overlying blister roof. Cell death may involve a single cell or groups of cells, or may be confluent necrosis. The dermal infiltrate is mostly lymphocytes with a few macrophages involving the superficial and mid-dermal vessels. There is also diffuse infiltrate within the basal layer. Similar to TEN, severe cases of EM may demonstrate sparse infiltrate with confluent necrosis of the detached overlying epidermis.
Direct immunofluorescence reveals intraepidermal cleft bodies, signifying degenerated keratinocytes that stain in a homogenous pattern usually with IgG and occasionally with C3. There is frequent granular staining for C3 along the dermoepidermal interface. In early lesions, this staining may also be found in papillary dermal vessels. Properdin may be present and suggests activation of the alternate complement pathway. Immunohistochemistry also reveals expression of matrix metalloproteinases 2, 9, and 11.

Frozen section allows rapid diagnosis of EM and differentiation from the other desquamative dermatoses we have considered. The need for rapid intervention in patients with EM was highlighted by a recent study showing that 21% of patients had severe fibrotic mucous membrane consequences. For example, some patients may experience esophageal stenosis, severe airway disease, and vaginal synchia. EM secondary to *Mycoplasm pneumoniae* infection was associated with the more severe sequelae.

**Cutaneous aspergillosis**

*Aspergillus* infections of immunocompromised individuals pose a serious threat. Among patients with cancer, opportunistic infection with *Aspergillus* is second in frequency only to *Candida*. Although it usually involves the lungs, *Aspergillus* rarely affects the skin. In addition, *Aspergillus* infection of the skin usually occurs as part of a systemic infection in immunocompromised patients. Primary cutaneous aspergillosis (PCA), wherein cutaneous lesions are the only manifestation, is a rare phenomenon. The development of PCA is commonly associated with preexisting leukemia, with lesions located at sites of intravenous cannulae or the associated dressings. PCA may also be seen in preterm infants. It rarely occurs in immunocompetent hosts.

Secondary cutaneous aspergillosis (SCA) follow hyphae seeding the skin from the blood.

Cutaneous *Aspergillus* infection may present as a single or multiple violaceous nodules or plaques with rapid secondary escharotic evolution [Figure 4]. Plaques may be studded with pustules. *Onychomycosis* has also been recorded. Though *Aspergillus flavus* is the most common isolate, *Aspergillus fumigatus*, *Aspergillus ustus*, and *Aspergillus niger* have also been culprits. Rarely, pyoderma gangrenosum and burns may be secondarily infected with *Aspergillus*.

Upon histopathologic examination, there may be areas of suppuration and abscess formation, well-developed granulomas, or masses of fungi with minimal mixed inflammatory infiltrate. The type of change depends on the host response. Hyphae may be found within the walls of dermal blood vessels, creating thromboses and possible necrosis. Under low power, the hyphae may be so confluent that they mimic normal skin architecture. *Aspergillus* species are detected as dichotomously branching, septate hyphae. Silver methenamine stain best demonstrates the organism [Figure 5]. Moreover, the overlying epidermis may exhibit pseudopitheliomatous hyperplasia.

Rapid initiation of treatment (i.e., within hours) is crucial, necessitating evaluation via frozen section of a punch biopsy. Patients tend to respond well to treatment, especially if they are immunocompetent. The *Aspergillus* lesions tend to arise in hours, not days, and may kill the patient within hours if it is not treated. Recent work suggests the 3-month survival rate for PCA is 100% and 30% for SCA. However, the mortality of PCA in another recent study was recorded as 31.5%, with disease dissemination more common in patients with underlying systemic disease. Nearly one-third of patients had PCA at the time of death. Patients who survive may live for years afterwards, so treatment is more than an academic exercise. Therefore, early and aggressive treatment should be enacted upon histopathologic diagnosis of cutaneous aspergillosis to maximize survival, especially in patients with immune deficiencies.

**Tinea/Candida overlying fracture**

According to a recent case report, a patient with a history of refractory onychomycosis of the toe nails developed osteomyelitis at the site of repair of a right distal tibia fracture. The repair involved an external fixator but no signs of superficial dermatophytes were present when the pins were later removed. Beginning around 8 weeks postoperatively,
Surgeons should take caution to examine infections prior to incising bone to minimize the chance of the patient's skin to look for possible signs of fungal skin infections. He developed increased lucency over the right calcaneus, which worsened over the following 4 weeks with pain, mild fluctuance, and erythema over the area. Twelve weeks after the initial external fixation, intraoperative cultures taken during debridement grew *Trichophyton rubrum* after 13 days of incubation. He was then treated with itraconazole 200 mg twice daily for 3 months with no recurrence of symptoms at the 14-month follow-up.

Some dermatophyte as well as Candida species grow preferentially not only in skin, hair and/or nails but also, importantly, in bone marrow. The presence of signs suggestive of a dermatophyte or Candida lesion at the time of a fracture repair should not be overlooked. Although the authors of the above cited report did not note signs of dermatophyte infection at the site of pinning, the presence of treatment-refractory onychomycosis served as a clue to the source of the eventual osteomyelitis. Out of caution, the infected nails perhaps should have been avulsed or otherwise isolated prior to the pinning. Other cases have been reported of patients who developed osteomyelitis after manipulating bone, including reports of candidal sternal osteomyelitis after sternotomy, and candidal osteomyelitis following open reduction and internal fixation of an open fracture of the distal phalanx of a thumb. Surgeons should take caution to examine the patient’s skin to look for possible signs of fungal skin infections prior to incising bone to minimize the chance of fungal osteomyelitis. If surgery needs to be done quickly, a frozen section with evaluation for Candida species and dermatophytes may be indicated (i.e. dermatopathologic emergency) [Figures 6 and 7].

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Conflicts of interest
There are no conflicts of interest.

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**Figure 6:** Tinea infection of the skin of the knee (Gömöri methenamine silver stain, ×976.5)

**Figure 7:** Tinea infection of the skin of the knee (H and E, ×976.5)
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