Case Report

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Case Presentation of Stevens–Johnson Syndrome / Toxic Epidermal Necrolysis

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ABSTRACT

Stevens-Johnson syndrome (SJS) is a type IV (subtype C) hypersensitivity reaction that involves the skin and the mucous membranes. The classic manifestation of SJS consists of initial "flu-like" symptoms as malaise, fever, and anorexia in the prodromal phase, followed by cutaneous and mucous membrane inflammation and pain, and other systemic involvement. Symptoms usually begin 4-28 days after the onset of drug intake. SJS can affect many organs as oral mucosa, nasal mucosa, eye, vagina, urethra, gastrointestinal, and lower respiratory tract. SJS is a serious systemic disorder with the potential for severe morbidity and even death. Drugs and malignancies are most often implicated as the etiology in adults and elderly persons. The most common drugs which can induce SJS are phenytoin, carbamazepine, lamotrigine, barbiturates, modafinil, allopurinol, TNF- alpha antagonists (eg, infliximab, etanercept, adalimumab, oxcarbazepine (Trileptal), and valproic acid. Pediatric cases are related more often to infections as Epstein-Barr virus, enteroviruses, Group A beta-hemolytic streptococci, diphtheria, and brucellosis. It can also occur idiopathically. An idiosyncratic, delayed hypersensitivity reaction has been implicated in the pathophysiology of Stevens-Johnson syndrome. Certain population groups appear more susceptible to develop SJS than the general population. Without treatment, the symptoms can become very severe and be life threatening. Severe cases of (SJS) must be treated in an intensive care unit (ICU) or burns unit. The overlap between Stevens- Johnson syndrome (SJS)/ Toxic Epidermal Necrolysis (TEN) is considered when the lesions affected between 10% to 30 % of total body surface area (TBSA).

Abbreviations: SJS: Stevens-Johnson Syndrome; ICU: Intensive Care Unit; TEN: Toxic Epidermal Necrolysis; TBSA: Total Body Surface Area; TSS: Toxic Shock Syndrome; BSA: Body Surface Area; CDC: Center for Disease Control and Prevention; IgG: Immunoglobulin G; SSSS: Staphylococcal Scalded Skin Syndrome

Case Report

30- year-old, African male, came to the ER with fever which was associated with numerous bullous eruptions in the face, trunk, upper and lower extremities, and oral mucosa. The symptoms started since one week after a certain drug which was not be remembered well by the patient.

O/E

The patient was ill, feverish, had malaise, hemorrhagic bullous lesions in the face, trunk, upper and lower extremities. Some lesions showed target or iris lesions in the center. He had also erosions in the oral mucosa as shown in plates 1-2. His eyes were free. The patient was admitted, hydrated by I.V. fluids, treated with appropriate systemic and topical antibiotics with dressing to ruptured bullae, and

systemic cyclosporin.Stevens-Johnson syndrome is a minor form of toxic epidermal necrolysis, with less than 10% body surface area (BSA) detachment. Overlapping Stevens-Johnson syndrome/toxic epidermal necrolysis is considered when the detachment of 10- 30% of the body surface area (BSA). Toxic epidermal necrolysis (TEN) (Figures 1 & 2) is considered when the detachment of more than 30% of the BSA [1]. The lesions of our patient were about 15% of his body, so we considered the case as Stevens- Johnson syndrome (SJS)/ Toxic Epidermal Necrolysis(TEN).

Figure 1: Showed multiple ruptured bullous lesions in the upper extremity and R. axillae, and erosions in the lips.

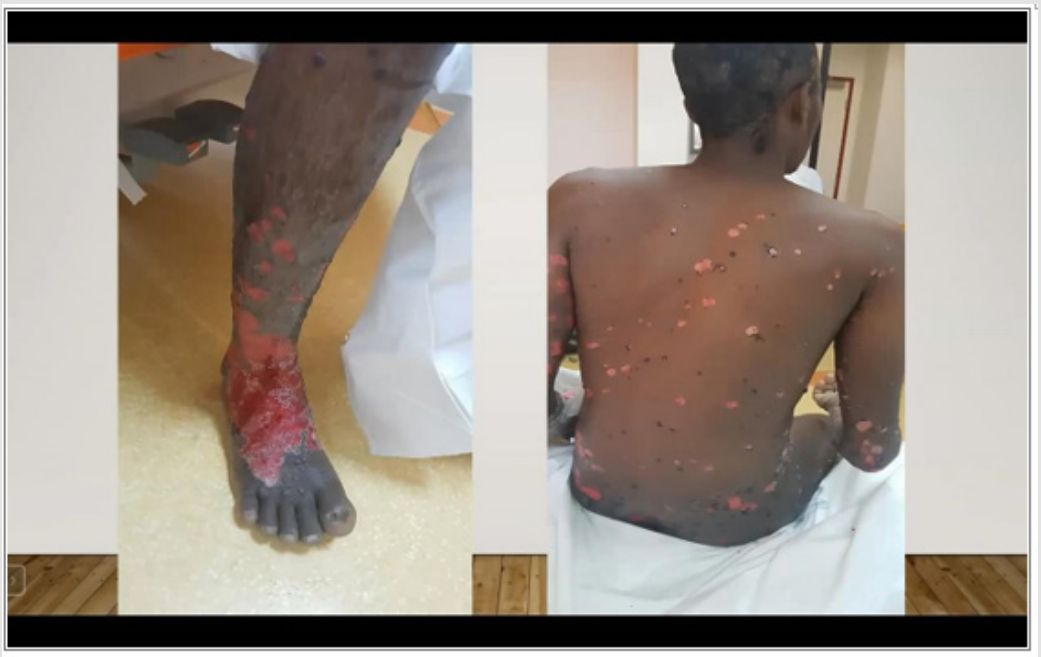

Figure 2: Showed ruptured bullous lesions in the R. leg, R. foot, back and upper extremities.

Histopathological Examination

(Figures 3-7).

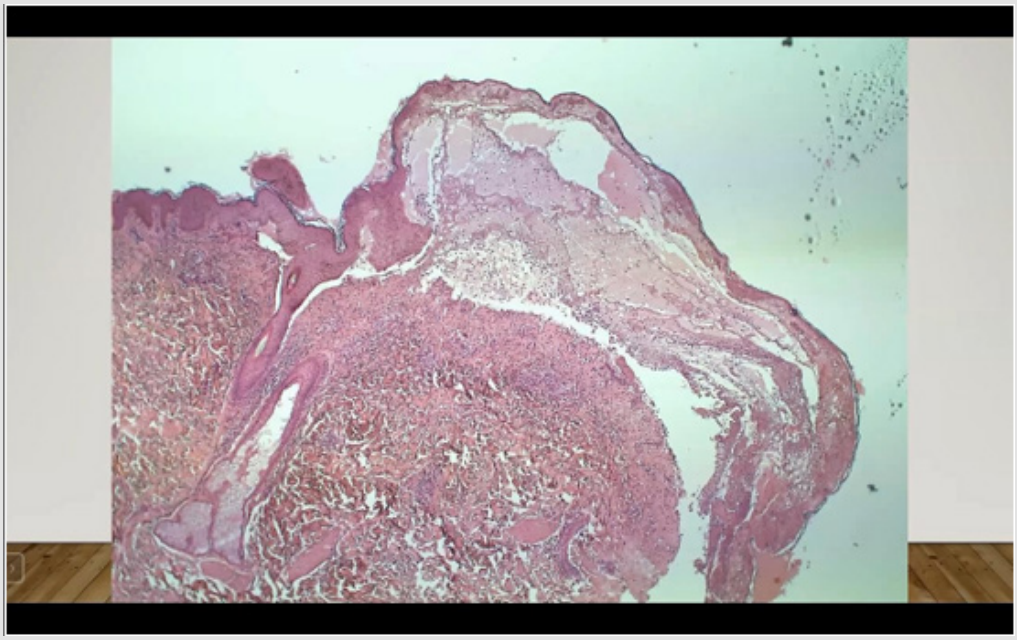

Figure 3: Showed vascular interface dermatitis with apoptotic keratinocytes and satellite cell necrosis and inflammatory cells in the upper dermis.

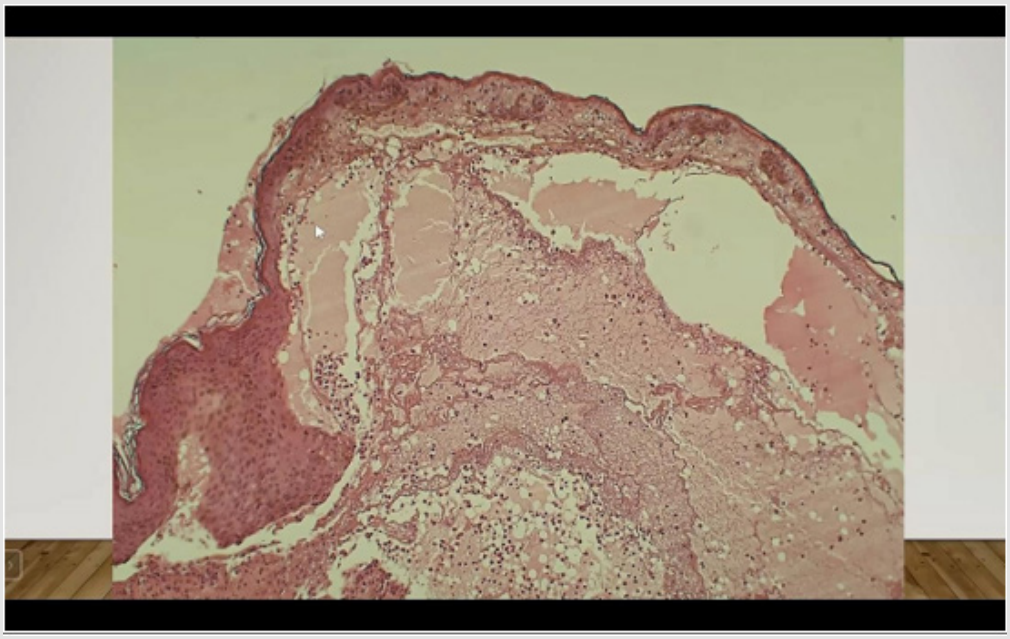

Figure 4: Showed full thickness epidermal necrosis with intraepidermal and subepidermal blisters which are filled with serum and some inflammatory cells. It showed also papillary dermal edema, RBCs extravasation in the blister cavity, and pathological features in the eccrine ductal epithelium.

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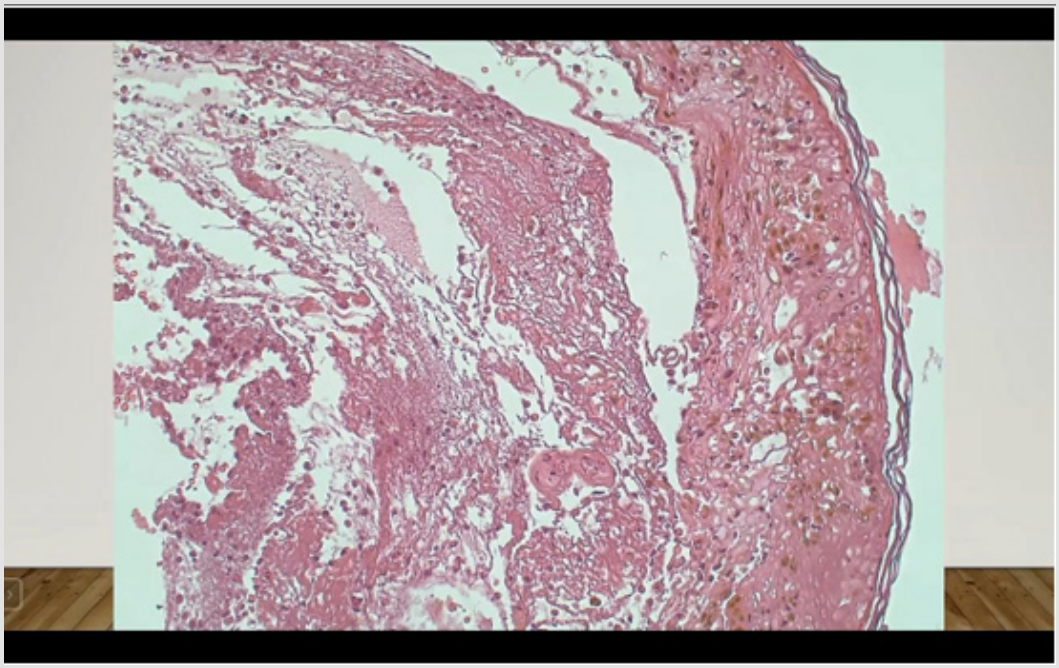

Figure 5: Showed high power shows: parakeratosis, satellite cell necrosis (which means that necrotic keratinocytes are surrounded by few lymphocytes).

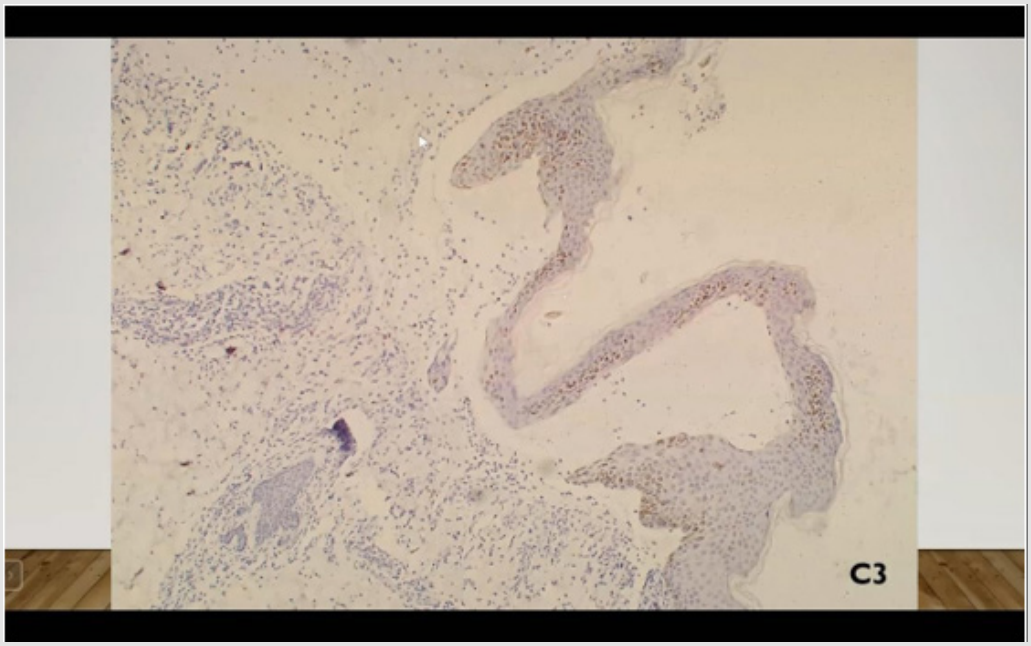

Figure 6: Showed immunohistological staining of IgM and C3 in the dermoepidermal junction and superficial dermal vessels.

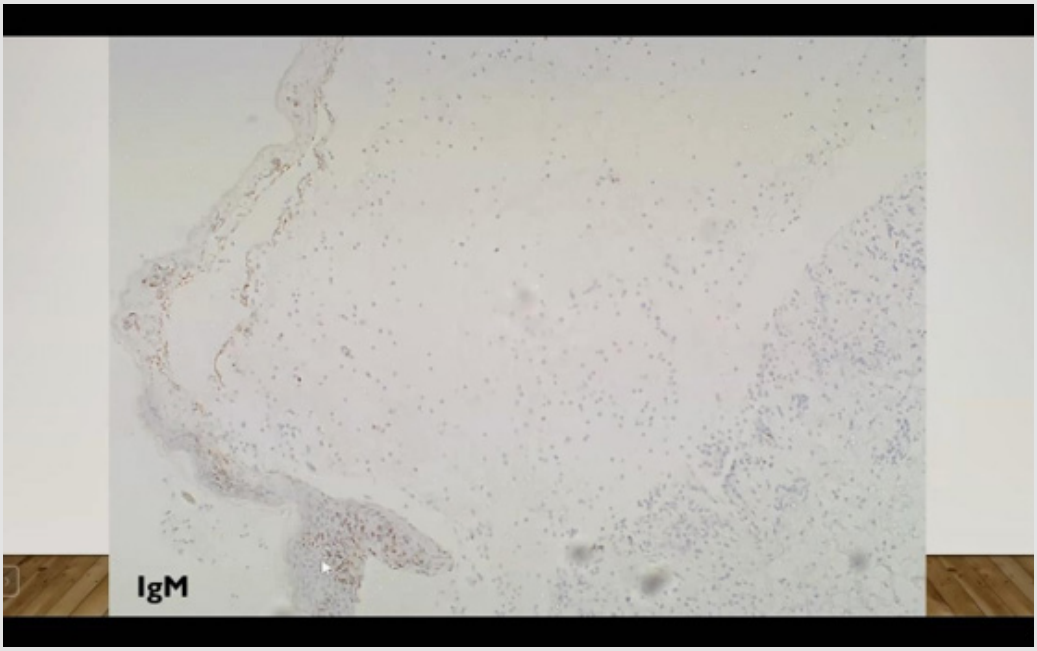

Figure 7: Showed immunohistological staining of IgM.

Differential Diagnoses

1. Chemical Burns
2. Exfoliative Dermatitis
3. Toxic Shock Syndrome
4. Bullous pemphigoid
5. Pemphigus foliaceus
6. Staphylococcal scalded skin syndrome

Chemical Burns: Chemical burns can be caused by acids or bases that contact with tissue. Most acids produce a coagulation necrosis by denaturing proteins, forming a coagulum (eg, eschar) that limits the penetration of the acid. Bases typically produce a more severe injury known as liquefaction necrosis. This involves denaturing of proteins as well as saponification of fats, which does not limit tissue penetration. Hydrofluoric acid is somewhat different from other acids in that it produces a liquefaction necrosis. There are many industrial products contain toxic concentrations of acids, bases, or other chemicals that can cause burns. In skin injured by chemical burns, we usually consider the size, depth, location, and area surrounded the burns. In the presence of periorbital dermal burns, we examine the scleral and corneal lesions as ulcerations and leakage of vitreous humor [2,3].

Exfoliative Dermatitis: Exfoliative dermatitis, or erythroderma, is erythematous, scaly dermatitis involving at least 90% of the skin surface. The diagnosis of exfoliative dermatitis is based on skin findings on physical examination and not on the underlying etiology for the dermatitis, which is variable and may be idiopathic. The pathophysiologic processes resulting in exfoliative dermatitis vary with the underlying disorder responsible for the dermatitis. However, common to all conditions that cause exfoliative dermatitis is an increased rate of skin turnover. Normal epidermis has a continual turnover of epithelial cells. Cell division occurs near the basal layer. As cells move toward the periphery, they become well-keratinized. This process requires approximately 10-12 days. Cells subsequently remain in the stratum corneum for another 12-14 days prior to being sloughed. In exfoliative dermatitis, the number of cells in the germinative layer and their mitotic rate is increased. The transit time of cells through the epidermis is shortened. As a result, the exfoliated scales are incompletely keratinized and contain material normally retained by the skin, including proteins, amino acids, and nucleic acids, which may result in a negative nitrogen balance [4,5]. Another common pathophysiologic process to all forms of exfoliative erythroderma is increased blood flow to the skin, which, in combination with impaired skin barrier function, results in increased insensible fluid loss through transpiration. Dehydration and reflex tachycardia are common. In severe cases, high-output cardiac failure may occur. Increased cutaneous blood flow also leads to increased heat loss, which may lead to compensatory hypermetabolism and cachexia. The patient is usually presented with tachycardia, hyperthermia, and hypothermia. Tachycardia is reflexive in nature, occurring from increased insensible fluid losses and third spacing

of fluid. Skin examination usually showing significant erythema and scaling of at least 90% of the skin area. In acute exfoliative dermatitis, erythema may precede exfoliation by 2-6 days. The character of the scale may provide clues to the underlying etiology: fine in atopic dermatitis and dermatophytosis, greasy in seborrheic dermatitis, large exfoliative scale in drug eruptions, and crusted in pemphigus foliaceus [4].

Toxic Shock Syndrome (TSS): TSS is a toxin-mediated disease that is caused by toxin-producing streptococci or S. aureus. These superantigens bypass the normal pathway for activation of T cells resulting in over-activation of cytokines and inflammatory cells. This then leads to the presenting signs and symptoms of fever, rash, hypotension, and end-organ failure due to capillary leak. Streptococcus pyogenes (GAS) has other toxins that play a role in necrotizing fasciitis and streptococcal toxic shock syndrome. The Center for Disease Control and Prevention (CDC) clinical criteria for TSS includes fever, rash, hypotension, and multisystem organ involvement [6]. Classically, the rash is a diffuse, blanching, macular erythroderma. Initially it may be a transient macular rash, predominantly on the chest. The rash desquamates one to two weeks later followed by full-thickness peeling. There may be mucosal involvement with strawberry tongue and ulceration of the vaginal mucosa or conjunctival erythema. Patients may exhibit disorientation or altered mental status without focal deficits [7].

Bullous Pemphigoid: In bullous pemphigoid patient, IgG autoantibodies bind to the skin basement membrane. The binding of antibodies at the basement membrane activates complement and inflammatory mediators. Activation of the complement system is thought to play a critical role in attracting inflammatory cells to the basement membrane. These inflammatory cells are postulated to release proteases, which degrade hemidesmosomal proteins and lead to blister formation. Eosinophils are characteristically present in blisters as demonstrated by histopathologic analysis, although their presence is not an absolute diagnostic criterion [8]. The onset of bullous pemphigoid may be either subacute or acute, with widespread, tense blisters. Significant pruritus is frequently present and may be the only manifestation of the disease, especially in older patients [9]. In some patients, the blisters arise after persistent urticarial lesions. Bullous pemphigoid has been reported following several nonbullous, chronic, inflammatory skin diseases, such as lichen planus and psoriasis. Bullous pemphigoid has been reported to be precipitated by ultraviolet irradiation, x-ray therapy, and exposure to some drugs as furosemide, ibuprofen and other nonsteroidal anti-inflammatory agents, captopril, penicillamine, and antibiotics. Bullous pemphigoid has been reported to develop shortly after vaccination, particularly in children [10].

Pemphigus Foliaceus: Pemphigus foliaceus (PF) is an autoimmune skin disorder characterized by the loss of intercellular adhesion of keratinocytes in the upper parts of the epidermis (acantholysis), resulting in the formation of superficial blisters which are characterized by positive Nikolsky sign. PF is a benign variety of pemphigus and has a chronic course. It is characterized with little or no involvement of the mucous membranes [11]. The blisters in pemphigus foliaceus are induced by immunoglobulin G (IgG) (mainly IgG4 subclass) autoantibodies directed against a cell adhesion molecule, desmoglein 1 (160 kd), expressed mainly in the granular layer of the epidermis. The mechanism of acantholysis induction by specific autoantibodies may involve phosphorylation of intracellular proteins associated with desmosomes. Complement activation does not play a pathogenic role in pemphigus foliaceus. A polyclonal mixture in pemphigus foliaceus patients of anti-Dsg1 IgG antibodies enhances pathogenic activity for blister formation, with not only pathogenic antibodies, but also nonpathogenic antibodies, contributing to blister formation [12]. Drug-induced pemphigus foliaceus is mostly associated with penicillamine, penicillin, cephalosporins, antihypertensive agents as nifedipine and captopril, medications with a cysteine like chemical structure and piroxicam [13].

Staphylococcal Scalded Skin Syndrome (SSSS): Staphylococcal scalded skin syndrome (SSSS) is caused by an exfoliative toxin produced by roughly 5% of Staphylococcus aureus. As the syndrome evolves, an initial infection occurs, commonly at a site such as the oral or nasal cavities, throat, or umbilicus [14]. Epidermolytic toxins are produced by the infecting Staphylococcus species; these toxins act at a remote site leading to a red rash and separation of the epidermis beneath the granular cell layer. Bullae form, and diffuse sheetlike desquamation occurs. Two types of staphylococcal scalded skin syndrome are thought to exist: a localized form, in which there is only patchy involvement of the epidermis, and a generalized form, in which significant areas are involved, remote from the initial site of infection [15]. Two exfoliative toxins (ETA and ETB) have been isolated and characterized, but the exact mechanism by which they initiate exfoliation is still uncertain. The toxins likely act as proteases that target the protein desmoglein-1 (DG-1), an important keratinocyte cell-to-cell attachment protein found only in the superficial epidermis [16-18]. SSSS is a syndrome of acute exfoliation of the skin typically following an erythematous cellulitis. Severity of staphylococcal scalded skin syndrome varies from a few blisters localized to the site of infection to a severe exfoliation affecting almost the entire body. A mild form of the illness involving desquamation of just the skin folds following impetigo has been described [19]. The patient is usually presented with general malaise, fever, irritability, dehydrated, his skin is tender, and presented with, macular erythema followed by diffuse epidermal exfoliation. A prodromal localized S aureus infection of the skin, throat, nose, mouth, umbilicus, or GI tract occurs. The patient is usually presented with facial edema, conjunctivitis, perioral crusting, but mucous membranes are spared. Nikolsky sign is + ve [20,21].

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