Autoimmunity

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Abbreviations

ACLE	Acute cutaneous lupus erythematous
ANA	Anti-neutrophilic antibody
BMI	Body mass index
BP	Bullous Pemphigoid
BP180	Bullous Pemphigoid Antigen 180
BP230	Bullous Pemphigoid Antigen 230
CCLE	Chronic cutaneous lupus erythematosus
CNS	Central nervous system
DIF	Direct Immunofluorescence
DLE	Discoid lupus erythematous
EM	Erythema Multiforme
IgE	Immunoglobulin E
IIF	Indirect Immunofluorescence
IVIG	Intravenous immunoglobulins
LE	Lupus erythematous
LP	Lichen planus
MAC	Membranolytic attack complex
PMLE	Polymorphic light eruption
PV	Pemphigus Vulgaris
SCLE	Subacute cutaneous lupus erythematous
SLE	Systemic lupus erythematous

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1 Introduction

Autoimmune disorders arise from a failure of self-tolerance, or immunologic unresponsiveness to an individual's own antigens, in genetically susceptible individuals. The mechanisms that result in tissue damage in autoimmune diseases parallel the normal responses of adaptive immunity and may include autoantibodies, immune complexes and/or autoreacting T lymphocytes. The clinical manifestations of autoimmune disorders are extremely varied but tend to be long-lasting and progressive. Immune responses may be directed against a single tissue resulting in organ specific disease such as bullous pemphigoid (BP). In contrast, some autoimmune disorders target a widespread antigens resulting in diseases like systemic lupus erythematous (SLE). We aim to introduce the reader to a better understanding of some common autoimmune diseases, as well as appropriate treatment approaches.

Case 1

An 80-year-old male with a past medical history of hypertension and atrial fibrillation presented to the outpatient clinic for evaluation of a new rash. His rash had started 3 months prior, with small punctate lesions scattered over his body. Initially, the patient went to the emergency department and was given a course of oral prednisone, which did improve his symptoms for a brief time. He tried topical over-the-counter moisturizers which did not help. He saw dermatology 1 month after his rash started and was given a topical steroid cream which did not improve his symptoms. At the time of presentation, he had blisters extending from his neck to his toes. He reports that the blisters would burst and ooze a clear liquid. He denied any new household or personal products (Fig. 1).

Further subjective history was negative for any autoimmune conditions to the patient's knowledge. Family history was also unremarkable. The patient was a nonsmoker.

His vitals identified a healthy body mass index (BMI) (23.7, normal range [NR] 18.5–24.9 kg/m^2). The physical

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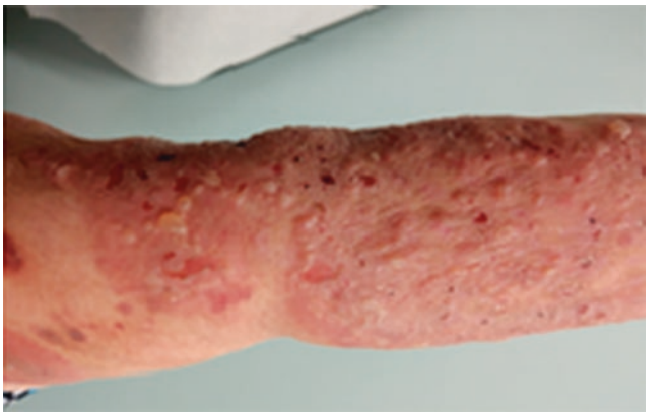

Fig. 1 Picture of the patient's skin lesion

examination revealed an erythematous, macular rash with thin-walled blisters. No evidence of oral mucosal lesions or ocular findings.

At his evaluation, the patient had a skin biopsy revealing subepidermal vesicles containing a dense infiltrate of inflammatory cells including eosinophils. Direct and indirect immunofluorescence (DIF and IIF) studies revealed linear deposition of IgG and C3 along the basement membrane.

Question 1

Based on the biopsy results the most likely diagnosis would be:

A. Erythema multiforme
B. Pemphigus vulgaris
C. Mucous membrane pemphigoid
D. Bullous pemphigoid
E. Lichen planus

Answer: D

The patient in this case is presenting with bullous pemphigoid, an autoimmune disorder characterized by blistering (Table 1). It presents with urticarial and eczematous lesions on the trunk and upper legs that progress to tense bullae. The most common age of onset for BP is 80-years old; however, drug-induced pemphigus can also be seen in the pediatric population, and young adults. BP is the most frequently encountered autoimmune blistering disease and is caused by autoantibodies directed against the hemidesmosomal proteins, BP antigen 180 (BP180) and BP antigen 230 (BP230). The diagnosis can be made with a perilesional biopsy with staining and direct immunofluorescence. A skin biopsy demonstrates subepithelial vesicles with mixed inflammatory infiltrate containing eosinophils. DIF microscopy shows linear IgG and/or C3 staining along the basement membrane zone.

Erythema Multiforme (EM) is an acute inflammatory reaction of the skin, with rare involvement of the mucous membranes, that presents as erythematous macules that classically evolve into targetoid lesions on the extensor extremities. It represents a cell-mediated immune reaction associated with infections (mainly Herpes Simplex Virus), drugs, vaccinations, and autoimmune disorders. The histological features in EM are nonspecific with perivascular inflammation, interface dermatitis, and epidermal necrosis. Unlike BP, DIF is nonspecific and IIF would be negative, making this answer choice incorrect.

Table 1 Characteristics of common blistering skin disorders

Disease	Clinical features	Histology	Autoantibody target	Immunofluorescence
Erythema Multiforme	Sudden onset. Variable lesions: Erythematous macules, target lesions, vesicles. Located on extensor extremities → spread centripetally. Mucous membranes are sometimes involved	Nonspecific. Perivascular inflammation, interface dermatitis, epidermal necrosis with intra and subepithelial vesicular formation	Nonspecific	Nonspecific
Pemphigus vulgaris	No sudden onset. Painful, flaccid bullae with erosions on skin and mucosa. Nikolsky sign is positive	Intraepithelial vesicles with acantholytic keratinocytes, intact basal layer	Epidermal desmosomes (Desmoglein-1 and Desmoglein-3)	Intercellular, reticulated IgG and C3
Mucous membrane pemphigoid	No sudden onset. Vesiculoulcerative lesions involving the mucosa only. May lead to scarring	Perivascular inflammation with subepithelial vesicles	BP230, BP180, α6-integrin, Laminin 5, Laminin 6, b4-integrin, type 7 collagen	Linear IgG and IgA along basement membrane
Bullouspemphigoid	No sudden onset. Pruritic, tense bullae with rare mucosal involvement	Perivascular infiltrate with eosinophils and subepithelial vesicles	BP230, BP180	Linear IgG and C3 along basement membrane
Lichen planus	No sudden onset. Pruritic, flat topped papules and plaques with involvement of the skin (flexor extremities), hair, nails, and mucous membranes	Hyperkeratosis, hypergranulosis, interface dermatitis, saw-toothed epithelial vacuolation with apoptosis	None/unknown	Fibrin deposits along the basement membrane

Pemphigus Vulgaris (PV) is a chronic, autoimmune blistering disease of the skin and mucous membranes. In contrast to BP, PV presents at an earlier age (40–60 years old) with painful, flaccid bullae that rupture easily to form erosions. In addition, the mucosa is almost always involved compared to BP. The primary defect in PV is IgG autoantibodies directed against keratinocyte adhesion proteins resulting in loss of cell adhesion or acantholysis. In turn, DIF demonstrates intercellular deposits of IgG in a reticular pattern around keratinocytes making this an incorrect answer choice.

Mucous Membrane Pemphigoid is a rare, antibody-mediated blistering disorder that only affects the mucous membranes, making this answer choice incorrect. In addition, although DIF would demonstrate linear bands of IgG deposited along the basement membrane, IIF is usually negative.

Lichen planus (LP) is an idiopathic inflammatory disorder of the skin. The skin lesions of LP are characterized by the "6P's" including purple, pruritic, planar, polygonal, papules, and plaques with an overlying reticulated, fine scale known as Wickham striae. The wrist and ankles are common sites of involvement, but any location may be affected including the hair, nails, and mucous membranes. Characteristic histological features of LP include a band-like lymphocytic infiltrate along the dermal-epidermal junction, saw-toothed epithelial vacuolation, and apoptosis with a thickened granular cell layer and stratum corneum making this an incorrect answer choice. In addition, LP will have a negative IIF.

Question 2

What are possible complications of bullous pemphigoid?

A. Neurologic disorders
B. Malignancy
C. Thrombosis
D. A and B
E. All the above

Answer: E

There have been studies that have demonstrated an association between BP and neurologic disorders. A recent systematic review with meta-analysis evaluated 14 studies. Results of the analysis indicated that individuals with BP were five times more likely to develop neurologic disorders such as dementia, epilepsy, multiple sclerosis, Parkinson's disease, and stroke. This review also found that the neurologic disorder typically precedes the onset of BP by 5.5 years. The most common associated neurologic disorder is multiple sclerosis with a 5–12 time risk of development of BP. Unfortunately, the pathogenesis linking BP and neurologic disorders is still not completely understood.

Another study found that bullous pemphigoid antigen (BP180 and BP230) are expressed both in the central nervous system (CNS) and skin. This may be the common feature which connects the clinical manifestations of BP to the CNS. It is postulated that any insult to the CNS can trigger increased levels of anti-BP180. Increases in these levels have been found to correlate with the severity of dementia in patients with Alzheimer's disease.

There is conflicting data regarding BP association with malignancy. Two Japanese studies found higher rates of malignancy in their BP subjects when compared to age-matched controls. One study demonstrated a rate of 5.8% of their BP subjects with malignancies including lymphoma, gastric, colorectal, prostate, lung, and uterine cancers.

In addition to its association with neurologic disorders and malignancy, BP also has been associated with an increased thrombotic risk. BP promotes a dysregulated immune response mediated by Th1 and Th2 cells resulting in an increased synthesis of IL-1B, TNF-α, IL-5, IL-6, IL-8, IL-10, and IL-15. The production of these pro-inflammatory cytokines upregulates vascular endothelial growth factor and E-selectin which results in endothelial cell activation. These patients also have been found to have increased circulating levels of prothrombin and D-dimer as well as overexpression of tissue factor in lesional skin. These levels have been shown to return to normal with disease control. Together this evidence suggests a prothrombotic state exists in the BP patient. This may lead to a higher risk of thromboembolic events, including pulmonary embolism and stroke in comparison to age-matched controls.

Question 3

Which of the following would be the first-line treatment in a patient diagnosed with mild to moderate BP?

A. Doxycycline
B. Low potency topical corticosteroid
C. High potency topical corticosteroid
D. Oral prednisolone
E. Methotrexate

Answer: C

BP is a chronic disease that can persist for many years with a risk of relapse. The main purpose of treatment is to promote healing of the skin lesions as well as to decrease itching and prevent recurrence to improve patients' quality of life.

The first-line treatment in BP depends on the disease severity and spread. For localized and moderate forms of BP the current first-line treatment consists of super potent topical corticosteroids (e.g., clobetasol propionate). The effectiveness of topical clobetasol propionate cream was proven in extensive BP with less mortality and side effects when compared with oral prednisone in a randomized control trial. Limitations of extensive topical steroid use include skin atrophy and difficult application for the elderly person.

In the case of extensive and advanced BP, systemic corticosteroids are considered the first line of treatment. Other alternative therapies may be considered to counteract the systemic effects of oral steroids. For patients who fail to respond to corticosteroids or who develop side effects, other therapeutic options are available.

Doxycycline has proven effective as an alternative to steroids. In a randomized control trial of 253 patients with BP, Doxycycline was noninferior to oral prednisolone for short-term blister control.

The patient was started on an oral prednisone taper and empiric mycophenolic acid (Cellcept) 750 mg twice daily for treatment for BP.

Despite starting mycophenolic acid, the patient had persistent symptoms and reported increased pruritus. He completed two 10-day prednisone tapers and started hydroxyzine 10 mg three times daily as needed for pruritus. There was minimal improvement in his rash and his blisters were in various stages of healing.

After a 26-day trial of mycophenolic acid, the patient elected to stop treatment due to persistence of his rash. Alternative treatment options were considered and discussed with the patient.

Question 4

Which of the following would be the next best step in management for a patient who has failed corticosteroids and corticosteroid-sparing therapy?

A. Intravenous immunoglobulins (IVIG)
B. Cyclosporine
C. Methotrexate
D. Doxycycline
E. Topical urea

Answer: A

Addition of an oral immunosuppressive agent (cyclosporine, methotrexate, mycophenolic acid. Etc.) can be considered with severe disease. However, in cases refractory to corticosteroids and corticosteroid-sparing therapy, biological therapies should be considered. Various biologic therapies can be used including rituximab, omalizumab, dupilumab, and IVIG (Table 2). Therefore, the next most appropriate choice in treatment in this case would be IVIG. Multiple treatment cycles are typically needed for disease improvement. Studies have shown that IVIG leads to a decline in serum levels of BP180 and BP230 antibodies.

The patient was started on 70 g of IVIG daily for 2 consecutive days to treat his resistant disease state. Over the next 6 weeks, he had near complete resolution of his rash and associated symptoms. Monthly IVIG infusions were continued for disease maintenance.

Table 2 Biologic therapies available for refractory BP

Biologic agents	Target	Average response rate based on case series (%)
Rituximab	CD20	85
Omalizumab	Immunoglobulin E (IgE)	84
Dupilumab	IL-4 and IL-13	92
Intravenous immunoglobulin (IVIG)	BP180 and BP230 antibodies	86

Question 5

By what mechanism does IVIG affect autoimmune disorders in general?

A. Modulation of pathogenic autoantibodies
B. Inhibition of complement activation and interception of membranolytic attack complex (MAC) formation, an action relevant to the complement-mediated mechanisms
C. Modulation of the inhibitory or activation Fc receptors on macrophages invading targeted tissues
D. Downregulation of pathogenic cytokines and adhesion molecules
E. All the above

Answer: E

Many mechanisms have been suggested to account for the beneficial action of IVIG in autoimmune and inflammatory disorders including blockade of Fc receptors on cells of the reticuloendothelial system, the neutralization of pathogenic autoantibodies, and the attenuation of complement-mediated tissue damage. The major role of IVIG in these disorders appears to be through its effects on Fc receptors. FcRn blockade leads to an accelerated neutralization and clearance of autoantibodies. The blockade of activating FcγRIII results in reduced opsonization of antigens and decreased pro-inflammatory responses from innate effector cells. Furthermore, sialylated IgG exerts anti-inflammatory effects by upregulated inhibitory FcγRIIB on macrophages. Still other mechanisms of IVIG may include the downregulation of pro-inflammatory genes in macrophages, modulation of dendritic cell maturation and function, and inhibition of lymphocyte autoreactivity. The pleiotropic role and effect of IVIG on autoimmune disease such as BP has yet to be completely elucidated.

Case 2

A 35-year-old female presents to the outpatient clinic for evaluation of a new skin rash. The rash started 4 months prior with scaling, erythematous lesions on the upper trunk. She was seen at a local urgent care clinic and was given an oral

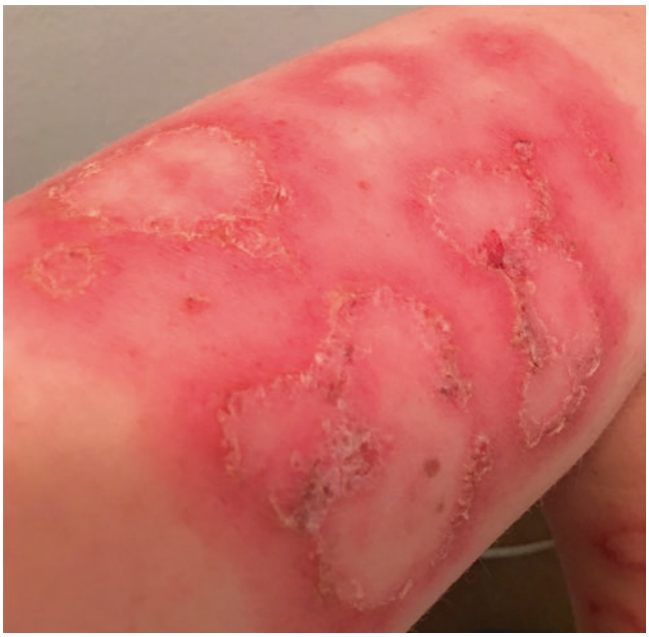

Fig. 2 Picture of the patient's skin lesion

prednisone taper with temporary resolution of her symptoms. The lesions have since progressed with involvement of the extremities. She has been working as a lifeguard for the past year and notes the lesions are exacerbated by the sun. She denies any symptoms other than occasional pruritis. Her medical history is significant for Hashimoto's thyroiditis for which she takes levothyroxine. She has no known allergies. She is a nonsmoker without any recent travel history or sick contacts. Her father has a history of psoriasis limited to the scalp.

Her vital signs were stable. Skin examination revealed erythematous, annular plaques with central clearing forming polycyclic patterns. There are variable amounts of scale-crust at the margins as shown in Fig. 2. There are similar lesions symmetrically distributed over the neck and trunk; however, the face is spared. There are no mucosal lesions or joint swellings present. The remainder of the physical exam was unremarkable.

Laboratory results at the time of evaluation revealed a positive anti-neutrophilic antibody (ANA), but normal blood cell counts and urinalysis. A skin biopsy was performed and demonstrated lymphocytic infiltrate along the dermal-epidermal junction with vacuolar basal cell degeneration. DIF was performed and revealed granular deposits of IgG and C3 along the dermal-epidermal junction.

Question 1

Which of the following is the most likely diagnosis:

A. Discoid lupus erythematous
B. Subacute cutaneous lupus erythematosus
C. Psoriasis
D. Lichen planus
E. Polymorphic light eruption

Answer: B

Lupus erythematous (LE) is a multisystemic autoimmune disorder characterized by the formation of autoantibodies that cause tissue injury mainly through the deposition of immune complexes as well as binding of antibodies directly to cells. Cutaneous manifestations are frequently the initial presentation of LE and can occur with or without systemic disease. LE-specific skin disease includes acute cutaneous lupus erythematous (ACLE), subacute cutaneous lupus erythematous (SCLE), and chronic cutaneous lupus erythematosus (CCLE). Although all types share similar histologic features like interface dermatitis and deposits of immunoglobulin and complement, they differ in clinical presentation, association with systemic disease, and long-term complications.

The clinical vignette above describes a case of SCLE. SCLE occurs most common in middle aged females. Two morphologic variants of SCLE exist: annular and papulosqamous. In the annular variant, scaling, erythematous, plaques with central clearing coalesce to form polycyclic configurations. The papulosqamous variant resembles plaque psoriasis. SCLE is a photosensitive rash and exacerbations occur with sun exposure. In turn, the most affected areas are sun exposed skin like the neck, upper trunk, and extensor portion of the upper extremities; however, the face is usually spared. SCLE heals without scarring or atrophy. Post inflammatory hypopigmentation may result, but usually resolves overtime.

Discoid lupus erythematous (DLE) is the most common type of CCLE. It presents as well-defined, round, erythematous plaques with an adherent scale that involves the hair follicles. Unlike SCLE, the lesions scar as they evolve into atrophic plaques with central hypopigmentation and peripheral hyperpigmentation, making this an incorrect answer choice. In addition, the head and neck are common sites of involvement. Lesions of the scalp can result in permanent alopecia.

Psoriasis is a chronic inflammatory disorder of the skin characterized by well-defined erythematous plaques with overlying silvery scales. It commonly affects the scalp, elbows, knees, and intergluteal cleft but any site may be affected. The nails and joints may also be involved. Psoriasis is not usually exacerbated by UV-radiation, but instead may be beneficial. In fact, phototherapy may be used as a treatment modality in severe disease. Laboratory evaluation in psoriatic patients would demonstrate a negative ANA. The histological findings of psoriasis are characterized by parakeratosis, a decreased granular layer, and a neutrophilic infiltrate in the dermis. DIF would also be negative.

Lichen planus is an idiopathic inflammatory disorder of the skin. The lesions manifest as pruritic, flat-topped papules and plaques with an overlying reticulated scale known as Wickham striae. The wrist and ankles are common sites of involvement, but any location may be affected. The rash is typically not photosensitive. Characteristic histological features of LP are described in Table 1. Both ANA and DIF would be negative.

Polymorphic light eruption (PMLE) is an idiopathic inflammatory disorder of the skin. The lesions can take many morphologies including erythematous macules, papules, plaques, or vesicles that occur after sun exposure. PMLE is a diagnosis of exclusion that may resemble the cutaneous features of lupus erythematous; however, DIF would be negative in PMLE, making this answer choice incorrect.

Question 2

Which of the following is most likely to be positive in this patient:

A. Anti-SSA/Ro antibody
B. Anti-dsDNA antibody
C. Anti-histone antibody
D. Anti-Jo-1 antibody
E. Anticentromere antibody

Answer: A

Detection of serum autoantibodies can aid in the diagnosis of autoimmune diseases. SCLE is strongly associated with Anti-SSA/Ro antibodies. Studies have shown that 70% of patients are positive for anti-SSA/Ro and 70–80% are positive for ANA. In addition, half of the patients with SCLE will be positive for Anti-SSB/La. In contrast to systemic lupus erythematous, only 5% of patients are positive for anti-dsDNA.

Anti-histone antibodies are associated with drug-induced lupus which presents with acute onset fever, arthralgias, and serositis after starting the causative drug. Common culprits are hydralazine, procainamide, isoniazid, and TNF-alpha inhibitors. Unlike SLE, Drug-induced lupus is less likely to have a cutaneous, central nervous system, or renal involvement.

Anti-Jo-1 antibodies are specific for inflammatory myositis, which presents as progressive proximal muscle weakness and atrophy. Dermatomyositis can also present with similar skin manifestations as SLE.

Anticentromere antibodies are associated with disease limited systemic sclerosis or CREST syndrome, which usually presents with fibrosis of the skin limited to fingers and face, calcinosis cutis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias.

The patient was started on an oral prednisone taper supplemented with 0.1% tacrolimus cream. She was advised to apply broad spectrum sunscreen (SPF of at least 50) 20–30 min before sun exposure. The rash resolved without scarring and minimal dyspigmentation.

One year later the rash returned despite extensive photoprotection and continued topical maintenance therapy. In addition to the recurrence of the annular erythematous plaques, the patient also now complains of fatigue, joint pains, and oral ulcers.

The laboratory evaluation revealed an elevated ANA, hemoglobin of 13, and platelet count of 120,000. Urinalysis was normal.

Question 3

What percentage of patients will progress to systemic lupus erythematous?

A. 5%
B. 10%
C. 25%
D. 50%
E. 90%

Answer: D

Cutaneous lupus erythematosus is a common initial manifestation of LE and can occur with or without systemic disease. Fifty percent of patients with SCLE will eventually meet the criteria for systemic disease outlined by the American College of Rheumatology. However, systemic symptoms are mild and most commonly include a photosensitive rash, oral ulcers, arthritis, and positive serology. Most patients do not have central nervous involvement or lupus nephritis. The progression of chronic cutaneous lupus erythematosus to systemic disease is even rarer. In contrast, acute cutaneous lupus erythematosus is almost always associated with systemic disease.

Question 4

Which of the following is the best next step in treatment for this patient?

A. Hydroxychloroquine
B. Methotrexate
C. Mycophenolate mofetil
D. Rituximab
E. Acitretin

Answer: A

The first-line treatment for cutaneous lupus erythematous includes photoprotection, topical or oral steroids (depending on the extend of the disease), and hydroxychloroquine. For localized disease, topical steroids or topical calcineurin inhibitors can be used. For disease that is widespread, scarring or refractory to topicals, hydroxychloroquine is considered the drug of choice. Methotrexate, mycophenolate mofetil, rituximab, and acitretin may be considered in cases refractory to hydroxychloroquine.

Question 5

Which of the following should be monitored while taking this medication?

A. Liver function tests
B. Visual acuity
C. Blood cell counts
D. Thyroid function tests
E. Lipid panel

Answer: B

Hydroxychloroquine is the drug of choice for systemic lupus erythematosus as well as cutaneous lupus erythematous that is widespread, severe or refractory to other first-line treatments. Although hydroxychloroquine is normally well tolerated, there is an increased risk of retinopathy after 5–7 years of use. The American Academy of Ophthalmology recommends a baseline examination for patients starting hydroxychloroquine with annual eye examinations after 5 years.

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