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# DERMATOLOGY

Open Journal

| December 2016 | Volume 1 | Issue 3 |



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DERMATOLOGY

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ISSN 2473-4799 Open Journal http://dx.doi.org/10.17140/DRMTOJ-1-113

Case Report

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***Volume 1 : Issue 3***
***Article Ref. #: 1000DRMTOJ1113***

***Article History***
**Received:** September 17th, 2016
**Accepted:** September 28th, 2016
**Published:** September 28th, 2016

***Citation***
Hannawi S, Al Salmi I. Guttate psoriasis can present with psoriatic arthritis after urinary tract infection: Case report. *Dermatol Open J.* 2016; 1(3): 47-50. doi: 10.17140/DRMTOJ-1-113



# Guttate Psoriasis Can Present With Psoriatic Arthritis after Urinary Tract Infection: Case Report

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## ABSTRACT

**Introduction:** Psoriasis and psoriatic arthritis (PsA) are serious, poorly understood, diseases. As many as 10-30% of psoriasis patients develop an inflammatory arthritis termed psoriatic arthritis which is progressive and leads to destruction of the joints if it is not treated assertively. Several triggering factors may elicit or aggravate the expression of psoriasis, of which focal infections is a well-established triggering factor, in particular infections of the upper respiratory tract. Guttate (eruptive) psoriasis, known to have a better prognosis than other types of psoriasis with rapid involution and longer remission, but its clinical course has barely been studied. We are presenting a case of guttate psoriasis with sever onset and association with nail psoriasis, scalp psoriasis and psoriatic arthritis, all which started unexpectedly after urinary tract infection
**Case Presentation:** We are presenting a young woman of 32-years-old who presented to our service with a typical guttate psoriasis lesion after urinary tract infection. Her guttate psoriasis exhibited unusual sever course with associated onset of nails psoriasis, scalp psoriasis, conjunctivitis and psoriatic arthritis. All the symptoms started few days after urinary infection symptoms.
**Conclusion:** Guttate psoriasis that occurs after urinary tract infection, may exhibit sever onset and rapid progression to psoriatic arthritis.

**KEYWORDS:** Psoriasis; Psoriatic arthritis; Guttate; Urinary tract infection.

**ABBREVIATIONS:** PsA: Psoriatic arthritis; HIV: Human Immunodeficiency Virus; WBC: White Blood Cell; MCV: Mean Cell Volume; RBC: Red Blood Cells; ESR: Erythrocyte Sedimentation Rate; ASO: Anti-Streptolysin O; TPHA: Treponema pallidum hemagglutination.

## INTRODUCTION

Psoriasis and psoriatic arthritis (PsA) are chronic inflammatory diseases that have a major impact on health.

As many as 10-30% of psoriasis patients develop an inflammatory arthritis termed psoriatic arthritis which is progressive and leads to destruction of the joints if it is not treated assertively.[1] Environmental risk factors including streptococcal pharyngitis, stressful life events, low humidity, drugs, human immunodeficiency virus (HIV) infection, trauma, smoking and obesity have been associated with psoriasis and psoriatic arthritis.[2]

Of psoriasis, guttate psoriasis is a distinct eruptive dermatosis that classically occurs in children and young adults following upper respiratory tract infection.[3] It might present as either the initial manifestation of psoriasis in individuals previously unaffected by psoriasis or as an acute exacerbation in individuals with pre-existing chronic plaque psoriasis. Guttate psoriasis is strongly associated with antecedent or concomitant streptococcal infection and of-

ISSN 2473-4799 Open Journal http://dx.doi.org/10.17140/DRMTOJ-1-113

ten occurs 1 to 2 weeks after streptococcal pharyngitis or a viral upper respiratory infection.[4] Typically, they manifests as multiple scaly, well-demarcated, salmon-pink to erythematous, drop like round to oval papules ranging in size from 1 mm to 10 mm in diameter, appearing primarily on the trunk and extremities, sparing the palms and soles.[5] Fine silvery scale is often present on more established lesions.[6]

Although, limited information is available about the long-term prognosis of individuals with first-manifestation of guttate psoriasis.[5] Ko et al[3] reported that patients have two distinguishable clinical courses, a rapid involution course with long-term remission and a chronic course without remission. Others reported that approximately 33% of patients with guttate psoriasis might eventually develop chronic plaque psoriasis.[7] The diagnosis of guttate psoriasis is essentially a clinical diagnosis, and a careful history regarding recent illness or medication use can help to clarify the condition from other differential diagnosis.[5]

Here, we present unusual case of sudden onset of guttate psoriasis with nail psoriasis, scalp psoriasis, conjunctivitis and psoriatic arthritis, without preceding history of upper respiratory tract infection.

## CASE HISTORY

Our case is a 32-year-old woman, who presented with typical skin lesions of guttate psoriasis after urinary tract infection. Her guttate psoriasis exhibited unusual scenario with concomitant development of nails psoriasis, scalp psoriasis, and psoriatic arthritis.

The patient presented with 2 weeks chief complains of abrupt onset of eruptive scaly rashes over her body, scaly lesion over the scalp, eyes soreness and a painful swollen right wrist and left knee. Patient reported a difficult and painful mouth opening that started with her right wrist and left knee swelling. Few days earlier to her symptoms development she noticed darkness of her urine with burning micturation. Ten days after the rashes inception she developed painful left knee swelling and sore redness of both eyes. It's the first attack of its type with no significant previous medical history or similar familial history. There was no preceding upper respiratory tract infection or bowel motion disturbance.

Examination revealed a young woman in severs' pain and inability to walk because of left knee pain. Temperature was 38 ºC, arterial blood pressure 128/84 mmHg, heart rate 89 beats per minute and respiratory rate 22 per minute. Conjunctivitis was evident in both eyes (Figure 1). There was no peripheral lymphodenopathy. The scalp was full of dry scales (Figure 2). First and third right nails were yellow in color with onycholysis (Figures 3A and 3B). There was a scaly eruptive lesion over the trunk and all the four extremities with spare of palms and soles. Rashes were erythematous papules with fine silvery scales that can be seen over some of the lesions. Dermatological consultation confirmed the nature of the skin lesions as a guttate psoriasis (Figure 4). Left knee and right wrist were red and swollen. Both

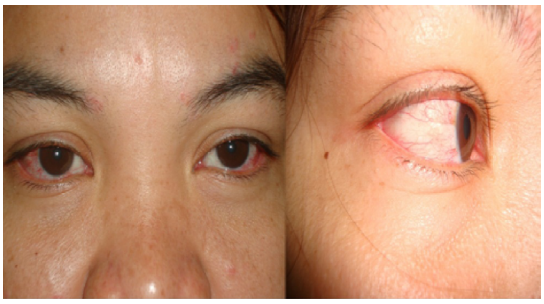

**Figure 1:** Conjunctivitis; Inflammation of the conjunctiva bilaterally.

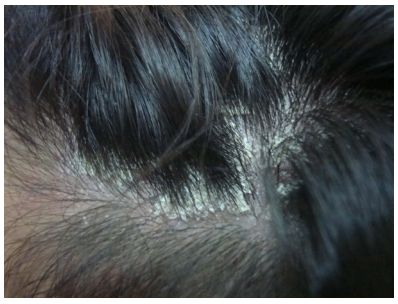

**Figure 2:** Scalp Psoriasis. Plaque psoriasis characterized by elevated lesions covered with silvery white dry scales.

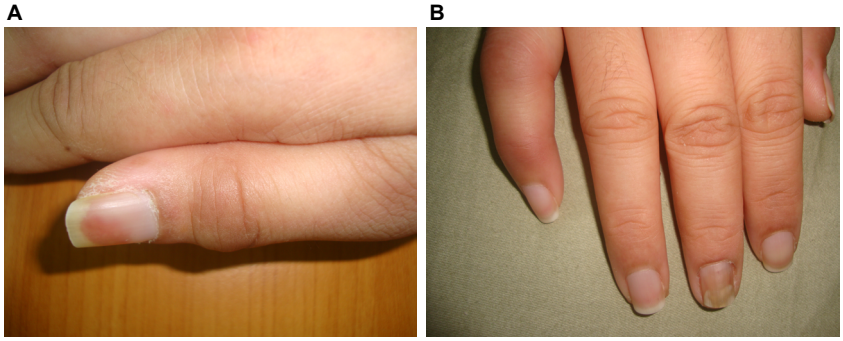


**Figure 3:** Finger nails psoriasis. (A) Discoloration of the nail plate and onycholysis; (B) Separation of the right first and the third nails from its nail bed, and inflammation of the first interphalangeal joint.

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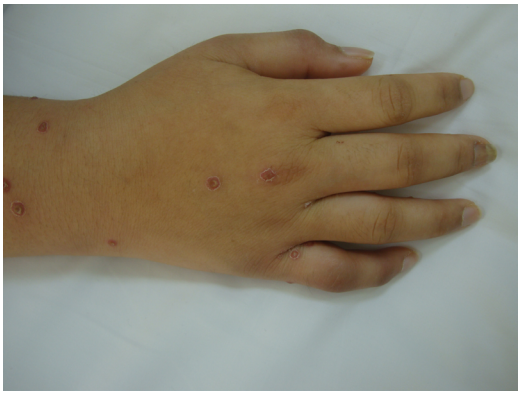

**Figure 4:** Guttate psoriasis; well demarcated, multiple, discrete, drop like salmon-pink lesions and fine scale with dactylitis; sausage digit (on the first day of presentation to the hospital).

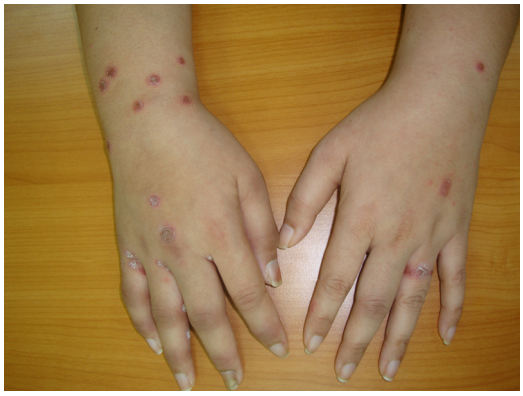

**Figure 5:** Guttate psoriasis. Multiple, small, discrete, well demarcated, salmon color raindrop-shaped lesions with silvery scale of both hands with dactylitis; sausage shape right digit (on day 4 of presentation to the hospital).

temporo-mandibular joints were tender and very painful to mild touch. Right hand showed dactylitis of the little finger with sausage shape look (Figure 3B).

Investigations revealed high white blood cell (WBC) count of 14.3×10*3/ul, with neutrophilia of 10.6×10*3/ul, Hb 11.8 g/dl, mean cell volume (MCV) 95.3 fl and platelet 466. There were no particular alterations in the electrolytes, renal or liver functions. Urine showed a pus cells over the full field, 2-4/hpf red blood cells (RBC) and squamous epithelial cells (three plus). A high inflammatory marker with erythrocyte sedimentation rate (ESR) of 130 mm/hr and C-reactive protein of 175.4 mg/l. Negative anti-streptolysin O (ASO) titer, HIV I+II+0+p24 antigen and Mantoux test. Rapid plasma regain antibody and treponema pallidum hemagglutination (TPHA) were non-reactive. Brucella abortus and melitensis antibodies were 1:80. Aerobic and anaerobic blood cultures showed no growth. A chest, hands and knees X-rays were normal.

A diagnosis of psoriasis and psoriatic arthritis had been made based on the characteristic body lesion, scaly scalp, bilateral eye conjunctivitis, nail psoriasis, polyarthritis and dactylitis.

Two triamcinolone injections were given in the right wrist and in the left knee. Antibiotics eye ointment and drops were given for the conjunctivitis. Skin lesion treated with local application of coal tar preparations, topical corticosteroids and Fusidic acid cream. Urinary tract infection was covered with a course of antibiotics. Methotrexate of 15 mg/wk and folic acid 5 mg/wk were started after hepatitis screen came negative for both hepatitis B and hepatitis C.

On the 4th day of treatment the psoriatic lesion became clearer with more silvery scales that can be appreciated over more lesions (Figure 5).

## DISCUSSION

Psoriasis is a chronic inflammatory disease affecting 1-3% of the world's population. Joints can be affected in up to 30% of patients.[8]

As psoriasis has a large spectrum of clinical features and evolution, classification of its clinical features has been a controversial subject among investigators. Thereafter, no complete agreement on the classification of the clinical variants exists.[8]

It's reported that psoriasis can be provoked or exacerbated by a variety of different environmental factors, particularly infections and drugs.[9] Despite that it has been reported that various microorganisms are associated with the provocation and/or exacerbation of psoriasis, their roles in the disease pathogenesis are unknown.[10-12]

Knowledge of the factors that may trigger, psoriasis is of primary importance in clinical practice. Extensive evidence supports that the disease can be triggered by a variety of different environmental factors, particularly streptococcus pyogenes, which has been recognized for at least 50 years and implicated in both acute and chronic forms of the disease.[9,13,14] The link between psoriasis and infections is probably explained by the "superantigen theory", that superantigens are the products of bacteria, virus or fungi, which can bypass normal immunological pathway and cause powerful stimulation of the immune system.[15] Wang et al[15] suggested that cell-wall-deficient bacterial infection may be a virtual triggering factor in psoriasis by regulating T-cell activation. To the best of our knowledge, this is the 1st case report of guttate psoriasis after urinary tract infection. More, it's the 1st case to have abrupt onset of guttate psoriasis, nail and scalp psoriasis and psoriatic arthritis.

## CONCLUSION

There are conflicting views in the literature regarding the triggering infection factors and the efficacy of anti-streptococcus antibiotics on psoriasis. Hence, other organism and different kinds of infection factor could be implicated in psoriasis development. Organisms causing urinary tract infection could trigger

ISSN 2473-4799 Open Journal http://dx.doi.org/10.17140/DRMTOJ-1-113

psoriasis through the same mechanism as streptococcus bacteria of upper respiratory infection do.

## COMPETING INTERESTS

The authors declare that they have no competing interests.

## AUTHORS CONTRIBUTIONS

HS wrote the manuscript and compiled the figures. AI edited the manuscript. Both authors analyzed and interpreted the patient data. Both authors read and approved the final manuscript.

## CONSENT

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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ISSN 2473-4799 Open Journal http://dx.doi.org/10.17140/DRMTOJ-1-114

*Clinical Review*

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***Volume 1 : Issue 3***
***Article Ref. #: 1000DRMTOJ1114***

***Article History***
**Received:** August 22nd, 2016
**Accepted:** October 14th, 2016
**Published:** October 19th, 2016

***Citation***
Mohamed H, Al Lenjawi B. Triangle of wound assessment made easy: Revisited. *Dermatol Open J*. 2016; 1(3): 51-55. doi: 10.17140/DRMTOJ-1-114



# Triangle of Wound Assessment Made Easy: Revisited

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**ABSTRACT**

**Objective:** We have provided evidence based critical review of the "*Triangle of wound assessment made easy*".
**Background:** Wound assessment is a vital step in managing patients with acute and chronic wounds in daily clinical practice. The natural progression of most wounds is to heal naturally in a coherent and timely manner, although a minority of wounds will fail to heal. The aim of treating recalcitrant wounds that fail to heal is to control symptoms and delay or prevent complications. One vital step in managing wounds is proper and comprehensive evidence based wound assessment.
**Methods:** We have carried out literature review including systemic reviews, met analysis pertaining wound assessment including international guidelines.
**Results:** We have found few gaps in the proposed "Triangle *of wound assessment made easy*" which have been addressed accordingly. We have revised the concept of (infection) i.e. "*raised white blood cell (WBC) count as a sign of infection*" and argued that in up to one-half of patients, even with severe diabetic foot infection raised temperature, WBC count, or sedimentation rate are absent. A second point of concern is the omission of "*probing to bone sign*" in the diagnostic criteria of local signs of infection. Recent clinical studies have demonstrated that in the presence of a clinically infected ulcer, a positive Probe-to-Bone Test (PTB) test is highly suggestive of osteomyelitis, but a negative test does not rule out the diagnosis; conversely, in the situation of an apparently uninfected foot wound, a positive PTB test is not specific for osteomyelitis, but this diagnosis is unlikely if the PTB test is negative. Lastly, the authors have suggested reducing wound bio burden/manage infection through the use of topical antimicrobial therapy-including antiseptic agents. Topical antiseptics have inconclusive proof of efficacy in various etiology wounds and concern remain regarding their residual cytotoxicity when in contact with newly forming granulating tissues especially when highly concentrated rinse solutions is the common practice in developing countries of the world.
**Conclusion:** On the basis of these analysis, we propose revising the "*Triangle of wound assessment made easy*" in order to address these gaps and maximize its utility in clinical practice.

We read the article of Dowsett et al,[1] "Acute wounds, Assessment and diagnosis, Complex wounds" published in the May 2015 issue of Wound International Journal with interest.

A wound occurs as a result of the disruption of the normal structure and function of the skin and soft tissue structure secondary to a variety of etiologies and mechanisms.[2] Initial assessment of a wound starts by differentiating its etiology whether it's acute or chronic in nature. The orderly physiologic cascade of inflammation, proliferation and maturation occur as healing is expected to occur in an acute wound,[3,4] whereas in chronic wounds the cascade is impaired due to many reasons including impaired cellular mechanism, proliferation, migration, dysfunctional angiogenesis and impaired innervation among other reasons.[5] Examples of chronic wounds include diabetic, arterial ulcers, venous ulcers, and infected wounds including surgical site infections.[6,7]

ISSN 2473-4799 Open Journal http://dx.doi.org/10.17140/DRMTOJ-1-114

Although, the majority of wounds heal without difficulty. Some wounds, however, will become chronic and non-healing. In these circumstances, the aim is to manage symptoms and delay or prevent complications.

Before initiating treatment of any wound a diagnostic hypothesis must be in place to ensure optimal healing outcome. A comprehensive clinical history of wound duration, history of trauma, previous ulceration, wound characteristics (site, size, pain, periwound area characteristics, odor, presence of infection or not and (discharge or exudate), family history of ulceration, skin temperature, current medical history (for example, diabetes mellitus, cardiovascular disease, neuropathy, autoimmune disease, venous insufficiency), previous surgery, smoking history, medications, radiation and allergic reactions to dressings and medications and quality of life (QoL).

Wound assessment is vital in formulating a management plan in order to achieve wound healing and patient well-being. The authors of the wound triangle made a considerable effort in devising a simple and practical assessment tool for clinician's worldwide. However, there are few shortcomings that need to be examined when utilizing this tool in daily practice and these include (Figure 1):

Under the section (infection) raised WBC are documented as a sign of infection.

Although this is true in most situations however in patients with diabetes the clinical diagnosis of diabetic foot ulcer infection poses a complex issue to most clinicians and the ideal method to identify localized diabetic foot ulcers (DFU) infection with certainty remains elusive. Many patients with diabetes may not feel pain, do not suffer from fever, and will not have raised WBC count or raised erythrocyte-sedimentation rate.[8-10]

The presence of virulent pathogens and extensive tissue damage usually mount systemic signs or symptoms in the host, however in up to one-half of patients, even with severe diabetic foot infection raised temperature, WBC count, or sedimentation rate are absent. None the less worse clinical outcomes of treatment is predicted when these markers are elevated.[11]

Two recent prospective clinical studies[12,13] of patients with a diabetic foot ulcer have demonstrated that procalcitonin levels were more sensitive markers of clinical evidence of infection than levels of WBC, C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR). Clinically uninfected wounds can be differentiated accurately from those with mild or moderate infections based on the combined levels of CRP and procalcitonin.[12] Therefore, the inclusion of raised WBC count is insensitive marker and may delay the diagnosis of diabetic foot infections if it was taken into consideration as a sign or marker of infection in patients with diabetes.

A second point to concern is the omission of "*probing to bone sign*" in the diagnostic criteria of local signs of infection. There is high suspicion of osteomyelitis in a wound which fails to heal after at least 6 weeks of adequate wound therapy and offloading a patient with an adequate blood supply to the affected site. Both the presence of a deep wound area and any exposed bone increase the likelihood of osteomyelitis.[14] Nonetheless, the likelihood of osteomyelitis is not influenced by either elevated WBC count nor the presence of signs of infection of the wound.[14,15]

Baseline and serial measurements of the wound size (length, width or area, and depth), appearance and location, will help to establish a baseline for treatment and monitor any response to interventions.[12,13] The method of measurement should be used consistently to aid meaningful tracking of changes over a specifi number of days (e.g. 7-14 days).[14] Problems identifi in the wound bed may extend beyond the wound edge to the surrounding skin (e.g. maceration, erythema, swelling).

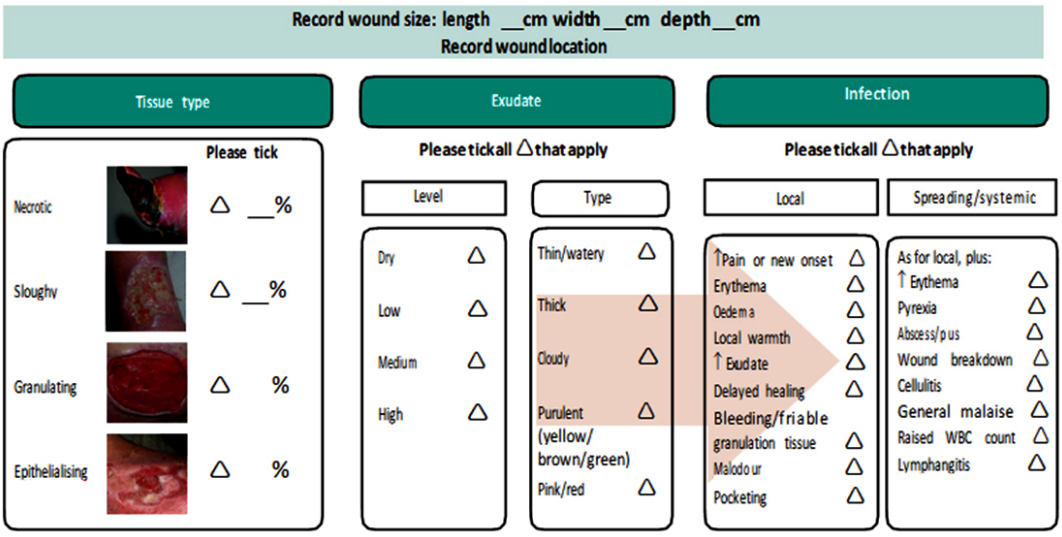


**Figure 1:** Using the triangle of wound assessment-wound bed.

ISSN 2473-4799 Open Journal http://dx.doi.org/10.17140/DRMTOJ-1-114

According to a recent clinical study, independent risk factors for osteomyelitis in a patient with lower limb infection were, previous history of a wound, wounds that extended to bone or joint and multiple or recurrent wounds.[16] Osteomyelitis can be differentiated from cellulitis by combining together laboratory data and clinical findings (ulcer depth>3 mm or CRP>3.2 mg/dL, ulcer depth>3 mm or ESR>60 mm/hour).[17] Currently, there is no specific clinical criteria to diagnose osteomyelitis in the lower limb of patients with diabetes, although the presence of "sausage toe" (swollen, erythematous, and lacking normal contours) is highly suggestive of the diagnosis.[18]

Health care practitioners need to be aware that the true depth of a wound is often not clinically apparent, so a sterile blunt metal probe must be introduced into the wound at each visit (the PTB test). Any wound with a visible bone or with either a positive PTB test (i.e., palpable hard, gritty bone) is highly likely to be osteomyelitis until proven otherwise.[17]

The accuracy of the probe to bone test in predicting or excluding osteomyelitis is, however, directly related to the pretest likelihood (i.e., the prevalence in the population under study) of osteomyelitis. Recent clinical studies have demonstrated that in the presence of a clinically infected ulcer, a positive PTB test is highly suggestive of osteomyelitis, but a negative test does not rule out the diagnosis; conversely, in the situation of an apparently uninfected foot wound, a positive PTB test is not specific for osteomyelitis, but this diagnosis is unlikely if the PTB test is negative.[19-25]

This clinical sign is of great importance since early reports in 1995, Grayson et al[16] who explored the possibility of osteomyelitis in wounds by the use of a sterile blunt metal probe. They concluded that the PTB test had a positive predictive value of 89%. Later on in 2007, Lavery et al[17] followed-up 247 patients with suspected osteomyelitis concluded that the positive predictive value was only 57% in a population with a lower prevalence of osteomyelitis.[17] However, in 2014 in an outpatient setting, Morales Lozano et al[18] followed-up 132 of patients with clinical suspicion of osteomyelitis over a 36 months concluded that the PTB test had an efficiency of 94%, sensitivity of 98%, specificity of 78%, positive predictive value of 95%, and negative predictive value of 91% ($p$<0.001, κ 0.803); the positive likelihood ratio was 4.41, and the negative likelihood ratio was 0.02 (95% CI).[18] Therefore, the inclusion of "probe to bone test (PTB)" is a vital component in assessing any chronic wound especially in patients with diabetic wounds of more than 4 week duration where the suspicion of the possibility of osteomyelitis is high.

The third point which is worth considering is mentioned under "setting treatment goals" (reduce wound bioburden/manage infection (e.g. topical antimicrobial therapy-including antiseptic agents-may be used for local infection and combined with antibiotic therapy for spreading or systemic infection).

The term topical antimicrobial is a vague term and may imply the use of topical antibacterial creams and ointments. The use of topical antibiotics among patients with diabetic wounds is not justified since most wounds in patients with diabetes have polymicrobial colonization.

Topical antiseptics have inconclusive proof of efficacy in various etiology wounds and concern remain regarding their residual cytotoxicity when in contact with newly forming granulating tissues especially when highly concentrated rinse solutions is the common practice in developing countries of the world. Some authors have even warned against the routine use of antiseptic solutions due to their cytotoxicity and lack of demonstrated benefit over saline irrigation.[31] Furthermore, recently the International Working Group on Diabetic Foot Management (IWGDF) has warned against the use of topical antimicrobial dressing with the goal of improving wound healing or preventing secondary infection.[20] They went even further by saying that "currently supporting data are too limited to recommend topical antimicrobial therapy".[20-22] The use of antimicrobial dressings for DFUs was recently assessed *via* a systemic review which concluded that current evidence base is too weak to suggest any specific antimicrobial dressing.[23] The management of diabetic foot ulcers pose a challenge to attending clinicians and some advanced and expensive topical antimicrobials have been in use through the last few decades.[24] On the other hand, alternative modalities such as natural honey have been in use for a millennia and recently a new interest by clinicians worldwide have surfaced through the publications of case series and case studies highlighting its efficacy in various types of wounds.[25-32] This is quite important since natural honey offers an efficacious and cost effective alternative option characterized by its ability to provide moisture, antimicrobial cover and anti-inflammatory properties.[32] This is quite important especially in developing countries where diabetes has reached epidemic proportions and the incidence of diabetic wounds is likely to rise too thereby posing a huge economic burden on already stretched out economies. Additionally, health practitioners worldwide have over utilized antimicrobials, particularly topical antiseptics as a result of coining the controversial idea of excess wound bio burden in the medical literature, despite little evidence substantiating any benefit of these dressings over conventional therapy.[33-37] In addition to their potential for causing local reactions and expense, bacterial resistance may emerge as a consequence to the arbitrary use of these antimicrobials.[38,39] Due to these inherent risks, and a lack of sound clinical evidence of any advantages, the use of topical antimicrobials for clinically uninfected wounds is not recommended.[33] Furthermore, current data does not support any benefit to using advanced wound products such as silver-based dressings for clinically infected wounds.[40]

We believe there is an urgent need for head to head large scale multicenter randomized controlled trials to clarify the role of antimicrobial therapies in various etiology wounds and we believe that this knowledge is imperative before universal suggestions regarding wound assessment and management

could be advised.

## HIGHLIGHTS

- A revised version of the "*Triangle of wound assessment made easy*" is urgently needed
- Specific areas of improvement of the "*Triangle of wound assessment made easy*" is proposed.
- The mechanism relies on stabilization changes of anionic ubiquinone intermediates.
- The validity and reliability of "*Triangle of wound assessment made easy*" should be tested through double-blinded randomized controlled trials controlled during turnover.

## CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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ISSN 2473-4799 Open Journal http://dx.doi.org/10.17140/DRMTOJ-1-115

Research

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*Volume 1 : Issue 3*
*Article Ref. #: 1000DRMTOJ1115*

***Article History***
**Received:** September 17th, 2016
**Accepted:** October 26th, 2016
**Published:** October 27th, 2016

***Citation***
Ecra EJ, Kouassi YI, Kouassi KA, et al. Analysis of mortality in a dermatological affections referral center in sub-Saharan Africa, Abidjan, République de Côte d'Ivoire. *Dermatol Open J*. 2016; 1(3): 56-59. doi: 10.17140/DRMTOJ-1-115



# Analysis of Mortality in a Dermatological Affections Referral Center in Sub-Saharan Africa, Abidjan, République de Côte d'Ivoire

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## ABSTRACT

**Objectives:** To document patients who died in Dermatology Department at University Teaching Hospital (UTH) of Treichville; describe epidemiological aspects; indicate the various dermatological diseases associated; specify the immediate causes; identify the determinants.
**Materials and Methods:** This was a cross-sectional study with descriptive and analytical referred. Included were all hospitalized patients died in the Dermatology and Venereology service of Treichville University Hospital from January 2000 through December 2014.
**Results:** One thousand seven-hundred and thirty-five patients were hospitalized. The hospital mortality was 10.26% (178 deaths). The average age of the death was 43.16 years; the sex ratio was 0.83. Patients who had no source of income were the most numerous (61.53%). The average hospital stay was 20.05 days. Patients had at the entrance an altered condition in 49.43% of cases and 46.62% in middle condition. Those who regularly bought their drugs were 58.21%. Those who died in the second half of the month were the most numerous (55.61%). Dermatosis groups associated deaths were: infectious dermatosis 41.57%, 29.77% tumor dermatitis and drug eruptions 16.85%. Of the 178 deaths, the 1st 3 are pathologies associated fasciitis (50 cases), Kaposi's sarcoma (46 cases) and toxic epidermal necrolysis (17 cases). Respiratory distress (41.31%) and septic shock (36.52%) were the main immediate causes of death. Anemia (41.40%), tuberculosis (10.82%) and diabetes (10.19%) were the major comorbidities. Serology was positive in 92.5% of dead patients who have realized their HIV status (n=80). Significantly associated determinants were essentially the regular bought of drugs ($p$=0.013), the altered condition ($p$=0.033), death hours ($p$=0.023) and comorbidities ($p$=00000).
**Conclusion:** Mortality is a reality in the Dermatology and Venereology at UTH of Treichville. These determinants are numerous and some need to be better studied to identify true risk factors in order to make appropriate recommendations.

**KEYWORDS:** Mortality; HIV; Dermatosis.

## INTRODUCTION

Dermatological diseases are not among the most common causes of death in sub-Saharan Africa.[1] However, since the advent of human immunodeficiency virus (HIV) infection which is one of the causes of death in sub-Saharan Africa, some skin diseases have become very common while others have seen their prognosis serious. Data on overall mortality from skin dis-

ISSN 2473-4799 Open Journal http://dx.doi.org/10.17140/DRMTOJ-1-115

eases in hospital services remain very partial references in the literature. So we conducted this study to analyze mortality in a Dermatology Department of black Africa. It will specifically to describe the epidemiological aspects, indicate the various associated dermatological disease, specify the immediate causes of death, identify the determinants and measures the scalability of deaths from 2000 to 2014.

## MATERIALS AND METHODS

This was a descriptive and analytical cross study of hospitalized patients from January 2000 to December 2014 (15 years) in the Dermatology and Venereology Department of University Hospital of Treichville. Were included in the study, all patients died during the study period, regardless of the age, sex and pathology. Were not included deceased patients registered in the register of Dermatology and whose records could not be found. Data were collected from patient records on a survey sheet. The seizures and analyzes were made on the EPI-INFO 3.5.1 software. The test of chi-square ($X^2$) was used for comparison of proportions and *t*-student for the comparison of averages.

## RESULTS

### Epidemiological Aspects

During this period of 15 years we registered in 1735 inpatients, including 178 deaths or a hospital mortality of 10.26%. The average age of patients who died was 43.16 years, ranging from 2 to 89 years. There was a male predominance with a sex ratio (M/F) of 1.19. Patients live as a couple in 51.87% of cases and by followed singles with 31.25%. They had no source of income at 61.53% and 29.48% worked in the informal economy.

### Cause of Death

Infectious skin diseases were the leading cause of death (41.57%), followed tumor dermatoses (29.77%) and drug reactions (16.85%). The list of 1st 10 diseases causing deaths is shown in Table 1 and the immediate causes in Figure 1. From 2000 to 2006, 3 leading causes of death were in ascending order Kaposi's disease, fasciitis and burili ulcer. From 2007 fasciitis has become the leading cause of death followed by Kaposi's

| Pathologies | Frequency |
|---|---|
| 1. Fasciitis | 50 |
| 2. Kaposi disease | 46 |
| 3. Lyell Syndrome | 17 |
| 4. Steven Johnson | 10 |
| 5. No necrotizing bacterial cellulitis | 9 |
| 6. Squamous cell carcinoma | 7 |
| 7. Pyodermitis | 6 |
| 8. Diabetic gangrene | 5 |
| 9. Escarres | 4 |
| 10. Buriliulcer | 3 |
| 10ex Bullouspemphigoide | 3 |

**Table 1:** The first 10 causes of death, Dermatology and Venereology of Treichville University Hospital Service, Abidjan, from 2000 to 2014.

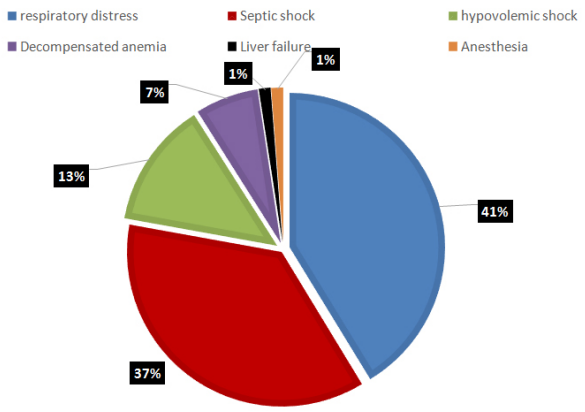


**Figure 1**: Distribution of deceased patients according to the immediate cause of death, Dermatology and Venereology of Treichville University Hospital Service, Abidjan, from 2000 to 2014.

ISSN 2473-4799 Open Journal http://dx.doi.org/10.17140/DRMTOJ-1-115

| Measured parameters | Variable 1 | Variable 2 | Statistical test |
|---|---|---|---|
| Regular purchase of medicines | Yes: 58.21% | No: 41.78% | $p$=0.013 |
| Altered general condition | Regular purchase of drugs: 41.17% | Irregular purchasing medicines: 59.01% | $p$=0.033 |
| Altered general condition | Regular purchase of drugs: 35 | Irregular purchasing medicines: 36 | $p$=0.033 |
| Good and medium general condition | Regular purchase of drugs: 50 | Irregular purchasing medicines: 25 | |
| Death hour | 08 H 30 am- 04 H 30 pm: 38.04% | 04 H 30 pm - 08 H 30 am: 61.95% | $p$=0.023 |
| Week days | Working day: 74.71% | Non-working day: 25.28% | $p$=0.000 |
| Month period | 1 au 15: 44.38% | 15 au 31: 55.61% | $p$=0.15 |
| Morbidity condition | Morbidity: 85.35% | No morbidity: 14.64% | $p$=0.00000 |

**Table 2:** Statistical tests performed in patients who died, Dermatology and Venereology of Treichville University Hospital Service, Abidjan, from 2000 to 2014.

disease in 2nd place and Lyell's syndrome in third. Anemia, tuberculosis and diabetes were the main comorbidities associated of death with respectively 41.40%, 10.82% and 10.19%. HIV status was requested in 80 cases or 44.9% achievement rate. It was positive in 74 patients who died according to 92.5%.

### Determinants of Mortality

The average hospital stay was 20.05 days, with a range from 1 to 143 days. Deceased patients were 1st hospitalized in service in 93.25% of cases. Their general condition was impaired or medium at the entry with respectively 49.43% and 46.62%. They regularly bought their drugs in 58.21%. Comorbidity was associated in 85.35% of cases. The patients who died were in 61.95% between 4:30 pm to 8:30 am; in 74.71% they died at working days of the week; 55.61% in the second half of the month. The determinants significantly associated with death ($p$<0.05) are shown in Table 2.

## DISCUSSION

The death rate found in our study was slightly higher than that of Tollhupp-Journet et al[2] in France and Keita et al[3] in Guinea with 9% and 7.90%, far higher than Nair et al[4] 3.58% in India in Dermatology services. Compared to those of studies conducted in Côte d'Ivoire in other services, our mortality rate substantially corresponds to that found by Dekou A et al[5] (10.1%) in a urology Abidjan. This high mortality rate could be explained by the fact that the patients arrived at a very advanced stage. Indeed, nearly half of deceased patients (49.43%) came in an altered condition. The average age of the deceased patients in our study was 43.16 years. In France, according Tollhupp-Journet et al[2] the average is 71. This age difference could be partly explained by the unfavorable socio-economic and structural conditions in developing countries, unlike France where most patients supported was the end-of-life for metastatic melanoma. Life expectancy is highest in France with regard to the quality of life (QoL) and care, life expectancy in Côte d'Ivoire being 54.1 years according to the National Institute of Statistics (NIS).[6] In our study, patients who died live as a couple were the most numerous with 83 cases or 51.87%. This high rate of cohabitants, highlighted the socio-cultural and economic problems of widows, widowers and orphans in our country after the death. This is consistent with the study of Channon Mandal in South Africa which took place in KwaZulu-Natal,[7] which found a high mortality rate among the living cohabiting couples compared to legally married couples. Deceased patients who regularly bought their medicines were the most numerous in 58.21% of cases, with a significant difference compared with those deceased who do not regularly bought their medication ($p$=0.013, Table 2). Among the deceased patients who regularly bought their drugs, there was far more infectious and tumorous skin with 42.35% and 37.64% respectively. It also noted many more patients with a general altered health or medium to entry with respectively 39.77% and 54.21%. Can we understand the severity of the condition and severity of disease would condition the purchase of medicines? Further studies will allow us to better argue this because there is a significant difference between the regular purchase medication or not depending on whether the condition is altered or good and moderate ($p$=0.033, Table 2). The patients died more frequently between 4:30 pm to 8:30 am (61.95%) with a significant difference compared to those who died between 8:30 am to 4:30 pm ($p$=0.023, Table 2). This time slice corresponds to a period where there are no doctors in the service. The service then based on a nursing care with coverage of medical emergencies, themselves already overwhelmed. Regarding the period of death in the month, patients who died in the second half of the month were the most numerous with 99 cases or 55.61%. The second half of the month is always difficult financially for workers especially in African countries due to multiple responsibilities. Would this position responsible for the large number of deaths? We do not think so because the regular purchase of drugs did not influence deaths in our service but rather the impaired general condition and therefore the consultation delay. Indeed, the observed difference is not statistically significant compared to the other half of the months ($p$=0.15, Table 2). Among the patients who died of infectious skin diseases were noted much of necrotizing fasciitis with 67.56% and 12.16% with erysipelas. Both dermatosis alone accounted for 79.72% of death among infectious dermatosis. Infectious diseases, although there is a decline in their hand, are a leading cause of death.[8] Infectious skin diseases are a place where 1st cause of death in service (Table 1). Acute bacterial dermohypodermitis that are fasciitis and erysipelas are dermatological emergency with a high death rate of about 27.7% from necrotizing fasciitis.[8] These deaths are significantly related to complications or HIV positive land according to studies carried out in service.[8] Indeed in our study, 92.5% of deceased patients tested for HIV were positive. Among the patients who died of

ISSN 2473-4799 Open Journal http://dx.doi.org/10.17140/DRMTOJ-1-115

tumor dermatosis we noted much of Kaposi's disease with 46 cases or 86.79% (Table 1). This condition is related to HIV with a predictive value in the Dermatology Department at University Hospital of Treichville 87.5%.[8]

## CONCLUSION

Mortality is a reality in the Dermatology and Venereology of Treichville University Hospital. From 2000 to 2014 the rate was 10.26%. Infectious skin diseases and tumor are the main causes with as main immediate causes respiratory distress and septic shock. These determinants are numerous and some need to be better studied to identify true risk factors in order to make appropriate recommendations.

## CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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ISSN 2473-4799 Open Journal http://dx.doi.org/10.17140/DRMTOJ-1-116

Case Report

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***Volume 1 : Issue 3***
***Article Ref. #: 1000DRMTOJ1116***

***Article History***
**Received:** October 18th, 2016
**Accepted:** November 4th, 2016
**Published:** November 7th, 2016

***Citation***
Giménez-García R. Syphilis maligna (lues maligna): A case report. *Dermatol Open J*. 2016; 1(3): 60-62. doi: 10.17140/DRMTOJ-1-116



# Syphilis Maligna (Lues Maligna): A Case Report

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## INTRODUCTION

Syphilis is a sexually transmitted disease (STD) produced by *Treponema pallidum*, an anaerobic filamentous spirochete, which has a tropism for several organs and tissues in the body. A rare form of detructive syphilide, with deeply ulcerative covered with thick crust lesions was described under the name malignant syphilis (lues maligna).[1] Most of the cases, resulting from human immunodeficiency virus (HIV)-induced suppression of cell mediated immunity, have been reported in HIV positive patients[1-20] but some cases occur in individuals with poor health, alcoholic or immunocompetent patients.[21,22]

## CASE REPORT

A 49-year-old promiscuous man presented to our department with multiple nodular ulcerative lesions on his arms and legs (Figure 1), and a healing genital ulcer. Laboratory tests including syphilis serology showed a Venereal Disease Research Laboratory (VDRL) titre of 1:32 and a positive treponema pallidum hemagglutinatoin (TPHA). HIV (ELISA method) was positive. His $CD^{4+}$ count was 425/mm³ and his HIV viral load 63,420 copies/ml. Histopathological study of skin lesion revealed an epithelial hyperplasia, and perivascular infiltrate containing plasma cells and endothelial thickening of blood vessels throughout dermis extending into the subcutaneous tissue. Periodic acid-Schiff, Grocott´s and Warthin-Starry stains were all negatives in cerebrospinal fluid (CSF) examination showed 1 cell/mm³; protein 35 mg/dL; glucose 57 mg/dL; VDRL negative. Patient was diagnosed to have malignant syphilis associated with HIV infection and he was given injection benzathine penicillin 2.4 per week for 3 weeks. A Jarisch-Herxheimer reaction occurred in the course of therapy. Lesions healed in a month with hypopigmented macules. Viral load dropped to undetectable levels following antiretroviral treatment.

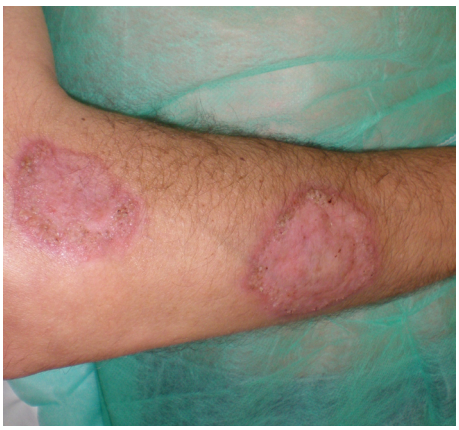

**Figure 1:** Rupioid plaques on the right arm.

ISSN 2473-4799 Open Journal http://dx.doi.org/10.17140/DRMTOJ-1-116

## DISCUSSION

Early syphilis (recently acquired or less than 2 year's duration) is the more contagious stage and includes the primary and secondary forms and the early latent period. Primary syphilis is often asymptomatic and the initial lesion-chancre is extragenital in much cases. Secondary syphilis and latent infection is the most usual forms of presentation in HIV positive patients. Lues maligna is a severe form of secondary syphilis. In these patients syphilis presents an atypical clinical course with severe constitutional symptoms and unusual nodules, necrotic or rupiod skin lesions, organ involvement and a great tendency to develop neurosyphilis and ocular involvement.[20] Serology for syphilis in HIV infection can be falsely negative and biopsy is commonly needed to establish the diagnosis.[6-9]

Histological findings in malignant syphilis are similar to those of secondary syphilis but lymphocytic predominance superficial and deep perivascular infiltrate containing plasma cells, epithelial hyperplasia, perineural plasma cellular infiltrate and thickening of lamina propia blood vessels have been seen in lues maligna in HIV-infected patients. The abundance of plasma cells is a good indicator of malignant syphilis on skin histological analyses, in some cases, the plasma cell count may be very low and cutaneous T-cell lymphoma could be misdiagnosed.[14] No differences in a comparative immunohistologic study were observed between HIV patients and patients who were HIV negative.[12]

Diagnosis of malignant lues should be considered in all HIV-infected individuals who have nodules.[1] $CD^{4+}$ cell count is not the only determinant factor for the occurrence of lues maligna and propably interaction between *T. palidum* and HIV lead to defects of both cell-mediated and humoral immunity.

After the effective control of acquired immune deficiency syndrome (AIDS) in the US and Europe, preventive measures relaxed and in the last years a resurgence of syphilis has been reported in several countries as US, Spain, England, France, Eastern Europe, Russia and China. The main reason for the increase in prevalence is unprotected anogenital and oral sex. Epidemiological changes are related to sexual promiscuity, prostitution, drug abuse, increased travel and migration. New cases occur especially among men who have sex with men (MSM) and are strongly associated with HIV coinfection.[8,9]

A high clinical index of suspicion should be maintained to prevent development of late syphilis or tertiary disease characterized by skin, cardiovascular, neurological, liver, spleen, bones or other organs manifestations. Syphilis is usually diagnosed on the basis of serology test, as detection of treponemes by dark-field microscopy tends to be unreliable. Non-treponemal tests (VDRL, rapid plasma reagin (RPR)) are inexpensive, rapid and commonly used for screening but develop late in primary syphilis. Treponemal test (FTA-ABS y TPHA) are specific antibody test.[2,9] Diagnostic criteria for malignant syphilis include strongly positive serologic test titre, a severe Jarisch-Hersheimer reaction, characteristic microscopic morphology and excellent response to antibiotics therapy.[3,6]

Benazthine penicillin G or aquous procaine penicillin G remains the drug of choice for all forms of syphilis. Oral tetracycline, or doxycycline 100 mgr orally twice, for 14 days are also effective for allergic to penicillin patiens with early syphilis.

HIV patients with primary and secondary syphilis can be treated in the same way as seronegative patients but some authors recommend a more aggressive treatment (as 3 doses of 2.4 million units of benzathine penicillin intramuscularly at weekly intervals) and an accurate follow-up.[9,13]

## CONCLUSIONS

Because of increasing syphilis rates the importance of recognizing the early clinical manifestations needs to be re-emphasized.

Diagnosis of syphilis in HIV patients is based in a clinical-pathological correlation together with serological studies. Screening is simple and inexpensive and treatment is highly effective.

## CONFLICTS OF INTEREST

The author declares that there are no conflicts of interest.

## CONSENT

Author has recieved oral informed consent from the patient whose photograph is involved in this manuscript.

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ISSN 2473-4799 Open Journal http://dx.doi.org/10.17140/DRMTOJ-1-116

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DERMATOLOGY

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ISSN 2473-4799 Open Journal http://dx.doi.org/10.17140/DRMTOJ-1-117

Review

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***Volume 1 : Issue 3***
***Article Ref. #: 1000DRMTOJ1117***

***Article History***
**Received:** October 10th, 2016
**Accepted:** December 28th, 2016
**Published:** December 30th, 2016

***Citation***
Nada HR. Fas receptor: An overview. *Dermatol Open J*. 2016; 1(3): 63-71. doi: 10.17140/DRMTOJ-1-117



# Fas Receptor: An Overview

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**ABSTRACT**

The FAS receptor (FasR), also known as apoptosis antigen 1 (APO-1 or APT), cluster of differentiation 95 (CD95) or tumor necrosis factor receptor superfamily 6 (TNFRSF6) is a protein that in humans is encoded by the FAS gene. Engagement of the cell death surface receptor Fas by Fas ligand (FasL) results in apoptotic cell death, mediated by caspase activation. Cell death mediated *via* Fas/FasL interaction is important for homeostasis of different cell types. In this review, we want to highlight the role of Fas receptor in different dermatologic disorders. This would definitely help our understanding of its important role in dermatology that can open a new era in using anti-Fas biologic therapy in the future management of such disorders.

**KEYWORDS:** Apoptosis; FasL; Fas; TNF-α; Death receptor.

**ABBREVATIONS:** TNFR: Tumor Necrosis Factor Receptor; TNFRSF 6: Tumor Necrosis Factor Superfamily; AIF: Apoptosis Inducing Factor; IAP: Inhibitors of Apoptosis.

## INTRODUCTION

Fas [APO-l/CD95/tumor necrosis factor superfamily 6 (TNFRSF6)/APT-1] is a transmembrane receptor expressed in particular in brain, heart, kidney, liver, pancreas, thymus and lymphoid tissues. It belongs to the death receptor family, a subgroup of the Tumor Necrosis Factor (TNF)/ Nerve Growth Factor (NGF) receptor superfamily,[1,2] and acts as the target of cell death-inducing antibodies.[3]

These cell surface cytokine receptors are able to initiate an apoptotic signaling cascade after binding a group of structurally related ligands or specific antibodies. In addition to its apoptotic function, it has other cellular responses including migration, invasion, inflammation, and proliferation. The members of this family are type I transmembrane proteins with a C-terminal intracellular tail, a membrane-spanning region, and an extracellular N-terminal domain rich in cystein. Through interaction with the N-terminal domain, the receptors bind their cognate ligands (called death ligands).[4] Although soluble forms of the receptor also exist, whose functions are still largely unknown, the membrane-bound form is largely predominant and highly biologically active.[5]

Fas is one of the members of the TNFR superfamily, currently comprising 29 receptors that are mirrored by only 19 ligands, representing the cognate TNF ligand superfamily. This already indicates that a single ligand might be capable to bind to more than one receptor and/or that there still exist orphan receptors.[6]

Activation of CD95-associated intracellular signaling pathways is not a simple consequence of ligand binding but is the fine-tuned result of a complex interplay of various molecular mechanisms that eventually determine the strength and quality of the CD95 response.[3]

In order to avoid unnecessary activation of the apoptotic pathway, Fas expression and localization are tightly regulated through a variety of mechanisms. The minimum amount of Fas is expressed on the plasma membrane in unstimulated cells (whereas the majority of the

ISSN 2473-4799 Open Journal http://dx.doi.org/10.17140/DRMTOJ-1-117

receptor localizes in the cytosol, in particular, in the golgi complex and the trans-golgi network).[7] Then, after a proapoptotic stimulus, Fas-containing vesicles translocate to the cell surface, increasing Fas expression on the plasma membrane and initiating the apoptotic signal. This mechanism provides an effective tool to regulate the plasma membrane density of the death receptor, and avoid its spontaneous activation.[7,8]

Fas can also be modulated at a post-translational level, by glycosylation of the receptor,[9] as well as at the transcriptional level, by direct regulation of Fas expression. A composite binding site for the transcription factor nuclear factor kappa B (NF-κ B) is located in the Fas gene promoter,[10] and a p53-responsive element has been identified within the first intron of the Fas gene, which co-operates with three sequences in the promoter to up-regulate Fas receptor expression.[11]

In eczema, spongiosis is predominantly located in suprabasal epidermal layers, suggesting an anti-apoptotic mechanism protecting basal KCs. CD95 is slightly up-regulated on KCs throughout all epidermal layers in eczematous dermatitis as compared with healthy skin.[12,13] Thus, differential CD95 expression may basically account for the increased susceptibility of KCs to CD95-mediated apoptosis in eczema, but does not explain the apoptosis resistance of basal KCs. The differential expression of pro- and anti-apoptotic factors, which may influence the susceptibility to CD95-mediated apoptosis, might provide an explanation for the restriction of spongiosis to suprabasal epidermal layers.[14]

## MECHANISM

In non-stimulated cells Fas pre-aggregates in the form of complexes due to its amino-terminal pre-ligand-binding assembly domain.[10,15]

Fas death receptor is physiologically activated through binding to its cognate ligand, Fas ligand (FasL). Fas/FasL interaction induces oligomerization and aggregation of Fas receptor, leading eventually to apoptosis after protein-protein interactions with adaptor and effectors proteins.[16] Binding of CD95 or agonistic antibodies to CD95 leads to formation of a receptor complex at the cellular membrane, which was named death-inducing signal complex (DISC).[17]

The DISC consists of oligomerized receptors, the death domain (DD)-containing adaptor molecule fas-associated death domain/mediator of receptor-induced toxicity (FADD/MORT1), procaspase-8 [FADD-like interleukin-1 beta-converting enzyme (FLICE), MACHa, Mch5], procaspase-10 and the cellular Flice like inhibitory protein (c-FLIP) (Figure 1). The DD of the receptor interacts with the DD of FADD, whereas the death effector domain (DED) of FADD interacts with the N-terminal tandem DEDs of procaspase-8, procaspase-10 and c-FLIP. As a result of

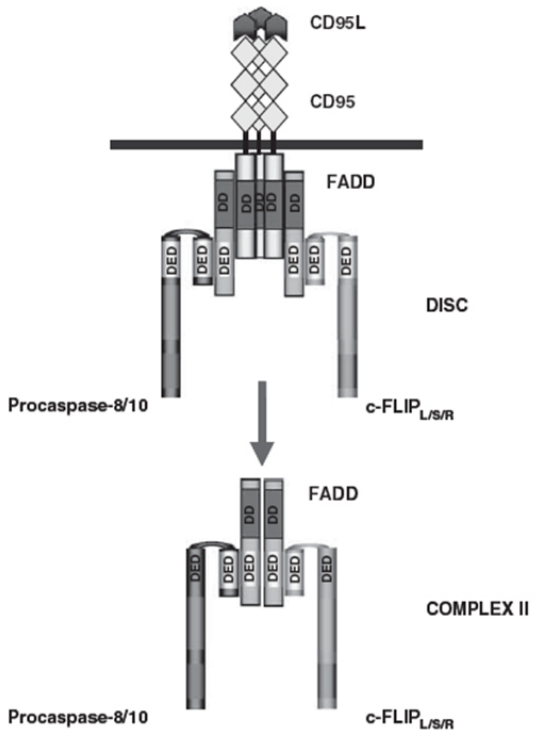


**Figure 1:** The CD95 DISC and complex II. The DISC consists of CD95, FADD, procaspase-8/procaspase-10 and c-FLIP. Complex II comprises FADD, procaspase-8/10 and c-FLIP. The interactions between the molecules at the DISC and complex II are based on homotypic contacts. The DD of CD95 interacts with the DD of FADD while the DED of FADD interacts with the N-terminal tandem DEDs of procaspase-8, procaspase-10 and c-FLIP.[18]

ISSN 2473-4799 Open Journal http://dx.doi.org/10.17140/DRMTOJ-1-117

DISC formation procaspase-8 is activated at the DISC resulting in the formation of the active caspase-8, which leads to apoptosis.[18]

While FADD binds directly to the DD of Fas by its own C-terminal DD, procaspase-8 is indirectly recruited to Fas *via* FADD, which interacts *via* its N-terminal DED with the corresponding structure in procaspase-8. This FADD-mediated recruitment into the DISC allows the transient formation of enzymatically active procaspase-8 dimers that convert by autoproteolytic processing to mature active caspases-8 heterotetramers, mature caspase-8 is released from the DISC and, dependent on the cell type, can trigger the execution phase of apoptosis by two pathways, the extrinsic and the intrinsic pathway.[19]

Extrinsic pathway of apoptosis is induced by the signal molecules-known as ligands–which are released by other cells, and which bind to the transmembrane death receptors of the target cell. For example, the immune system's natural killer cells posses the FasL on their surface: the binding of the FasL to Fas receptors (Fas-R) (a death receptor) on various target cells will trigger the aggregation of multiple receptors on the surface of that target cell.[20] The aggregation of these receptors then leads to the recruitment of an adapter protein, known as FADD, on the cytoplasmic side of the receptors. FADD, in turn, recruits caspase-8 (an initiator protein), forming the DISC.[21]

The intrinsic pathway is triggered by cellular stress–specifically, mitochondrial stress caused by various factors, such as Deoxy Ribonucleic Acid (DNA) damage. The stress signal will cause the pro-apoptotic proteins found in the cytoplasm–BAX (pro-apoptotic, cytoplasmic protein) and BID–to bind to the outer membrane of the mitochondria and signal the release of the internal mitochondrial content. However, the signal of BAX and BID is not enough to trigger a full release of the mitochondrial content: BAK, a pro-apoptotic protein found in the mitochondria, is also needed to fully promote the mitochondrial release; it is important to note that the mitochondrial content also includes cytochrome C. (Figure 2). Besides cytochrome C, the mitochondrial content released also contains the apoptosis inducing factor (AIF) which facilitates DNA fragmentation, preventing the activity of the inhibitors of apoptosis (IAP).[22,23]

The ligation of Fas by FasL causes the activation of target cell enzymes to degrade target cell nuclear DNA with concomitant fragmentation of the target cell nucleus, leading to programmed cell death. When FasL binds Fas, Fas trimerizes and activates its "death" domain that interacts with the "death" domains of several cytosolic proteins including FADD. Activation of FADD triggers the activation of a series of cysteine proteases known as caspases, resulting in apoptosis of the cell with the consequent morphological changes (reduction of cell volume, plasma membrane blebbing, condensation of chromatin, and fragmentation of DNA).[2,24,25]

Phosphatidylserine, normally found on the cytosolic surface of plasma membranes, is redistributed during the process of apoptosis to the EC surface. Phagocytic cells recognize this aberrant placement and remove the dying cells without the induction of inflammation. Cell removal is followed by a reset of the activated T-lymphocytes to initiate another Fas/FasL interaction.[2,26]

## FAS LIGAND (FasL)

FasL (CD178/TNFRSF6/APTILG1) is a trimeric type II transmembrane protein that plays an important immune-regulatory role in limiting the host immune response.[27]

The human FasL gene was mapped on chromosome lq23 by *in situ* hybridization. The FasL gene consists of approximately 8.0 kb and is split into four exons.[28]

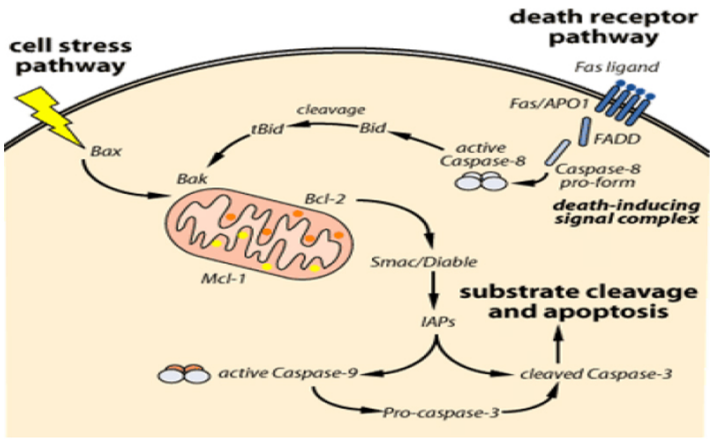


**Figure 2:** The intrinsic and extrinsic pathways leading to apoptosis.[21]

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FasL is predominantly expressed on activated T-lymphocytes and natural killer cells but also at immune privileged sites. Similar too many other members of the TNF ligand superfamily, FasL can be cleared by metalloproteinases in its EC domain to release the soluble trimetric ligand.[27] Both forms are capable to bind to Fas, but only membrane bound FasL is efficient in induction of cytotoxicity.[29]

As soluble FasL competes with the membrane-bound counterpart, however, it can act even as an antagonist preventing apoptosis induction by the membrane integrated form of the ligand.[30,27] On the other hand, soluble FasL binds effectively to fibronectin of the EC matrix, which results in retention of the molecule and an enhanced capacity to induce apoptosis.[31] Besides its role in the blockage of apoptosis the soluble form of FasL has been shown to function as a strong chemo-attractant, and to enhance neutrophil and phagocyte migration to inflammatory sites (Figure 3).[32,33]

Binding of membrane FasL to Fas triggers the re-organization of these complexes into signaling competent ligand-receptor aggregates. These aggregates are capable to interact with cytoplasmic signaling molecules. In sensitive cells this "active" Fas complex inducing apoptosis has been named DISC.[34]

## ROLE OF FAS

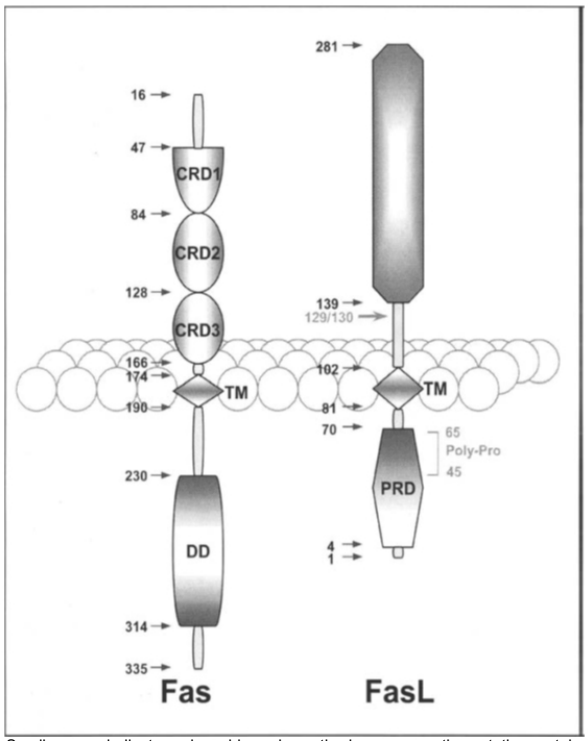
### Fas/FasL: Key Role in Autoimmunity

Normally, in order to eliminate auto-reactive T-cells (mature T-lymphocytes that recognize self-antigens), interaction between auto-reactive T-cell Fas and activated T-lymphocytes Fas L induces apoptosis of the auto reactive T-cells. In adequate removal of self-reactive T-lymphocytes permits the production of pathogenic auto-antibodies that characterize auto immune diseases.[35]

This negative regulation of T-cells contributes to the elimination of T-lymphocyte-activated auto-reactive B-cells, in the absence of presentation of the auto-antigen by the auto-reactive T-cell.[24]

By virtue of elimination of these cells, the immune system remains safe and effective. Thus, normal Fas/FasL function results in normal lymphocyte homeostasis and controlled auto-reactivity. An alteration in Fas/FasL structure results in impaired immune tolerance and in uncontrolled lympho-proliferation.[36,37]

Fas-mediated apoptosis plays a critical role in the removal of mature auto-reactive B- and T- lymphocytes as well




Small arrows indicate aminoacid numbers, the larger arrow the putative metalloproteinase cleavage site.

**Figure 3:** Schematic representation of Fas and FasL. Fas is a type I and FasL a type II transmebrane protein. The upper parts of both molecules represent the extracellular domains.
CRD=cysteine rich domain; TM=transmembrane domain; DD=death domain; PRD=proline rich domain.

ISSN 2473-4799 Open Journal http://dx.doi.org/10.17140/DRMTOJ-1-117

as in the elimination of infected or malignant cells.[24] A dysfunctional apoptotic pathway may lead to the development of cancers. Due to the sensitivity of the intrinsic pathway, tumors arise more often through the intrinsic pathway dysfunction than the extrinsic pathway.[38]

#### Fas / FasI: Role in Tumor Surveillance

It has been assumed that Fas and FasL works as tumor suppressors, since mutations that down regulate normal function of Fas have been proposed as a mechanism by which tumor cells avoid apoptosis or destruction by the immune system.[26]

However, a single point mutation of the Fas gene can change Fas/FasL interaction from tumor suppression to tumor promotion by induction of pro-survival genes through non-apoptotic pathways. This dual role of Fas/FasL is found in advanced cancer in humans, resulting in apoptosis resistance and activation of tumorigenic pathways.[39]

Stimulation of CD95 has been also reported to trigger non-apoptotic pathways.[40] However, details of CD95-mediated non-apoptotic pathways remain largely unknown. Importantly, it has been shown that membrane-bound CD95L is essential for the cytotoxic activity, whereas soluble CD95L appears to promote autoimmunity and tumorigenesis *via* induction of non-apoptotic pathways, in particular NF-κ B.[41] Future studies are needed to show more details on the mechanism of non-apoptotic action of CD95.[42]

#### Fas/FasL: Role in inflammation

Inflammatory biomarkers might help to identify specific inflammatory disturbances. Therefore, targeting specific biomarkers of inflammation might represent new therapeutic approaches.[43] Both Fas and FasL proteins exert a wide range of pro-inflammatory functions by inducing secretion of cytokines and chemokines.[44]

Beyond activating apoptosis, the activation of the Fas "DD" can initiate multiple non-apoptotic signaling pathways, including inflammatory responses.[2,25] Furthermore, Fas/FasL increases cell removal from areas of chronic inflammation,[25] through its role in the blockage of apoptosis the soluble form of FasL has been shown to function as a strong chemo-attractant and to enhance neutrophil and phagocyte migration to inflammatory sites.[32]

Activation-induced cell death (AICD) down-modulates the immune response.[45] Therefore, plays a key role in the prevention of inflammatory and auto immune responses. AICD of T-cells, B-cells, and macrophages is mediated by Fas.[46]

#### Role in eczematous dermatitis

The clinical features of eczemaare related to increased blood flow in the vessels (erythema), augmented vascularperme ability (edema), invasion of T-cells into the tissue (infiltration), epidermal spongiosis (vesiculation), and a release of mediators (pruritus). During these eczematous diseases, the resident structural elements in the skin (for example, KCs, fibroblasts, endothelial cells) tightly interact with cells that are actively recruited from the blood in response to inflammatory stimuli. A complex interaction of numerous chemokines controls the recruitment of T-cells from the blood vessels and their migration into the dermis and epidermis.[47]

The early acute phase of AE is characterized by a Th2 immune response with a distinct cytokine profile. As the disease progresses, there is a shift to a Th1 response, characterized by CD4+Th lymphocytes and the release of high levels of pro-inflammatory cytokines such as interferon-gamma (IFN-γ), which also helps modulate the transition from acute to chronic inflammation.[48] The Th1 cytokines released by T-cells in skin, including IFN-γ, can up-regulate Fas expression and increase KC susceptibility to apoptosis.[49] Additionally, IFN-γ works synergistically with TNF-related apoptosis-inducing ligand (TRAIL) receptor 2 antibody, soluble TRAIL and TNF-α.[50] In AE, it has been found that T-cells induce the expression of death receptor Fas on the surface of KCs.[13]

FasL, either secreted from activated T-cells or present on their surface, interacts with up-regulated Fas on KCs resulting in apoptosis. KC apoptosis induced by T-cells disrupts the integrity of the skin leading to altered barrier function that favours invasion of allergens, with subsequent production of inflammatory cytokines and amplification of epithelial damage.[51]

The eczematous inflammation of the epidermo-dermal unit is caused by the intricate interaction of T-cells and KCs with T-cell-derived inflammatory cytokines, IFNs, and other immune regulatory mediator produced by KCs. Thus the local response of KCs together with the reaction of endothelial cells, T-cells, mast cells, and dendritic cells finally leads to the characteristic clinical and histological symptoms of eczema. It has been suggested that the death Lig and Fas expressed on activated T-cells plays a crucial role in KC death during the elicitation phase of eczematous dermatitis.[14] However, only single KC undergo apoptosis in acute eczema; T-cell-mediated apoptosis of single KCs is a key feature of epidermal pathology in acute eczematous dermatitis.[14] This supports a concept in which the resistance to death Lig and mediated apoptosis may rather define an alternative response of KCs to death receptor ligation.[13]

Damage of KCs decreases the effectiveness of the epidermis as a barrier against invasion by infectious agents. Furthermore, damage to the epidermis might allow greater access of allergens and super-antigens to Langerhans cells, dermal dendritic cells and T-cells, serving to amplify the inflammatory process. Thus, the apoptosis of KCs and damage to the epidermis might play a pivotal role in the development of chronic eczema.[13]

ISSN 2473-4799 Open Journal http://dx.doi.org/10.17140/DRMTOJ-1-117

In the skin of patients with eczema, the basal layer of KCs and the basement membrane are morphologically intact. It seems probable that during the course of eczema, KC stem cells located directly at the basal membrane are protected from T-cell induced apoptosis. It has been demonstrated that postmitotic, suprabasal KCs are damaged relatively easily, whereas basal stem cells have strong anti-apoptotic defense mechanisms.[52]

CD95 is not only needed for a silent end of the life of KCs during eczema but may rather contribute to a "going out with an (inflammatory) bang" intracellular inhibition of effect or caspases or mitochondrial signaling pathways of apoptosis downstream of caspase-8 activation by Bcl-2 family members or inhibitor-of-apoptosis proteins (IAPs).[53] might interfere with apoptotic, but not non-apoptotic, signals by death receptors. This scenario may ultimately result in a uncontrolled activation of CD95-mediated inflammation in the skin, but this hypothesis awaits further experimental studies**.** It will be interesting to determine under which conditions apoptosis may predominate over CD95-mediated inflammation in KCs. This difference subtle at first glance of a death receptor-mediated signal might prove to be highly relevant to the quantitative response in the skin as the target organ of eczematous inflammation.[13]

A common histopathological feature of eczemasis the formation of exudative epidermal vesicles that are disruptive to the normal barrier function of the skin. Although vesicle formation in eczemas has been largely attributed to rupturing of KCs attachments as a result of inter cellular edema (spongiosis). Recent findings suggest that KC death plays a major role in vesicle formation.[54] This KCs death appears to be apoptotic and to be mediated by FasL, delivered to the epidermis by in filtrating T-lymphocytes and acting on Fas whose expression on the surface of KCs is induced by T-lymphocyte-derived IFN-γ.[13]

These findings clearly demonstrated the important role of FasL in the epidermal destruction in inflammatory skin diseases. However, whether FasL is directly involved in the inflammatory process is not known. We demonstrate here that FasL elicits a pro-inflammatory reaction in human KCs by triggering the expression of stress-responsive transcription factors, inflammatory cytokines, chemokines, and the adhesion molecule ICAM-1, KC; as a target of Fas-induced apoptosis, provides evidence that this form of cell death contributes to the pathogenesis of eczematous dermatitis. KCs normally express low-levels of Fas, but IFN-γ up-regulates Fas on these cells. Secretion of IFN-γ by T-lymphocytes, which promotes Fas up-regulation in KCs, is a crucial early step in this pathway. Therefore, in this case KC apoptosis occurs only in association with an inflammatory reaction; but it is important to mention that the inflammatory infiltrate is not the consequence but the cause of apoptosis.[55]

From the pathophysiological point of view, it is interesting that the same mechanism is demonstrated in AD and ACD, since these dermatoses are usually regarded as mutually exclusive, AD being a classic example of a Th2-mediated and ACD of a Th1-mediated process.[56]

Some authors speculated that IFN-γ expression *via* up-regulation of the intercullar adhesion molecule 1 (ICAM-1) contributes to the subsequent accumulation of inflammatory cells. Consistent with this suggestion, the present findings imply that the high expression of IFN-γ also propagates the inflammatory process *via* disruption of the epidermal barrier. Interestingly, in histologic sections of AD and ACD lesions alike, the majority of apoptotic KCs were found not in spongiotic regions, but in areas that retained normal cohesion of epidermal cells. Hence, one can speculate that apoptosis precedes spongiosis and, further, that apoptotic death of KCs promotes spongiosis by enabling the in-

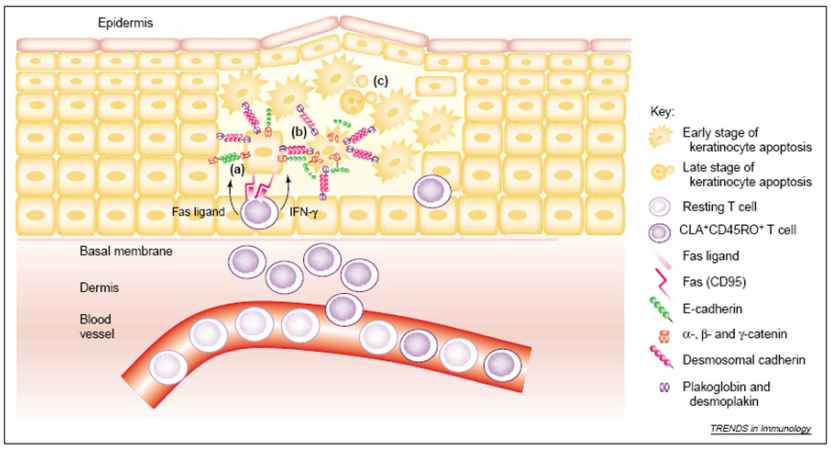



**Figure 4:** T-cells attack keratinocytes (KCs) in the elicitation phase of eczematous dermatitis. The infiltration of activated $CD4^+$ and $CD8^+$ T-cells into the dermis and epidermis results in eczematous changes to the epidermis. The apoptosis of KCs is characterized by impairment of the cohesion between KCs (spongiosis). The key pathogenic steps are as follows. (a) Interferon γ (IFN-γ) secreted by activated T-cells ($CLA^+CD45RO^+$) enhances the expression of Fas on KCs. Membrane-bound and soluble Faslig and produced by activated T-cells triggers Fas on the KCs. (b) During the early stages of the apoptosis of KCs, E-cadherin is cleaved by caspases that remove the β-catenin-binding domain from its cytoplasmic tail. By contrast, desmosomal cadherins (e.g. desmogleins and desmocollins) remain intact. The intracellular domain of E-cadherin is linked to actin microfilaments through its association with α-catenin, β-catenin and γ-catenin (plakoglobin). Desmosomal cadherins bind to the cytoplasmic proteins plakoglobin and desmoplakin,and are linked to keratin intermediate filaments.[13] (c) Finally, DNA is fragmented and apoptotic bodies form.
Abbreviation: CLA, cutaneous lymphocyte-associated antigen.

ISSN 2473-4799 Open Journal http://dx.doi.org/10.17140/DRMTOJ-1-117

flux of EC fluid into the epidermis (Figure 4).[13,57-60]

Activated transcription factors, such as nuclear factor kappa B (NF-κ B), activator protein 1 (AP-1), nuclear factor of activated T-cells (NF-AT) and signal transducer and activator of transcription (STAT) factors, induce inflammation and favor the recruitment of $CLA^+$T cells to the skin through chemokines and cell-adhesion molecules (e.g. vascular-cell adhesion molecule 1 and E-selection). During the final process of migration, some T-cells penetrate the basal membrane and reach the intercellular space of epidermal KCs. Superfluous and damaged T-cells are removed by apoptosis, promoting the resolution, rather than progression, of inflammation. An increased level of apoptosis controls the number of activated, skin-homing T-cells in peripheral blood, but cytokines (e.g. IL-2,IL-4 and IL-15) and components of the EC matrix (e.g. fibronectin, laminin, tenascin and collagen IV) in eczematous skin prevent T-cell apoptosis. Therefore, the prolonged survival of T-cells, due to components of the skin micro-environment, causes more-pronounced tissue damage and might contribute to chronicity in eczema.[47,61]

## CONCLUSION

It is now clear up that Fas receptor plays an important role in the pathogenesis of some dermatologic diseases. Its role cannot be rolled out as a contributing factor to others. So, better evaluation of such role can help in understanding the pathogenesis of such diseases and also can open a new hope of management of such diseases and the possible use of anti-Fas antibodies in the future.

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