Pooya Khan Mohammad Beigi

A Clinician's Guide to Pemphigus Vulgaris

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To my real hero
Mohammad Khan Mohammad Beigi
who inspired me to achieve and succeed by focusing only ever on the goal and never on the obstacles

and

To my real teacher
Parvin Mojabi
to whom I owe my life and all that I have accomplished and become

and

To my real companion
Sherry Jalalian
who unceasingly encouraged me with her patience, without which I would not have been able to persevere in spite of my humanity

Foreword

In the Old Testament, Job's faith is tested by a terrible blistering disease that assails his skin. "From the sole of his foot to the crown of his head," he is blanketed with boils. Of his plight, he laments, "I am decaying like a rotten thing, like a garment that is moth-eaten."

To patients who developed pemphigus vulgaris throughout history, the story of Job must have come to mind, though unlike Job, their predicament was almost universally lethal. As late as the 1950s, this blistering disease of seemingly Biblical wrath was considered a death sentence within a short period of time. We can imagine the countless individual cases coalescing into a representative narrative, the horror of recognition when the relentlessly advancing rash is diagnosed and given a prognosis, the oral and mucosal ulcers so widespread that they prevent eating or drinking, or the grim struggle of the patient and physician to preserve the integrity of the skin as it sloughed off in sheets. Inevitably, infection and sepsis followed, and then death.

The development and widespread use of corticosteroids provided the first flicker of hope for patients with this disease. While the side effects of prolonged high-dose steroids are numerous, these drugs afforded some measure of control for patients suffering with the disease. More recently, with the development of other immunosuppressants, the use of IVIG, and the advent of biologic agents, patients with pemphigus have been offered hope that they may live with a degree of comfort or even achieve remission. Yet many of the newer treatments are available only in developed countries and even then to patients with insurance or the means to purchase expensive therapies. There is still work to be done in the service of a cure, but much has been achieved, and there is abundant cause for gratitude.

Dr. Beigi's monograph summarizes much of what is known about the varieties of blistering disease including pemphigus. As a clinical dermatologist, his firsthand experience with patients who have blistering diseases comes through in this work. He joins the succession of talented physicians who have devoted their time and energy to the study of maladies and to the very real betterment of individual lives.

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Disclaimer

The texts, tables, charts, and pictures in this book are for education, guidance, and information purposes only. Responsibility remains in the hands of the clinician diagnosing and treating their own patient to determine the correct care plan. No one who took part in creating this collection can be held legally responsible for any of the information contained in the book. It is also important to note that new and improved diagnoses and care plans are being constantly discovered due to the great advancements in medical science. Therefore, we invite all readers to keep up with the recent research besides utilizing this text.

Pooya Khan Mohammad Beigi, MD, MSc

Preface

One of the greatest joys in the life of a medical professional is to see the smile on a patient's face when told they have recovered or improved.

Thanks to medical advancements, many patients easily move on with their lives; however, in the past, many patients were faced with severe and debilitating conditions due to the lack of proper treatment. With the help of the aforementioned medical advancements, profound changes have been made to eliminate etiologies and cure diseases as the underlying causes are now identifiable.

Nevertheless, some diseases have unknown causes. That is why the prevention of these diseases is difficult and sometimes even impossible; among this group of diseases whose exact causes are currently unidentified are autoimmune diseases. An autoimmune disease occurs when the body identifies a part of itself as an intruder and begins to attack or destroy the cells associated with that particular area of the body.

Pemphigus is one such type of autoimmune disease. In the past, many pemphigus patients were faced with severe complications, and the rate of morbidity and mortality was high. Today, thanks to advances in medical research, patients have seen major improvements in their quality of life.

As with many diseases like pemphigus, there are high rates of complication; therefore, these diseases should be diagnosed and treated as soon as possible. Unfortunately, pemphigus has symptoms that are similar to many other diseases, which often makes its diagnosis difficult. Doctors have to use other diagnostic methods and tools and utilize the help of experts and specialists for the correct diagnosis. Despite tremendous advancements in diagnostic medicine, the increased cooperation of experts, and the use of modern tools, misdiagnosis still occurs.

Upon misdiagnosis, many patients undergo treatment plans and receive medications that do not improve their health but may also result in the deterioration of symptoms or the formation of non-compensable effects. Misdiagnosis and errors in treatment in diseases such as pemphigus can also lead to early patient mortality and morbidity.

As previously mentioned, medicine is a progressive science, and new medications and information become available daily; there are increasingly accurate and

efficient diagnostic and therapeutic tools being discovered.[1] It is my hope that this book will be a significant step in enhancing the knowledge of physicians and other healthcare providers involved in the diagnosis and treatment of pemphigus.

This book begins with a definition of the basement membrane by briefly discussing the functions and structural components of this cellular structure.

Next, the pemphigus group of diseases is introduced. Details regarding each type of the diseases' immune response, such as expression of antibodies against proteins on the surface of epidermal cells, as well as the different variants and their clinical characteristics are provided to give the reader a comprehensive understanding of this group of autoimmune diseases. It then proceeds to discuss one specific type: pemphigus vulgaris.

To provide an overview of pemphigus vulgaris, the history, origin of discovery, epidemiology, and etiology of this disease are included before proceeding to an in-depth analysis of this skin disease. To aid physicians in their decisions about when and which treatment(s) to start, the activity levels of pemphigus vulgaris are discussed in detail. Subsequently, the strategies in effectively diagnosing the disease, as well as the histological and physical examinations that must take place, are also detailed in this book.

Since pemphigus vulgaris is a rare autoimmune disease of which many health practitioners are still unaware due to its low rate of incidence, it is often misdiagnosed. Thusly, ineffective treatments may worsen the patient's outcome. Differentials for this disease are also discussed to reduce incidents of misdiagnosis and to help with the recognition of the clinical traits that are indicative of either pemphigus vulgaris or another similar disease.

Finally, the treatment options for pemphigus vulgaris are discussed in this book. Available medications and their recommended dosages and side effects are provided to the reader. Alternate options, in which the signs of recovery are not observed or where complications arise, are also briefly illustrated to provide the reader with a broader perspective of the types of treatments available for this type of skin disease.

Numerous articles and books have been published in the field of pemphigus disease, but unfortunately, due to the rarity of the disease and the inherent difficulty in studying rare diseases, a comprehensive reference for pemphigus disease is hard to find. The goal of this book is to review and examine all of the verified studies on this disease along with the results of the studies conducted on several of my patients. This book intends to present this information as a unified and complete reference.

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Introduction

Pemphigus can be a severe and sometimes lethal disease. The diagnosis is frequently very delayed because this disease is rare and poorly known, even by the dermatologists. Hence, this book will be a valuable auxiliary.

The variety of pemphigus diseases and their clinical variants, as well as many possibilities of differential diagnosis, may also explain the difficulties of diagnosis. Skin is not the only involved organ and mucosa are also frequently affected.

Pemphigus is the manifestation of circulating autoantibodies against the intercellular adhesion structures of the epidermis, desmosomal proteins desmogleins 3 and 1. However, there is accumulating evidence that indicates that pemphigus vulgaris also targets other, nondesmoglein, molecules. The pathophysiology of pemphigus is not fully elucidated.

Without any treatment, the prognosis for pemphigus vulgaris is very bleak, and people would die within 2–5 years. Nonetheless, treatments can also induce severe side effects. Whereas the corticosteroids were the reference treatment, therapeutic alternatives like rituximab are very promising.

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Part I
Overview of Disorder

Chapter 1
Background

Basement membranes are thin layers of extracellular connective tissue that divide epithelial cells from the underlying connective tissue or from different types of cells [1]. Basement membranes are very complex structures that play different roles and have different compositions and structures, depending on the type of tissue they are found in. Functionally, basement membranes play many different roles. For instance, they are the site of attachment for many cells; can influence the behavior of cells such as their growth, apoptosis, development, and differentiation; and can also be the backbone structure for cell and tissue repair. The basement membrane can also regulate the extracellular environment of cells by acting as a selectively permeable structure. In this book, we will specifically be discussing the structure of the epidermal basement membrane, because many of the diseases that we will discuss will require a basic understanding of this important type of basement membrane.

The epidermal basement membrane consists of four major layers [2]. The first layer is called the basal keratinocyte layer, and it consists of the plasma membrane of the basal layer of keratinocytes, the hemidesmosomes, and cytoskeletal keratin intermediate filaments inside the keratinocyte, which connect to the hemidesmosomes. The second layer is called the lamina lucida, and it contains the extracellular connections, also known as anchoring filaments, that run between the hemidesmosomes and the lamina densa [3]. The lamina densa, also known as the basement membrane proper, is the next layer of the basement membrane found beneath the lamina lucida. The fourth layer of the basement membrane is the sublamina densa region, which consists of anchoring fibrils, microfibrils, interstitial collagens, micro-thread-like fibers, and anchoring plaques, which are components of the papillary dermis that connect it to the lamina densa above (Fig. 1.1).

Acquired immune vesiculobullous diseases are diseases in which the body starts to produce autoantibodies against protein antigens in the epidermis or in the basement membrane associated with the epidermal cells [4]. Acquired immunobullous diseases can be divided into epidermal pemphigus or subepidermal pemphigoid diseases. Pemphigus diseases involve autoantibodies against proteins in the epidermis,

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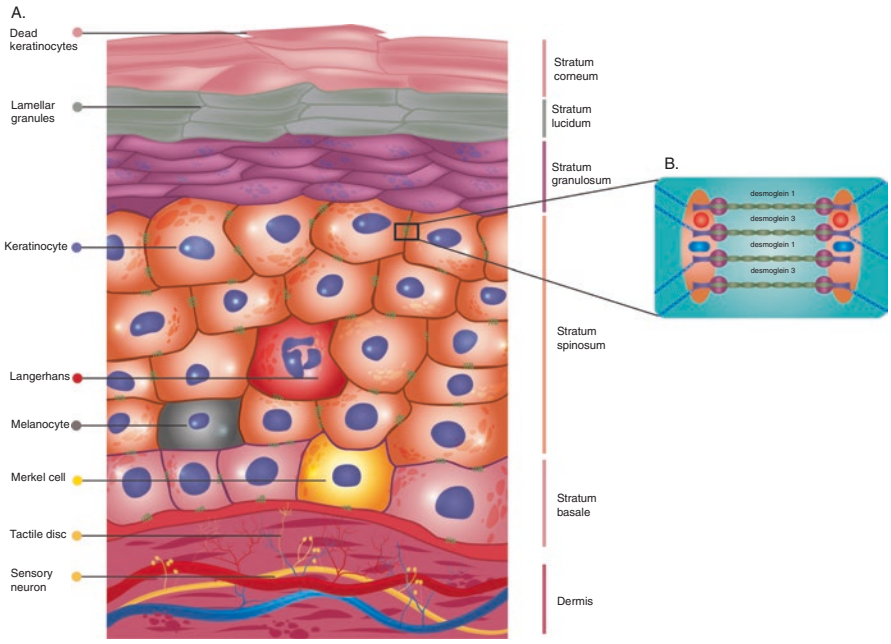

Fig. 1.1 Anatomy of the basement membrane. (**a**) The five layers of epidermis, which include the superficial layer of stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and the innermost layer of stratum basale. Stratum corneum is made up of dead keratinocytes that are linked together with proteins. Stratum lucidum contains dead keratinocytes that have not completely finished the keratinization process. Stratum granulosum is the layer containing keratinocytes that contain keratohyalin granules. Stratum spinosum is characterized by the presence of desmosomes that results in an impermeable junction between keratinocytes as seen in section B of this image. Stratum basale is the deepest layer of epidermis, which contains a single layered column of epidermal stem cells. Moreover, the epidermis also contains specialized cells that are most prominent in stratum spinosum. For example, Langerhans are present in all stratums except stratum corneum, and their primary function is to fight skin infections by becoming antigen-presenting cells. Melanocytes are melanin-producing cells responsible for skin color. Merkel cells contain mechanoreceptors responsible for the detection of light touches. (**b**) The desmosome junction between keratinocytes that is created by the binding of desmoglein 1 (dsg1) and desmoglein 3 (dsg3) antibodies that attach to cell surface (Source: Pooya Khan Mohammad Beigi)

whereas the pemphigoid group of diseases involves subepidermal autoantibodies against proteins in the basement membrane associated with the epidermis.

Pemphigus

The pemphigus group of diseases are immune diseases involving immunoglobulin G (IgG) autoantibodies against various proteins found on the surface of epidermal cells [1]. This group of diseases is divided into three main disease groups:

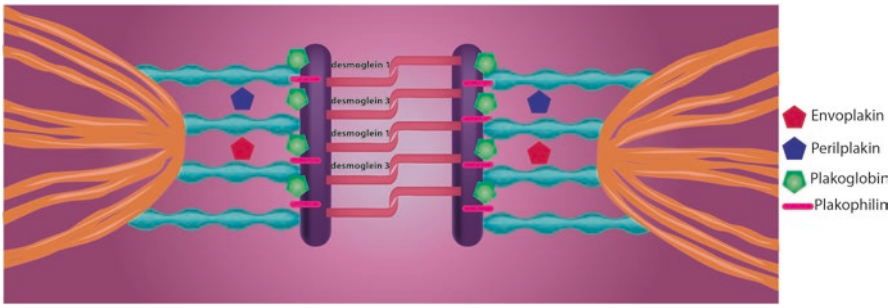

Fig. 1.2 The junction between keratinocytes that is characterized by desmosomes, which create an impermeable junction between the cells. The desmosome junction is created by the binding of desmoglein 1 (dsg1) and desmoglein 3 (dsg3) antibodies that attach to cell surface. As seen in the image, the junction is created with the help of additional proteins. For example, envoplakins interact with periplakins in order to serve as an intermediate filament in the desmosome junction. The plakoglobin serves as the cytoplasmic component. Lastly, plakophilins are proteins that link cadherins to intermediate filaments in the junction (Source: Pooya Khan Mohammad Beigi MD)

pemphigus vulgaris, pemphigus foliaceus, and paraneoplastic pemphigus. Pemphigus foliaceus involves autoantibodies against desmoglein 1 proteins, and paraneoplastic pemphigus involves autoantibodies against both desmoglein and plakin. There are two different variants of pemphigus vulgaris: one is the mucocutaneous variant and the other is the mucosal dominant variant [1]. The mucosal dominant variant of pemphigus vulgaris involves autoantibodies against only desmoglein 3, whereas the mucocutaneous variant involves autoantibodies against both desmoglein 1 and 3 (Fig. 1.2).

Desmoglein Compensation Hypothesis of Pemphigus Disease Presentation

On mucosal surfaces, both desmoglein 1 and 3 are expressed; however, desmoglein 3 dominates in terms of its expression in the mucosa compared to desmoglein 1 [5]. In the skin epidermis, desmoglein 1 is expressed everywhere, but is mainly expressed in the superficial upper layers of the skin epidermis, whereas desmoglein 3 is expressed in the basal lower layers of the epidermis. These differences have been hypothesized to explain the clinical features of various presentations of pemphigus based on the autoantibodies involved [6]. For instance, pemphigus vulgaris involves autoantibodies primarily directed against desmoglein 3 proteins, and since these proteins are rendered dysfunctional by the antibodies, the keratinocytes in the lower basal layers of the epidermis become detached from one another, resulting in the blisters in the basal layers of the epidermis [5]. In pemphigus foliaceus, the skin blisters are more superficial, and this can be explained by the fact that this disease involves autoantibodies to desmoglein 1, which is mainly expressed in the

superficial layers of the epidermis. Pemphigus foliaceus has no mucosal erosions simply because desmoglein 3 dominates in terms of its expression in the mucous membranes [5].

Pemphigus vulgaris has two primary clinical variants, and the clinical features of these two variants can also be explained based on desmoglein expression. The mucocutaneous variant that involves autoantibodies against desmoglein 1 and 3 causes mucosal erosions and deep skin blisters [5]. The mucosal dominant variant that involves antibodies against desmoglein 3 only causes mucosal erosions and no skin lesions, because the desmoglein 1 in the lower epidermal layers makes up for the lack of desmoglein 3; however, in the mucous membranes, there is not enough desmoglein 1 to make up for the lack of desmoglein 3, since desmoglein 3 is expressed in greater quantity than desmoglein 1 in the mucous membranes [5]. There is a minority of patients that have cutaneous-only disease expression (i.e., no current or history of mucosal lesions) that cannot be fully explained by the desmoglein 3/1 compensation hypothesis. Recent literature indicates that pemphigus vulgaris patients harbor antibodies to other, nondesmoglein, targets [7–9].

Types of Pemphigus Diseases

Pemphigus Vulgaris (Explained in Detail in the Next Section)

Pemphigus Vegetans

Pemphigus vegetans is a clinical variant of pemphigus vulgaris that involves erosions that form fungoid or papillomatous growths. These fungoid or vegetative growths are mainly seen on the scalp or face. This clinical variant is fairly rare and involves two subtypes: mild Hallopeau and severe Neumann types [1].

Pemphigus Foliaceus

Pemphigus foliaceus only has cutaneous erosions and does not involve any mucosal erosions. It is an autoimmune disease in which the body produces IgG autoantibodies against desmoglein 1 proteins on the surface of keratinocytes in the superficial upper layers of the epidermis. The erosions look crusted and scaly in appearance and are transient in nature. These erosions also have an erythematous base. These erosions are found mainly on the upper trunk, scalp, and face [10].

Pemphigus foliaceus is similar to pemphigus vulgaris with respect to the fragile blisters that are rarely ever found intact; thus, we only see the crust and scaly erosions left over from the ruptured superficial vesicles [10]. In this disease, the Nikolsky sign is present. The Nikolsky sign involves pushing the top of a blister and observing whether the top epidermal layers of the blister move laterally. This would indicate the absence of intercellular connections holding the top layers of epidermal cells together. Patients that have this disease often complain of painful burning lesions.

Pemphigus Erythematosus

This is also known as the Senear-Usher syndrome [1]. This is considered to be a type of pemphigus foliaceus that is only found on the malar region of the face. So it is a variant of pemphigus foliaceus, in which the crusted lesions only appear on the nose and malar regions.

Paraneoplastic Pemphigus

Paraneoplastic pemphigus is a disease associated with the presence of benign or malignant neoplasms [11]. The most commonly associated neoplasms include non-Hodgkin's lymphoma and chronic lymphocytic leukemia, which account for around 67% of all the paraneoplastic pemphigus cases. Castleman's disease is associated with about 10% of the paraneoplastic pemphigus cases. This disease is not associated with common tumors, such as breast or colon carcinomas.

The structure of the blisters can range from being flaccid and fragile, like in pemphigus vulgaris, to being stronger more tense blisters, such as the one seen in bullous pemphigoid [11]. Erosions can also be more vegetative in nature. However, a key clinical feature that can be used to distinguish from pemphigus vulgaris is the presence of the reddened lesions and vesicles on the patient's palms and soles, which is a very rare observation in pemphigus vulgaris patients [11].

At the onset of the disease, the most common clinical sign of paraneoplastic pemphigus is intractable stomatitis, in which erosions and ulcerations are found on the oropharynx up to the vermillion lip [11]. This disease also commonly causes pseudomembranous conjunctivitis, which may become more and more severe until it destroys the conjunctival fornices. There are also erosions commonly seen in the genital mucosal areas, as well as the nasopharyngeal areas [11].

Herpetiform Pemphigus

This is seen as a clinical variant of pemphigus foliaceus in most cases and can also be a clinical variant of pemphigus vulgaris [12]. The clinical presentation of herpetiform pemphigus is milder than the presentation in both pemphigus foliaceus and involves red itchy erosions and blisters in a herpetiform pattern. It also involves subcorneal pustules and eosinophilic spongiosis [12]. Unlike PV and PF, no acantholysis is seen histologically. Depending on which clinical variant it is, the disease will involve IgG antibodies to desmoglein 1 or 3 and will have a milder clinical presentation of pemphigus foliaceus or pemphigus vulgaris, respectively [12].

Drug-Induced Pemphigus

Patients may produce antibodies to desmoglein proteins in response to some drugs, or these drugs may affect the function of the desmoglein proteins to induce pemphigus [1]. These drugs include penicillamine and captopril. Penicillamine is usually used in rheumatoid arthritis treatment and in Wilson's disease, or to treat cystinuria, and can cause pemphigus foliaceus or pemphigus vulgaris [1]. However, it is four times more likely to cause pemphigus foliaceus than pemphigus vulgaris. Captopril is an angiotensin-converting enzyme (ACE) inhibitor, which also can cause pemphigus. Usually when the patient is taken off the drug, the pemphigus goes into remission, but this is not always the case [1].

Immunoglobulin A Pemphigus

Unlike all other types of pemphigus, immunoglobulin A (IgA) pemphigus involves IgA autoantibodies against antigens on the cell surface of keratinocytes [13]. This disease is classified into two subtypes: subcorneal pustular dermatosis (SPD) and intraepidermal neutrophilic (IEN) type. In the SPD type, patients have an annular pattern of red pustules with crusting found in the center of the ring pattern of pustules [13]. In the IEN type, the arrangement of the red pustules resembles a sunflower. The pustules and lesions are often pruritic and are most commonly found in the axilla and groin areas. These lesions can also be found on the trunk, on the lower abdomen, and on the proximal parts of arms and legs [13].

Pemphigoid Group of Diseases

The pemphigoid group of diseases includes two major diseases: bullous pemphigoid and cicatricial pemphigoid. Pemphigoid diseases involve subepidermal autoantibodies against proteins in the basement membrane associated with the epidermis.

Bullous Pemphigoid

Bullous pemphigoid is the most common type of disease involving antibodies targeting subepidermal antigens [4]. This is also a chronic blistering disease like pemphigus vulgaris; however, it mainly affects people over the age of 60, and the blisters mainly cover the arms and legs, as well as the trunk area of the patients [4, 14]. In this condition, the blisters are itchy, unlike the ones in pemphigus foliaceus, and they are rarely found in the mucous membranes of the mouth [14]. It has spontaneous exacerbations and remissions and has a high rate of morbidity. It involves pruritic lesions that affect the skin in large generalized areas, and it affects the whole body; however, in its early stages in rare variants of the disease, it can be misdiagnosed because the lesions are more eczematous and may be more localized [4]. The antigens targeted by the autoantibodies in this disease are parts of hemidesmosomes, which are the junctional complexes found between the epidermis and basement membrane. This disease has two distinct phases: the non-bullous phase and the bullous phase. In the non-bullous phase, this disease is quite non-specific and involves mild to severe intractable pruritic skin [4]. There may also be eczematous or urticarial lesion involvement, and this ranges from weeks to months. Then in the bullous phase, tense, clear fluid-filled blisters take up an annular arrangement on the abdomen, limbs, and lower trunk. These lesions are between 1 and 4 cm in diameter [4].

Cicatricial Pemphigoid

Cicatricial pemphigoid, unlike bullous pemphigoid, mainly affects the mucous membranes [1]. It most commonly affects the oral and conjunctival mucosae and is a chronic disease that can cause long-term complications due to scarring. Histological and immunofluorescence studies can help to distinguish this from pemphigus vulgaris, which also mainly affects oral mucosa.

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Chapter 2
Overview of Pemphigus Vulgaris

Overview of Pemphigus Vulgaris

Introduction

Pemphigus is originated from the Greek word *pemphix* meaning bubble or blister. Pemphigus vulgaris (PV) is a life-threatening chronic autoimmune disease where the serum autoantibodies respond to the cell surface antigens resulting in a loss of epidermal cell cohesion [1]. This can be characterized as the manifestation of circulating autoantibodies against the intercellular adhesion structures, desmosomal protein desmoglein (DSG) 3, and in some cases DSG1. However, there is accumulating evidence that indicates that pemphigus vulgaris also targets other, nondesmoglein, molecules. The functional role of these other specificities and their impact on disease expression are yet to be fully elucidated [2–4].

Disruption of the cell-cell and cell-matrix adhesion due to the circulating autoantibodies results in acantholysis, which could result in Tzanck phenomenon—the rounding of single epidermal cells due to the loss of cell-cell attachment [1].

Desmoglein proteins are a type of cadherin, which is a transmembrane protein that binds with other cadherins to form junctions known as desmosomes between cells [5]. These desmoglein proteins thus hold cells together, but when the body starts producing antibodies against desmoglein, these junctions break down, and this results in subsequent blister or vesicle formation.

Initially, PV is expressed in the form of intraoral lesions, which then spread to other mucus membranes and skin, causing cutaneous and mucosal blistering. This disease is commonly seen in the elderly population, and 50 % of the cases primarily display oral lesions in the form of blisters (within the epidermis) that quickly rupture causing patients to suffer excruciating erosions [6]. Patients can develop lesions anywhere within the oral cavity; however, the soft palate, buccal mucosa, and lips are shown to be more commonly involved [6].

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There are two dominant clinical variants of pemphigus vulgaris: one is the mucocutaneous variant and the other is the mucosal dominant variant [7]. The mucosal dominant variant of pemphigus vulgaris involves autoantibodies against only desmoglein 3, whereas the mucocutaneous variant involves autoantibodies against both desmoglein 1 and 3. Pemphigus vulgaris has the two variants, and the clinical features of these two variants can also be explained based on desmoglein expression. The mucocutaneous variant that involves autoantibodies against desmoglein 1 and 3 causes mucosal erosions and deep skin blisters. The mucosal dominant variant that involves antibodies against desmoglein 3 only causes mucosal erosions and no skin lesions, because the desmoglein 1 in the lower epidermal layers makes up for the lack of desmoglein 3. However, in the mucous membranes, there is not enough desmoglein 1 to make up for the lack of desmoglein 3, since desmoglein 3 is expressed in greater quantity than desmoglein 1 in the mucous membranes. There are, however, a small group of patients that never had mucosal lesions (no current or history of mucosal lesions), classified as cutaneous-only pemphigus vulgaris, whose disease presentation cannot be fully explained by the distinct expression patterns of desmoglein 3 or 1. It remains to be determined if this group of patients is linked to the presence of autoantibodies to nondesmoglein targets.

If left untreated, pemphigus vulgaris can be fatal. This may be due to the complications of ulceration. For instance, if the erosions get infected, it may cause the patients to become septic [8]. The erosions stem from a lack of cohesion among the epidermal or mucosal layer of cells, and this disrupts the function of these cells to retain water, thus resulting in fluid loss as a complication of the disease [7]. Since the blisters are very fragile and rupture easily, physicians rarely are able to find intact blisters [7].

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Chapter 3
History of Pemphigus Vulgaris

Pemphigus was derived from the Greek word *pemphix*, which means vesicle or blister [1]. There are many different types of pemphigus, all involving vesicle formation at some stage, but the most common of all of them is pemphigus vulgaris. All types of pemphigus involve acantholysis, which means the breaking apart of intercellular connections through an autoantibody-mediated response. It was in 1964 that researchers first found that antibodies were responsible for breaking the intercellular connections between keratinocytes leading to this disease. Then, in 1971 through immunofluorescent staining, it was found that the body produces immunoglobulin G (IgG) autoantibodies against the intercellular substance that holds epithelial cells together.

Pemphigus vulgaris used to be an indefinitely fatal disease before the introduction of corticosteroids as the primary form of treatment in the 1940s [2]. Even though the mortality rate had decreased significantly with the help of corticosteroids, pemphigus vulgaris was still known as the fourth most common cause of death due to a skin disorder in 1998.

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Chapter 4
Epidemiology and Etiology

Epidemiology

Pemphigus vulgaris (PV), an autoimmune blistering disease, is a rare disease with an estimated worldwide yearly incidence of 0.1–0.5 per 100,000 populations [1, 2]. PV is also the most common form of pemphigus. The occurrence is mostly common in middle-aged and older adults between the ages 50 and 60 years, although there have been a few cases in children [1]. PV has a male-to-female ratio of 1:2, showing a higher incidence in women [3]. A study conducted by Gupta et al. in 2011 also found that more women than men suffer from PV and they resonated this to the female predominance reported in several other autoimmune diseases [2]. Nonetheless, it was noted that there are restricted number of studies on pemphigus that do not depict female supremacy. Though PV can occur in people of all racial and ethnic backgrounds, it has the highest incidence in Ashkenazi Jews. PV is known as one of the most common pemphigus diseases, accounting for about 70% of all pemphigus cases in India, China, Malaysia, and the Middle East [4].

Etiology

The etiology of pemphigus vulgaris is still unknown. It is a complex disease, where susceptibility is multifactorial, involving both genetic and environmental factors (most of which are unknown) [5, 6]. PV involves the body creating antibodies to desmoglein cadherin proteins that form the intercellular junctions between epithelial cells, but the specific cause of attack by the immune system is not known [1]. It has been speculated that viral infections may be involved in the production of autoantibodies. The more frequent occurrence of PV in Ashkenazi Jews and those of Mediterranean origin may point toward a strong genetic basis [3]. PV has also been found to demonstrate a strong association with certain human leukocyte antigen

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(HLA) class II alleles [3]. There seems to be a strong genetic link between pemphigus vulgaris and having the HLA-DR4 and HLA-DR6 HLA types, since about 95% of people who have pemphigus vulgaris also have one or both of these HLA types [5, 6].

On the other hand, environmental factors may also play a role in the progression of this life-threatening blistering disease. Some initiating factors include foods with high garlic content, infections, neoplasms, and drugs—in particular those in the thiol group such as captopril, penicillamine, and rifampicin [3]. A survey study of 126 PV patients found that patients who were smoking cigarettes experienced an improvement in PV, while nonsmokers experienced worsening in their condition [7]. This can be explained by the antiestrogenic effects of smoking, which seem to be contributing to the protective effect in PV. Furthermore, activation of nicotinic cholinergic receptors on keratinocytes stimulates calcium influx, which increases cell-cell adhesion and promotes lateral migration of keratinocytes improving the symptoms of PV [7]. The study also found an increase in the risk of developing PV with increased exposure to pesticides and metal vapor. Pesticides may contribute to the disease process due to its estrogenic effect. It is yet to be determined whether preventing exposures to pesticides and metal vapor may be advantageous in the clinical context [7]. There have also been hypothesized drug triggers for PV, which include medications that contain thiol groups, for example, rifampicin. Neoplasms have also been hypothesized to trigger pemphigus vulgaris in some cases. Other environmental factors have also been hypothesized to play a part in autoimmune antibody formation, for example, ultraviolet (UV) rays and stress [4]. All in all, there seems to be an interaction between genetic and environmental factors in the development of PV.

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Chapter 5
Analysis of Pemphigus Vulgaris

Clinical Variants of Pemphigus Vulgaris

There are two main different variants of pemphigus vulgaris: one is the mucocutaneous variant and the other is the mucosal dominant variant [1]. The mucosal dominant variant of pemphigus vulgaris involves autoantibodies against only desmoglein 3, whereas the mucocutaneous variant involves autoantibodies against both desmoglein 1 and 3. Some patients, however, report never having musocal lesions and are classified as having cutaneous-only disease.

Pemphigus vegetans is also a clinical variant of pemphigus vulgaris that involves erosions that evolve into fungoid or papillomatous growths [1]. These fungoid or vegetative growths are mainly seen on the scalp or face. This clinical variant is fairly rare and involves two subtypes: mild Hallopeau and severe Neumann types.

Classification of Pemphigus Disease Activity

According to the "Consensus Statement on Definitions of Disease Endpoints and Therapeutic Response for Pemphigus," all pemphigus diseases can be classified according to the level of disease activity [2]. Knowing the disease activity level of pemphigus vulgaris can aid physicians in their decisions about which treatment to start and when in the course of the disease.

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Early Endpoints

The classification of disease activity is divided into four big categories: (1) early endpoints, (2) late endpoints, (3) relapse or flare, and (4) treatment failure [2]. Early endpoints include three stages of disease activity: baseline, control of disease activity, and end of consolidation phase. The baseline is referred to as the level of disease activity on day 1 of when the doctor begins the treatment on the patient with pemphigus vulgaris. Control of disease activity is when the current lesions that the patient has are starting to heal and there are no new lesions cropping up. The end of the consolidation phase of disease activity is when the patient has had no new lesions for at least 2 weeks, and the already existing lesions have healed over. This stage is clinically important because the physician may be able to start weaning the patient off of the immunosuppression therapies at this point.

Late Endpoints

The second part of this classification includes the late endpoints [2]. Late endpoints of pemphigus diseases include complete remission off therapy, complete remission on therapy, partial remission off therapy, and partial remission on minimal therapy. Complete remission off therapy is the classification that we give the disease when there have been no new lesions and/or established lesions for at least a period of 2 months without any treatment. The "complete remission on therapy" classification is a bit more complicated however. It simply means that there are no new lesions cropping up and no previously established lesions present while the patient is on treatment.

Complete remission on therapy can be further divided into the following categories: minimal therapy and minimal adjuvant therapy [2]. When the patient has complete remission on minimal therapy, the guidelines are referring to the "minimal therapy" as up to a maximum of 10 mg/day of prednisone, an equivalent treatment, or the use of "minimal adjuvant therapy" for at least 2 months. Minimal adjuvant therapy is when half the full therapeutic adjuvant dose is given to the patient.

Partial remission off therapy is when a patient, who has received no forms of treatment for a period of at least 2 months, gets new lesions that then heal within a period of a week without restarting any forms of treatment. Partial remission on minimal therapy is when a patient gets new lesions that heal within 1 week of erupting [2].

Relapse/flare is the third type of disease activity. It is when a patient gets three new lesions within the time frame of a month and they do not heal within a week without any treatment. It also can be defined as a patient who has been in the "control of disease activity" early endpoint, whose established lesions start getting worse instead of healing [2].

Treatment failure is the last type of disease activity discussed in the guidelines. It is basically defined as the failure of bringing the patient to the "control of disease activity" early endpoint despite using the maximum therapeutic doses accepted by the guidelines [2].

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Chapter 6
Overview of Diagnosis

Diagnosis

Patients with pemphigus vulgaris (PV) are seen to initially suffer from oral erosions and then successively develop cutaneous involvement. Mucous membrane erosions precede cutaneous expressions of the disease and often result in a lengthened course of misdiagnosis with illnesses such as aphthous ulceration [1]. As seen in some cases of PV, painful oral ulceration may appear to be the only indicator of the disease. Common mucosal surfaces that are involved in the manifestation of the disease include the gingiva, soft and hard palate, floor of the mouth, tongue, esophagus, oropharynx, nasal, larynx, urethra, vulva, and cervix [1, 2]. Conjunctiva involvement is less frequently observed in PV. PV patients also demonstrate dysphagia accompanied with weight loss [2].

Oral involvement remains isolated for months before the occurrence of cutaneous lesions that could be localized or generalized. Commonly involved skin lesions occur on the trunk, groins, axillae, scalp, face, and various pressure points of the body [1]. These sites develop flaccid blisters that amalgamate and eventually rupture resulting in agonizing erosions. The addition of new blisters to adjacent skin upon slight pressure (direct Nikolsky) and shearing of the skin as a result of rubbing on normal skin (indirect Nikolsky) may be a suggestive sign of PV but not a 100% reliable diagnosis [1]. Other clinical manifestations are nail dystrophy, paronychia, subungual hematomas, and neonatal pemphigus vulgaris [1]. Additionally, association of the periungual areas can contribute to chronic perionyxis, onychomadesis, onychoschizia, and onycholysis [2]. Skin lesions are also predominantly found on areas with scars and radiotherapy.

There are three major and two minor criteria for the diagnosis of PV (Fig. 6.1). The three major criteria consist of the clinical picture, biopsy/histopathology, and direct immunofluorescence (DIF). First, the dermatologist performs a comprehensive physical exam of the patient, paying close attention to clinical factors such as nonscarring, fragile vesicles, and bullae involving the mucosae and varying degree

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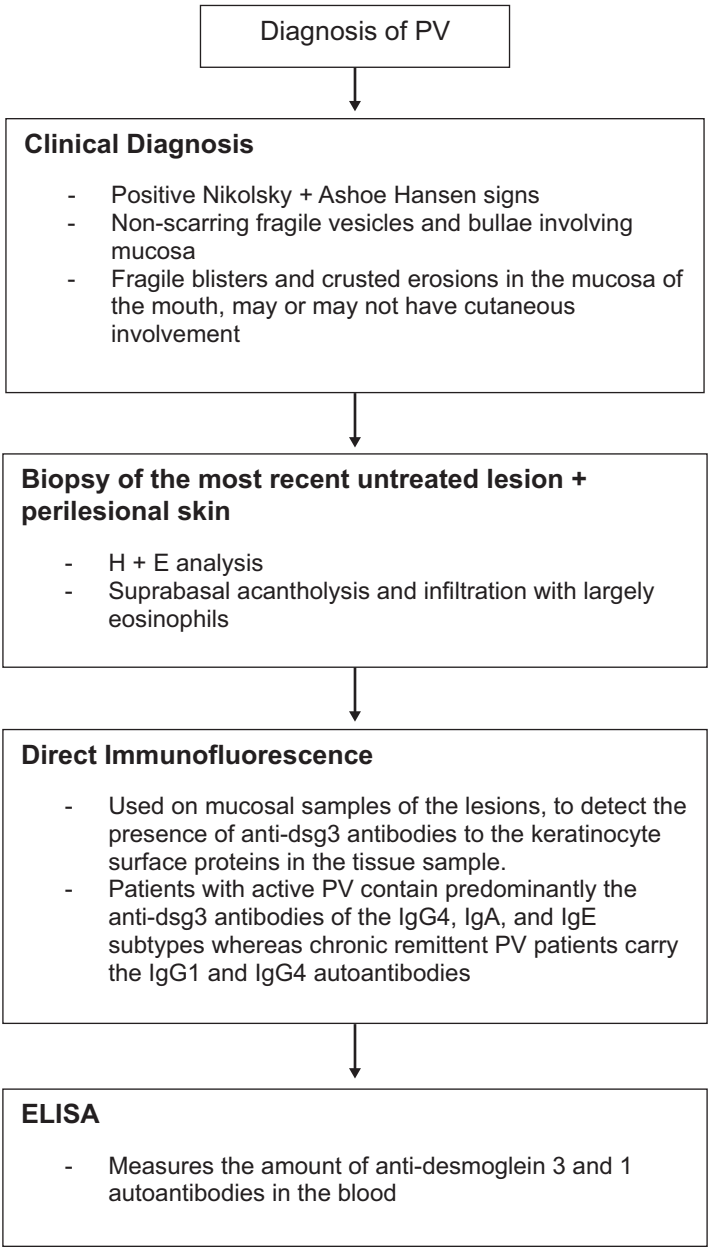

Fig. 6.1 Algorithm for diagnosing pemphigus vulgaris

of cutaneous involvement [1]. Second, a biopsy of the most recent untreated lesional and perilesional skin is executed. Hematoxylin and eosin (H+E) analysis is conducted to differentiate the existence and degree of blistering or acantholysis. H+E analysis is best performed from tissues that can be sent for direct immunofluorescence testing to determine the presence of autoantibodies within the epidermis. Although PV lesions are typically paucicellular, the density, type, and amount of inflammatory infiltrate—particularly eosinophils—can contribute to determining a diagnosis of PV [1]. Individuals suffering from isolated mucosal disease must have the H+E and direct immunofluorescence executed on the lesional and perilesional biopsies to confirm for PV. Third, if the DIF shows deposition of immunoglobulin G (IgG) and (complement component 3) C3 on the epithelial cell surface, it is strongly indicative of PV. The two minor criteria consist of indirect immunofluorescence (IF) and enzyme-linked immunosorbent assay (ELISA). Using IF, we also look for deposition of IgG and C3 on the epithelial cell surface, as it is strongly indicative of PV. The ELISA test can be utilized to measure the amount of anti-desmoglein 3 and 1 autoantibodies in the blood. These values are in general, but not perfectly aligned with the level of disease activity [1].

Laboratory Diagnosis (Blood, Urine, etc.)

Serum samples can be obtained and tested using indirect immunofluorescence and ELISA techniques to discover the presence of any desmoglein 1 or desmoglein 3 autoantibodies. These two techniques are both diagnostic for pemphigus vulgaris if the samples are positive for the autoantibodies [3–5].

Histopathology Diagnosis (Biopsy, Microscopic Study, etc.)

Direct Immunofluorescence

Direct immunofluorescence techniques are used on mucosal samples obtained of the lesions, to detect the presence of IgG antibodies to the keratinocyte surface proteins in the tissue sample.

Findings from the direct immunofluorescence microscopy suggest that there is a netlike distribution of the tissue-bound IgG, C3, immunoglobulin M (IgM), or immunoglobulin A (IgA) within the epidermis [1]. Direct immunofluorescence findings suggest that IgG or C3 attaching to the intercellular cement substance in the mid-lower or whole epidermis of perilesional skin or mucosa is typical [1]. The autoantibodies in PV target primarily desmoglein (DSG) 3 proteins and the anti-DSG3 antibodies belong to the IgG4 subclass. Individuals displaying primarily mucosal manifestations carry antibodies merely against DSG3, although there are patients who contain DSG1 autoantibodies [1]. Patients with active PV contain

predominantly the anti-DSG3 antibodies of the igG4, IgA, and immunoglobulin E (IgE) subtypes, whereas chronic remittent PV patients carry the IgG1 and IgG4 autoantibodies [1].

Biopsy and Histological Examination

Using the biopsy method, a sample of the tissue is taken and then observed under a microscope after being stained by the H+E stain [4]. The histological structure of the tissue is then examined. If acantholysis and epidermal vesicles are present above the basal layer of the epidermis, it is highly indicative of pemphigus vulgaris. Suprabasilar acantholysis of keratinocytes, with no present keratinocyte necrosis, is a finding indicative of pemphigus vulgaris. Even though there is acantholysis present in the suprabasilar region, there also may be intraepithelial separation higher in the stratum spinosum [6]. The cells appear as a "row of tombstones," because they are attached to the basement membrane through hemidesmosomes, but are no longer attached to the cells adjacent to them via desmosomal connections. The H+E analysis from the biopsy of PV lesions indicates suprabasal acantholysis and infiltration with large neutrophils and eosinophils [1]. In the blister cavity, there are few eosinophils present, and in the dermis, there is a moderate amount of mononuclear cell infiltrate, along with eosinophils.

The biopsy should be taken from the active border of an early lesion. The Tzanck smear can be used to prove acantholysis; however, further histological examination will prove if there is a primary or secondary cause behind the acantholysis.

Reflectance Confocal Microscopy

Although immunologic and histopathologic tests are the gold standard in diagnosing pemphigus vulgaris, reflectance confocal microscopy (RCM) is a quick way to rule in pemphigus in the initial stages of narrowing down the differential diagnosis (DDx) list. There are three major RCM criteria. First, there should be intradermal clefts with acantholytic cells in the RCM of a lesion. Second, the RCM of the healthy-appearing skin adjacent to the lesion should also show intradermal clefts. Third, the RCM of a lesion should show multiple dilated blood vessels. The presence of two of the three criteria can be a quick way to diagnose pemphigus with RCM. However, this technique cannot differentiate between pemphigus vulgaris and pemphigus foliaceus and is rather a rapid technique that can be used to rule in pemphigus, before subsequent immunologic and histopathologic investigations.

Clinical Diagnosis (Physical Exam, etc.)

The clinical diagnosis involves clues from the history and physical exam [4]. Usually the patients will describe blisters in their mouth area in the earlier stages of the disease. These blisters burst easily, leaving chronic painful erosions in the mouth of the patients. They may describe symptoms associated with painful erosions in the mouth, such as dysphagia or odynophagia.

The erosions themselves are very painful and may have a crusted appearance [4]. These erosions are of different sizes and do not have regular well-defined borders. The erosions leave a dark mark when they heal over. The blisters are filled with a clear fluid, which can then become cloudy, bloody, or pus filled. In most patients, the blisters initially present in the mouth area and then in a period of weeks to months may transition to other epidermal surfaces of the body. This disease can affect areas such as the pharynx, larynx, conjunctivae, genital areas, anus, and nails and can also affect general skin areas. If there are erosions in the area of the larynx, this may result in hoarseness of the voice.

There are two physical exam techniques that can be used to help with the clinical diagnosis: the Nikolsky and the Asboe-Hansen signs. The Nikolsky sign involves pushing the top of a blister and observing whether the top epidermal layers of the blister move laterally. This would indicate the absence of intercellular connections holding the top layers of epidermal cells together. The Asboe-Hansen sign involves putting pressure on the fluid inside the vesicles and observing whether it moves laterally and beneath nearby epidermal layers. If the fluid slips between and into these layers, this again indicates the absence of intercellular connections holding epidermal cells together [4].

Differential Diagnosis

PV is a rare autoimmune disease and many health practitioners are still unaware of it. Due to its low incidence, it is often misdiagnosed where ineffective treatments may even worsen the outcome. The differentials for PV mucosal lesions are stomatitis secondary to herpes simplex virus (HSV), lichen planus, aphthous ulcers, paraneoplastic pemphigus, lupus erythematous, or dermatitis herpetiformis [1]. The cutaneous lesions, on the other hand, are mistaken for pemphigus foliaceus, pemphigus vegetans, IgA pemphigus, paraneoplastic pemphigus, bullous pemphigoid, linear IgA disease, erythema multiforme, Grover disease, and Hailey-Hailey disease [1].

Differential Diagnosis of Mucosal Lesions

Acute Herpetic Stomatitis

HSV infections can cause lesions in the mouth, gums, and oropharyngeal membranes [6]. These initially present as painful and red vesicles, which then become ulcerations or pustules. Then in a period of 2–6 weeks, these painful ulcerations crust over and peel off. Viral cultures and direct immunofluorescence studies can help with the diagnosis of HSV infection.

Erythema Multiforme

Usually patients with erythema multiforme have a previous HSV infection history [6]. This is a self-limited skin disease in which there are characteristic skin lesions that are target shaped—there is an outer circle of redness surrounding blisters and lesions centrally. These target-shaped lesions have fast onset and appear within a period of 24 h.

Cicatricial Pemphigoid

Cicatricial pemphigoid belongs in the pemphigoid group of diseases [6]. Pemphigoid diseases involve subepidermal autoantibodies against proteins in the basement membrane associated with the epidermis. This disease, unlike bullous pemphigoid, mainly affects the mucous membranes. It most commonly affects the oral and conjunctival mucosae and is a chronic disease that can cause long-term complications due to scarring. Histological and immunofluorescence studies can help to distinguish this from pemphigus vulgaris, which also mainly affects the oral mucosa. This disease has a scarring tendency and mainly affects mucosal sites. In a small percentage of cases, it may also have skin involvement, in which case the head and upper trunk are most commonly affected.

Bullous Lichen Planus

Lichen planus is a T-cell-mediated disease in which keratinocytes start presenting antigens hypothesized to be modified by viral infection or drug exposure [6]. It affects middle-aged adults most commonly and has characteristic flat-topped, itchy, violaceous papules, which most commonly are found in areas such as the forearms, wrists, genitalia, and lower extremities. It may develop into bullous lichen planus if

the subepidermal layer becomes exposed to autoantibodies and the alloreactive T cells. In this case, the lichen planus characteristic lesions become vesiculobullous in nature, resembling the lesions in bullous pemphigoid.

Aphthous Stomatitis

Aphthous stomatitis causes painful, recurrent oral ulcers and most commonly affects younger people [7]. In the general population, the ulcers caused by this condition are commonly called canker sores. It starts off with macules, which become papules. The papules eventually rupture, giving way to round yellowish white ulcers that are surrounded by erythema [7]. These are painful, and healing time depends on the size of the ulcer. The cycling periodicity of this disease helps differentiate it from other diseases. These ulcers can heal in a period of days to weeks and recur around three to six times a year.

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Chapter 7
Differential Diagnosis of Cutaneous Lesions

Bullous Pemphigoid

Bullous pemphigoid is also a chronic blistering disease like pemphigus vulgaris; however, it mainly affects people over the age of 60 and the blisters mainly cover the arms and legs, as well as the trunk area of the patients [1, 2]. In this condition, the blisters are itchy, unlike those seen in pemphigus foliaceus, and they are rarely found in the mouth area [2]. This disease is subepidermal in nature, whereas pemphigus vulgaris is epidermal [2].

Erythema Multiforme

Usually patients with erythema multiforme have a previous herpes simplex virus (HSV) infection history [3]. This is a self-limited skin disease in which there are characteristic skin lesions that are target shaped; there is an outer circle of redness surrounding blisters and lesions centrally. These target-shaped lesions have fast onset and appear within a period of 24 h.

Hailey-Hailey Disease

Hailey-Hailey is a rare autosomal disease in which a mutation exists in the gene for an ATP-dependent Ca 2+ transporter in Golgi bodies [3]. This disrupts intracellular Ca 2+ signaling. In this disease, flaccid blisters and erosions can be seen cutaneously. The most common places to find the blisters are the neck, axillae, and groin.

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Linear Immunoglobulin A Bullous Dermatosis

Linear immunoglobulin A (IgA) bullous dermatosis is a group of subepidermal blistering diseases belonging to the pemphigoid group of diseases [3]. This disease occurs in both adults and children. In adults, the signs and symptoms of this disease are very similar to those in bullous pemphigoid. In children, this disease is given the term "chronic bullous disease of childhood" or CBDC. In children, this disease has blisters and erythema in a characteristic annular shape, found mainly in the groin, and on the thigh and lower trunk areas.

Transient Acantholytic Dermatosis (Grover's Disease)

Grover's disease mainly affects Caucasian males older than 40 years old and presents as itchy papulovesicular dermatitis, mainly on the trunk area and proximal extremities [3]. The pruritic nature of the dermatitis gets worse with sunlight exposure, heat, rubbing, and sweat.

Pemphigus Diseases

Pemphigus Vegetans

Pemphigus vegetans is a clinical variant of pemphigus vulgaris, which involves erosions that form fungoid or papillomatous growths [3]. These fungoid or vegetative growths are mainly seen on the scalp or face. This clinical variant is fairly rare and involves two subtypes: mild Hallopeau and severe Neumann types.

Pemphigus Foliaceus

Pemphigus foliaceus only has cutaneous erosions and does not involve any mucosal erosions [3]. It is an autoimmune disease in which the body produces IgG autoantibodies against desmoglein 1 proteins on the surface of keratinocytes in the superficial upper layers of the epidermis. The erosions look crusted and scaly in appearance and are transient in nature. These erosions also have an erythematous base. These erosions are found mainly on the upper trunk, scalp, and face.

Pemphigus foliaceus is similar to pemphigus vulgaris with respect to the fragile blisters that are rarely ever found intact; thus, we only see the crust and scaly erosions left over from the ruptured superficial vesicles [3]. In this disease, the Nikolsky sign is present. The Nikolsky sign involves pushing the top of a blister and observing whether the top epidermal layers of the blister move laterally. This would

indicate the absence of intercellular connections holding the top layers of epidermal cells together. Patients who have this disease often complain of painful burning lesions.

Pemphigus foliaceus has a similar autoimmune mechanism as pemphigus vulgaris; however, it can be differentiated using the enzyme-linked immunosorbent assay (ELISA) technique [4]. If the patient has both autoantibodies to the desmoglein 1 and desmoglein 3 proteins or just to the desmoglein 3 proteins, it is indicative of pemphigus vulgaris, but if the patient only has autoantibodies to the desmoglein 1 protein, it is indicative of pemphigus foliaceus [5].

Pemphigus Erythematosus

Pemphigus erythematosus is also known as the Senear-Usher syndrome [3]. This is considered to be a type of pemphigus foliaceus that is only found on the malar region of the face. So it is a variant of pemphigus foliaceus, in which the crusted lesions only appear on the nose and malar regions.

Paraneoplastic Pemphigus

Paraneoplastic pemphigus is a disease associated with the presence of benign or malignant neoplasms [3]. The most commonly associated neoplasms include non-Hodgkin's lymphoma and chronic lymphocytic leukemia, which account for around 67% of all the paraneoplastic pemphigus cases. Castleman's disease is associated with about 10% of the paraneoplastic pemphigus cases. This disease is not associated with common tumors, such as breast or colon carcinomas.

The structure of the blisters can range from being flaccid and fragile, like in pemphigus vulgaris, to being stronger more tense blisters, such as the one seen in bullous pemphigoid [3]. Erosions can also be more vegetative in nature. However, a key clinical feature that can be used to distinguish from pemphigus vulgaris is the presence of the reddened lesions and vesicles on the patient's palms and soles, which is a very rare observation in pemphigus vulgaris patients.

At the onset of the disease, the most common clinical sign of paraneoplastic pemphigus is intractable stomatitis, in which erosions and ulcerations are found on the oropharynx up to the vermillion lip [3]. This disease also commonly causes pseudomembranous conjunctivitis, which may become more and more severe until it destroys the conjunctival fornices. There are also erosions commonly seen in the genital mucosal areas, as well as the nasopharyngeal areas [3].

Herpetiform Pemphigus

Herpetiform pemphigus is seen as a clinical variant of pemphigus foliaceus in most cases and can also be a clinical variant of pemphigus vulgaris [3]. The clinical presentation of herpetiform pemphigus is milder than the presentation in pemphigus foliaceus and involves red itchy erosions and blisters in a herpetiform pattern. It also involves subcorneal pustules and eosinophilic spongiosis [3]. Unlike PV and PF, no acantholysis is seen histologically. Depending on which clinical variant it is, the disease will involve IgG antibodies to desmoglein 1 or 3 and will have a milder clinical presentation of pemphigus foliaceus or pemphigus vulgaris, respectively.

Drug-Induced Pemphigus

Patients may produce antibodies to desmoglein proteins in response to some drugs, or these drugs may affect the function of the desmoglein proteins to induce pemphigus [3]. These drugs include penicillamine and captopril. Penicillamine is usually used in rheumatoid arthritis treatment and in Wilson's disease, or to treat cystinuria, and can cause pemphigus foliaceus or pemphigus vulgaris. However, it is four times more likely to cause pemphigus foliaceus than pemphigus vulgaris [3]. Captopril is an angiotensin-converting enzyme (ACE) inhibitor that also can cause pemphigus. Usually when the patient is taken off the drug, the pemphigus goes into remission, but this is not always the case.

Immunoglobulin A Pemphigus

Unlike all other types of pemphigus, immunoglobulin A (IgA) pemphigus involves IgA autoantibodies against antigens on the cell surface of keratinocytes [3]. This disease is classified into two subtypes: subcorneal pustular dermatosis (SPD) and intraepidermal neutrophilic (IEN) types. In the SPD type, patients have an annular pattern of red pustules with crusting found in the center of the ring pattern of pustules [3]. In the IEN type, the arrangement of the red pustules resembles a sunflower. The pustules and lesions are often pruritic and are most commonly found in the axilla and groin areas. These lesions can also be found on the trunk, on the lower abdomen, and on the proximal parts of arms and legs.

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Chapter 8
Overview of Treatment

Treatment Options

Prognosis with No Treatment

Without any treatment, the prognosis for pemphigus vulgaris (PV) is very bleak, and people usually die within 2–5 years due to the complications of the disease, such as the blistering and erosions that then can lead to dehydration and infection [1, 2].

Corticosteroids with Adjuvants

Corticosteroids are first-line therapy for this condition (Fig. 8.1) [1, 3]. Initially, the patient should be started off on prednisone 1 mg/kg/day, and then when the patient reaches the control of disease activity level, the patient can then be weaned off of this systemic corticosteroid slowly [1]. Basically, physicians have to measure the levels of autoantibodies in the blood using enzyme-linked immunosorbent assay (ELISA) or indirect immunofluorescence and taper off the corticosteroids accordingly [2]. If the patient does not respond in 3–7 days, with corticosteroid and an adjuvant such as mycophenolate mofetil (MMF) or azathioprine, an alternate adjuvant with corticosteroids should be tried, such as plasma exchange, intravenous (IV) immunoglobulin (Ig), or rituximab. Corticosteroids should only be used in the short term because of the dangerous side effects of these drugs. They suppress the immune system and thus may increase the risk of malignancies, infections, and sepsis [1]. Corticosteroids are effective, have rapid onset, and are administered orally [3].

From the start of the therapy, an adjuvant has to be used with the corticosteroids to ensure that the disease stays in the control of disease activity phase. This shortens the duration and dose of the corticosteroids that have adverse side effects if taken

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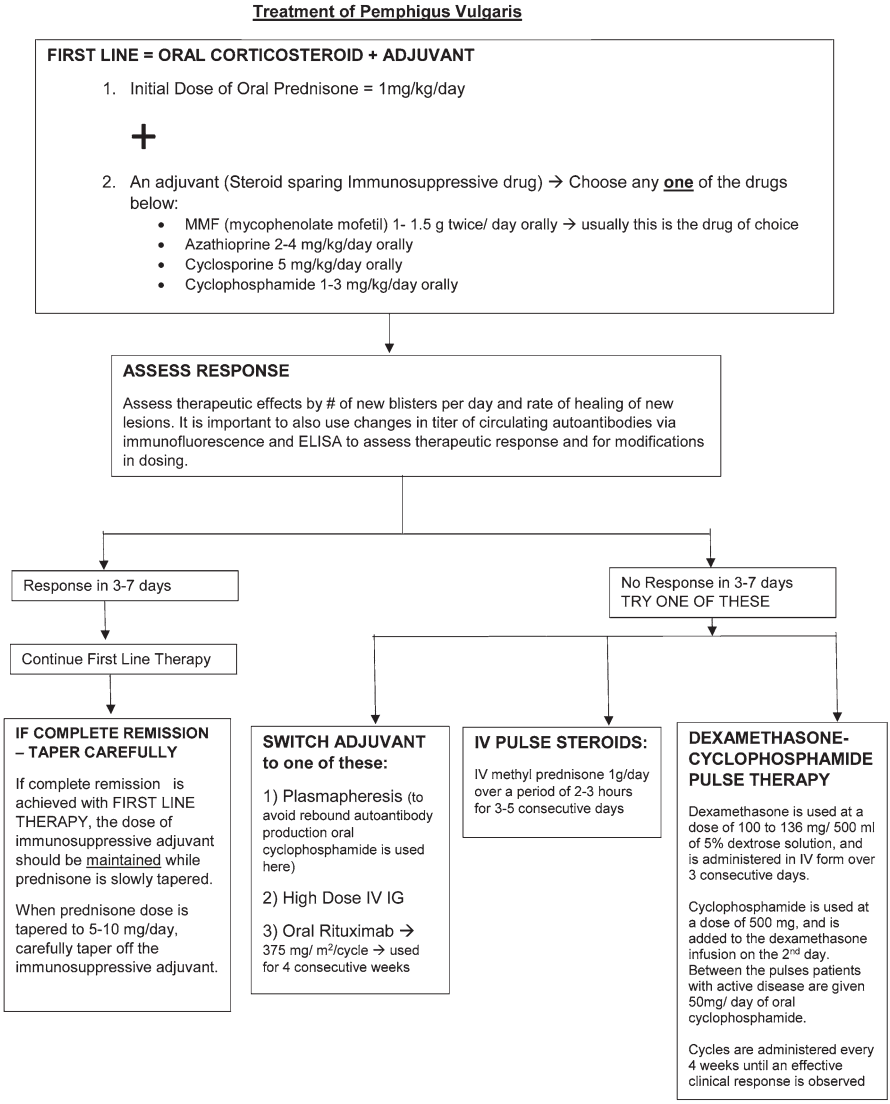

Fig. 8.1 Treatment algorithm for pemphigus vulgaris

over long periods of time. The most popular adjuvant used by physicians is mycophenolate mofetil, which is given at a dose of 1–1.5 mg/day [1]. The mechanism of action of MMF is that it inhibits the growth of B and T cells by preventing purine synthesis. Azathioprine is also a popular adjuvant choice as well, is cheaper than MMF, and is given at a dose of 2–4 mg/kg/day [1, 2]. Oral corticosteroids have faster onset of action than adjuvant immunosuppressants, which is why they are used acutely [3]. Azathioprine causes dose-dependent myelosuppression and

nausea; MMF, on the other hand, causes less myelosuppression, but more gastrointestinal toxicity [2]. MMF is more expensive than azathioprine, but it has less side effects and is well tolerated [3]. If the patient has complete remission of the disease on combined therapy, the corticosteroids can be tapered off, while keeping the dose of the immunosuppressive adjuvant the same [2]. When the corticosteroid dose reaches 5–10 mg/day, physicians should taper off of the immunosuppressive adjuvant as well [2].

Cyclophosphamide is also another adjuvant that may be used, instead of MMF or azathioprine, at a dose of 1–3 mg/kg/day. However, this drug has many side effects, such as hemorrhagic cystitis, sterility, and leukopenia [2].

Plasma Exchange, Intravenous Immunoglobulin Therapy, and Rituximab as Alternative Adjuvants Used with Corticosteroid Therapy

In cases where it is difficult to bring the disease into remission with corticosteroids and adjuvants, it may be necessary to try plasma exchange, intravenous Ig therapy, or rituximab as adjuvants to the corticosteroids (Fig. 8.1) [1, 4].

Plasma exchange involves direct and rapid removal of IgG, and therefore removal of PV antibodies. However, some of the disadvantages of this treatment method are that you can get rebound PV antibodies after plasma exchange. It is also a very labor-intensive process and requires central venous access [3].

IV Ig therapy has fast onset in terms of improving the patient's condition; however, this therapy is short-lived, and the patient must undergo this treatment several times under very high doses [3]. During IV Ig infusion, patients can get self-limited symptoms such as chills, tachycardia, high blood pressure, muscle pains, and pyrexia [3].

Rituximab (anti-CD20), which targets the majority of B lymphocytes (barring plasma cells), has been shown to be effective in significant numbers of patients [5] and is being considered more commonly as second- or even first-line therapy. For therapy with rituximab, a 375 mg/m^2/cycle is used weekly for four consecutive weeks [6].

Pulsed Intravenous Steroids (Alternative to Oral Corticosteroids)

These may be used in cases where it is difficult to bring the disease into remission, particularly if the disease is unresponsive to high oral doses of corticosteroids (Fig. 8.1). It is relatively inexpensive and has rapid onset; however, it has to be administered through IV and can cause mood flashes and flushing [3, 7]. In pulse IV

steroids, a 1 g/day dose of IV methyl prednisone is used over a period of 2–3 h for three to five consecutive days [2].

Dexamethasone-Cyclophosphamide Pulse Therapy

This is used in cases where the PV is refractory to treatment with first-line oral prednisone or in people who develop adverse side effects to first-line oral steroid therapy (Fig. 8.1) [8].

Dexamethasone is used at a dose of 100–136 mg/500 ml of 5% dextrose solution and is administered in IV form over three consecutive days. Cyclophosphamide is used at a dose of 500 mg and is added to the dexamethasone infusion on the second day. Between the pulses, patients with active disease are given 50 mg/day of oral cyclophosphamide. Cycles are administered every 4 weeks until an effective clinical response is observed.

Treatment Complications (Treatment in Pregnancy, Failure of Treatment, etc.)

The complications of taking corticosteroids are vast. Some of the side effects are diabetes, osteoporosis, and hypertension, and so patients should be supplemented with vitamin D and bisphosphonates and should be monitored for these changes [1].

The patient also should be monitored for sepsis, as patients with pemphigus vulgaris are prone to infection through the ulcerations [1].

A major side effect of using corticosteroids and immunosuppressive drugs is malignancies. This factor should be taken into consideration with the dosing and duration, especially in the younger patients [2]. In elderly patients, for whom corticosteroids are contraindicated, or those with limited disease, immunosuppressive therapy can be used alone [2].

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Part II
Pathology

Chapter 9
Pathology

Introduction

Pemphigus vulgaris (PV) is a life-threatening chronic autoimmune disease where the serum autoantibodies respond to the cell surface antigens resulting in a loss of epidermal cell cohesion [1]. This can be characterized as the manifestation of circulating autoantibodies against the intercellular adhesion structures, desmosomal protein desmoglein (Dsg) 3, and in some cases Dsg1. Disruption of the cell-cell and cell-matrix adhesion due to the circulating autoantibodies results in acantholysis, which could result in Tzanck phenomenon—the rounding of single epidermal cells due to the loss of cell-cell attachment [1].

The main histological finding, acantholysis, is known as the loss of coherence of epidermal cells and their subsequent detachment. Observing under light microscopy indicates that this process begins by the development of edema among keratinocytes located above the stratum basale. Proceeding this in the next stage, a suprabasal crevice appears and widens to give rise to a bulla. In cellular material collected from the base and sides of a bulla, typical acantholytic cells can be found by a cytological examination known as the Tzanck test. Immunofluorescence methods can also be used to detect immunoglobulin G (IgG) antibodies in the intercellular space of the epidermis or epithelium and circulating antibodies in serum [2].

In PV, the disruption of suprabasalar adhesion results in a single layer of basal keratinocytes bound to the dermoepidermal basement membrane. Detection of IgG antibodies by direct immunofluorescence is the gold standard test for diagnosis of pemphigus vulgaris. In this chapter, we will discuss the pathogenesis, morphologic, histomorphologic, and histopathology of pemphigus vulgaris and several diseases in the differential for PV.

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Pemphigus Vulgaris: From a Morphologic View

Pathogenesis (Mechanism) of the Morphologic Feature

Pemphigus vulgaris is a rare autoimmune intraepithelial blistering disease produced by circulating autoantibodies against keratinocyte desmogleins (Dsg) resulting in the loss of keratinocyte adhesion, through a process called acantholysis [3]. Autoantibodies against desmoglein 3 (Dsg3), prominent in the lower epidermis, are the main pathogenesis of PV. Keratinocyte detachment in the lower epidermis and tight attachment of basal keratinocytes to the basement membrane by hemidesmosomes give the appearance of suprabasal blisters (bullae) commonly seen in PV. Other autoantibodies include anti-desmocollin [4] and anti-desmoglein 1 (present in the upper epidermis). It should be underlined that the presence of anti-desmoglein 1 in serum leads to acantholysis of superficial keratinocytes similar to pemphigus foliaceus (PF).

Histomorphologic Feature

The earliest change in PV is epidermal edema (spongiosis) and exocytosis of eosinophils into spongiotic epidermis (eosinophilic exocytosis) (Fig. 9.1a). Acantholysis in the lower epidermis leads to the formation of slit-like suprabasal cleft or lacuna containing some acantholytic cells. Attachment of basal keratinocytes to the basement membrane and subsequent suprabasal acantholysis gives the characteristic appearance of a “tombstone” layer, in which a layer of basal keratinocytes is preserved (Fig. 9.1b). The suprabasal bulla may extend up to form an intraepidermal bulla or blister, which is interpreted as the regeneration of basal keratinocytes as the disease progresses. Epidermal necrosis, intraepidermal bulla, and extension of acantholysis into the adnexal structures may be seen in the progression of the disease (Fig. 9.1c) [3–5].

Dermal changes are non-specific, and the papillary dermis usually protrudes to the blister cavity, which is more prominent in the mucosal areas (Fig. 9.1d). Dermal inflammation is mild and consists of mixed inflammatory cell infiltrate including lymphocytes, neutrophils, and eosinophils around superficial vessels [6].

Immunohistochemistry Study

Immunohistochemistry staining by anti-desmoglein (anti-Dsg) monoclonal antibody 32-2B, which detects desmogleins 1 and 3, distinguishes drug-induced pemphigus from idiopathic pemphigus. A patchy pattern of staining was observed in idiopathic pemphigus, whereas drug-induced pemphigus shows normal pattern in

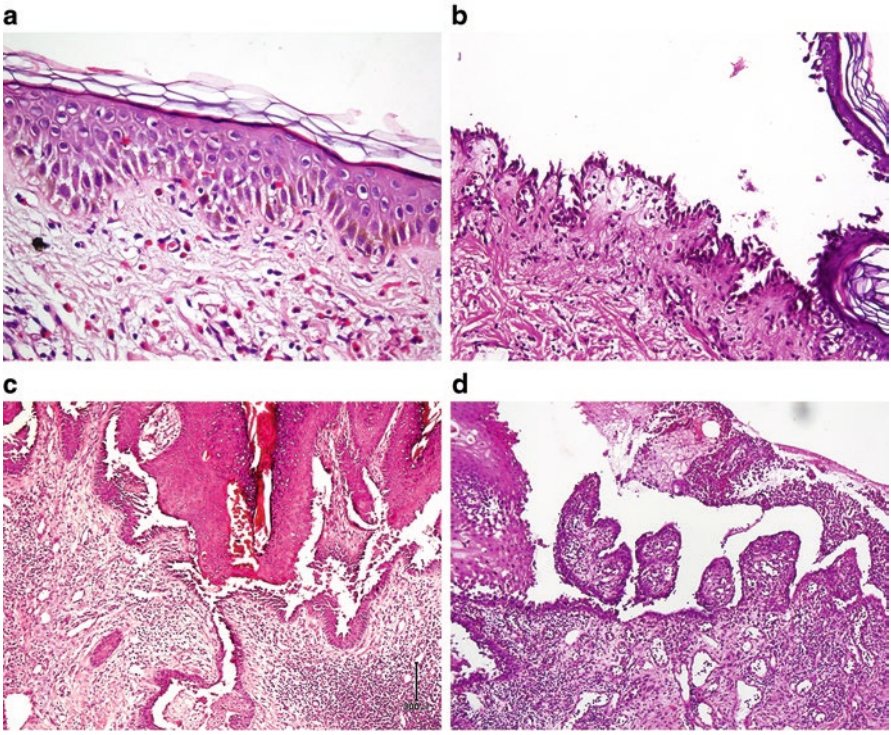

Fig. 9.1 (**a**) Eosinophilic spongiosis in pemphigus vulgaris (H&E × 20). (**b**) Suprabasal bulla with acantholysis and tombstone feature (H&E × 20). (**c**) Extension of the acantholytic blister into the follicular structure (H&E × 20). (**d**) Mucosal involvement with marked papillomatosis (H&E × 10) (Source: Alireza Ghannadan MD)

70% of cases and a patchy pattern in 30% of the cases. Normal pattern of staining is an indicator of a good prognosis in drug-induced pemphigus [7].

Immunolabeling with C3d and C4d in paraffin blocks was positive in 82% of pemphigus vulgaris cases, which roughly mirrors the intercellular pattern for IgG and complement seen by direct immunofluorescence [8].

The direct immunofluorescence (DIF) test could be replaced by immunohistochemistry staining of IgG4 and C3d on paraffin blocks in situations in which the DIF test is not available [9].

Immunofluorescence Study

Detection of IgG antibodies by direct immunofluorescence is the gold standard test for the diagnosis of pemphigus vulgaris. In pemphigus vulgaris, IgG usually deposits in intercellular spaces of keratinocytes leading to a network or chicken wire

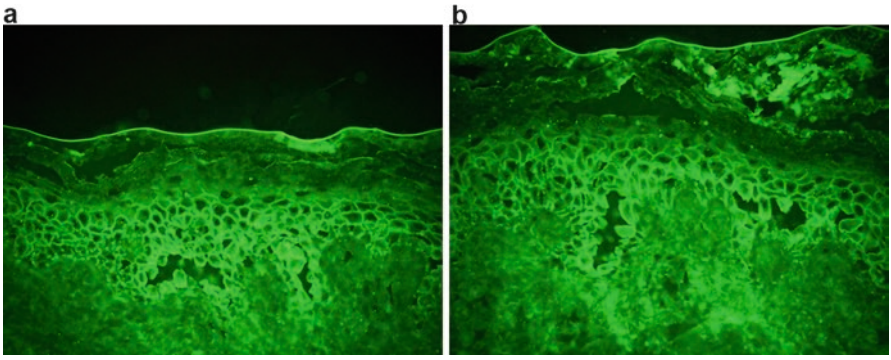

Fig. 9.2 Direct immunofluorescence for (**a**) IgG and (**b**) C3 in pemphigus vulgaris shows network or chicken wire pattern (Source: Alireza Ghannadan MD)

feature of the epidermis (Fig. 9.2). C3, IgM, and IgA are less common antibodies that react in the epidermis [10, 11]. Negative DIF is a predictor of immunologic remission in pemphigus vulgaris. Plucked hair may be used as a substrate for the DIF test in the remission period, and it had 79% sensitivity, 48% specificity, 61% positive predictive value, and 68% negative predictive value [12]. Patients in clinical remission who had positive DIF are more prone to relapse than those with negative DIF [13–15].

Circulating antibodies bind to epidermal keratinocytes present in 80–90% of pemphigus vulgaris patients and are detected by the indirect immunofluorescence (IIF) test. In pemphigus vulgaris, monkey esophagus is a better substrate for the IIF test (react with anti-Dsg3 antibodies), whereas in pemphigus foliaceus, guinea pig esophagus or human skin is a better substrate (react with anti-Dsg1 antibodies) [16–19]. These antibodies have been reported in many inflammatory dermatoses, including burns [20].

Histopathologic Differential Diagnosis

Histopathologic differential diagnosis of pemphigus vulgaris includes acantholytic dyskeratosis conditions such as *Hailey-Hailey disease*, *Darier's disease*, and *Grover's disease* (transient acantholytic dermatosis) [5, 6]. Acantholysis is associated with dyskeratotic cells, and immunofluorescence (DIF and IFF) tests are negative in acantholytic dyskeratotic diseases. More extensive suprabasal acantholysis in Hailey-Hailey disease gives the appearance of a "dilapidated brick wall" (Fig. 9.3a) [3, 5, 6]. Dyskeratotic cells are more commonly seen in Darier's disease and Grover's disease than in Hailey-Hailey disease (Fig. 9.3b). Dermal infiltration is more common in pemphigus vulgaris, and eosinophilic spongiosis is not a feature of acantholytic dyskeratotic diseases [5].

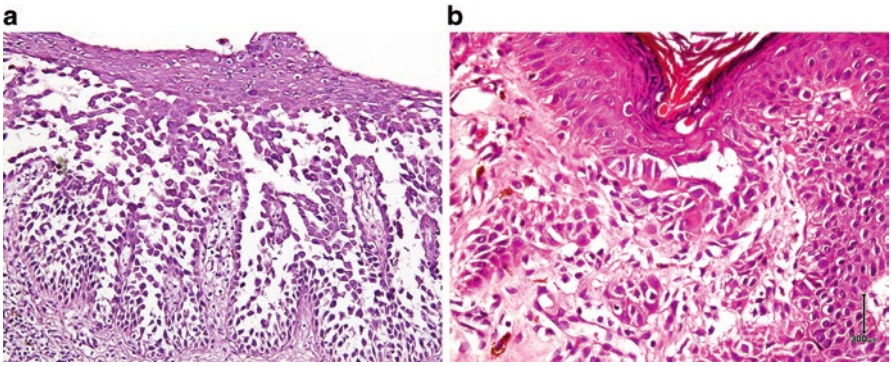

Fig. 9.3 (**a**) Marked acantholysis in Hailey-Hailey disease gives the appearance of dilapidated brick wall (H&E × 20). (**b**) Darier's disease with suprabasal acantholysis and scattered dyskeratotic cells in upper epidermis (H&E × 40) (Source: Alireza Ghannadan MD, Pooya Khan Mohammad Beigi MD)

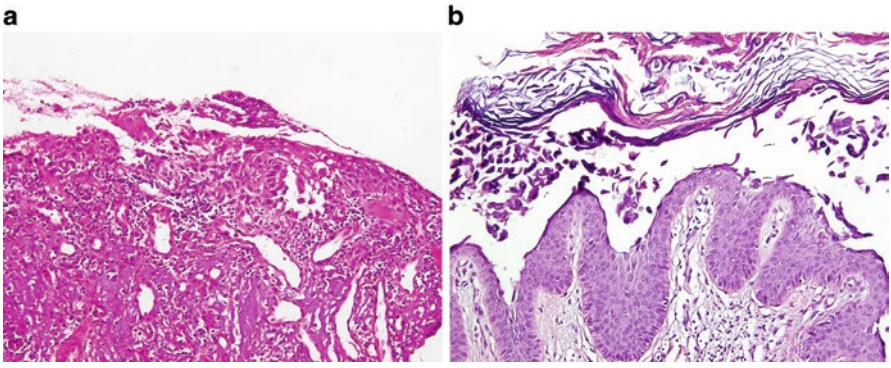

Fig. 9.4 (**a**) Paraneoplastic pemphigus in oral mucosa shows lichenoid interface reaction and suprabasal acantholysis (H&E × 20). (**b**) Pemphigus foliaceus with subcorneal bulla and superficial acantholysis (H&E × 20) (Source: Alireza Ghannadan MD, Pooya Khan Mohammad Beigi MD)

Paraneoplastic pemphigus (PNP) simulates pemphigus vulgaris clinically and histologically. Direct immunofluorescence shows an IgG intercellular deposition in network pattern and C3 deposition in lower epidermis and along basement membrane in a linear pattern (reminiscent of pemphigus erythematosus). In pemphigus vulgaris, anti-Dsg3 subclasses of IgG4 are usually found; however, in PNP subclasses of IgG1 and IgG2 are usually found [21]. PNP may represent other histopathologic findings in combination with the suprabasal or superficial acantholysis (PV-like or PF-like), including lichenoid interface pattern (lichen planus-like), erythema multiforme-like changes, focal epidermal spongiosis, subepidermal clefting (pemphigoides pattern), and linear IgA dermatosis-like changes (Fig. 9.4a, b) [5].

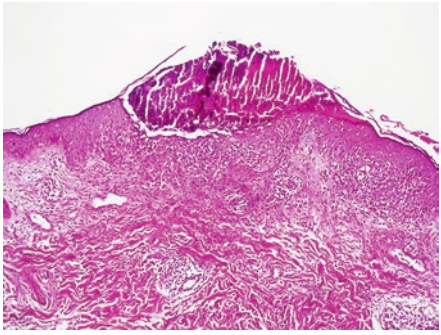

Fig. 9.5 IgA pemphigus with subcorneal pustule containing neutrophils and scattered acantholytic cells (H&E × 10) (Source: Alireza Ghannadan MD, Pooya Khan Mohammad Beigi MD)

IgA pemphigus rarely simulates pemphigus vulgaris and usually represents subcorneal and intraepidermal pustules with neutrophilic spongiosis. Two distinct subtypes of IgA pemphigus are recognized: subcorneal pustular dermatosis (SPD type), in which IgA is confined to the superficial epidermis, and intraepidermal neutrophilic dermatosis (IEN type) in which IgA is distributed through the entire epidermis (Fig. 9.5). Acantholysis is rare in IgA pemphigus [5, 6].

IgG/IgA pemphigus is another histopathologic differential diagnosis in which IgA and IgG antibodies target the epidermis [5, 6]. The case reports usually show IgG and IgA intercellular deposits in the DIF and/or IIF studies. Histologically, IgG/IgA pemphigus is more similar to pemphigus and should be regarded as a variant of IgG pemphigus and distinct from IgA pemphigus [22].

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Part III
Clinical Research 1

Chapter 10
Clinical Research Introduction

Introduction

Pemphigus vulgaris (PV) is a chronic autoimmune disease of cutaneous blisters with a high rate of death. Autoimmune pemphigus has three types: pemphigus vulgaris, pemphigus foliaceous, and paraneoplastic pemphigus.

Studies have shown that the age of disease onset, phenotype, severity, and also the rates of disease differ in different types of pemphigus diseases [1–3]. Pemphigus vulgaris is a severe autoimmune disease diagnosed by painful erosions and extensive blistering of the skin and mucous membranes. The clinical disease is the result of disruption in keratinocyte cell adhesion, called acantholysis, and is caused by autoantibodies against the desmosomal components [4, 5]. With a prevalence of 81.2%, pemphigus vulgaris is the most common blister autoimmune disease in Iran. It affects one to five people in one million, but it is higher in Ashkenazi Jews and eastern countries. In 2005, its prevalence in Iran was 30 in 100,000 people, and its incidence was 1 in 100,000 people per year [6, 7]. Pemphigus vulgaris affects both men and women to the same extent; however, its prevalence under age 20 is higher among women [8].

Race, sex, and onset age are important epidemiologic factors influencing the incidence of the disease [9, 10]. Some studies show that smoking has a protective role in the emergence of pemphigus vulgaris [11–13].

Some studies mentioned the age of disease onset is an important factor in disease advancement [14]. While a study by Savin et al. indicated that early treatment of pemphigus vulgaris results in higher risk of death [9], Herbst et al. showed that the initial response to the treatment has a crucial role in determination of remission [15]. The location of erosions and disease severity are also among the effective factors in remission. It was seen that the disease improvement was better in the patients whose erosions occurred on the skin [16, 17]. And the patients with mild to moderate severity (at the time of diagnosis) had two times more chance of long-lasting remission [15].

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Pemphigus vulgaris can be diagnosed by four main criteria: (1) clinical findings, (2) optical microscopy, (3) direct immunofluorescence, and (4) indirect immunofluorescence [18]. Anti-epicutaneous autoantibodies are among the most important factors in pemphigus vulgaris, and among them desmoglein (DSG) 1 and 3 are of particular importance. It seems that anti-desmoglein antibodies cause acantholysis and activation of cell signaling.

There is no specific gold standard for assessment of disease severity in PV patients, and this could be due to the rarity of the disease.

It was observed that anti-DSG1 is accompanied with higher severity, and that in the patients with positive levels of anti-DSG1 and anti-DSG3, the disease is faster and more extensive [19]. In a study conducted by Harman et al., anti-DSG1 was positive in 75% of Indian and 46% of European patients with PV [19]. In the study of Barnadas et al., anti-DSG1 was positive in 36% of PV patients from Spain [7]. Differences in anti-DSG antibody distribution could be due to racial and phenotypic differences of disease.

Although anti-desmoglein 1 and 3 autoantibody levels are two factors capable of predicting disease activity, these tests are not usually used. Studying the amount of circulating antibodies with specific enzyme-linked immunosorbent assay (ELISA) kits is instead preferably used for diagnosis and tracking the autoimmune patients. Especially, in pemphigus vulgaris patients, tracking anti-desmoglein 1 or 3 of the serum is in accordance with the clinical type and severity of the disease. ELISA has high sensitivity and has made diagnosis of pemphigus subgroups possible, and its results can be used for determination of disease activity and controlling the response to treatment [20].

The Pemphigus Disease Area Index (PDAI) is an independent assessment method for disease activity that shows the extent of disease. PDAI is designed by the International Pemphigus Committee. PDAI has three components: one related to skin, one related to scalp, and one related to mucosal membranes.

The activity score is specific for the skin allocated to the number of erosions, blisters, or new erythema. Twelve anatomic points will be evaluated, and by summing these points, the final score will be obtained (Table 10.1) [21].

Currently, several studies have already investigated the relationship between ELISA analysis of circulating autoantibodies and the clinical type and severity of the disease at the time of diagnosis, as well as its relation with disease activity. In a recent study, the prognostic role of the ELISA analysis of circulating autoantibodies in association with the duration of the disease and the time required for disease remission are assessed. However, up until now, there has been no research conducted specifically for investigating the relationship between the serum level of these two with the time required for the management of disease activity in pemphigus vulgaris patients.

The aim of the author's own study is to investigate the relationship between the levels of anti-desmoglein 1 and 3 autoantibodies, measured by ELISA, in the new cases of pemphigus vulgaris and the timeline of the disease activity among the patients hospitalized in Razi Hospital, Tehran, Iran, during 2013–2014.

Table 10.1 Pemphigus Disease Area Index (PDAI)

	Skin	Scalp	Mucous membrane	
	Activity rating scale	Activity rating scale	Activity rating scale	
Activity				
For skin and scalp, activity = erosions/blisters or new erythema	**0 =** absent	**0 =** absent	**0 =** absent	
For mucous membranes, activity = erosions/blisters	**1 =** 1–3 lesions, up to one > 2 cm diameter, none >6 cm	**1 =** in one quadrant	**1 =** 1 lesion	
	2 = 2–3 lesions, at least two >2 cm in diameter, none >6 cm	**2 =** two quadrants	**2 =** 2–3 lesions	
	3 = >3 lesions, none >6 cm diameter	**3 =** three quadrants	**5 =** >3 lesions or 2 lesions >2 cm	
	5 = >3 lesions, and/ or at least one >6 cm diameter	**4 =** affects whole skull	**10 =** entire area	
	10 = >3 lesions, and/or at least one lesion >16 cm diameter or entire area	**10 =** at least one lesion >6 cm		
	☐ Ears _____		☐ Ears _____	
	☐ Nose _____		☐ Nose _____	
	☐ Rest of face _____		☐ Buccal Mucosa _____	
	☐ Chest _____		☐ Hard palate _____	
	☐ Neck _____		☐ Soft palate _____	
	☐ Abdomen _____		☐ Upper gingiva _____	
	☐ Back, buttocks _____		☐ Lower gingiva _____	
	☐ Arms _____		☐ Tongue _____	
	☐ Hands _____		☐ Floor of mouth _____	
	☐ Legs _____		☐ Labial mucosa _____	
	☐ Feet _____		☐ Posterior pharynx _____	
	☐ Genitals _____		☐ Anogenital _____	
	Total activity score for skin: _____/120	Total activity score for scalp: _____/10	Total activity score for mucosa: _____/120	**Total activity score:** _____

(continued)

Table 10.1 (continued)

	Skin	Scalp	Mucous membrane	
	Activity rating scale	Activity rating scale	Activity rating scale	
Damage				
Damage is post inflammatory hyperpigmentation or erythema from resolving lesion	☐ Ears _____			
0 absent	☐ Nose _____			
1 present	☐ Rest of face _____			
	☐ Chest _____			
	☐ Neck _____			
	☐ Abdomen _____			
	☐ Back, buttocks _____			
	☐ Arms _____			
	☐ Hands _____			
	☐ Legs _____			
	☐ Feet _____			
	☐ Genitals _____			
	Total damage score for skin: _____/12	Total damage score for scalp: _____/1	N/A	**Total damage score** (skin+ scalp) = _____

Number of lesions if ≤3	☐ Ears _____	Number of lesions: _____	☐ Ears _____	
	☐ Nose _____		☐ Nose _____	
	☐ Rest of face _____		☐ Rest of face _____	
	☐ Chest _____		☐ Chest _____	
	☐ Neck _____		☐ Neck _____	
	☐ Abdomen _____		☐ Abdomen _____	
	☐ Back, buttocks _____		☐ Back, buttocks _____	
	☐ Arms _____		☐ Arms _____	
	☐ Hands _____		☐ Hands _____	
	☐ Legs _____		☐ Legs _____	
	☐ Feet _____		☐ Feet _____	
	☐ Genitals _____		☐ Genitals _____	

Adapted from [21]

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Chapter 11
Research Objectives

The Main Objective

Determination of the relationship between the levels of anti-desmoglein 1 and 3 autoantibodies, measured by enzyme-linked immunosorbent assay (ELISA) in the new cases of pemphigus vulgaris, with the timeline of the disease activity among the patients hospitalized in Razi Hospital, Tehran, Iran, during 2013–2014.

Minor Objectives

- Determination of the severity of pemphigus vulgaris by Pemphigus Disease Area Index (PDAI) in new cases of this disease
- Measurement of the levels of anti-desmoglein 1 and 3 autoantibodies by ELISA in the new cases of pemphigus vulgaris
- Determination of the time required for the management of disease activity of new cases of pemphigus vulgaris under treatment
- Examination of the relationship between the levels of anti-desmoglein 1 and 3 autoantibodies, measured by ELISA in the new cases of pemphigus vulgaris, and the severity of cutaneous and mucosal involvement
- Investigation of the relationship between the severity of new pemphigus vulgaris cases, measured by PDAI, and the control time of disease activity
- Comparing the extent of association between the levels of anti-desmoglein 1 and 3 autoantibodies measured by ELISA in the new cases of pemphigus vulgaris and the control time of the disease activity
- Determining the relationship between the severity of disease in new cases of pemphigus vulgaris measured by PDAI and the control time of activity

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Practical Objectives of the Project

- Determining the prognostic role of the level of circulating anti-desmoglein 1 and 3 autoantibodies measured by ELISA method in controlling the activity of the disease
- Identification of pemphigus vulgaris subgroups that need a longer period of hospitalization and higher dosages of prednisolone for disease control

Questions and Hypotheses of the Research

1. The level of anti-desmoglein 3 autoantibodies in new cases of pemphigus vulgaris has association with the time needed for controlling the activity for mucosal forms of disease.
2. The level of anti-desmoglein 1 autoantibodies in new cases of pemphigus vulgaris has association with the time needed for controlling the activity of cutaneous form of disease.
3. The level of anti-desmoglein 1 and 3 autoantibodies at the onset of disease is associated with the severity of cutaneous and mucosal involvement.
4. The severity of cutaneous and mucosal involvement in new cases of pemphigus vulgaris is related to the time needed for controlling cutaneous and mucosal disease.
5. Does the relationship between the times needed for controlling the disease have a stronger relation with the levels of desmoglein autoantibodies or the severity of the disease?
6. The level of anti-desmoglein 1 autoantibodies in new cases of pemphigus vulgaris is associated with the severity of the cutaneous form of disease.
7. The level of anti-desmoglein 3 autoantibodies in new cases of pemphigus vulgaris is associated with the severity of the mucosal form of disease.

Chapter 12
Literature Review

In a study conducted by Daneshpazhooh et al. in 2014, the levels of anti-desmoglein (anti-DSG) 1 and 3 autoantibodies were tested in 73 patients, and they were compared with the clinical symptoms of the patients [1]. Anti-DSG1 was found in 56 (76.7%) of the patients, and anti-DSG3 was detected in 69 (94.5%) of the patients. Anti-DSG1 was also found in 48 (94.1%) of the patients with the mucocutaneous form of the disease, and anti-DSG3 was found in 50 patients (98%) with the mucocutaneous form.

DSG1 and DSG3 were detected in 2 (12.5%) and 15 (93.7%) of the patients with the mucosal form, respectively. DSG1 was detected in 6 (100%) and DSG3 was detected in 4 (66.7%) of the patients with the cutaneous form of the disease. The average levels of DSG1 in the patients with cutaneous, mucosal, and mucocutaneous forms of the diseases were 136.8 ± 28.5, 11.4 ± 3.3, and 131.4 ± 7.8, respectively ($P < 0.001$). Also, the average levels of DSG3 in the patients with cutaneous, mucosal, and mucocutaneous forms of the diseases were 117.3 ± 44.4, 236 ± 48, and 457.2 ± 26.2, respectively ($P < 0.001$). The extent of cutaneous involvement has a significant positive relationship with DSG1 (r-0.74 and $P < 0.001$). Additionally, a weak positive association was observed between the extent of cutaneous involvement and DSG3 ($P < 0.001$ and r-0.38).

In a study by Hallaji et al., 50 pemphigus vulgaris patients were investigated; 37 patients had the mucocutaneous form of the disease, 11 of them had the mucosal form of the disease, and 2 patients had the cutaneous form of the disease. Anti-desmoglein 3 and 1 sensitivity was 94% and 72%, respectively. Salivary sensitivity of anti-desmoglein 3 and 1 was 94% and 70%, respectively [2].

In a study by Rahbar et al., 100 pemphigus vulgaris patients were examined. Pemphigus Disease Area Index (PDAI), Autoimmune Bullous Skin Disorder Intensity Score (ABSIS), and Pemphigus Vulgaris Activity Score (PVAS) along with desmoglein 1 and 3 levels were tested. The results show that a PDAI value greater than two is another criterion in the evaluation of the disease severity [3].

In the work of Saha et al., 95 pemphigus patients (79 pemphigus vulgaris and 16 pemphigus foliaceus) were tested [4]. The results showed that the duration of the

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disease is significantly longer in Indo-Asian patients in comparison with Caucasian-British patients. Also, young age at the time of disease onset was accompanied with bad prognosis. The average age of the patients at the time of disease onset among the patients whose disease lasted less than 5 years was 49, and among the patients whose disease lasted more than 5 years, the age of symptoms onset was 40 years ($p = 0.03$). High titers of antibodies at the time of disease onset were accompanied with a longer time period to remission. Furthermore, high levels of desmoglein 3 at the beginning of examination resulted in longer duration of the disease [4].

Harman et al. examined the relationship between anti-DSG1 and 3 autoantibody levels with the severity of pemphigus vulgaris in 2001 [5]. Enzyme-linked immunosorbent assay (ELISA) was performed on 424 serum samples from 80 pemphigus vulgaris and 24 pemphigus foliaceus patients. The anti-DSG1 level had strong correlation with severity of cutaneous involvement, while anti-DSG3 levels had a relationship with the extent of mucosal involvement. Anti-DSG1 levels, even after adjustment for the effect of anti-DSG3, had no relationship with oral involvement [5].

Belloni-Fortina et al., in a study published in 2009, with the aim of determining the relationship between levels of autoantibodies and the extent of mucocutaneous lesions, examined 20 pemphigus vulgaris patients at the time of diagnosis and tracking [6]. In the case of mucosal lesions, there was a relationship between the extent of mucosal lesions and anti-DSG1 and 3 titers, while in the case of cutaneous lesions, there was a significant association between cutaneous lesions and anti-DSG3 titer but not an association with anti-DSG1 levels [6].

In a retrospective study conducted by Herrero-González et al. in Spain and published in 2010, the serum of 33 pemphigus vulgaris patients and 7 pemphigus foliaceus patients were tested by ELISA and indirect immunofluorescence [7]. While there was no correlation between the indirect immunofluorescence titer and disease severity, in pemphigus vulgaris patients, the level of anti-DSG3 and 1 had significant relationship with the extent of mucosal and cutaneous involvement, respectively. High titer of anti-DSG3 before beginning of treatment is predictive of worse clinical consequences [7].

In the study by Cozzani et al. of 20 patients including 3 mucosal pemphigus vulgaris, 9 patients with mucocutaneous form, and 8 cases of cutaneous form, there was no relationship between anti-DSG1 and 3 autoantibodies and the severity of the disease [8]. It was only in mucosal pemphigus vulgaris, where the autoantibodies profiles were correlated with mucosal involvement [8].

In a study by Patsatsi et al., circulating autoantibody titers in the serum of 35 pemphigus vulgaris patients were assessed by the ELISA method [9]. They found that anti-DSG1 shows the extent of disease activity in cutaneous and mucocutaneous forms better. Anti-DSG3 is good for diagnosis, but it does not seem to correlate consistently with disease activity [9].

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Chapter 13
Research Methods

- Population under study: 52 pemphigus vulgaris patients
- Location: Razi Hospital in Tehran, Iran
- Time: 2013–2014

Method

The author's previously unpublished study presented herein is a cohort study of 52 new pemphigus vulgaris patients who were examined while hospitalized in the Razi Hospital during 2013–2014.

The inclusion criteria were:

1. New pemphigus vulgaris patients with optical microscopy biopsy findings in accordance with pemphigus vulgaris disease and direct immunofluorescence in accordance with pemphigus vulgaris in the last month
2. No history of receiving systemic corticosteroids with immunosuppressive dosages before the treatment (1 mg per kg of body weight for more than 5 days, 2 weeks before the treatment)
3. Active cutaneous or mucosal disease such as blisters, crest erosions, and mucosal erosions
4. Patients under treatment with prednisolone with dosage of 1 or 2 mg per kg of body weight, with or without adjuvant

Exclusion criteria:

1. A subgroup of pemphigus that is not pemphigus vulgaris
2. History of receiving systemic corticosteroids with immunosuppressive dosage
3. Treated patients or old erosions (in the case of cutaneous diseases, it only includes hyperpigmentation after inflammation, and for mucosal erosions it only includes old ulcers)

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4. Severe disease cases, which are candidates of receiving drugs other than prednisolone in addition to normal immunosuppressive adjuvants (azathioprine, methotrexate, and mycophenolate mofetil), such as intravenous immunoglobulin (Ig), and biologic drugs such as rituximab
5. Patients who leave the hospital or who are discharged from hospital due to different reasons such as personal reasons or transferring to other departments

Venous blood samples were taken from the patients on the first day, the serum of the patients' samples were kept at −70 °C until the performance of an enzyme-linked immunosorbent assay (ELISA) test. The serums were thinned by 1:100 and analyzed by ELISA kit according to the instruction of the manufacturer (Euroimmun AG, Luebeck, Germany). Then anti-desmoglein (DSG) 3 and anti-DSG1 titers were reported for each sample. Numbers above 20 relative units (RU)/ml were taken as positive. For values higher than 200 RU/ml, the patients' serum was thinned by 1/400 and the index value was calculated.

The severity of cutaneous and mucosal disease was calculated by Pemphigus Disease Area Index (PDAI) before beginning of the treatment. The intensity of the cutaneous disease was calculated by PDAI, as the sum of the cutaneous severity score plus severity of scalp. The total severity was calculated as the sum of the cutaneous and mucosal scores.

Management (control) time of the disease activity was defined in 2008 as the time at which the patient has no new erosions and the old ones are dried or being improved. It was determined by daily examination by a separate dermatologist. From the day of treatment with prednisolone (1 or 2 mg per kg of body weight) to the day that the patient has no new erosions, the old cutaneous erosions are dried, and the mucosal erosions form white-gray pseudomembranes is known as the time it takes to achieve control of disease activity.

Data Collection and Tools

All the data regarding the variables and demographic features were recorded in data collection forms, the severity of the disease upon hospitalization was examined by a dermatologist, and PDAI for each type of cutaneous and mucosal involvement was recorded (Table 13.1). The time needed for controlling the disease was also evaluated by asking the patient and through examination by a dermatologist. Anti-desmoglein 3 and 1 titers were also analyzed by the ELISA method and recorded as a continuous numerical variable.

Table 13.1 Study variables

	Variable type		Quantitative		Qualitative			
Variable	Independent	Dependent	Continuous	Discrete	Nominal	Ranking	Definition	Measurement method
Age	*		*					
Sex	*			*				
Weight	*		*					
Prednisolone dosage	*		*					
Mucosal disease by PDAI method	*		*					
Cutaneous disease with PDAI method	*		*					
Cutaneous disease activity control		*	*					
Mucosal disease activity control		*	*					
Anti-DSG1 antibody	*		*					
Anti-DSG3 antibody	*		*					
Mucosal symptom onset	*		*					
Cutaneous symptom onset	*		*					

Source: Pooya Khan Mohammad Beigi
PDAI Pemphigus Disease Area Index, *DSG* desmoglein

Sample Volume Calculation

As all the patients who had the inclusion criteria were entered into the research study in a 1-year interval, the sampling was performed by the census method and 52 patients were studied.

Ethical Considerations

The personal information of the patients was kept confidential, and the type of study does not involve any financial, mental, or body damages. The patients were under normal treatment of pemphigus vulgaris, and they were not deprived of useful treatment. The blood tests were done in normal form as with the other pemphigus vulgaris patients, and no excess measures were taken in this study. There was no specific ethical consideration.

Data Analysis

The data were analyzed by SPSS 11 software. All the comparisons were performed in binary form and with numerical scales. The Pearson correlation coefficients were separately considered for investigating the levels of anti-DSG1 and 3 with cutaneous and mucosal involvement. The correlation between anti-DSG1 and 3 autoantibody levels and the time needed for controlling the activity of cutaneous and mucosal disease were separately calculated. Also the relationship between the severity of cutaneous and mucosal disease and the time needed for controlling the cutaneous and mucosal forms were separately calculated, and $P < 0.05$ was considered as the significance level.

Chapter 14
Research Results

Fifty-two pemphigus vulgaris patients were investigated in the author's previously unpublished study. The average age of the patients was 46 (±13.6) years, and the average weight of the patients was 72 (±14.9) kg. Of the patients, 29 were male (55.8%) and 23 of them (44.2%) were female (Fig. 14.1).

Four cases (7.7%) had the cutaneous form, only 7 cases had the mucosal type (13.5), and 41 cases had the mucocutaneous form of disease (78.8%) (Fig. 14.2).

The average time until remission was 7.7 ± 2.9 days for the cutaneous type, and the average Pemphigus Disease Area Index (PDAI) of these patients was 19.5 ± 16.3. In the mucosal type, the remission time was 10 ± 1 days and the average PDAI was 8.3 ± 2.8. For the mucocutaneous form of the disease, the average remission time was 8.9 ± 27 and 10.8 ± 4 days for cutaneous and mucosal types of lesions, respectively.

In the mucocutaneous form of disease, the average PDAI was 17.7 ± 8.3 and 9.7 ± 8.6 for cutaneous and mucosal types of lesions, respectively.

The average of desmoglein (DSG) 3 and DSG1 in the three forms of disease shows no statistically significant differences (Table 14.1).

For three of the four patients (75%) with the cutaneous form of the disease, remission occurred in less than 10 days, and for one out of the four patients (25%), remission took more than 10 days to occur (Table 14.2).

In six of seven (85.7%) cases of the mucosal form of the disease, remission occurred in less than 10 days, and one case (14.3%) needed more than 10 days for remission (Table 14.3).

Among 41 patients with the mucocutaneous form of the disease, 33 cases (80.5%) had cutaneous remission in less than 10 days, and in 21 cases (51.2%) mucosal remission occurred in less than 10 days. PDAI in the mucocutaneous group who had remission in less than 10 days had no significant difference with the PDAI value of the other group (Table 14.4).

Desmoglein 3 and cutaneous and mucosal PDAI in the patients who had mucosal remission in less than 10 days were significantly lower in the patients whose mucosal remission occurred in more than 10 days (Table 14.5).

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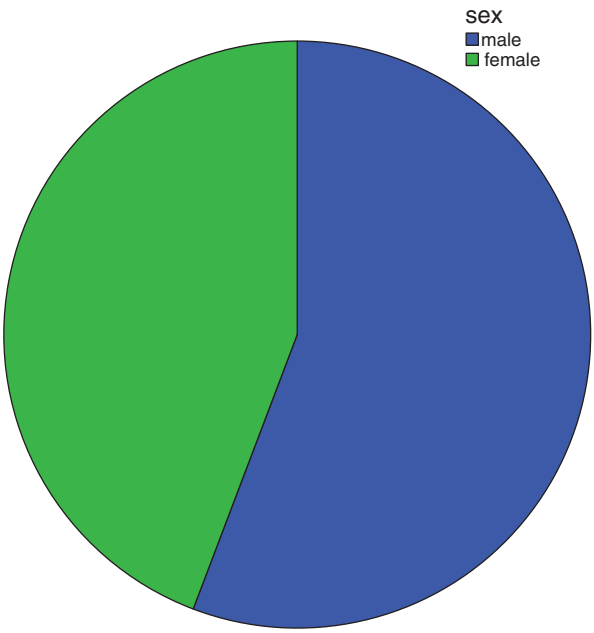

Fig. 14.1 Sex frequency of patients: 29 of the patients (58% of the patients) were males, and 23 patients (44.2% of the patients) were females (Source: Pooya Khan Mohammad Beigi)

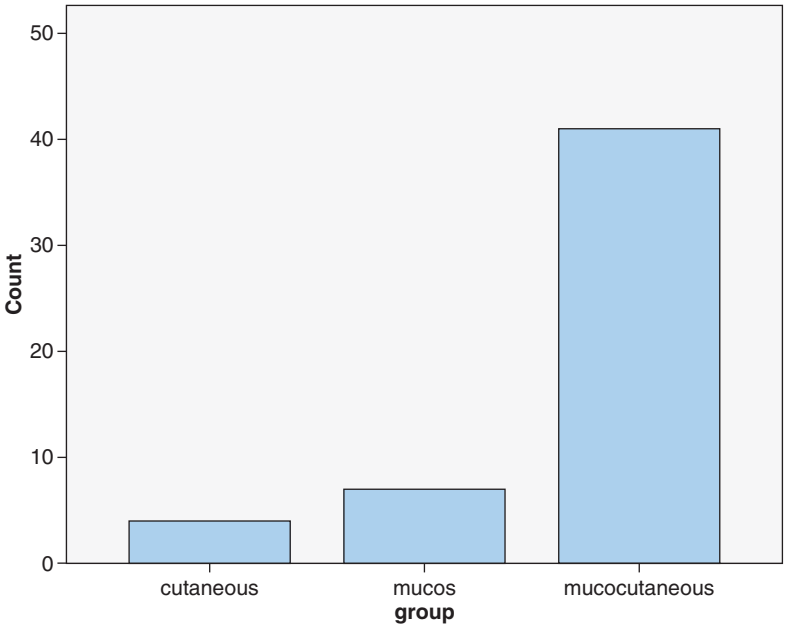

Fig. 14.2 Type frequency of disease: Four cases (7.7%) had the cutaneous form, only 7 cases had the mucosal type (13.5), and 41 cases had the mucocutaneous form of disease (78.8%) (Source: Pooya Khan Mohammad Beigi)

Table 14.1 Lab and clinical factors

	Cutaneous phenotype	Mucosal phenotype	Mucocutanous phenotype	P-value
Age	38 ± 9	25.5 ± 7.1	25.5 ± 7.1	0.4
Anti-Dsg1	297 ± 259	14.9 ± 22.1	294 ± 320	0.04
Anti-Dsg3	231.2 ± 264.1	704 ± 597	675 ± 455	0.1
Cutaneous PDAI	19.5 ± 6.3	- - -	17.7 ± 8.3	0.7
Mucous PDAI	- - -	8.4 ± 2.6	9.7 ± 8.6	0.6

Table 14.2 Clinical and lab factors of patients in the cutaneous form of disease

	Remission in 10 days or less	Remission in more than 10 days	P-value
Age	41 ± 9	29	0.08
Anti-Dsg1	262 ± 305	402	0.5
Anti-Dsg3	285 ± 295	70	0.3
PDAI	12 ± 8	42	0.07
Total corticosteroid dose	73.3 ± 20.8	110	0.09

Table 14.3 Lab and clinical factors in the patients with the mucosal form of the disease

	Remission in 10 days or less	Remission in more than 10 days	P-value
Age	46 ± 13.6	55	0.06
Anti-Dsg1	7.9 ± 13.3	57	< 0.001
Anti-Dsg3	614 ± 601	1240	0.05
PDAI	7.6 ± 1.8	13	0.001
Total corticosteroid dose	70 ± 16	120	0.001

Table 14.4 Lab and clinical factors of the patients in the mucocutaneous group who had cutaneous remission in less or more than 10 days

	Remission in 10 days or less	Remission in more than 10 days	P-value
Age	48.2 ± 13.8	39.6 ± 15.4	0.1
Anti-Dsg1	280.2 ± 256	597 ± 486	0.1
Anti-Dsg3	636 ± 482	838 ± 292	0.1
Cutaneous PDAI	16 ± 8	24.6 ± 7.8	0.008
Mucosal PDAI	10.1 ± 9.4	8 ± 3	0.5
Total corticosteroid dose	83.3 ± 18.9	100 ± 21	0.03

Table 14.5 Lab and clinical factors in the patients whose mucosal remission occurred in less or more than 10 days

	Remission in 10 days or less	Remission in more than 10 days	P-value
Age	45.9 ± 14.5	47.2 ± 14.5	0.7
Anti-Dsg1	355.8 ± 366.8	327.5 ± 299.5	0.7
Anti-Dsg3	443.4 ± 368	919.4 ± 415	< 0.001
Cutaneous PDAI	15 ± 6	20.6 ± 9.5	0.02
Mucosal PDAI	4.8 ± 3.7	14.8 ± 9.3	< 0.001
Total corticosteroid dose	85.7 ± 19.2	87.5 ± 21.7	0.7

Table 14.6 Correlation coefficient

	Correlation coefficient	*P* Value
Cutaneous PDAI and desmoglein 1	0.559	<0.001
Cutaneous PDAI and desmoglein 3	0.05	0.7
Mucosal PDAI and desmoglein 1	0.08	0.5
Mucosal PDAI and desmoglein 3	0.221	0.1
Cutaneous PDAI and cutaneous remission	0.67	<0.001
Cutaneous PDAI and mucosal remission	0.39	0.01
Mucosal PDAI and cutaneous remission	0.03	0.8
Mucosal PDAI and mucosal remission	0.48	<0.01
Cutaneous remission and desmoglein 1	0.43	0.003
Mucosal remission and desmoglein 1	0.16	0.27
Mucosal remission and desmoglein 3	0.25	0.09
Mucosal remission and desmoglein 3	0.447	0.001

Source: Pooya Khan Mohammad Beigi
PDAI Pemphigus Disease Area Index

Cutaneous PDAI and desmoglein 1, PD mucosal remission and desmoglein 3, and cutaneous remission and desmoglein 1 have significant positive relationships (Table 14.6).

Chapter 15
Discussion and Conclusion

The author's present study shows that the average levels of anti-desmoglein (DSG) 1 in the three phenotypes of pemphigus are significantly different. Furthermore, the cutaneous form had a higher average level of desmoglein 1 than 2 other forms. Also, in the patients with the mucosal form of the disease whose remission took more than 10 days, the average level of desmoglein 1 was significantly more than in the patients who needed less than 10 days for remission.

Considering the 52 patients in all 3 forms of disease, it was revealed that the level of desmoglein 3 and Pemphigus Disease Area Index (PDAI) was significantly lower in patients who had remission in less than 10 days when compared to the patients whose remission occurred in more than 10 days. As correlation coefficients showed, cutaneous PDAI and desmoglein 1, cutaneous PDAI and mucosal remission, and cutaneous remission and desmoglein 1 have positive significant relations.

In the study by Valikhani et al. in 2007, the level of anti-DSG 1 and 3 were tested in 73 pemphigus vulgaris patients and compared with the clinical symptoms of the patients [1]. The average levels of anti-DSG1 in the patients with cutaneous, mucosal, and mucocutaneous forms of the disease were 136.8 ± 28.5, 11.4 ± 3.3, and 131 ± 7.8, respectively ($P < 0.001$). Also, the average levels of anti-DSG1 in the patients with cutaneous, mucosal, and mucocutaneous forms of the disease were 117.3 ± 44.4, 236 ± 48 and 457.2 ± 26.2, respectively ($P < 0.001$). The severity of cutaneous involvement has a positive significant relation with DSG3 level ($P < 0.001$ and $r = 0.38$).

Harman et al. investigated the relationship between the levels of anti-DSG 1 and 3 autoantibodies with the severity of pemphigus vulgaris. The level of anti-DSG1 has a strong correlation with the severity of cutaneous involvement, and the level of auto-DSG3 has a strong correlation with the severity of mucosal involvement. The level of anti-DSG 1, even after adjusting for the effect of anti-DSG3, had no relationship with oral involvement [2].

In Iranian pemphigus vulgaris patients, anti-DSG 1 and 3 autoantibodies exist that result in a more severe form of the disease making the disease duration and time interval to the remission even longer.

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It has been hypothesized that the high emergence of pemphigus vulgaris in countries such as Iran and India is due to the overconsumption of garlic.

In our study, the age of the patients who had remission in less than 10 days had no significant difference compared to age of the patients whose remission occurred in more than 10 days. This result is in accordance with the results of Saha et al.'s study, in which remission was not associated with the age [3]. However, Savin reported that higher age at the time of diagnosis would be with worse prognosis [4].

Our study shows a positive significant relationship between the level of anti-DSG1 and cutaneous remission and between cutaneous PDAI and anti-DSG. However, in the study of Saha et al., the level of anti-DSG1 and cutaneous remission was not related to each other [3]. This difference in the results could be due to different methods of selecting patients and measurements.

In our study, the level of DSG3 and remission had positive significant relationships, and the level of DSG3 was significantly lower in the patients with the mucocutaneous form of the disease whose remission took less than 10 days.

In a study by Cozzani et al. of 20 patients—including 3 mucosal, 9 cutaneous, and 8 mucocutaneous forms of pemphigus vulgaris—there was no relationship between anti-DSG 1 and 3 autoantibodies and severity of the disease [5]. However, in the patients with the mucosal form, the autoantibody profile was in accordance with mucosal involvement [5].

In the study by Patsatsi et al., flowing autoantibody titers in the serum of 35 pemphigus vulgaris patients were assessed by the enzyme-linked immunosorbent assay (ELISA) method; they found that anti-DSG1 shows the extent of disease activity in cutaneous and mucocutaneous forms better. Anti-DSG3 is good for diagnosis, but it does not seem to show the activity of the disease [6].

Conclusion

The level of antibodies could be considered as a predictive factor for acute remission in the cutaneous and mucosal forms of pemphigus vulgaris.

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Part IV
Clinical Research 2

Chapter 16
Clinical Research Introduction

Introduction

Pemphigus is the name of a group of life-threatening blistering diseases of the skin and mucous membranes. The base of treatment for this disease is corticosteroids; however, recently, new drugs, such as rituximab, have been verified for more severe forms of it.

In the author's previously unpublished study, the effect of rituximab on variation in the laboratory indices of pemphigus vulgaris patients is addressed. After investigation of the files of pemphigus patients who received rituximab in Razi Hospital, Tehran, Iran, from 2008 to 2013, 39 patients were entered into the study. All patients had lab sheets containing CR (creatinine), urea, ALT (alanine aminotransferase), AST (aspartate aminotransferase), Plt (platelet), Hgb (hemoglobin), and WBC (white blood cell) before and after receiving rituximab. The patients received rituximab four times at a dosage of 500 mg in 4 successive weeks. The lab results before receiving the first dose of rituximab were compared to the results after receiving treatment. The effect of rituximab on the variation in lab indices with the adjustment effect of age, gender, disease duration, sites of involvement, received adjoins, and the background disease was also investigated.

In the initial analysis, rituximab only had a significant effect on urea reduction. In the CellCept® (mycophenolate mofetil) receiving subgroup, the mixed consumption of rituximab led to a significant reduction in WBC. In the subgroup having background disease, rituximab had a statistically significant impact on platelet reduction. In the subgroup having no background disease, rituximab had a statistically significant effect on urea reduction.

The lab indices were shown to have no significant relationship with age and disease duration. Thus, it can be predicted that disease duration and age would have no effect in the relationship between rituximab and lab indices' variations.

Although in stratified single-variable analysis for adjusting the effect of other variables (involvement sites and received adjoins) on the relation of rituximab and

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lab indices, some of these variables showed interacting effects with rituximab on the variations of lab indices. However, due to the low volume of sample and non-normal distribution of most of these variables, it was impossible to do multivariable analysis for investigation of their independent and interactive effects on variations of lab indices in an integrated manner; therefore, we cannot make certain comments about their relationships.

Types of Pemphigus

Pemphigus is the name of a group of life-threatening blistering diseases that have characteristic acantholysis leading to formation of intraepithelial blisters in mucus and skin [1]. The acantholysis process is induced via attachments of flowing autoantibodies to adhesion molecules in the cells [2]. Patients with pemphigus have mucosal erosions, blisters, papules, and cutaneous erosions.

The different types of pemphigus are pemphigus vulgaris, pemphigus foliaceus, immunoglobulin A (IgA) pemphigus, and paraneoplastic pemphigus. Different types of pemphigus are differentiated by clinical symptoms, related autoantigens, and histological methods. Pemphigus vulgaris has mucosal and mucocutaneous involvement. The blisters are acantholytic and suprabasal. The autoantibodies responsible for the disease are against desmoglein (DSG) 1 or both desmoglein 3 and 1.

Pemphigus foliaceus only involves the skin. The blisters are acantholytic and subcorneal. The responsible autoantibodies are against desmoglein 1.

IgA pemphigus has the form of grouped erythematous crusts, papules, and vesicle plucks. Blisters can be subcorneal or intraepithelial and acantholytic. The responsible autoantibodies are against desmocollin (DSC) 1 [3].

Paraneoplastic pemphigus involves vast and resistant stomatite along with different cutaneous findings. The responsible autoantibodies are against desmoplakin (DSP) or other desmosomal antigens.

Pemphigus vulgaris is the most common type of pemphigus, but is still very rare. The chance of its occurrence is between 0.1 and 0.5 per 100,000 people [4].

Pemphigus often occurs among adults and the average age of onset is 40–60 years old. It is very rare among children [5, 6]. Its prevalence is almost the same in the two sexes [7]. Almost all the pemphigus vulgaris patients have mucosal involvement. The mouth is the most common site of involvement and is often the first site of involvement. Other mucosal membranes such as conjunctivae, nose, esophagus, vulva, vagina, cervix, and anus are rarely involved [8]. As mucosal blisters are fragile and burst easily, in clinical examination it is difficult to find intact blisters, and instead the examiner tends to find mucosal erosions. Buccal and palatal mucosa are the most common sites of blister involvement in the mouth cavity [9].

Mucosal involvement can be very painful. This pain often increases by chewing and swallowing, which can result in improper alimentation and weight reduction. Most of the patients also have cutaneous involvement appearing in the form of soft

blisters in healthy skin or erythematosus. The blisters easily break, resulting in painful erosions. Pemphigus vulgaris rarely causes pruritis. Almost any part of body skin can be involved, but the palmar aspects of the foot and hands are rarely involved. The Nikolsky sign is often observed among these patients (mechanical pressure on the healthy skin results in blistering).

Pemphigus is diagnosed based on the clinical, histological, immunopathological symptoms and laboratory findings. Even in cases where the clinical symptoms are intensively supporting pemphigus, laboratory investigation is still needed to confirm the diagnosis, as other diseases may have the same symptoms.

The first line of treatment of pemphigus is systemic corticosteroids, and addition of adjuvants may also be needed. Patients who do not respond to the first line of treatment might need additional interventions. In such patients, cyclophosphamides, rituximab, intravenous immunoglobulin (IVIG), or plasmapheresis may be helpful.

Initial treatment of pemphigus vulgaris is systemic glucocorticoid, which is often applied in combination with other nonsteroidal immunosuppressants such as azathioprine and mycophenolate mofetil. Pemphigus resistant to treatment is a type of pemphigus that does not respond to the aforementioned treatments.

Pemphigus is a chronic disease that needs long-term treatment. A retrospective study was conducted during 1982–1993 on 40 patients [8]. On average, these patients achieved complete remission after 7.7 years; 25% had remission after 2 years, 50% after 5 years, and 75% after 10 years [8]. Most pemphigus vulgaris patients respond to initial treatments [9]. The first step, in the patients who do not respond to initial treatment, is increasing the dosage of systemic corticosteroids (1.5–2 mg/kg of prednisolone per day) or adjuvant drug. The adjuvant drug can also be changed (changing azathioprine to mycophenolate mofetil). In resistant cases, cyclophosphamides, rituximab, IVIG, and plasmapheresis could also be used.

As pemphigus is an autoimmune disease caused by autoantibodies, treatments that reduce B cells are investigated [10–13]. Rituximab is a monoclonal antibody that targets CD20, located on B lymphocytes, as its antigen. This drug has been shown to have profound effects on pemphigus treatments [13, 14]. In a multicenter study conducted on 14 pemphigus vulgaris patients and seven pemphigus foliaceus patients, both groups were resistant to systemic glucocorticoids and experienced several relapses during glucocorticoid tapering. They were then put on one cycle of rituximab with a weekly dosage of 275 mg/m^2 for 4 weeks, and this addition proved advantageous [15]. Although, severe infections were reported in the patients under rituximab treatment, its effect on risk of infection is not clear, as other immunosuppressants were also concurrently used. Reactions during injection are among the most common side effects of rituximab. Deep vein thrombosis (DVT), pulmonary embolism, long-term hypogammaglobulinemia, and neutropenia were also common among the patients under rituximab treatment. Regarding the excellent impact of this drug on treatment of resistant pemphigus, and also on other diseases such as idiopathic thrombocytopenic purpura (ITP), vasculitis, lymphocytic leukemia, and systemic lupus erythematosus (SLE), we decided to evaluate the effects of this drug on the variation of lab parameters such as white blood cell (WBC), hemoglobin (Hg), platelet (Plt), aspartate aminotransferase (AST), alanine aminotransferase

(ALT), urea, and creatinine (CR). So far, no study has been conducted on investigation of these variations due to receiving rituximab.

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Chapter 17
Research Objectives and Hypotheses

Objectives

Major Objective

The major objective was the investigation of laboratory variations after injection of rituximab in pemphigus vulgaris patients.

Minor Objectives

Minor objectives of the project were the determination of rituximab impact on:

- Laboratory indices
- Laboratory indices by adjusting for the effect of age
- Laboratory indices by adjusting for the effect of gender
- Laboratory indices by adjusting for the effect of other treatment methods
- Laboratory indices by adjusting for the effect of disease duration
- Laboratory indices by adjusting for the effect of disease in the involved sites
- Laboratory indices by adjusting for the effect of underlying disease

Application Objectives

- Enhancement of health level among pemphigus vulgaris patients and paying attention to laboratory effect of patients after rituximab consumption.

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Hypotheses

Research questions or hypotheses include how rituximab affects:

- The laboratory indices
- The laboratory indices with age effect adjustment
- The laboratory indices with gender effect adjustment
- The laboratory indices with disease duration effect adjustment
- The laboratory indices with previous treatment effect adjustment
- The laboratory indices with other disease effect adjustment
- The laboratory indices with involved sites' effect adjustment

Chapter 18
Literature Review

In 1997, rituximab was approved by the US Food and Drug Administration (FDA) as a treatment for non-Hodgkin's lymphoma of B cell that was resistant to chemotherapy. After that, it was applied for treatment for other diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Wegener's granulomatosis, idiopathic thrombocytopenic purpura (ITP), and Sjögren's syndrome. Ten years later, its impact on the treatment of blister diseases such as pemphigus was shown [1].

In a 2006 study by Larrar et al., two children with autoimmune hemolytic anemia who were treated with rituximab experienced acute thrombocytopenia and neutropenia [2]. They resolved in several days, which showed that these hematologic effects are directly dependent on the toxicity of rituximab.

In a study by Chairwatanatorn et al. in 2003, neutropenia following application of rituximab was tested in 53 patients [3]. All patients except one were under Hodgkin's lymphoma treatment. Eight cases of grade 4 neutropenia were observed after 1–5 months of rituximab treatment (five patients only received rituximab and three patients were also under additional chemotherapy); three patients advanced toward sepsis. Neutropenia was not related to other diseases or treatments and was related with reduction of neutrophil precursors, except for one of the patients whose bone marrow had hypoplasia. All cases of neutropenia occurred among the patients whose polymorphonuclear neutrophils (PMN) were normally or weakly reduced [3].

In a study by Tesfa et al. in 2008, neutropenia occurred 4 or more weeks after rituximab treatment in lymphoma patients [4]. However, the mechanism of how rituximab causes neutropenia is still unknown. In a retrospective study of 113 lymphoma patients under rituximab treatment (alone or along with chemotherapy), eight patients (7%) had neutropenia. The average onset was 88 days after receiving their last dosage of rituximab. The average time interval of neutropenia was 54 days. Four of the eight patients underwent stem cell transplantation, three patients had neutropenia with fever, and two of them needed granulocyte colony-stimulating

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factor (G-CSF) treatment. In the patients who had neutropenia, a cessation in maturation was observed in the promyelocytes category (the same as congenital neutropenia or Kostmann disease) [4].

A study by Otrock in 2005 addressed two patients who had acute thrombocytopenia after receiving rituximab [5]. One of the patients had hairy cell leukemia and the other one suffered from mantle cell lymphoma. In these patients, thrombocytopenia improved without the need of any treatment after several days. The reason for this is unknown.

A study by Leo et al. was conducted in 2004 for investigating the safety of rituximab [6]. In this study, the mixture of fludarabine, rituximab, and cyclophosphamide was applied for treatment of follicular lymphoma. Surprisingly, severe thrombocytopenia with World Health Organization (WHO) grades 3 and 4 were observed in the patients, which resulted in the end of trial. Cytological and serological analysis was based on direct toxicity of rituximab.

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Chapter 19
Research Methods

Investigation Method

Thirty-nine therapy-resistant pemphigus patients in Razi Hospital in Tehran, Iran, who had received rituximab from 2008 to 2012, were considered for inclusion in this retrospective cohort study. Data was collected before and after rituximab treatment. The variables included lab indices—white blood cell (WBC), hemoglobin (Hgb), platelet (Plt), aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, creatinine (Cr)—and age, gender, involved sites, previous therapies, underlying disease, and disease duration. Test sheets associated to before and after rituximab application, containing WBC, Hgb, Plt, AST, ALT, urea, and Cr, were compared.

Type of Study

This study is a retrospective cohort study conducted on the pemphigus patients resistant to therapies who had received rituximab in 2008–2012.

Studied Population

The study included 39 therapy-resistant pemphigus patients who were treated with rituximab in Razi Hospital, Tehran, Iran, in 2008–2012.

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Inclusion Criteria

Pemphigus patients who did not respond to the initial therapies (therapy-resistant pemphigus) were then treated with rituximab.

Exclusion Criteria

The following types of patients were excluded from the study:

1. Patients with no required tests before application of rituximab in their file
2. Patients with no follow-up after receiving rituximab
3. Patients whose first follow-up, after the last dosage of rituximab, was greater than 1 month.

Sampling Method

According to the available files, files of all the patients who had received rituximab from 2008 to 2012 were considered for inclusion.

Data Collection

The data collection tool included a checklist divided into two parts: one for the data before and one for the data collection after rituximab treatment. The variables included WBC, Hgb, Plt, AST, ALT, urea, and Cr, as well as age, gender, involved sites, previous therapies, underlying disease, and disease duration.

Project Implementation

After studying the files of therapy-resistant pemphigus patients, the patients who had the required data in their files were entered into the research. Rituximab treatment was defined as receiving four doses of 500 mg for 4 weeks, along with normal saline. Test sheets associated to before and after rituximab application, containing WBC, Hgb, Plt, AST, ALT, urea, and Cr, were compared. (The maximum time interval between the second test sheet and the last dosage of rituximab could be 1 month.)

Data Analysis

Finally, the finalized cases that had the inclusion criteria were analyzed in Stata statistical software (StataCorp, Texas, USA) in terms of variations in WBC, Hgb, Plt, AST, ALT, urea, and Cr after application of rituximab as the major variable and investigation of minor variables.

Problems and Limitations

As this research was based on filed files of the hospital, inadequacy of data either before or after rituximab application excluded a bunch of samples from the study in a way that among 105 available files, only 39 files had the required data.

Variables

Major Variables

Quantitative measurement before and after application of rituximab of:

- White blood cells (WBC)
- Hemoglobin (Hgb)
- Platelets (Plt)
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Urea
- Creatinine (Cr)

Minor Variables

- Gender
- Age
- Involved sites
- Previous therapies
- Underlying disease
- Disease duration

The data of variables were collected according to the positive findings in the patients' files (Table 19.1).

Table 19.1 Patient variables

	Variable type		Quantitative		Qualitative				
Title	Independent	Dependent	Continuous	Discrete	Nominal	Ranking	Scientific practical definition	Measurement method	Scale
WBC							Number of WBC per μ(mu)L of blood	File reading	Cell/mCl
Hgb							Amount of hemoglobin	File reading	Gr/dl
Plt							Number of plackets in patient blood	File reading	Cell/mcl
AST			*				Amount of AST	File reading	IU/L
ALT							Amount of ALT	File reading	IU/L
Urea							Microgram of urea per deciliter of blood	File reading	Mg/dl
Cr			*				Keratin amount	File reading	Mg/dl
Age			*				Years from birth	File reading	Year
Gender				*			According to patient phenotype	File reading	Male/female
Underlying disease				*			Existence of systemic disease	File reading	Having/not having
Previous therapies				*			Received adjoin before rituximab	File reading	Azathioprine, IVIG
									Cyclophosphamide
									CellCept®, methotrexate

Involved sites				*			Involved sites before starting rituximab	File reading	Upper body, lower body, face, genitalia, scalp, mucus
Disease duration							Months passed from onset to receiving rituximab	File reading	Month

Source: Pooya Khan Mohammad Beigi
WBC white blood cell, *Hgb* hemoglobin, *Plt* platelet, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *CR* creatinine, *IVIG* intravenous immunoglobulin

Chapter 20
Research Results

Results

Among 105 therapy-resistant pemphigus patients who received rituximab treatment in Razi Hospital, Tehran, Iran, from 2008 to 2012, only 39 patients managed to enter the study. The others were excluded due to inadequate data. Also in the included patient group, the maximum time interval between the last dosage of rituximab and follow-up was 1 month. The data of the remaining 39 patients were analyzed by Stata statistical software (StataCorp, Texas, USA), and the following results were obtained:

- The age of the patients ranged from 16 to 67 with a mean of 36.46 years.
- Their disease duration from the beginning of the disease until receiving rituximab ranged from 5 to 84 months with a mean of 39.30 months.
- Of the patients, 25 (64%) were men and 14 (36%) were women. It does not seem that the sex difference is related to therapy-resistant pemphigus; it is rather associated with the data collection method and exclusion of patients with incomplete files.

Investigation of the involved sites showed that 25 patients (64%) had mucosal involvement, 20 patients (51.3%) had upper body involvement, 18 patients (46.2%) had lower body involvement, 19 people (48.7%) had genitalia involvement, 23 people had facial involvement, 36 people (92%) had body involvement, and in 22 patients (56.4%) the scalp was involved. The lab result variations of the mentioned patients were investigated in terms of the involved sites.

The patients, before application of rituximab, were simultaneously under treatment with prednisolone and other adjoins. To summarize the unsuccessful treatments, 5 patients had cyclophosphamide, 18 of them received CellCept® (mycophenolate mofetil), 7 people (17.9%) had intravenous immunoglobulin (IVIG), 5 patients were treated with methotrexate, and 22 patients had azathioprine. All these patients did not respond to corticosteroids and had active disease.

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In terms of variation in lab test results after receiving rituximab, the patients were investigated in terms of the previous adjuvants as well. Among 39 patients, 12 of them (30.8%) had systemic underlying diseases such as hypertension (HTN), diabetes mellitus (DM), ischemic heart disease (IHD), and many more.

The major variables were white blood cell (WBC), hemoglobin (Hgb), platelet (Plt), aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, and creatinine (Cr) before and after application of rituximab.

Before Receiving Rituximab

- The WBC range was 4,000–14,800 with an average of 10,092.
- The Hgb range was 9.1–16.8 with an average of 13.8.
- The Plt range was 100,000–683,000 with an average of 243,384.
- The AST range was 6–64 with an average of 24.56.
- The ALT range was 10–143 with an average of 43.92.
- The urea range was 12–145 with an average of 37.25.
- The Cr range was 0.5–1.2 with an average of 0.87.

After Receiving Rituximab

- The WBC range was 5,400–19,000 with an average of 9,964.
- The Hgb range was 7.4–16.7 with an average of 13.42.
- The Plt range was 110,000–440,000 with an average of 232,512.
- The AST range was 10–121 with an average of 25.43.
- The ALT range was 12–144 with an average of 48.46.
- The urea range was 15–54 with an average of 29.12.
- The Cr range was 0.6–1.2 with an average of 0.85.
- The WBC had no statistically significant variations.
- The Hgb had no statistically significant variations.
- The Plt had no statistically significant variations.
- The AST had no statistically significant variations.
- The ALT had no statistically significant variations.
- The urea had statistically significant variations.
- The Cr had no statistically significant variations.

After receiving rituximab and adjusting for the effect of gender:

- The WBC had no statistically significant variations.
- The Hgb had no statistically significant variations.
- The Plt had no statistically significant variations.
- The AST had no statistically significant variations.
- The ALT had no statistically significant variations.

- The Cr had no statistically significant variations.
- In the case of urea, we concluded that it depends on gender, as in men the variation was significant, while in women the variations were not statistically significant.

When investigating the results with adjustment of the involved sites, the following results were obtained:

- In patients with lower body involvement, rituximab had no significant effect on WBC, Plt, AST, ALT, urea, and Cr, but it had significant impact on Hgb reduction.
- In patients whose lower body was not involved, urea significantly increased after receiving rituximab.
- In patients whose lower body was involved, rituximab caused a significant reduction in Cr, urea, and Hgb.
- In patients whose upper body was not involved, rituximab had no significant effect on the variables.
- In the patients with or without facial involvement, rituximab had no significant impact on any of the variables.
- In patients whose genitalia region was involved, rituximab has no significant impact on any of the major variables.
- In patients with no genitalia involvement, rituximab resulted in significant reduction of urea.
- In patients with body involvement, rituximab resulted in significant reduction of urea.
- In patients with scalp involvement, rituximab resulted in significant reduction of urea.

The adjustment of previous therapies was also addressed. As all the patients received prednisolone, the effect of adjoins (azathioprine, CellCept®, cyclophosphamide, IVIG, and methotrexate) was addressed:

- In patients who had received cyclophosphamide, rituximab has no statistically significant impact on the major variables.
- In patients who had not received cyclophosphamide, rituximab led to statistically significant reduction of urea.
- In patients who had received CellCept (mycophenolate mofetil), rituximab has statistically significant impact on reduction of urea and WBC.
- In patients who did not use IVIG adjoin, rituximab had a significant impact on reduction of urea.
- In patients who did not use methotrexate adjoin, rituximab had significant impact on reduction of urea.
- In patients who used azathioprine adjoin, rituximab had significant impact on reduction of urea.

The adjustment impact of systemic underlying diseases (such as HTN, DM, IHD) was also addressed:

- In patients with systemic underlying disease, rituximab had significant impact on platelet reduction.
- In patients with no systemic underlying disease, rituximab had significant impact on urea reduction.

There was no statistically significant relationship between the lab test result variations and disease duration and age (Tables 20.1, 20.2, 20.3, 20.4, 20.5, 20.6, 20.7, and 20.8).

Table 20.1 Age distribution in the studied patients

	Min	Max	Standard deviation	Average
Age	16	67	13.48	36.48

Source: Pooya Khan Mohammad Beigi

Table 20.2 Disease duration distribution in the studied patients

	Min	Max	Standard deviation	Average
Disease duration	5	84	20.28	29.30

Source: Pooya Khan Mohammad Beigi

Table 20.3 Absolute and relative frequency distribution of patients based on their sex

	Number	%
Men	25	64.1
Women	14	35.9
Total	39	100

Source: Pooya Khan Mohammad Beigi

Table 20.4 Absolute and relative frequency of involved sites at the time of rituximab injection

	Frequency	%
Upper body	20	51.3
Lower body	18	46.2
Face	23	59
Genitalia	19	48.7
Body	36	92.3
Mucus	25	64.1
Scalp	22	56.4

Source: Pooya Khan Mohammad Beigi

Table 20.5 Absolute and relative frequency of received adjoins before application of rituximab

	Frequency	%
Cyclophosphamide	5	12.8
CellCept® (mycophenolate mofetil)	18	46.2
IVIG	7	17.9
Methotrexate	5	12.8
Azathioprine	22	56.4

Source: Pooya Khan Mohammad Beigi
IVIG intravenous immunoglobulin

Table 20.6 Absolute and relative frequency of the patients based on having or not having underlying disease

	Frequency	%
With underlying disease	12	30.8
Without underlying disease	27	69.2
Total	39	100

Source: Pooya Khan Mohammad Beigi

Table 20.7 Distribution of lab variables of the patients before application of rituximab

	Min	Max	Standard deviation	Average
WBC	4000	14,800	2575	10,092/5
Hgb	9.1	16.8	1.84	13.8
Plt	100,000	683,000	99,365	243,384
AST	6	64	13.12	24.56
ALT	10	143	43.92	31.5
Urea	12	145	37.2	21.4
Cr	0.5	1.2	0.78	0.14

Source: Pooya Khan Mohammad Beigi
WBC white blood cell, *Hgb* hemoglobin, *Plt* platelet, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *CR* creatinine

Table 20.8 Distribution of lab variables of the patients after application of rituximab

	Min	Max	Standard deviation	Average
WBC	5400	19,000	3,041	9,964
Hgb	7.4	16.7	2.04	13.42
Plt	110,000	440,000	70,952	232,512
AST	10	121	17.9	26.43
ALT	12	144	29.62	48.46
Urea	15	54	7.86	29.12
Cr	0.6	1.2	0.14	0.85

Source: Pooya Khan Mohammad Beigi
WBC white blood cell, *Hgb* hemoglobin, *Plt* platelet, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *CR* creatinine

Chapter 21
Discussion and Conclusions

Discussion

White blood cells (WBC), hemoglobin (Hgb), platelets (Plt), aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, and creatinine (Cr) results, before and after administration of rituximab in pemphigus patients, were studied in the author's present work. This is the first study of its kind. It encompasses 39 therapy-resistant pemphigus patients who were treated at Razi Hospital, Tehran, Iran, from 2008 to 2012.

In the study of Chairwatanatorn et al. in 2003, neutropenia following application of rituximab was tested in 53 patients [1]. All the patients except one were under Hodgkin's lymphoma treatment. Eight cases of grade 4 neutropenia were observed after 1–5 months of treatment with rituximab. Neutropenia was related with a reduction in neutrophil precursors, except for one of the patients whose bone marrow had hypoplasia.

In a study by Tesfa et al. in 2008, neutropenia occurred 4 or more weeks after rituximab treatment in lymphoma patients [2].

In our study, we investigated the variation of total WBC counts, but variation of specific polymorphonuclear neutrophils (PMN) was not investigated separately. In this study, rituximab did not have a statistically significant effect on the number of WBCs. Also, even after adjustment for the effect of gender and underlying diseases, there is still no significant effect on the number of WBCs. Single-variable analysis showed that application of rituximab would result in significant reduction of WBCs in the patients who used CellCept® (mycophenolate mofetil), so it seems that simultaneous application of these two drugs has a synergistic effect on WBC reduction. Also, this study addressed the effect of rituximab on lab test result variations in the first month after receiving the last dosage of rituximab. While the previously mentioned studies addressed neutropenia after more than 4 weeks, this time interval was not of note in our own study.

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A study by Otrock in 2005 addressed two patients who had acute thrombocytopenia after receiving rituximab [3]. These patients had hairy cell leukemia and mantle cell lymphoma. In these patients, thrombocytopenia improved without the need of any treatment, after several days.

A study by Leo et al. was conducted in 2004 in which the mixture of fludarabine, rituximab, and cyclophosphamide was applied for the treatment of follicular lymphoma, and severe thrombocytopenia grades 3 and 4 were observed in the patients [4]. The cytologic and serological analysis was based on direct toxicity of rituximab [4].

In our own study, we do not have an exact number for Plt immediately after application of rituximab. But rather, Plt results before application of rituximab and first follow-up after application of rituximab were compared, in which the first follow-up of the patients was taken in 2–4 weeks after the last administration of rituximab. In our study, rituximab did not have a statistically significant effect on Plt variations.

The effect of rituximab on platelets (even after adjusting for the impact of involved sites and other received adjoins) was not statistically significant.

In our patients with systemic underlying disease, rituximab had a statistically significant impact on reduction of platelets, while in patients with no systemic underlying disease, it did not have any statistically significant effect on major variables. Therefore, it can be concluded that having an underlying disease could make patients vulnerable to platelet reduction as a result of rituximab application.

The author's study is the first to address the variations of Hgb, AST, ALT, urea, and Cr upon application of rituximab.

Rituximab did not have any statistically significant effect on variations of AST and ALT.

Also, by adjusting for the effect of sex, underlying disease, involved sites, and adjoins, rituximab did not have any statistically significant impact on Hgb variation.

Single-variable analysis showed the statistically significant impact of rituximab on Hgb reduction in patients with upper and lower body involvement.

Total analysis showed statistically significant impact of rituximab on urea reduction. By adjusting for the effect of gender, rituximab had a statistically significant impact on urea reduction among men; however, it did not show any statistically significant impact in women. It seems that sex has an interacting effect with rituximab in urea reduction. This suggests that without considering sex as a factor, impact of rituximab on urea variation is unclear.

Upon investigation of rituximab impact on urea variation with adjusting the effect of involved sites, the following results were obtained:

- A single-variable analysis of rituximab impact on the patients with lower body involvement showed a statistically significant impact of rituximab on urea increase.
- In patients with upper body and mucus involvement, rituximab had a statistically significant impact on urea reduction.

- In patients with body, scalp, and genitalia involvement, rituximab had a statistically significant effect on urea reduction.

Due to low sample volume and non-normal distribution of most of the variables, a multivariable analysis of independent effects of each involved site on lab test result variations was not statistically valuable. Therefore, we cannot definitively argue on the effect of involved sites on lab test results variations. By adjusting for the effect of underlying disease, the impact of rituximab on reduction of urea was statistically significant in the patients with no underlying diseases.

Conclusions

By adjusting the impact of received adjoins, we concluded that:

In a single-variable analysis on rituximab impact on the patients who received CellCept (mycophenolate mofetil) and azathioprine, it was concluded that rituximab had a statistically significant impact on urea reduction. Also, in patients who did not use intravenous immunoglobulin (IVIG), methotrexate, and cyclophosphamide, rituximab had statistically significant impact on urea reduction. Due to low sample volume and non-normal distribution of most of the variables, multivariable analysis of the independent effects of each adjoin on lab test result variations was not statistically significant. Therefore, we cannot make conclusions about the effect of adjoins on lab test results variations. Total analysis on impact of rituximab on Cr variation showed no statistically significant effect. Even after adjustment of sex and underlying disease, rituximab did not have any statistically significant effect on Cr variation. Investigation of rituximab impact on Cr variation, with involved sites impact adjustment, showed that a single-variable analysis on rituximab impact in patients with lower body involvement is indicative of rituximab's statistically significant impact on Cr reduction.

Investigating the effect of rituximab on Cr variation with adjoin effect adjustment by a single-variable analysis showed the statistically significant effect of rituximab on Cr reduction in patients who used IVIG.

Lab test result variations did not show any statistically significant relationship with duration of disease and age of patients. Therefore it can be predicted that these variables do not play an important role in the relationship between rituximab and lab test variation.

Summary

This study addressed the impact of rituximab on WBC, Hg, AST, ALT, urea, and Cr variation in pemphigus patients. The adjustment impact of involved sites, underlying diseases, gender, and received adjoins, was also studied. Furthermore, the

relation of lab test results with disease duration and patients' gender was also addressed.

Initial analysis only showed statistically significant impact of rituximab on urea reduction. And it did not have any statistically significant impact on other variables. In the subgroup who used CellCept (mycophenolate mofetil), simultaneous application of CellCept and rituximab resulted in statistically significant reduction of WBC. In the subgroup having underlying disease, rituximab had a statistically significant impact on platelet reduction; and in the subgroup with no underlying disease, rituximab had a statistically significant impact on urea reduction.

Lab test result variations with disease duration and age of patients were not statistically significant. Therefore, it is suggested that these variables do not play an important role in the relationship between rituximab and lab test variations.

The single-variable stratified analyses for adjustment of other variables' impact (involved sites, and adjoins) were conducted on rituximab relationship with lab indices, and some of these variables showed interactive impacts with rituximab on lab test results' variation. However, due to low sample volume and non-normal distribution of most of these variables, it was not possible to conduct a multivariable analysis for investigating the independent and interactive impacts of them on lab test result variations in a unified manner.

Suggestions

1. Due to the low sample volume, the investigation of rituximab impact on lab test results was not statistically significant. Therefore, it is suggested to conduct such investigation with a higher number of cases.
2. This study only investigates the lab test results' variations in a 2–4 week interval after the last dosage of rituximab; therefore, the effects due to direct toxicity and retarded effects of rituximab could not be studied. It is recommended to conduct a more regular and longer follow-up after rituximab administration.

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Part V
Clinical Case Photos

Chapter 22
Patient One

A 45-year-old man is under treatment with prednisone and azathioprine after diagnosis of pemphigus vulgaris (PV). During the last 2 years, the patient has had a history of two relapses when he was on 10 mg prednisone. The second time, methotrexate was added as the adjuvant. He is now on daily 7.5 mg of prednisone and weekly dosage of 12.5 mg of methotrexate.

Note: The photos were taken when symptoms were present (Figs. 22.1, 22.2, 22.3, and 22.4).

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https://doi.org/10.1007/978-3-319-67759-0_22

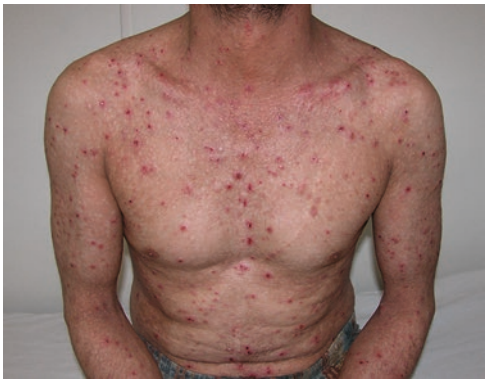

Fig. 22.1 The patient has many round secondary erosions distributed across the chest, abdomen, neck, and limbs. The erosions are round, raised, and erythematous (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

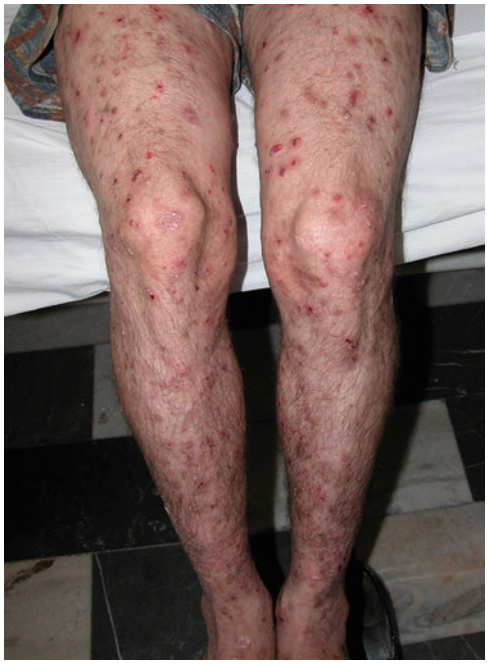

Fig. 22.2 The patient has many secondary excoriated erosions distributed across the thighs and legs. The erosions are round, raised, and erythematous (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

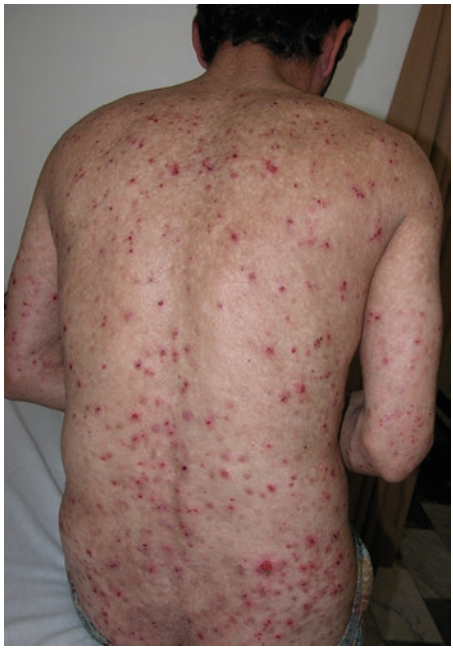

Fig. 22.3 The patient has many secondary excoriated erosions distributed across the back and arms (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

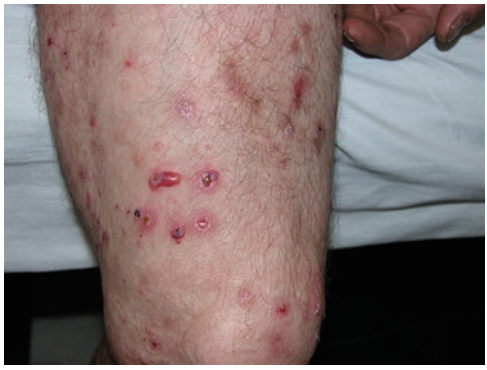

Fig. 22.4 Multiple well-defined vesicles and erosions on an erythematous base, seen on the distal thigh (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

Chapter 23
Patient Two

A 35-year-old woman, diagnosed with pemphigus foliaceus (PF) 3 years earlier, is under treatment with prednisone only. The patient's symptoms were controlled 3 weeks after application of 1 mg/kg/day of prednisone and the steroid got tapered. Since then she is under treatment with 5 mg/day of prednisone. Her direct immunofluorescence (DIF) control is still positive.

Note: The photos were taken when symptoms were present (Figs. 23.1, 23.2, 23.3, 23.4, 23.5, and 23.6).

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https://doi.org/10.1007/978-3-319-67759-0_23

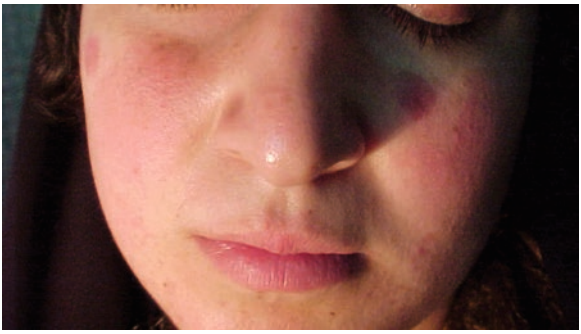

Fig. 23.1 Erythematous patches on the malar area of the face (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

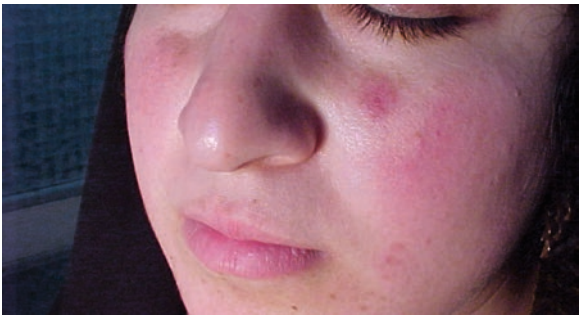

Fig. 23.2 The patient has a macule and erythematous patches in the malar area of her face (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

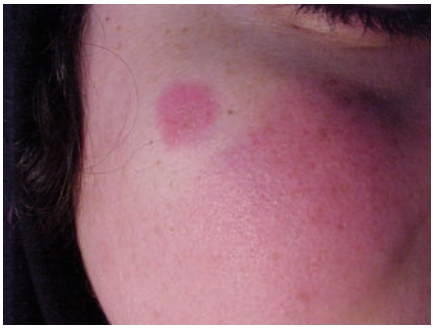

Fig. 23.3 The patient has an erythematous patch and macule in her malar area (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

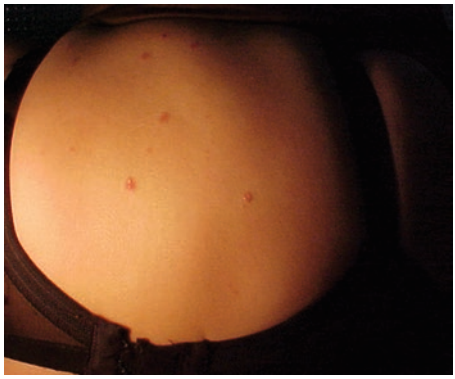

Fig. 23.4 Erythematous pustules, vesicles, and erosions on the back; these have an erythematous base (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

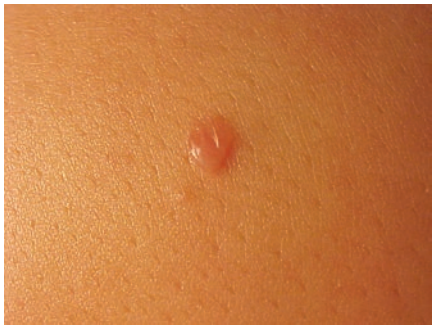

Fig. 23.5 Erythematous vesicle (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

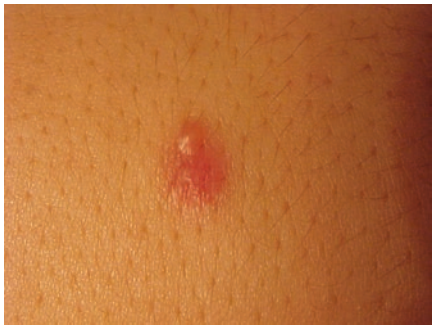

Fig. 23.6 Erythematous vesicle (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

Chapter 24
Patient Three

A 30-year-old man, diagnosed with pemphigus foliaceus (PF) 3 years earlier, is under treatment with prednisone and azathioprine. After 6 months, azathioprine was tapered and gradually stopped. Now he is under treatment with 7.5 mg/day of prednisone. He had one relapse when he was on 10 mg/day of prednisone.

Note: The photos were taken when symptoms were present (Figs. 24.1, 24.2, 24.3, and 24.4).

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https://doi.org/10.1007/978-3-319-67759-0_24

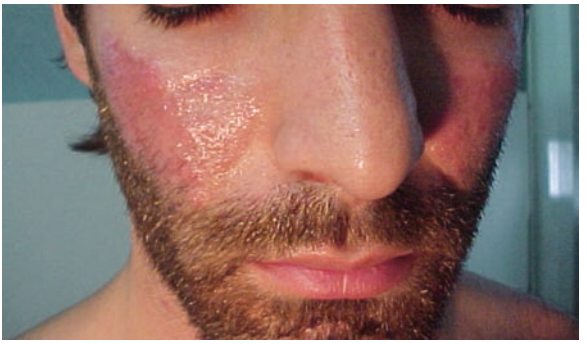

Fig. 24.1 Erythematous patches seen on the malar area of the face (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

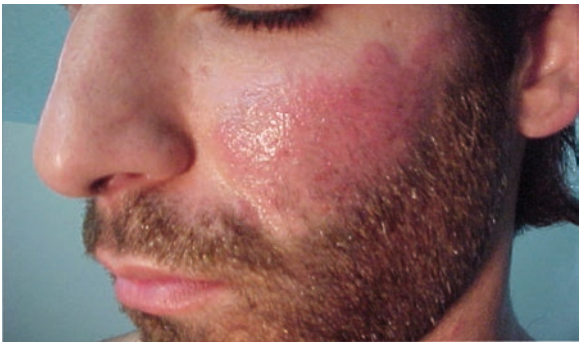

Fig. 24.2 Erythematous patch seen on the malar area of the face (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

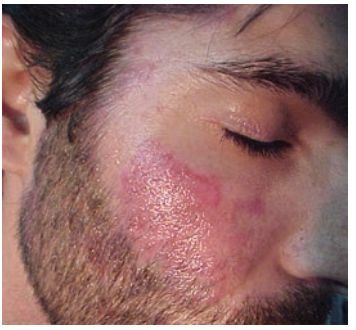

Fig. 24.3 Erythematous patches seen on the malar area of the face (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

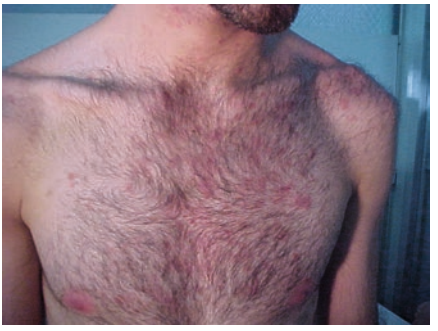

Fig. 24.4 Well-circumscribed, round erythematous papules widely distributed across the chest (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

Chapter 25
Patient Four

A 27-year-old man diagnosed with pemphigus foliaceus (PF) 2 years earlier is under treatment with a steroid only. He has been on 5 mg/day of prednisone and the symptoms are under control.

Note: The photos were taken when symptoms were present (Figs. 25.1, 25.2, 25.3, 25.4, and 25.5).

P. Khan Mohammad Beigi, *A Clinician's Guide to Pemphigus Vulgaris*,
https://doi.org/10.1007/978-3-319-67759-0_25

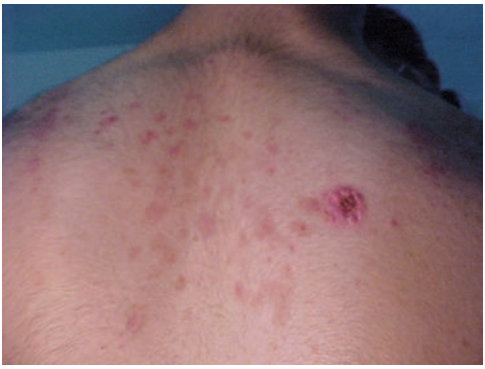

Fig. 25.1 Vesicles arranged concentrically with a crust present centrally. Macules are also widely distributed across the upper back (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

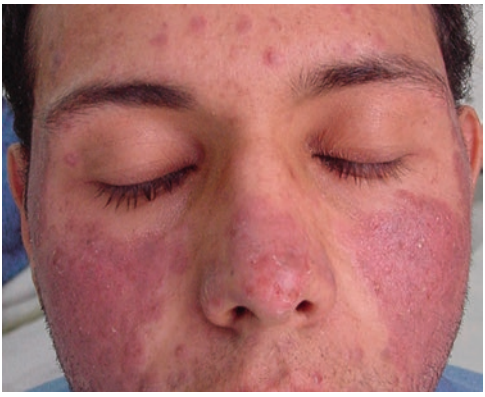

Fig. 25.2 Scaly crusted erosion on the nose and malar region of the face (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

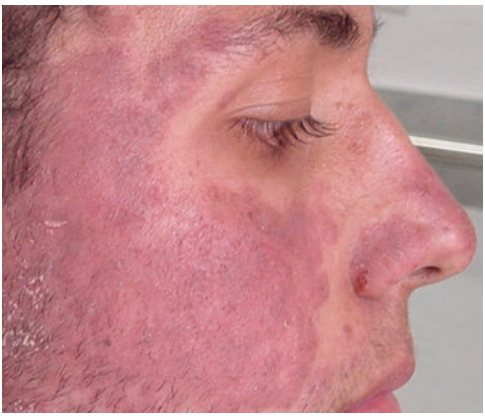

Fig. 25.3 Scaly crusted erosion on the nose and malar region of the face (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

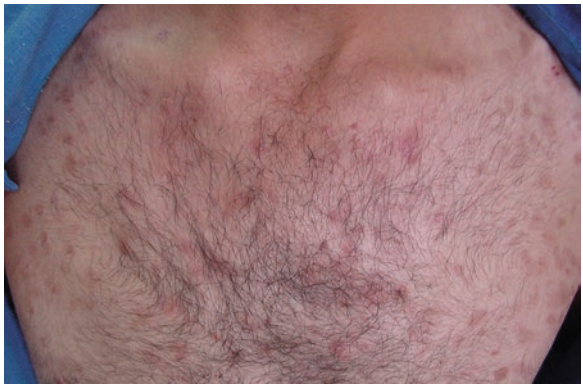

Fig. 25.4 Macules arranged in a random distribution across the chest area (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

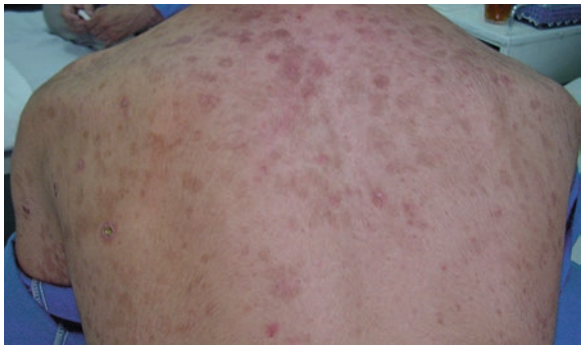

Fig. 25.5 Well-circumscribed, irregular macules are widely distributed across the upper back. There is also a pus-filled erosion on the left side of the upper back (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

Chapter 26
Patient Five

A 25-year-old woman has been under treatment after diagnosis of Senear-Usher syndrome for a year. This syndrome, which is called pemphigus erythematosus (PE), is the localized form of pemphigus foliaceus (PF) with clinical symptoms of lupus. Antinuclear antibody (ANA) of patient was reported positive. The treatment was initiated with 75 mg/day of prednisone and 2 g/day of mycophenolate mofetil. After control of symptoms, she was maintained on 5 mg/day of prednisone, which is still being continued.

Note: The photos were taken when symptoms were present (Figs. 26.1, 26.2, 26.3, 26.4, and 26.5).

P. Khan Mohammad Beigi, *A Clinician's Guide to Pemphigus Vulgaris*,
https://doi.org/10.1007/978-3-319-67759-0_26

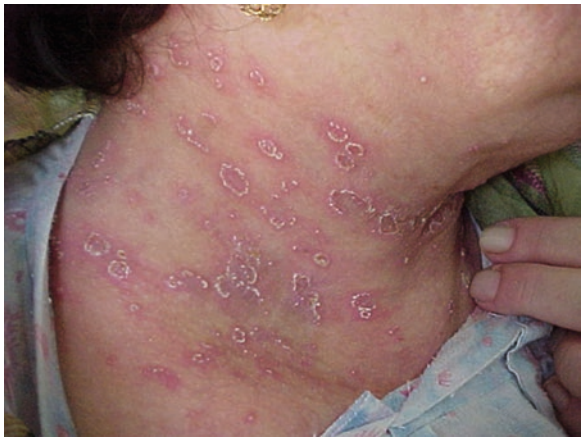

Fig. 26.1 Not well-circumscribed erosions with pustules arranged annularly around the erosions (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

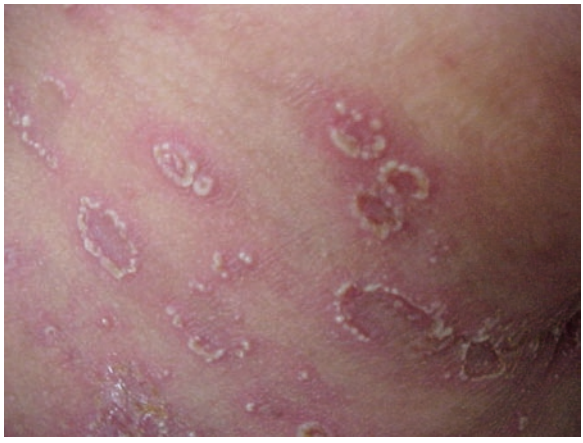

Fig. 26.2 Erythematous erosions with pustules arranged annularly around the erosions (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

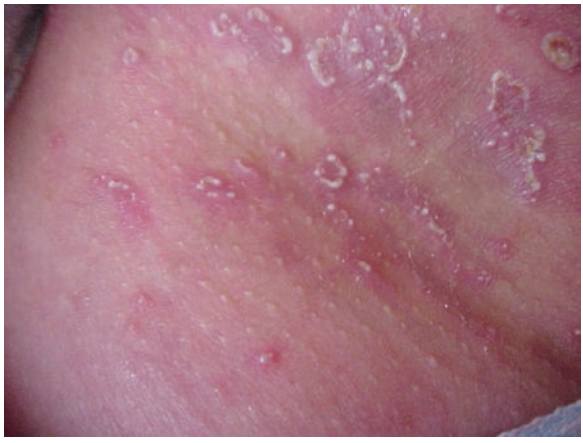

Fig. 26.3 Erythematous erosions with pustules arranged annularly around the erosions (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

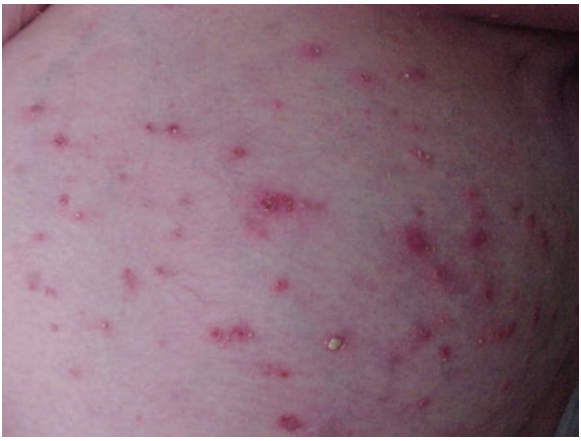

Fig. 26.4 Not well-circumscribed erythematous erosions. There is a single well-defined pustule in the field of view (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

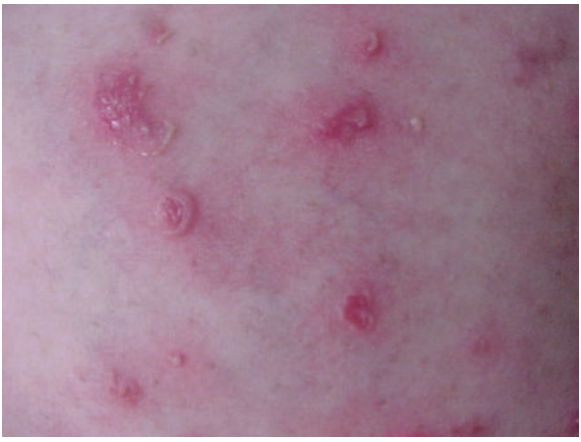

Fig. 26.5 Not well-circumscribed round, vesicles with an erythematous base (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

Chapter 27
Patient Six

A 26-year-old man diagnosed with pemphigus vulgaris (PV) has been under treatment for 1.5 years. The treatment was started with 80 g/day of prednisone along with 2 g/day of mycophenolate mofetil. During this period, after reduction of prednisone, in spite of simultaneous application of mycophenolate mofetil, the disease relapsed twice: when he was on 15 mg/day of prednisone and the other time when he was on 20 mg/day of prednisone. Due to several relapses, treatment with 2 g of rituximab was started 6 months ago, which controlled the symptoms. Now he is on 15 mg/day of prednisone without adjuvant and has had no relapses in the past 6 months. The dose of prednisone is now going to be tapered.

Note: The photos were taken when symptoms were present (Figs. 27.1, 27.2, 27.3, and 27.4).

P. Khan Mohammad Beigi, *A Clinician's Guide to Pemphigus Vulgaris*,
https://doi.org/10.1007/978-3-319-67759-0_27

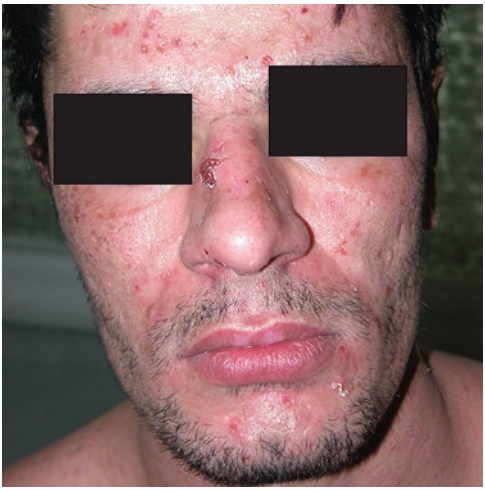

Fig. 27.1 Many well-defined round erosions on the face with an erythematous base (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

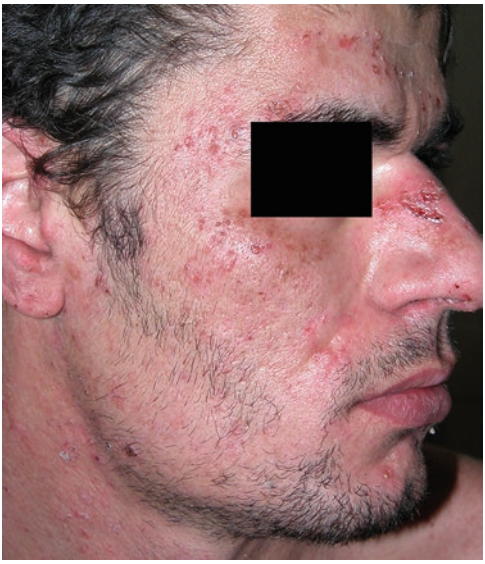

Fig. 27.2 Numerous well-defined erythematous/brown papules and an erosion on the nose (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

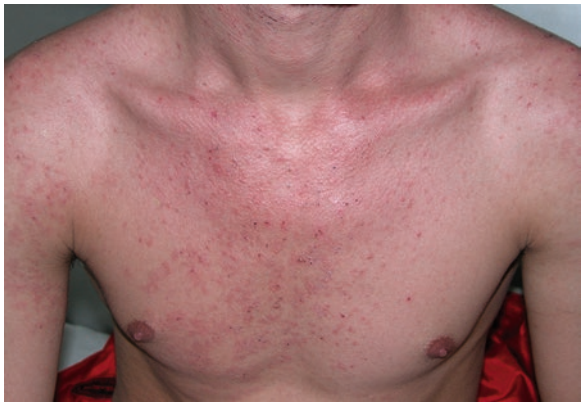

Fig. 27.3 Numerous erythematous macules and papules on the chest and proximal extremities (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

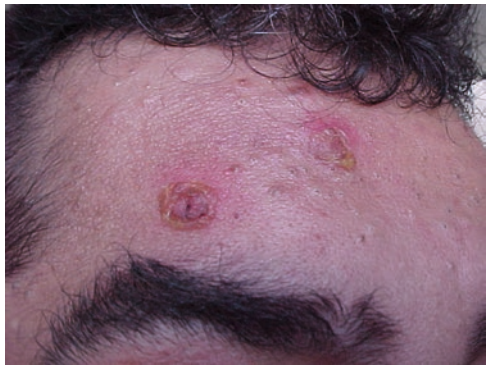

Fig. 27.4 Erythematous erosions with a pus-filled crust surrounding them (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

Chapter 28
Patient Seven

A 35-year-old man has been under treatment for 9 months after being diagnosed with pemphigus vulgaris (PV). The treatment was started with 100 mg/day of prednisone with 2 g of rituximab; by controlling the symptoms, prednisone was tapered. He is now under treatment with 7.5 mg/day of prednisone.

Note: The photos were taken when symptoms were present (Figs. 28.1 and 28.2).

P. Khan Mohammad Beigi, *A Clinician's Guide to Pemphigus Vulgaris*,
https://doi.org/10.1007/978-3-319-67759-0_28

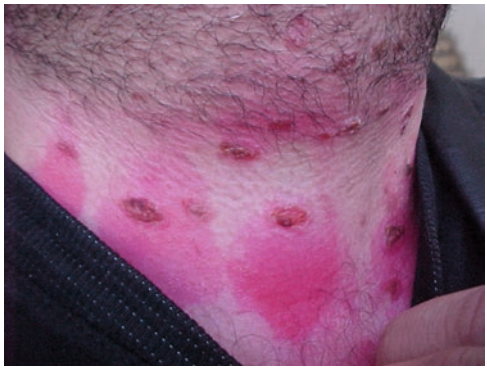

Fig. 28.1 Ill-defined, irregular *bright pink patches* and well-defined erosions (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

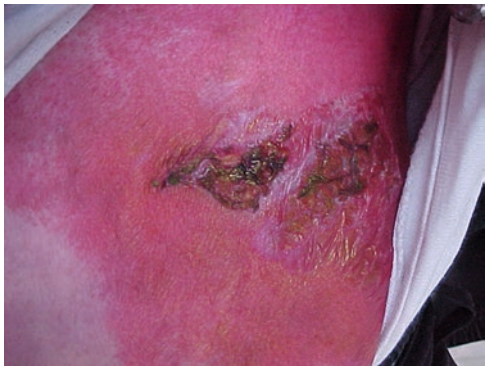

Fig. 28.2 Large well-defined irregular *bright pink patch* with large ulcer in the middle. The ulcer has a shiny texture to it (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

Chapter 29
Patient Eight

A 57-year-old man, who was diagnosed with pemphigus vulgaris (PV) 5 years earlier, has been under treatment with 30 mg/day of prednisone (oral) and local clobetasol. Currently, his symptoms are under control and he uses topical steroids as needed.

Note: The photos were taken when symptoms were present (Figs. 29.1, 29.2, and 29.3).

P. Khan Mohammad Beigi, *A Clinician's Guide to Pemphigus Vulgaris*,
https://doi.org/10.1007/978-3-319-67759-0_29

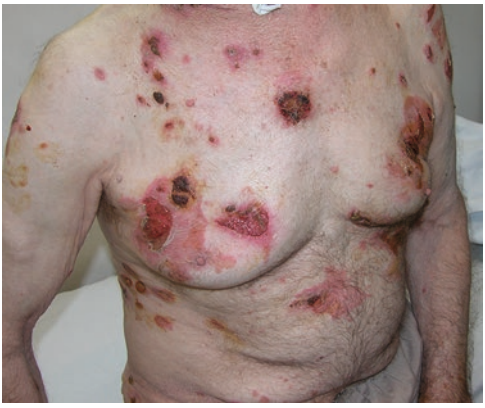

Fig. 29.1 Patient with many erythematous and brown crusted ulcers on the abdomen and limbs (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

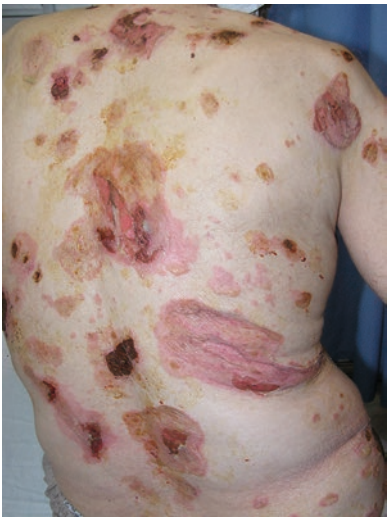

Fig. 29.2 Large erythematous patches and crusted erosions (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

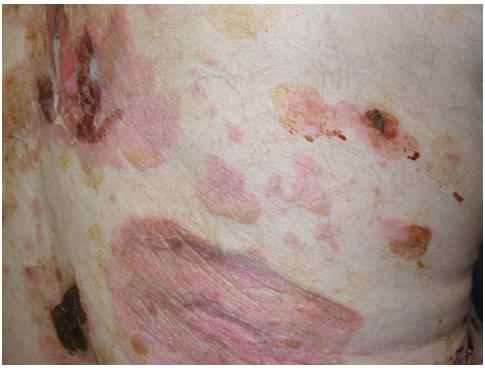

Fig. 29.3 Many crusted erosions and well-defined pink patches (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

Chapter 30
Patient Nine

A 45-year-old woman was diagnosed with pemphigus vulgaris (PV) 15 years ago. Treatment was first initiated with prednisone and azathioprine and was then substituted with mycophenolate mofetil. During her disease, the patient had relapses twice: when she was on 15 mg/day of prednisone and the other time when she received 20 mg/day of prednisone. Now she is under treatment with 7.5 mg/day of prednisone and her symptoms are under control.

Note: The photos were taken when symptoms were present (Figs. 30.1, 30.2, and 30.3).

P. Khan Mohammad Beigi, *A Clinician's Guide to Pemphigus Vulgaris*,
https://doi.org/10.1007/978-3-319-67759-0_30

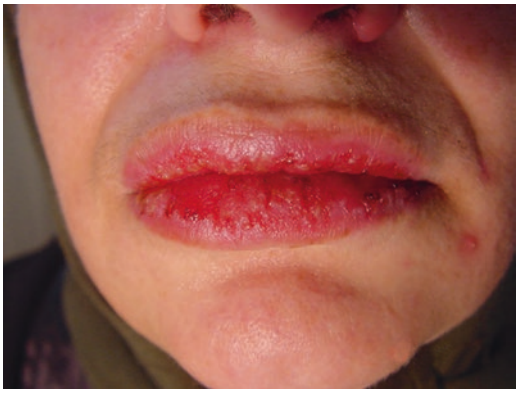

Fig. 30.1 Mucosal erosions on the lips (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

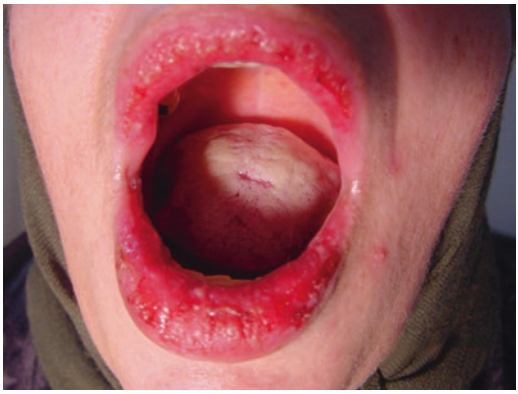

Fig. 30.2 Mucosal erosions of the lip and candidiasis of the tongue (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

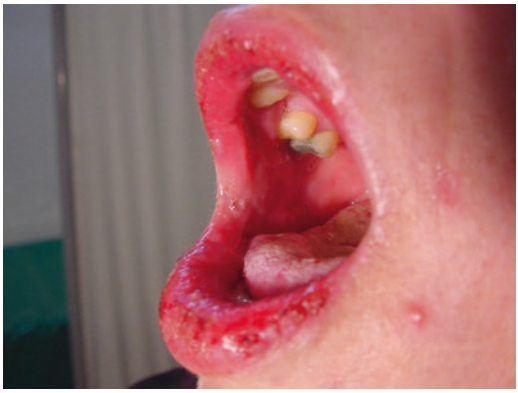

Fig. 30.3 Mucosal erosions and crusting on the lips (Source: Pooya Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

Chapter 31
Patient Ten

A 50-year-old man was receiving 80 mg/day of prednisone and 2 mg/day of mycophenolate mofetil when he was diagnosed with pemphigus vulgaris (PV) 9 months ago. Currently he is under treatment with 15 mg/day of prednisone and 75 mg/day of azathioprine.

Note: The photos were taken when symptoms were present (Figs. 31.1, 31.2, 31.3, and 31.4).

P. Khan Mohammad Beigi, *A Clinician's Guide to Pemphigus Vulgaris*,
https://doi.org/10.1007/978-3-319-67759-0_31

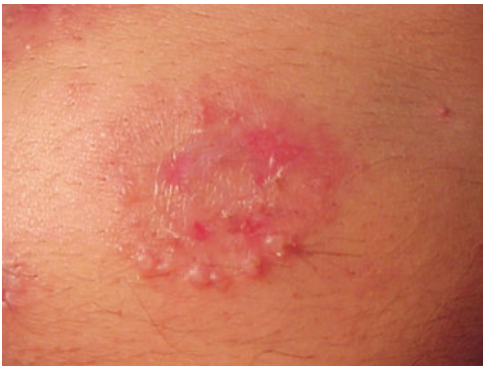

Fig. 31.1 Small skin-colored, round vesicles surrounding an erythematous ill-defined patch (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

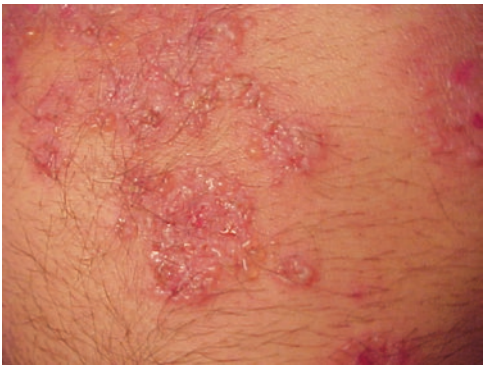

Fig. 31.2 Numerous fluid-filled vesicles on an erythematous base, with erosions (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

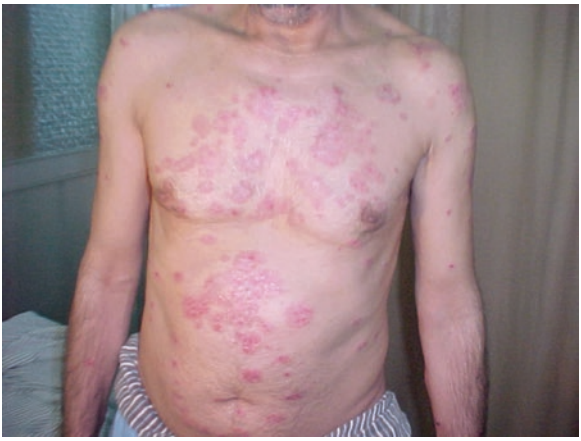

Fig. 31.3 Numerous erythematous erosions and patches on the abdomen and chest (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

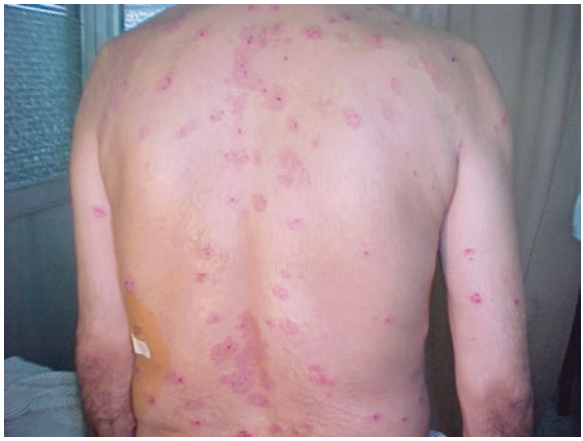

Fig. 31.4 Numerous erythematous erosions on the back and limbs (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

Chapter 32
Patient Eleven

The patient is a 55-year-old woman who was diagnosed with pemphigus vulgaris (PV) 5 years earlier. She was under treatment with 80 mg/day of prednisone along with 2 g/day of mycophenolate mofetil. She has not come to the clinic for 3 years, and in her last visit, she was under treatment with 12.5 mg/day of prednisone and 50 mg/day of azathioprine.

Note: The photos were taken when symptoms were present (Figs. 32.1 and 32.2).

P. Khan Mohammad Beigi, *A Clinician's Guide to Pemphigus Vulgaris*,
https://doi.org/10.1007/978-3-319-67759-0_32

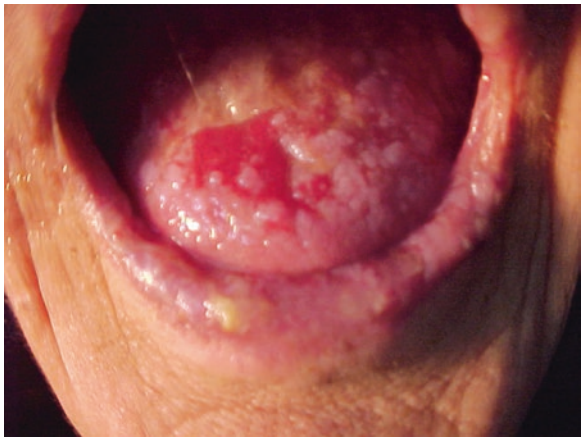

Fig. 32.2 Mucosal erosions and vesicles found inside the mouth (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

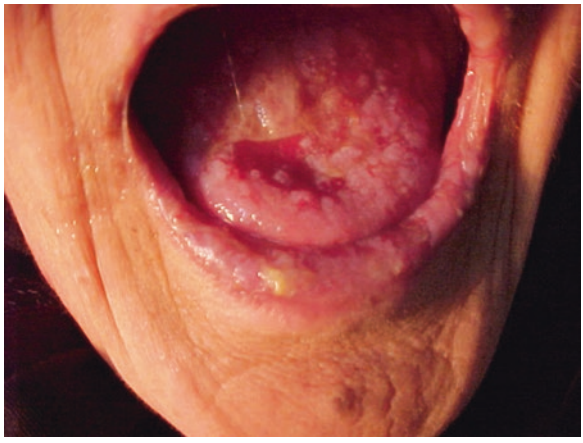

Fig. 32.1 Erythematous and *yellow* erosions found on the tongue and mucous membranes of the mouth (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

Chapter 33
Patient Twelve

A 28-year-old woman diagnosed with pemphigus vulgaris (PV) was initially treated with steroid and azathioprine 3 years ago. The patient has three histories of disease relapses: twice when she was on 7.5 mg/day and once she was on 12.5 mg/day of prednisone. Currently her symptoms are under control with 5 mg/day of prednisone.

Note: The photos were taken when symptoms were present (Figs. 33.1, 33.2, 33.3, 33.4, 33.5, and 33.6).

P. Khan Mohammad Beigi, *A Clinician's Guide to Pemphigus Vulgaris*,
https://doi.org/10.1007/978-3-319-67759-0_33

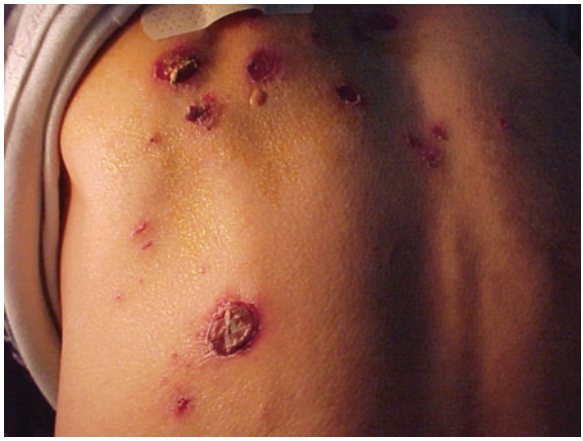

Fig. 33.1 Multiple round and erythematous erosions on the back. Some erosions are infected and pus filled (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

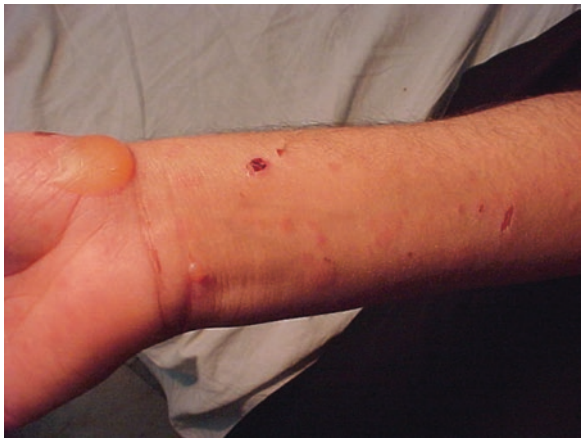

Fig. 33.2 Bulla is seen on the lateral aspect of the palm. There are some papules and excoriations on the forearm (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

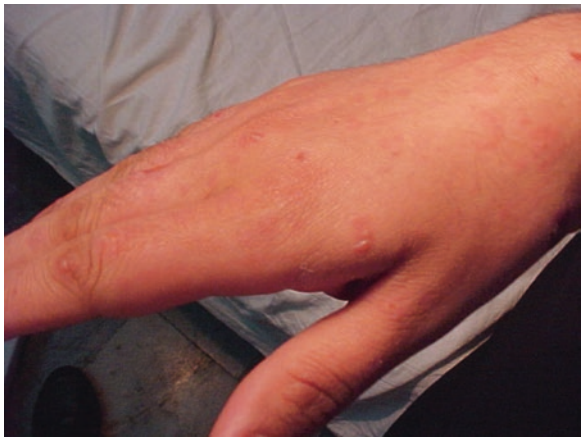

Fig. 33.3 Some vesicles found on the medial proximal interphalangeal (PIP) joint and near the thumb (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

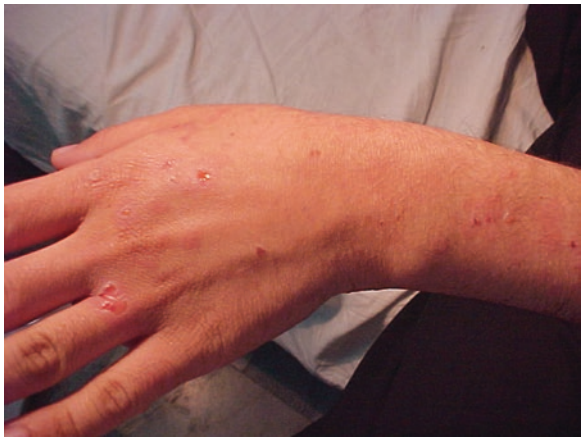

Fig. 33.4 Erythematous well-defined erosions are found on the dorsal aspect of the hand (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

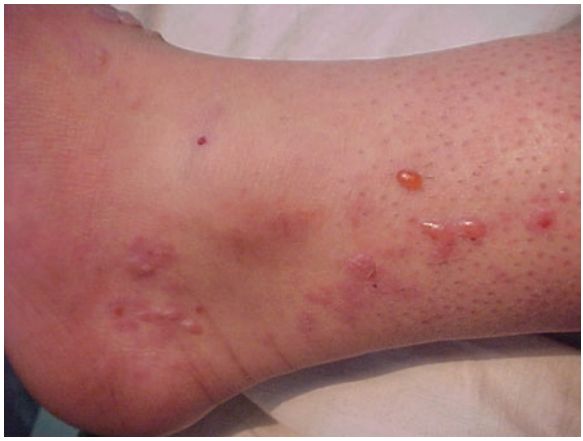

Fig. 33.5 Many round, well-defined, and erythematous vesicles and erosions are found on the lateral aspect of the foot, ankle, and leg (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

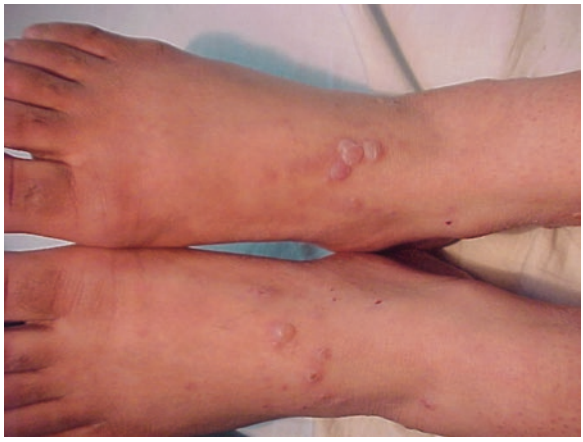

Fig. 33.6 Numerous round skin-colored bullae are found on the extensor surface of the foot (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

Chapter 34
Patient Thirteen

A 48-year-old woman diagnosed with pemphigus vulgaris (PV) has received 60 mg/day of steroid along with mycophenolate mofetil adjuvant. Now, the patient is under treatment with 5 mg/day of prednisone, which has controlled the symptoms.

Note: The photos were taken when symptoms were present (Fig. 34.1).

P. Khan Mohammad Beigi, *A Clinician's Guide to Pemphigus Vulgaris*,
https://doi.org/10.1007/978-3-319-67759-0_34

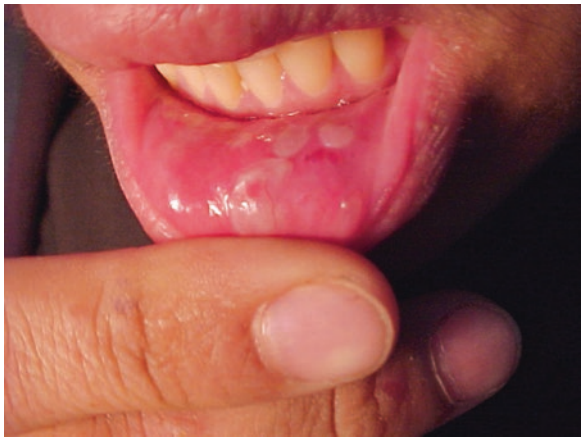

Fig. 34.1 Multiple round, well-defined vesicles are found on the mucous membranes in the mouth (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

Chapter 35
Patient Fourteen

A 37-year-old woman has been under treatment with 60 mg/day of prednisone and 100 mg/day of azathioprine when her pemphigus vulgaris (PV) was diagnosed 3 years ago. Now, she is on 5 mg/day of prednisone.

Note: The photos were taken when symptoms were present (Figs. 35.1, 35.2, 35.3, 35.4, and 35.5).

P. Khan Mohammad Beigi, *A Clinician's Guide to Pemphigus Vulgaris*,
https://doi.org/10.1007/978-3-319-67759-0_35

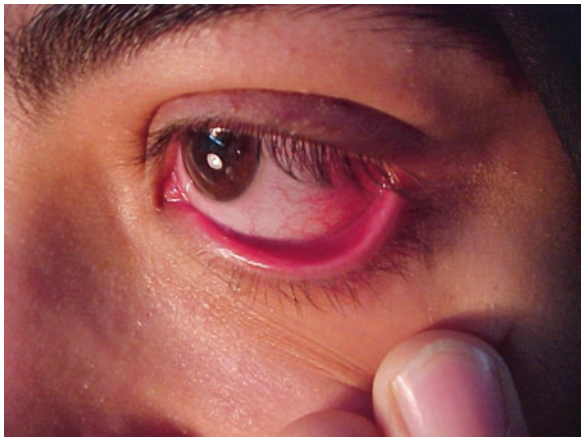

Fig. 35.1 The conjunctiva of the left eye is inflamed, and there is scleral inflammation as well (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

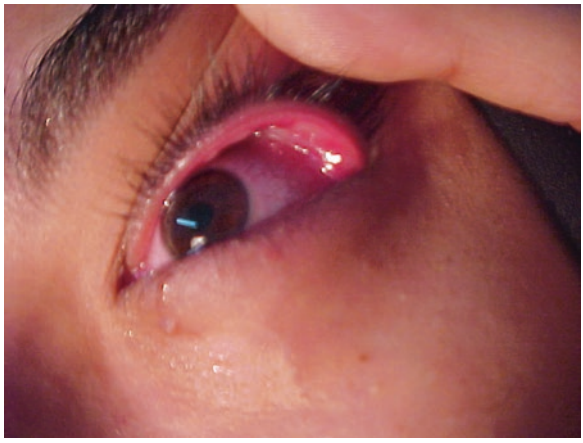

Fig. 35.2 Some vesicles can be seen in the mucous membrane of the upper eyelid of the left eye (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

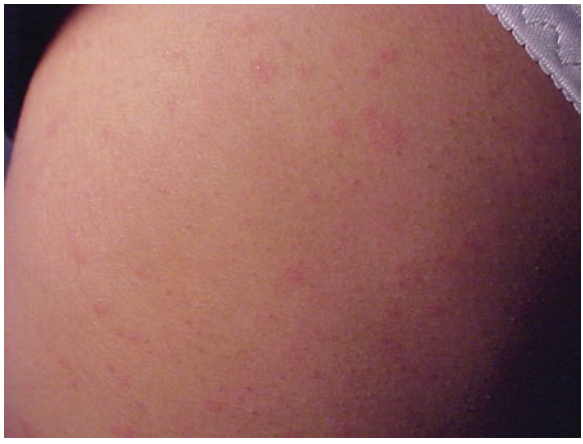

Fig. 35.3 Many round, well-defined erythematous papules are present (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

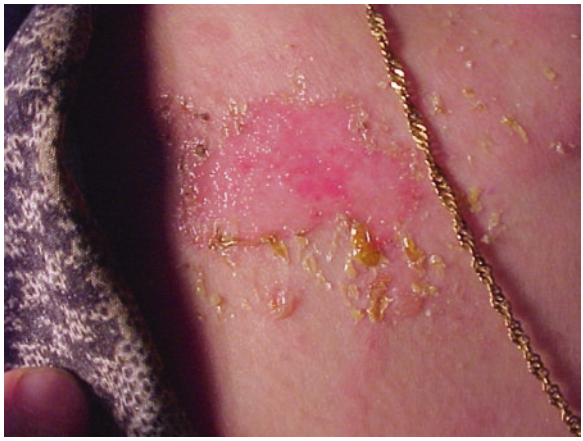

Fig. 35.4 Well-defined, erythematous erosion is present, with some pus and inflammation at the site of the erosion (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

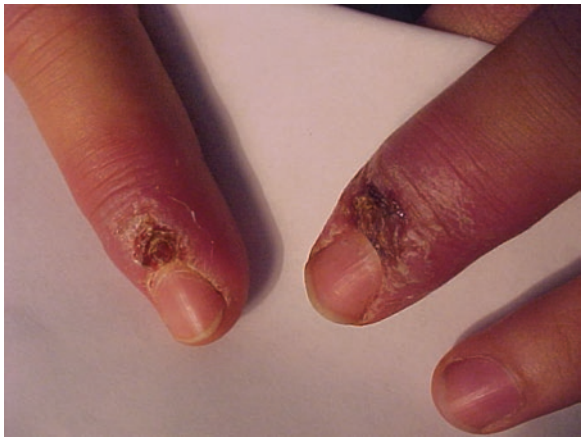

Fig. 35.5 Ill-defined and irregular erythematous and yellow erosions found on the skin below the nail bed. These erosions are crusted and scaly (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

Chapter 36
Patient Fifteen

A 25-year-old woman was diagnosed with pemphigus vulgaris (PV) 4 years ago, and her treatment was started with 55 mg/day of prednisone only. She had one relapse when the steroid was tapered. During that time, the dosage of steroid was 10 mg/day. After receiving treatment for 3 years with 3 mg/day of prednisone, it was tapered and now the symptoms are under control.

Note: The photos were taken when symptoms were present (Figs. 36.1, 36.2, 36.3, and 36.4).

P. Khan Mohammad Beigi, *A Clinician's Guide to Pemphigus Vulgaris*,
https://doi.org/10.1007/978-3-319-67759-0_36

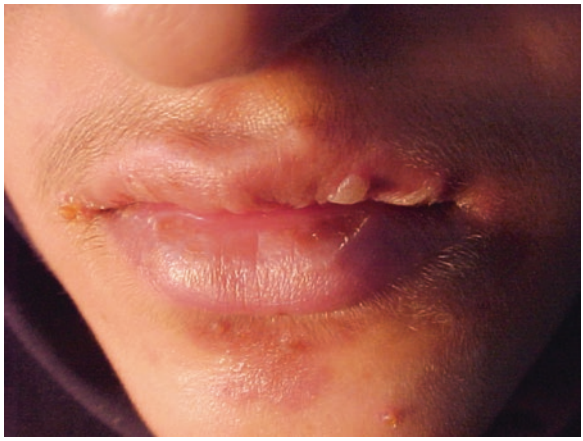

Fig. 36.1 Many erythematous and yellow vesicles found on the external surface of the lips. There is also an erythematous patch under the bottom lip (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

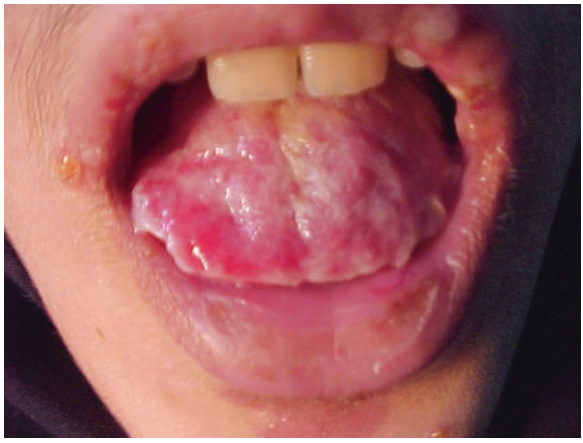

Fig. 36.2 Lots of erosions and inflammation inside the mouth. There are multiple vesicles and erosions on the external surface of the lips (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

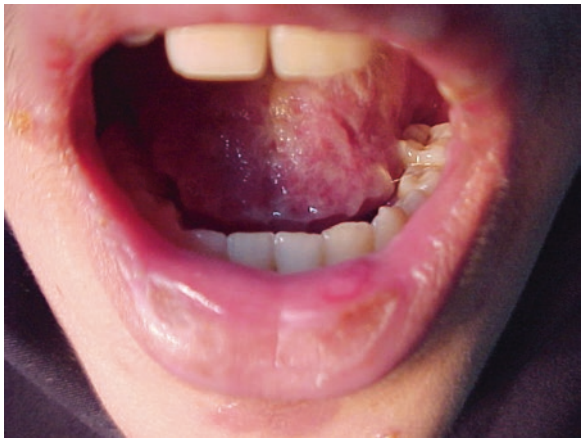

Fig. 36.3 Many round yellow vesicles on the tongue and some irregular yellow erosions on the lips. There is an erythematous, well-defined patch under the lower lip (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

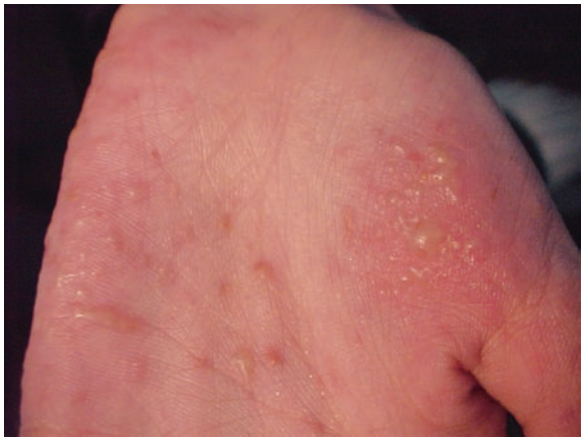

Fig. 36.4 Numerous round and well-defined vesicles found on the palmar aspect of the hand (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

Chapter 37
Patient Sixteen

A 35-year-old woman was diagnosed with pemphigus vulgaris (PV) a year ago and has been under treatment with 55 mg/day of prednisone and mycophenolate mofetil. She has had several disease recurrences when she was on 10 mg/day of prednisone and when she was on 15 mg/day of prednisone. Currently she is under treatment with 7.5 mg/day of prednisone and 15 mg/week of methotrexate.

Note: The photos were taken when symptoms were present (Figs. 37.1, 37.2, and 37.3).

P. Khan Mohammad Beigi, *A Clinician's Guide to Pemphigus Vulgaris*,
https://doi.org/10.1007/978-3-319-67759-0_37

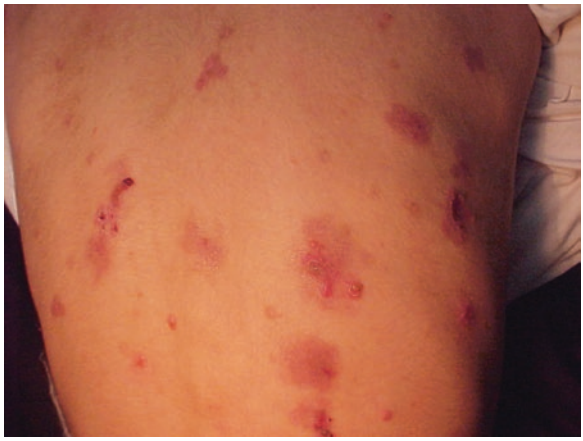

Fig. 37.1 Ill-defined erythematous erosions and patches on the back of the patient (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

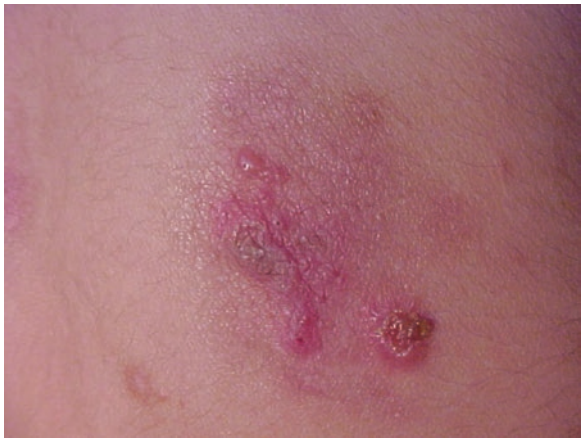

Fig. 37.2 An ill-defined erythematous patch of skin, containing a vesicle and multiple infected erosions on the skin (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

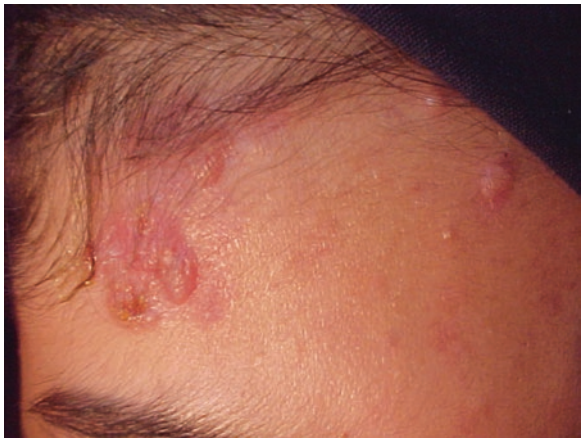

Fig. 37.3 Many vesicles on the forehead of the patient and erythematous infected erosions (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

Chapter 38
Patient Seventeen

The patient is a 27-year-old man diagnosed with pemphigus vulgaris (PV), who has been under treatment with 80 mg/day of prednisone and 2 mg/day of mycophenolate mofetil for 6 months. Now, the symptoms of disease are under control with 5 mg/day of prednisone.

Note: The photos were taken when symptoms were present (Figs. 38.1, 38.2, 38.3, and 38.4).

P. Khan Mohammad Beigi, *A Clinician's Guide to Pemphigus Vulgaris*,
https://doi.org/10.1007/978-3-319-67759-0_38

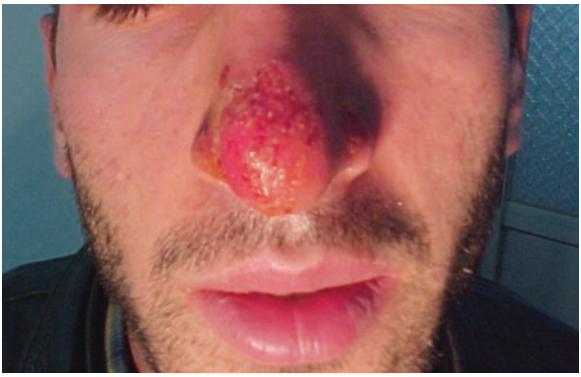

Fig. 38.1 The nose area has a large erythematous erosion that is infected (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

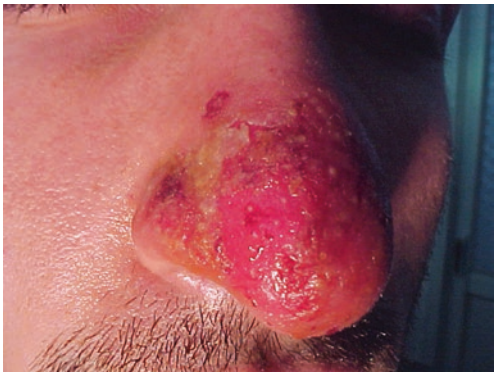

Fig. 38.2 The nose area is covered with erythematous erosions (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

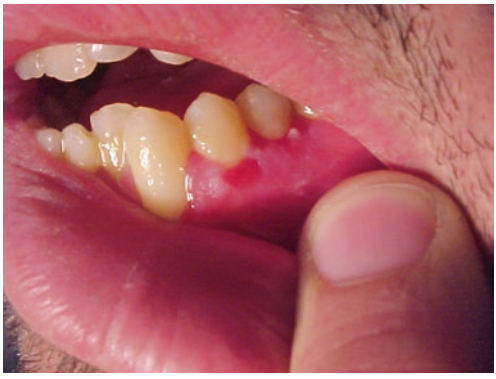

Fig. 38.3 There is an erythematous erosion on the gums (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

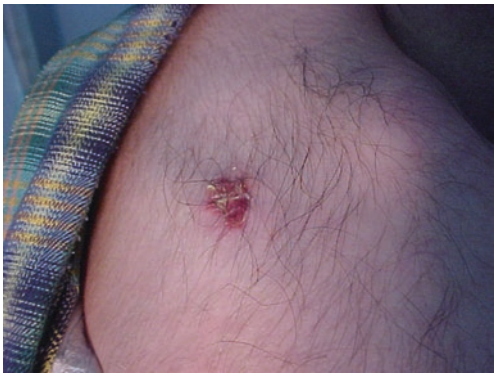

Fig. 38.4 A well-defined erythematous erosion with scaling and crusting (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

Chapter 39
Patient Eighteen

A 55-year-old man with pemphigus vulgaris (PV) has been treated with 55 mg/day of prednisone and 100 mg/day of azathioprine in the last year. The treatment was successful and the symptoms were well controlled. He has not been referred to clinic for 2 years and since then he has received 2 mg/day of prednisone with no adjuvant.

Note: The photos were taken when symptoms were present (Figs. 39.1, 39.2, 39.3, and 39.4).

P. Khan Mohammad Beigi, *A Clinician's Guide to Pemphigus Vulgaris*,
https://doi.org/10.1007/978-3-319-67759-0_39

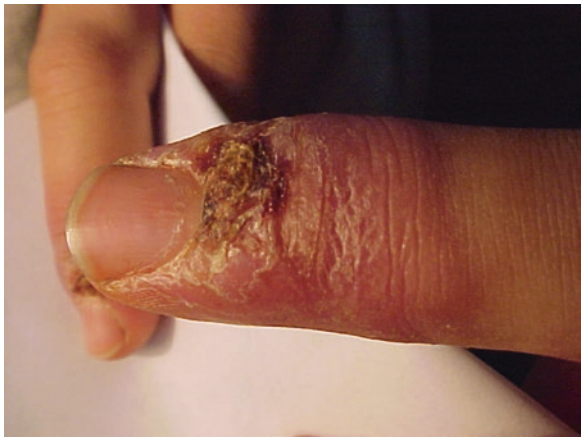

Fig. 39.1 A well-defined erythematous erosion, with pus crusting and scaling (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

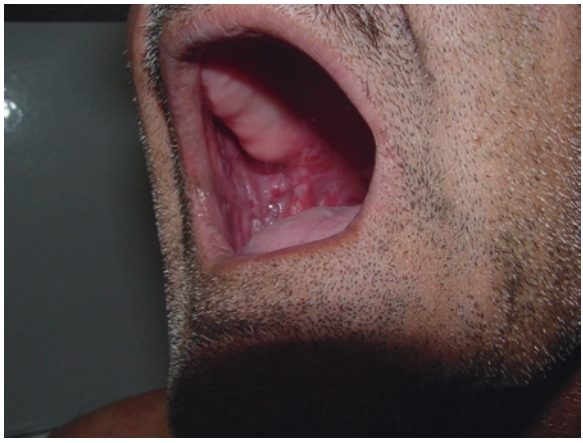

Fig. 39.2 Numerous well-defined, round vesicles and erythematous erosions involving the mucous membranes of the mouth (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

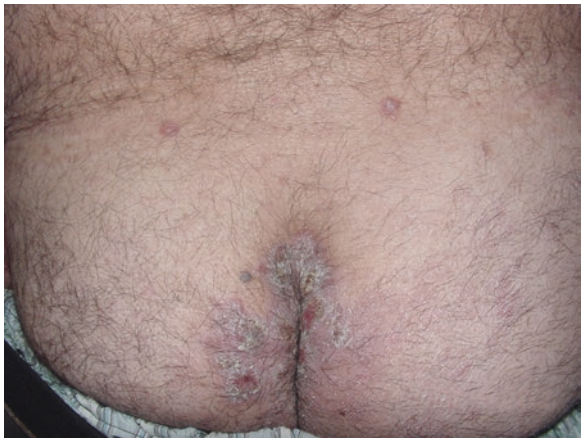

Fig. 39.3 Scaling and excoriation on an irregular ill-defined erythematous patch (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

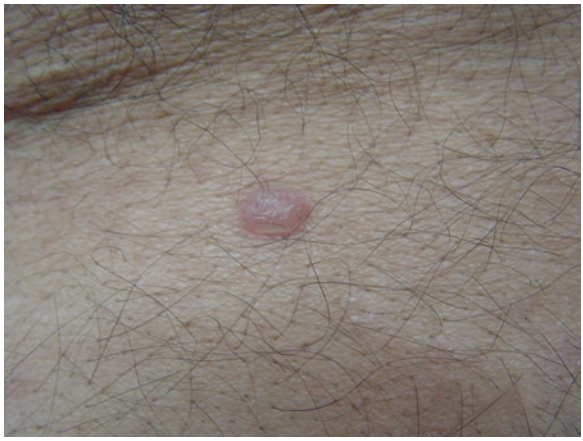

Fig. 39.4 Well-defined, round vesicle on an erythematous base (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

Chapter 40
Patient Nineteen

A 63-year-old woman was diagnosed with pemphigus vulgaris (PV) last year. Her treatment was started with 75 mg/day of prednisone and 2 g/day of mycophenolate mofetil. She has been treated with 15 mg/day of prednisone for the past 6 months and has had two recurrences on the same dosage. Now she has dispersed abortive lesions showing recovery and recurrence status. Therefore, steroid dosage has not been reduced lower than 15 mg.

Note: The photos were taken when symptoms were present (Figs. 40.1, 40.2, 40.3, 40.4, and 40.5).

P. Khan Mohammad Beigi, *A Clinician's Guide to Pemphigus Vulgaris*,
https://doi.org/10.1007/978-3-319-67759-0_40

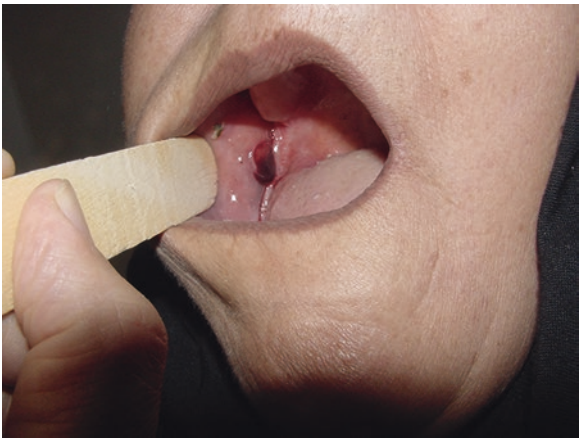

Fig. 40.1 A crusted green erosion in the mouth (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

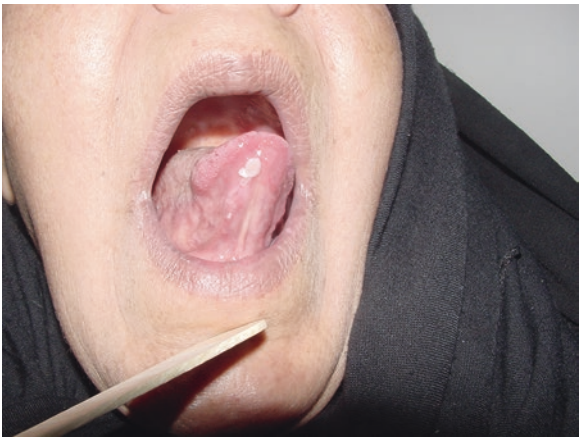

Fig. 40.2 Well-defined, round vesicle found on the bottom of the tongue (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

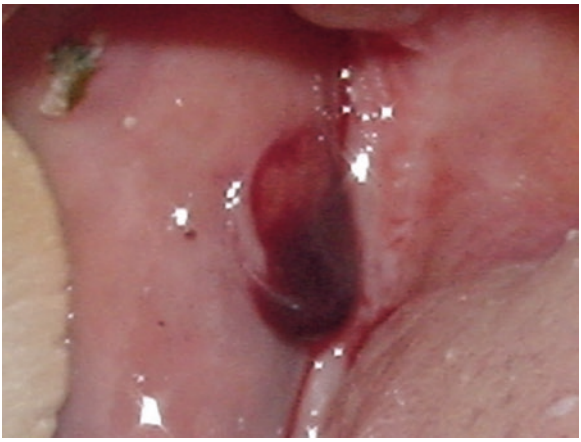

Fig. 40.3 Well-defined erythematous erosion in the mucous membranes of the mouth (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

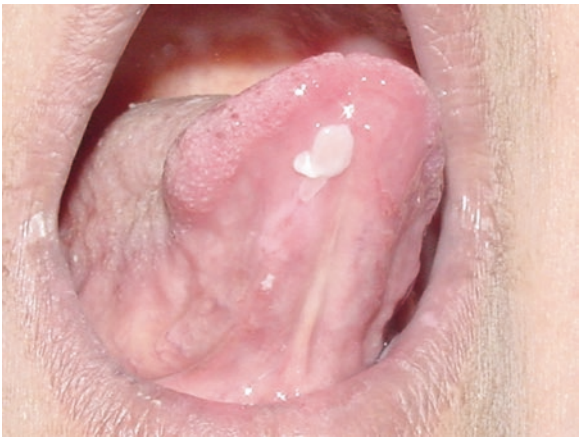

Fig. 40.4 A round and white well-defined vesicle (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

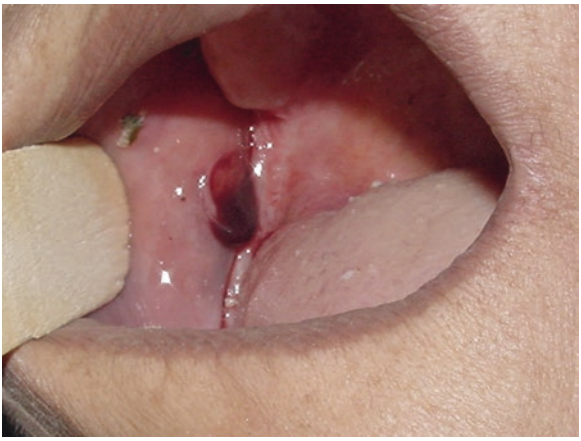

Fig. 40.5 Oval-shaped, well-defined erythematous mucosal erosion (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

Chapter 41
Patient Twenty

A 35-year-old female case of pemphigus vulgaris (PV) from 6 months ago was receiving 60 mg/day of prednisone and 2 mg/day of mycophenolate mofetil. After 8 months, prednisone dosage was reduced to 7.5 mg/day, while mycophenolate mofetil was continued with the same dosage. The next plan is to cautiously reduce the steroid dosage and gradually stop the adjuvant.

Note: The photos were taken when symptoms were present (Figs. 41.1 and 41.2).

P. Khan Mohammad Beigi, *A Clinician's Guide to Pemphigus Vulgaris*,
https://doi.org/10.1007/978-3-319-67759-0_41

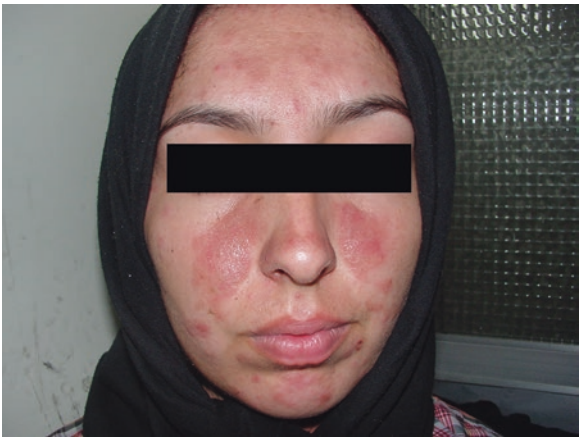

Fig. 41.1 Well-defined erythematous patches on the malar region of the face. There are also some erythematous macules and papules on the forehead and near the chin and lips (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

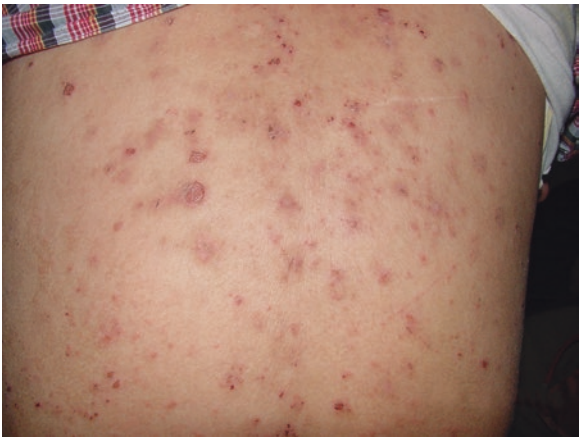

Fig. 41.2 Numerous ill-defined erythematous erosions on the back (Source: Pooya Khan Mohammad Beigi M.D., Pedram Nourmohammadpour M.D., Amirhoushang Ehsani M.D.)

Chapter 42
Patient Twenty-One

A 57-year-old female presented with vesicles and bullae in the upper chest, upper body, head, and mouth mucus and lower body for 3 months.

Note: The photos were taken when symptoms were present (Figs. 42.1, 42.2, 42.3, 42.4, 42.5, 42.6, 42.7, and 42.8).

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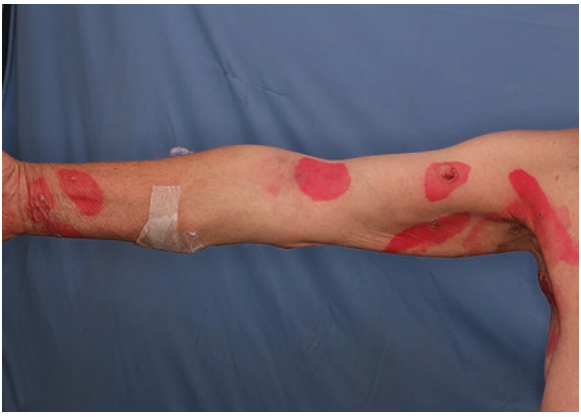

Fig. 42.1 *Bright pink*, well-defined patches, with central ulcerations (Source: Pooya Khan Mohammad Beigi M.D., Hassan Seirafi M.D.)

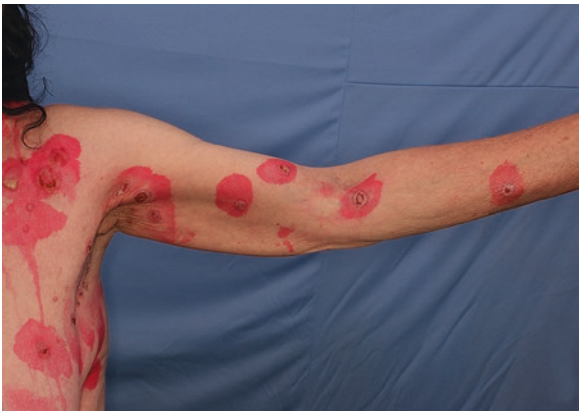

Fig. 42.2 *Bright pink*, well-defined patches, with central ulcerations (Source: Pooya Khan Mohammad Beigi M.D., Hassan Seirafi M.D.)

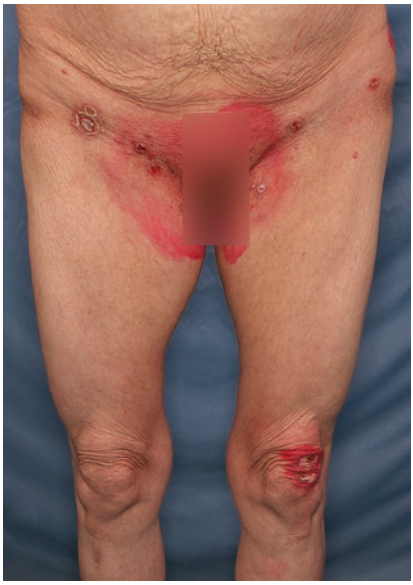

Fig. 42.3 *Bright pink*, well-defined patches in the groin area and on the left knee. There are also ulcerations with crusting present (Source: Pooya Khan Mohammad Beigi M.D., Hassan Seirafi M.D.)

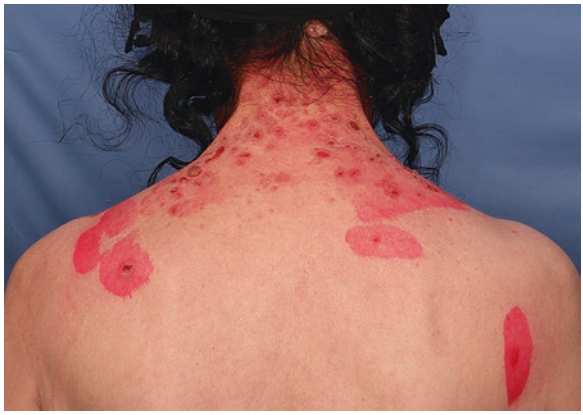

Fig. 42.4 *Bright pink*, well-defined patches on the back and neck. There are also ulcerations and erosions with crusting present (Source: Pooya Khan Mohammad Beigi M.D., Hassan Seirafi M.D.)

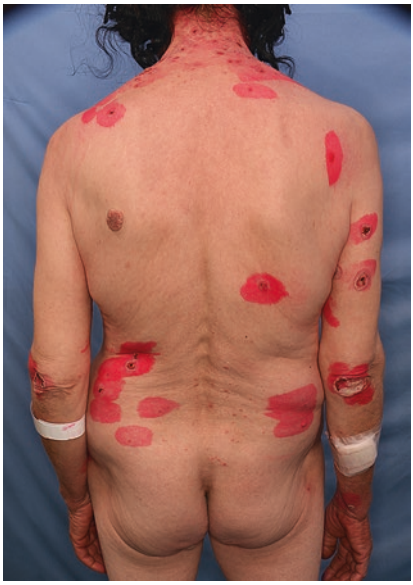

Fig. 42.5 *Bright pink*, well-defined patches on the neck, upper limb, and back. There are also ulcerations and erosions with crusting present on the neck, back, and upper limb. There is also a verrucous plaque on the upper left back (Source: Pooya Khan Mohammad Beigi M.D., Hassan Seirafi M.D.)

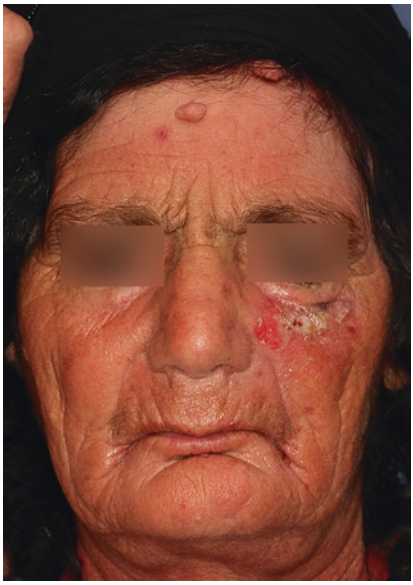

Fig. 42.6 Ill-defined erythematous ulcer with pus (Source: Pooya Khan Mohammad Beigi M.D., Hassan Seirafi M.D.)

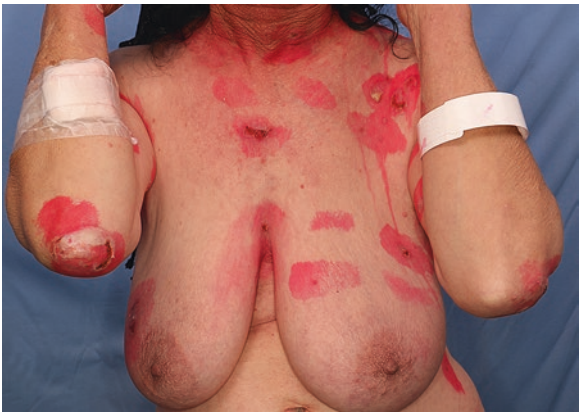

Fig. 42.7 *Bright pink*, well-defined patches with central ulcerations on the chest and elbows (Source: Pooya Khan Mohammad Beigi M.D., Hassan Seirafi M.D.)

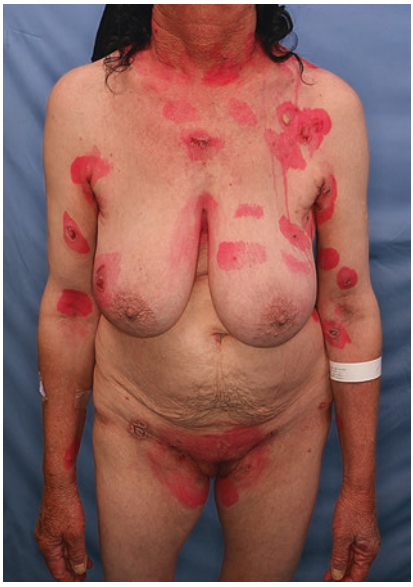

Fig. 42.8 *Bright pink*, well-defined patches with central ulcerations on the chest, upper arms, elbows, and groin area (Source: Pooya Khan Mohammad Beigi M.D., Hassan Seirafi M.D.)

Chapter 43
Patient Twenty-Two

A 50-year-old woman presents with vesiculobullous lesions. She has several blister lesions in her buccal mucous membranes, and several erosive lesions were also observed.

Note: The photos were taken when symptoms were present (Figs. 43.1, 43.2, 43.3, and 43.4).

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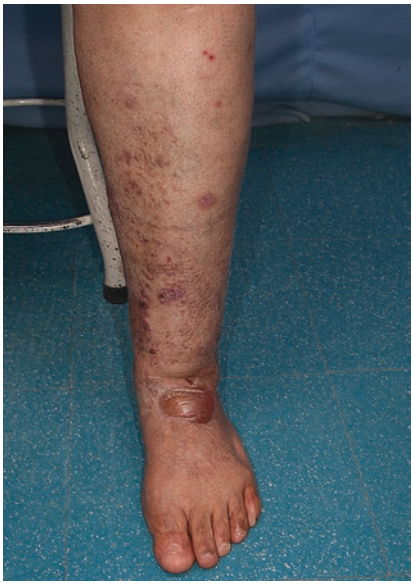

Fig. 43.1 Large skin-colored bulla on the foot and numerous erythematous erosions on the leg (Source: Pooya Khan Mohammad Beigi M.D., Hassan Seirafi M.D.)

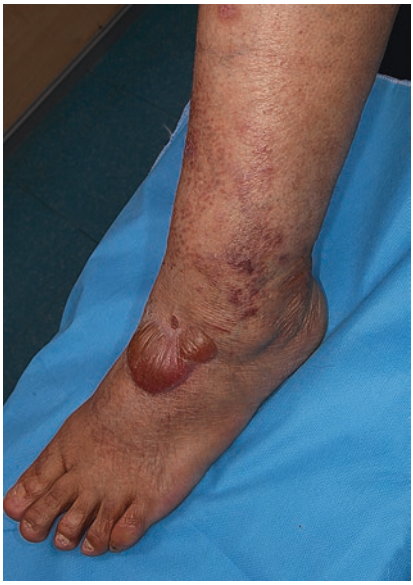

Fig. 43.2 Large skin-colored bulla on the foot and numerous erythematous erosions on the leg (Source: Pooya Khan Mohammad Beigi M.D., Hassan Seirafi M.D.)

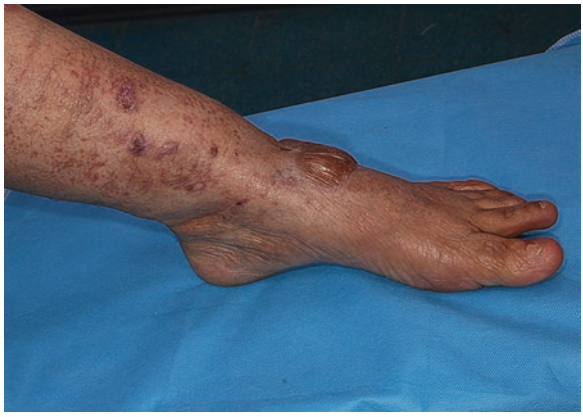

Fig. 43.3 Large skin-colored bulla on the foot and erythematous erosions on the leg (Source: Pooya Khan Mohammad Beigi M.D., Hassan Seirafi M.D.)

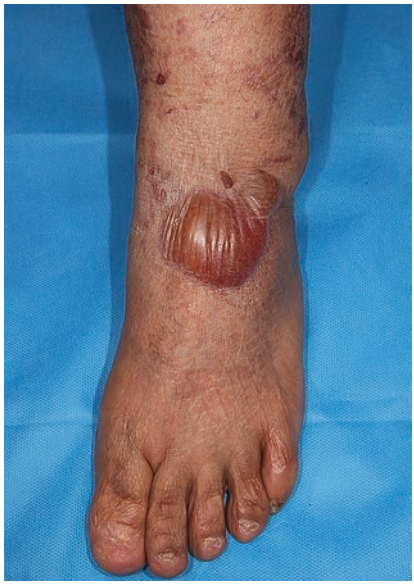

Fig. 43.4 Large skin-colored bulla on the foot and erythematous erosions on the leg (Source: Pooya Khan Mohammad Beigi M.D., Hassan Seirafi M.D.)

Chapter 44
Patient Twenty-Three

A 45-year-old female presents with a history of non-pruritic papulovesicular lesions, bullae, and erosions on her face, buccal mucosa, chest, leg, and genital region.

Note: The photos were taken when symptoms were present (Figs. 44.1, 44.2, 44.3, 44.4, 44.5, 44.6, and 44.7).

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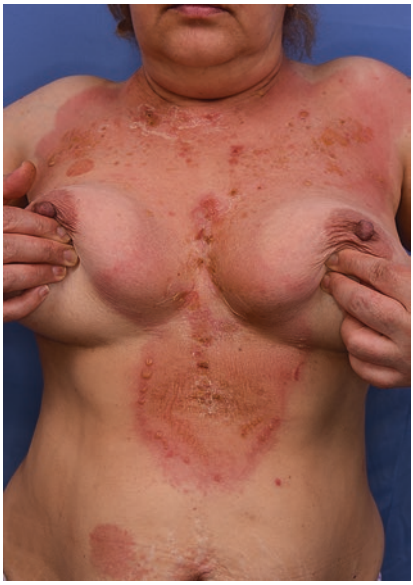

Fig. 44.1 Ill-defined erythematous patches on the chest and abdomen. Crusted erosions are found throughout the chest and abdomen (Source: Pooya Khan Mohammad Beigi M.D., Hassan Seirafi M.D.)

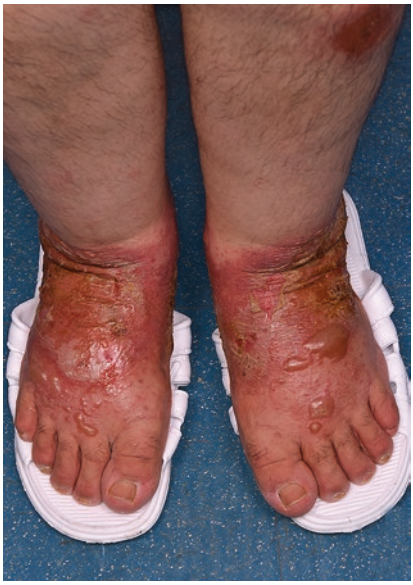

Fig. 44.2 Erythematous patches on both feet, with round epidermal bullae and yellow crusting (Source: Pooya Khan Mohammad Beigi M.D., Hassan Seirafi M.D.)

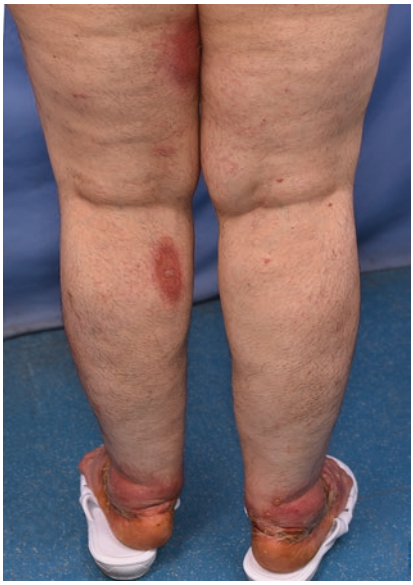

Fig. 44.3 The soles of the feet have erythematous patches (Source: Pooya Khan Mohammad Beigi M.D., Hassan Seirafi M.D.)

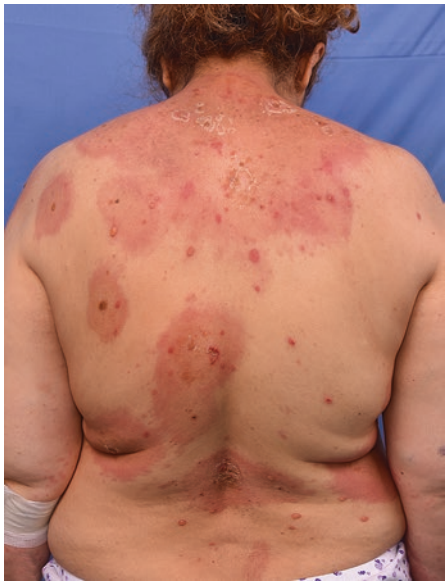

Fig. 44.4 Large well-defined patches with an erythematous base. There are central ulcerations and erosions with crusts and scaling present (Source: Pooya Khan Mohammad Beigi M.D., Hassan Seirafi M.D.)

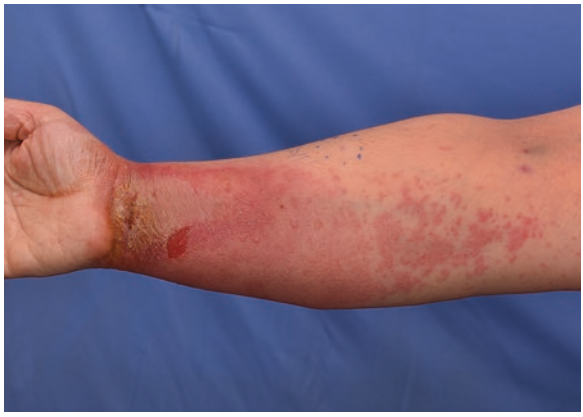

Fig. 44.5 Well-defined patches and macules with an erythematous base. There are also ulcerations and erosions with crusts and scaling present near the wrist (Source: Pooya Khan Mohammad Beigi M.D., Hassan Seirafi M.D.)

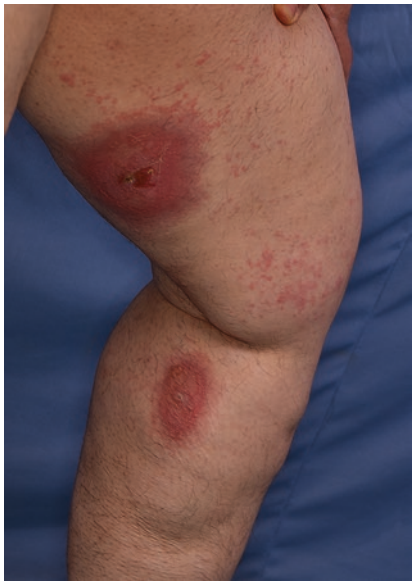

Fig. 44.6 Large ill-defined, round erythematous plaques with central ulceration (Source: Pooya Khan Mohammad Beigi M.D., Hassan Seirafi M.D.)

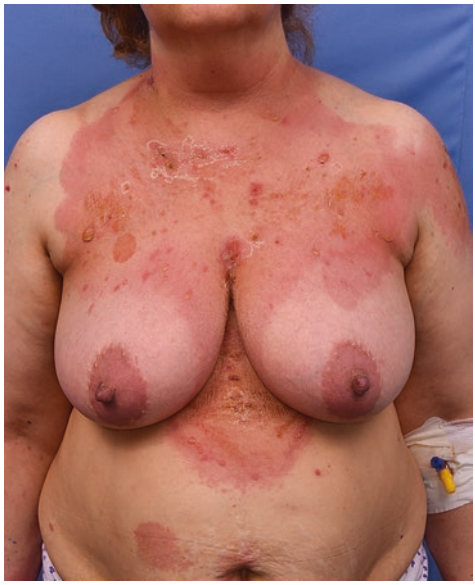

Fig. 44.7 Ill-defined erythematous patches on the chest and abdomen. Crusted erosions and ulcers are found throughout the chest and abdomen (Source: Pooya Khan Mohammad Beigi M.D., Hassan Seirafi M.D.)

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