Dermatologic Emergencies CME Part IV: Vesiculobullous diseases, connective tissue and rheumatological disorders

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ABSTRACT

This section reviews the emergency presentations of autoimmune blistering diseases, connective tissue and rheumatological disorders as well as common pitfalls associated with their diagnosis and management

Key words :*Vesiculobullous diseases; Systemic lupus; Dermatomyositis; Systemic sclerosis*

Vesiculobullous diseases are characterized by skin separation at various levels on histopathology. Autoimmune blistering diseases (AIBDs) are among the most common dermatologic emergencies, and they can have a dramatic clinical presentation with substantial morbidity and mortality. Connective tissue and rheumatological diseases can occasionally present as emergencies due to the disease process, internal organ damage, infection, and adverse effects of therapeutic agents.

• PEMPHIGUS

Pemphigus is a group of autoimmune diseases affecting stratified squamous epithelia, such as the skin and mucous membranes, in which acantholysis (the loss of cell adhesion) causes blisters and erosions [1]. Before the advent of immunosuppressive therapy, pemphigus was associated with high mortality and morbidity rates. Although pemphigus remains a possible dermatologic emergency with substantial morbidity, mortality rates have decreased due to the new therapeutic modalities [2,3].

Pemphigus vulgaris (PV) is the most frequent and severe form of pemphigus resulting from circulating autoantibodies against intercellular desmogleins (Dsg) 1 and 3 [4,5]. It is characterized by painful oral erosions with widespread flaccid skin blisters that break easily, resulting in extensive denuded skin and erosions [6,7]. Previously the disease was invariably fatal due to loss of body fluids and secondary bacterial infections; however, the outlook has dramatically changed since the introduction of immunosuppressives [8-10].

Pemphigus foliaceus (PF) results from circulating autoantibodies directed solely against Dsg1, leading to more superficial and fragile blisters with predominant erosions and scale-crust of a corn-flake like appearance [11,12]. PF predominantly affects the seborrheic areas without mucosal involvement [13]. Compared to PV, PF has a better prognosis except for occasional acute cases that can progress into exfoliative erythroderma [14,15].

Paraneoplastic pemphigus (PNP) is a fatal autoimmune blistering disease in patients with underlying neoplasms [16]. Castleman disease is the most commonly associated neoplasm in children, while in adults; it is frequently associated with non-Hodgkin lymphoma, chronic lymphocytic

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leukemia, thymoma, and Castleman's disease [17]. The disease is characterized by severe, recalcitrant oral stomatitis with polymorphous skin eruptions resembling lichen planus, erythema multiform, pemphigus vulgaris, or bullous pemphigoid. PNP has a poor prognosis with a 75% to 90% mortality rate [18-20]. The leading causes of death include underlying malignancy and respiratory failure (bronchiolitis obliterans) [21,22].

• BULLOUS PEMPHIGOID

Bullous pemphigoid (BP) is the most common immunobullous disease in Western Europe that more commonly affects the elderly and is characterized by subepidermal blistering. Bullae are generated when autoantibodies attack two main hemidesmosomal antigens, BP230 (BPAg1) and BP180 (BPAg2, collagen XVII) [23-25].

It is characterized by tense vesicles and bullae on apparently normal or erythematous skin. Bullae and/or erosions may be present in the oral and genital mucosa [26]. In the early stages, typical blistering lesions may be completely absent, and the patient may present with pruritus alone or associated with erythema and/or urticated plaques. Hence, bullous pemphigoid should be considered in all elderly patients with chronic pruritic skin eruptions [27,28].

BP has less aggressive course than pemphigus vulgaris. Complications in untreated patients may result from secondary bacterial infection, dehydration, electrolyte imbalance, and septicemia [29,30].

The exact diagnosis of autoimmune bullous disease (AIBD) is vital for prognosis and appropriate treatment decisions (Fig. 1). Clinical suspicion can be confirmed by freshly formed blisters (less than 48 h old) sampling and histopathological examination. Direct immunofluorescence (IF) microscopy of non-bullous perilesional skin (within 1 cm of the blister) is still the diagnostic gold standard in most cases. The circulating antibodies against specific autoantigens can be identified using indirect IF microscopy of organ substrates, enzyme-linked immunosorbent assay (ELISA), and newer techniques such as immunoblotting and immunoprecipitation. Patients with PNP should be screened for underlying neoplasms, and pulmonary function tests (PFTs) are essential for the diagnosis of bronchiolitis obliterans, a rare and serious complication of PNP [31-34]

Treatment

Systemic corticosteroids alone or with adjuvant immunosuppressants such as azathioprine and mycophenolate mofetil are the cornerstones of PV treatment [35]. For refractory cases, rituximab and/or intravenous immunoglobulin (IVIG) may be used as monotherapy or adjunctive treatment. Recent studies have shown promising results of rituximab (an anti-CD20 monoclonal biological agent) in the treatment of AIBD [36,37]. Good wound and oral lesion care is essential to prevent secondary infection. It is vital to identify and treat underlying neoplasms in patients with PNP. BP treatment aims to control symptoms with minimal adverse effects where possible. Both systemic and topical steroids remain the most widely used first-line treatments depending on the disease severity. Both PV and BP can be treated with the same immunosuppressive and immunomodulatory steroid-sparing agents [38].

Pitfalls in the diagnosis and management of AIBDs [39,40]

- The overlapping clinical and histological features of AIBDs in their early-stages
- The presence of unusual forms and clinical variants of AIBDs
- The prodromal non-bullous stage of bullous pemphigoid can mimic eczema or fixed urticaria
- Sampling the older BP lesions (more than 48 hours) could show re-epithelialization at the blister edge, epidermal necrosis and false-negative DIF findings due to secondary infection, causing diagnostic confusion.
- Sampling lesions from the lower extremity in BP has a higher false-negative result rate.
- Rapid tapering of corticosteroids before controlling the disease can result in a disease relapsing.

Practical pearls

An itchy eczematous, urticarial or prurigo-like rash affecting the distal extremities of elderly patients should raises the possibility of the non-bullous stage of BP. This non-specific rash can precede the classical blisters or be the only manifestation of the disease

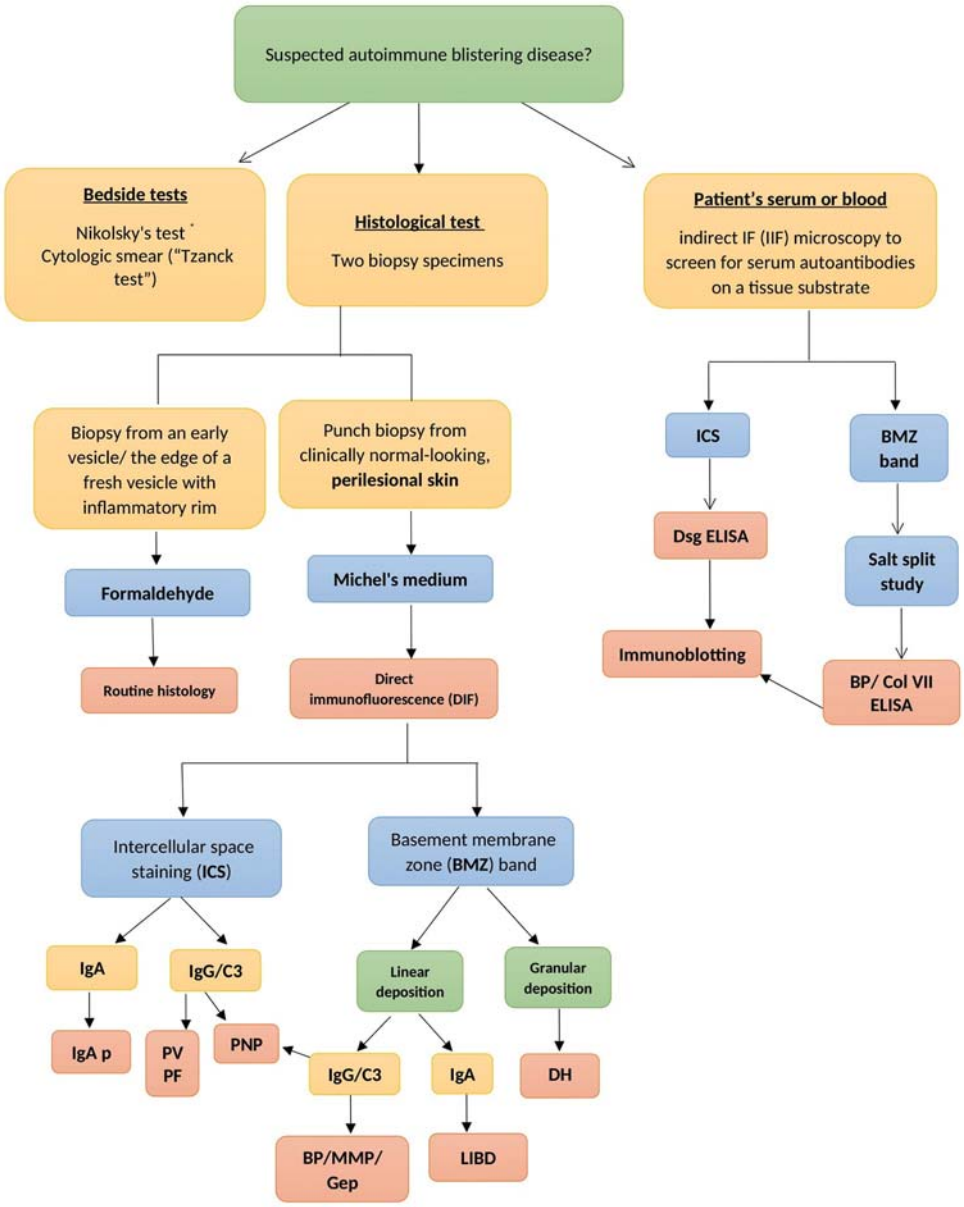

Figure 1:Autoimmune blistering diseases (AIBDs) Diagnostic approach to patients with immunobullous disease [41-43] *Applying lateral pressure with the index finger leading to shearing force to disrupt the intercellular adhesion (Nikolsky's sign) **ICS=** intercellular spaces, **BMZ=** basement membrane zone, **BP=** bullous pemphigoid, **IgA p=** IgA pemphigus, **PV=** pemphigus vulgaris, **PF=** pemphigus foliaceus, **PNP=** paraneoplastic pemphigus, **MMP=** mucous membrane pemphigoid, **Gep=** gestational pemphigoid, **DH=** dermatitis herpetiformis, **LIBD=** linear IgA bullous dermatosis.

CONNECTIVE TISSUE AND RHEUMATOLOGICAL DISORDERS

• Systemic lupus erythematosus (SLE)

Patients with SLE should be evaluated for internal organ involvement. It is **not uncommon** for patients with SLE to present with acute life-threatening complications that require emergency management. The patient with undiagnosed SLE may initially present to the emergency department with variable symptoms; hence, the physician should be alert to the broad-spectrum features of SLE [44] (Table 1).

SLE is usually diagnosed on clinical grounds in the presence of characteristic serological abnormalities [50].

Treatment

A multidisciplinary approach is essential for the effective management of acute emergencies associated with SLE. The management plan is guided by the

Pitfalls in the diagnosis of SLE [51]

- The clinical heterogeneity of SLE and lack of pathognomonic features
- Lack of gold-standard tests
- Difficulty in monitoring the disease activity and predicting flare-ups

Practical pearls

A high suspicion index is vital to consider the possibility of SLE in patients with multi-systemic clinical presentation

Table 1: The most common SLE complications that could be encountered at ER

Hematological	Profound thrombocytopenia can occur as part of the antiphospholipid syndrome or TTP*, and it can be refractory even to aggressive therapy, and it is an independent prognostic factor of survival [45]
Cardiopulmonary	The patient may present with chest pain, dyspnea or cyanosis, which may be secondary to underlying pericarditis, pericardial tamponade, pleural disease, interstitial lung disease (ILD), myocarditis, pulmonary embolism, hypertension and hemorrhage [46]
Renal	Lupus nephritis is the most common internal complication and a major predictor of poor prognosis associated with SLE. It presents with proteinuria, nephritic or nephrotic syndrome, and less commonly, a rapidly progressive glomerulonephritis [47]
Neuropsychiatric	Decreased consciousness, seizures, acute confusional state, and cerebrovascular accidents are considered a major cause of admission to hospital in lupus patients [48]
ASAP syndrome**	Acute life-threatening rare variant of cutaneous LE that is clinically and histopathologically indistinguishable from drug-induced Toxic epidermal necrolysis, hence a high index of suspicion is pivotal [49]

*TTP= Thrombotic Thrombocytopenic Purpura

**ASAP= Acute Syndrome of Apoptotic Pan-Epidermolysis

severity and risk of significant organ dysfunction. Unless contraindicated, **hydro**xychloroquine is recommended for all patients with SLE. High-dose intravenous steroids alone or in combination with other immunomodulatory agents are often required in acute, organ-threatening complications after exclusion of infection [52]. In RCT, belimumab a B lymphocyte stimulator (BLyS) inhibitor was associated with a significant reduction in severe SLE flare-up [53]. In the reported cases of Acute Syndrome of Apoptotic Pan-Epidermolysis (ASAP syndrome), corticosteroids, intravenous immunoglobulin and wound care are considered the cornerstones of treatment [54].

• DERMATOMYOSITIS (DM)

Dermatomyositis may present with a constellation of systemic features caused by internal visceral involvement including, the lung, heart and gastrointestinal tract. The major adverse prognostic factors in patients with DM are underlying malignancy, lung and cardiac complications, and infections [55] (Table 2).

Practical pearls

- Patients with dermatomyositis have about a 6-fold higher risk of soild organ and hematological malignancies than the general population, especially in the first two years after diagnosis [61]. Age-appropriate malignancy screening should be done in all patients with newly diagnosed DM
- Patients with dermatomyositis-associated ILD may present to ER with sudden onset chest pain, dyspnea, and swelling of the face and neck due to spontaneous pneumomediastinum.

When a DM diagnosis is confirmed, patients need to undergo further workup to identify systemic complications, especially interstitial lung disease and screening for potential underlying malignancies.

Treatment

The treatment of DM involves a multidisciplinary approach. Corticosteroids are the main component of treatment, either alone or with other immunosuppressive drugs. A few studies have suggested that rituximab and intravenous immunoglobulin (IVIG) are alternative therapeutic options for the treatment of steroid-refractory progressive ILD [62-65].

• SYSTEMIC SCLEROSIS (SSC)

Fibrosis and degenerative SSc changes may involve other internal organs, such as the lung, kidney, heart and gastrointestinal tract. The most common visceral complication is esophageal dysfunction, while lung involvement is the leading cause of morbidity and mortality in patients with SSc (Table 3).

The diagnosis of SSc-related ILD is primarily based on the clinical presentation and can be confirmed with high resolution computed tomography (HRCT) and pulmonary function testing. Scleroderma renal crisis

Table 2: Major causes of morbidity and mortality in patients with DM

Lung	Pulmonary involvement is considered the most common cause of mortality and morbidity and the primary reason for hospital admission in patients with DM. Patients with underlying antisynthetase syndrome* have a substantially higher risk for developing interstitial lung disease (ILD). Likewise, patients with anti-MDA5** DM are associated with an increased risk of ILD that could be rapidly progressive (RP-ILD) in some cases and associated with poor outcome [56,57]
Heart	Heart abnormalities are common in DM and associated with a poor prognosis. Patients may present to ER with chest pain, dyspnea, and syncope secondary to subclinical myositis, myocardial ischemia, conduction defects, or congestive heart failure [58]
GIT	Juvenile patients with DM may present with abdominal pain, vomiting and haematemesis that may indicate bowel ulceration and/or perforation due to vasculopathy involving the gastrointestinal tract [59]
Internal malignancy	Dermatomyositis is an independent risk factor of internal malignancy, particularly in the first two years after diagnosis [60]

*Antisynthetase syndrome: clinically heterogeneous form of inflammatory myositis, fever, arthritis, mechanic's hands and Raynaud's phenomenon in the presence of antisynthetase antibodies

**MDA5 DM: a subtype of DM with anti-melanoma differentiation-associated protein 5, previously known as clinically amyopathic dermatomyositis 140 (CADM140)

Table 3: Systemic Sclerosis life-threatening complications which may require admission to ICU

Lung	Interstitial lung disease (ILD) is the leading cause of death in SSc, in addition to pulmonary arterial hypertension (PAH) and subsequent life-threatening right heart failure. ILD is commonly associated with the diffuse type SSc, whereas the limited type SSc is considered a risk factor for PAH, particularly CREST syndrome*. Chronic microaspiration may result from persistent gastroesophageal reflux and it could end with pulmonary fibrosis. Pulmonary-renal syndrome, a combination of pulmonary hemorrhage, and acute renal insufficiency is another rare complication associated with SSc [66]
Kidney	Scleroderma renal crisis (SRC) is characterized by the abrupt onset of hypertension and impaired renal function. It is a relatively early complication that develops in patients with diffuse SSc and is adversely correlated with scleroderma mortality during the first 5 years. After the introduction of ACE inhibitors, SRC prevalence and mortality were significantly reduced [67]
Heart	Cardiac involvement is associated with a significant rise in mortality, especially in patients with diffuse SSc. Besides PAH, cardiac complications may include pericardial effusions, myocardial dysfunction, arrhythmias, and valvular diseases [68,69]

*CREST syndrome= Calcinosis cutis, Raynaud phenomenon, Esophageal dysmotility, Sclerodactyly, and Telangiectasia

(SRC) can be diagnosed based on the characteristic clinical findings and impaired renal function tests. The gold standard test for pulmonary arterial hypertension test is right heart catheterization, which shows elevated pulmonary artery pressure. Annual electrocardiograms and echocardiograms are recommended for the screening of cardiac complications [70].

Treatment

ACE inhibitors are the first-line agents for the treatment of scleroderma renal crisis, while renal replacement therapy is required for end-stage renal failure. Both mycophenolate mofetil and cyclophosphamide have shown potential clinical efficacy for SSc-ILD in randomized clinical trials [71]. Treatment of PAH includes the use of vasoactive agents such as endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, prostacyclin analogs and riociguat, a guanylate cyclase stimulant [72].

Practical pearls

- Diffuse skin involvement is the most critical factor for predicting systemic complications in SSc such as ILD, SRC and cardiac involvement.
- New-onset hypertension combined with a gradual decrease in renal function in a patient with SSc should raise the possibility of SRC. Normotensive patients may also experience SRC associated with a worse prognosis and higher mortality rate [73].
- Internal organs' involvement can remain asymptomatic for a long period and significantly contributes to increased mortality and morbidity; hence it is essential to screen all patients for lung, heart and renal involvement irrespective of symptoms.

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