Emergency in Dermatology

Mohammed Mohy El-Din Selim
Consultant - Dermatologist
Hamad Medical Corporation
Doha - Qatar.

Under this heading we will deal with some potentially fatal skin conditions where rapid diagnosis and proper management may decrease its morality.

The first emergency is Toxic Epidermal Necrolysis (TEN) :

Toxic epidermal necrolysis (TEN) is the most severe blistering disease with a mortality rate of 20-30% [1,2]. TEN is drug induced in 89% of cases [3]. Some of the drugs that were reported to cause TEN are phenytoin, phenobarbital, carbamazepine [4], valproic acid, sulfamethoxazole, trimethoprim and other sulfonamides [5,6], Naproxin, oxicam and other NSAIDs [7,6], aminopenicillins, quinolones, ciprofloxacin, cephalosporins, allopurinol, corticosteroids [6], Chlormezanone (Muskel-Trancopal pain killer)[8] cytosine arabinoside (cytarabine)[9], cymetidine[10], phenolphthalin [11], methotrexate [12], vitamins, minerals and natural medications [13]. There was no significant risk for thiazides, duiretics and hypoglycemic agents [6].

TEN affecting patients who give no history of drug intake, may be related to infection as varicella zoster virus [14], HIV infection where the incidence of TEN is 1 per 1000 per year reflecting an inherent high risk and more exposure of patients to sulfonamids [15], acute Graft Versus Host Disease (GVHD) [16,17]. Food additives, fumigants and contact with chemicals have been reported to cause TEN in few cases [18].

None of the drugs has an excess risk that exceeds five cases per million users per week [6].

Complications of TEN[19] include ulceration, dehydration, electrolyte abnormality, gastro-intestinal hemorrhage, acute tubular necrosis, secondary infection of the skin, pneumonia, bacterial conjunctivitis, keratitis, septic infarcts of internal organs, heterotropic ossification that resulted in multiple joint contrature.

The incidence of TEN was estimated in France[20], Germany [21], Italy [22] to be 1.3 per million per year.

Clinically TEN begins by a prodromal stage of 2-3 days or one day to 3 weeks. In the prodromal stage the patient gets signs and symptoms of upper respiratory tract infection; fever, anorexia, rheinitis, sore throat, cough, conjunctivitis and difficult micturation.

The prodromal stage is followed by the acute phase which lasts from 8-12 days. During the acute phase fever persists and mucous membranes are affected especially conjunctivae, oral, pharyngeal, tracheal, bronchial, nasal, anal, vaginal and urethra with urine retension. The skin lesions begin as burning, red, tender and painful eruption which usually begins on the face and upper body and spreads caudally [18], but predominates on the trunk and proximal part of the limbs. The skin shows large flaccid bullae, sloughing of the epidermis and positive Nicolsky's sign in large areas (Fig.1) and at sites of adhesive plaster or adhesive electrodes. The rash generally spreads rapidly and reaches maximal extension in 2-3 days and sometimes few hours and one in seven patients will get 100% loss of epidermis in less than 24 hours.

The acute phase is followed by a recovery phase which takes 1-2 or 3-4 weeks [18,23], during which mucous membranes and skin re-epithelialize even while the disease is still spreading to the lower limbs. No scarring occurs except in areas of pressure or infection. The thorax regenerates in few days while flexures and back heal more slowly. The mucous membranes take longer time and the glans penis may

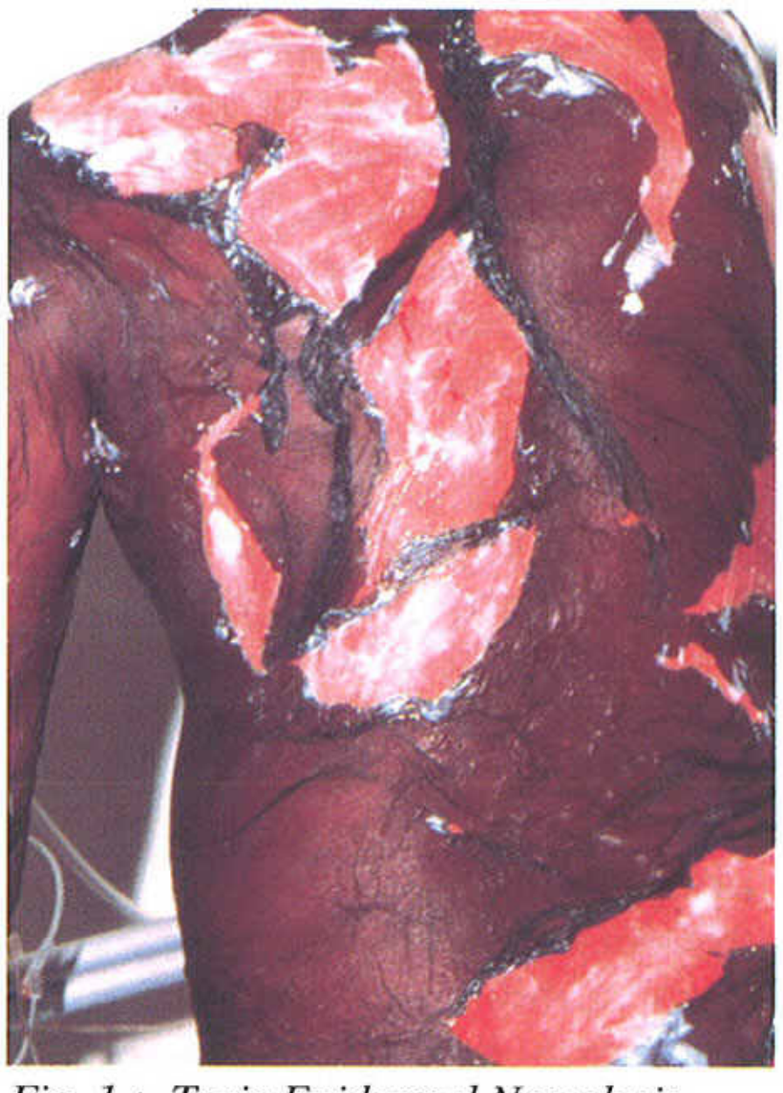

Fig. 1 : Toxic Epidermal Necrolysis

need 2 months to heal.

Approximately 30% of patients die [1], especially elderly patients and those with extensive lesions. Sepsis and pulmonary involvement are the most frequent causes of death. Multisystemic involvement is frequent and contributes to the severity of the process [24].

TEN may be complicated by [18,23] :-

1- Persistant,high fever and sudden drop rather than rise of temperature is more indicative of infection. Impaired thermal regulation may occur.
2- Skin infection, nail dystrophy and nail loss, hypohidrosis and dermal dessication, scarring alopecia, hypo or hyper pigmentation that may improve by time and may persist for more than 10 years.
3- Mucous membrane affection :
   One) Gastrointestinal tract: epidermal and intestinal epthelium undergo extensive apoptosis and mucosal death [25] leading to chronic mouth erosion and xerostomia, impairing alimentation, oesophageal bleeding and stricture, dysphagia, oesophageal rupture[26], profuse protein rich diarrhoea leading to increased fluid loss and hypoalbuminemia, severe chronic diarrhoea may occur and may require intestinal resection, overt hepatitis may occur in 10% of patients. Acute pancreatitis may occur with increase in serum amylase and serum lipase [27].
   Two) Respiratory complications occur in 30% of patients such as mucous retension, erosion and sloughing of tracheo-bronchial mucosa which when aspirated leads to shallow breathing, atelectasis, pneomonitis and pneumonia. Interstitial oedema due to increased alveolar capillary permeability and 10-20% of patients may need artificial ventilation. Involvement of bronchial epithelium must be suspected in patients with dyspnoea, bronchial hypersecretion and seem to indicate a poor prognosis [28]
4- Occular complications may occur in up to 50% of patients and they need special attention and include :
   One) conjunctivitis which may lead to pseudomembranous conjunctival erosions.
   Two) Photophobia
   Three) Ectropion, entropion and symblepharon,
   Four) Vascularization of the cornea, corneal opacities, ulceration and scarring.
   Five) Lacrimal duct destruction and chronic dry eye,
   Six) Conjunctival destruction with fusion of the eye lids to one another and to the globe leading to blindness.
5- Fluid loss: an adult with 50% of the body surface affected looses 3-5 liters of liquid from the skin with 40 grams of protein in each liter with electrolyte loss in the same concentration as in plasma. The fluid loss leads to hypokalaemia and kidney failure.
6- Blood: Normocytic hypochromic anaemia, lymphopenia, neutropenia which is seen in 30% of patients and is a poor prognostic sign, thrombocytopenia in 15% of patients, disseminated intravascular coagulopathy from release of lysosomal enzymes by sepsis.
7- Sepsis: Infection by staph aureus or pseudomonas aerogenosa may spread from skin and cause septicemia and septicaemic shock which is fatal. Central catheters and venous lines promote infection.
8- Kidneys may rarely show glomerulo nephritis, prerenal azotaemia and tubular necrosis.
9- Increased energy expenditure
   One) Hypermetabolic state produced by IL-I. Hypermetabolism is twice the basal metabolic rate when 50% or more of the body surface is affected.
   Two) Environmental temperature below 25°C increases the hypermetabolic state.
   Three) In an adult protein loss from skin surface and hypercatabolism may lead to protein loss upto 150-200 grams per day.
   Four) Inhibition of insulin secretion and or insulin resistance in peripheral tissue lead to glucosurea which leads to increased aminoacid break down which will cause more calory and fluid loss.
10- Miscellaneous: (a) Hypovolemia; (b) Hypoxic injury to the brain from hypotension; (c) Gastrointestinal haemorrhage; (d) Pulmonary emboli; (e) Sjogren syndrome; (f) Urinary tract infection;(g) valvovaginal and genital involvement is frequent with [29,30] chronic erosion of genitalia and phymosis; (h) Abnormal liver function [18,23,31], and hypocalcemia [32]. In TEN secretory sweat glands are not affected but there is significant reduction in sweat ducts. This is of

clinical importance because TEN affects 30-100% of the body surface [2].

A skin biopsy should be performed in every case of TEN and a frozen section usually rapidly confirms the diagnosis by showing necrotic detached epidermis, from a little-altered dermis. The diagnosis of autoimmune blistering disorders and staphylococcal scalded skin syndrome have to be ruled out.

TEN could be differentiated from erythema multiforme (EM) histopathologically because in EM there is dense T lymphocyte infiltration while in TEN there is poor cellular infiltrate with predominant macrophages and dendrocytes with strong immuno reactivity to tumour necrosis factor alpha (TNF-alpha) [33].

Pathogenesis :

Patients who develop TEN may have a low constitutive N-acelylating capacity and this predisposes them to adverse reaction to drugs that require N-acetylation [34]. Keratinocytes normally express death receptor Fas (CD 95). Keratinocytes from TEN express lytically active Fas ligand (FasL). Thus interaction between Fas receptor and FasL is involved in patholgenesis of TEN [35]. Keratinocytes in TEN undergo extensive apoptosis and so drugs that inhibit apoptosis may have a role in treatment of TEN for example cyclosporine A [36]. Soluble tumor necrosis factor alpha (sTNF alpha) and their receptors (sTNf-R1 and sTNF-R2) were high in blisters and serum of patients with TEN. The soluble TNF receptor 2 (sTNF-alpha-R2) enhances the cytotoxic effect of TNF alpha signifying a pathomechanism of TNF alpha system in epidermal necrosis and sloughing in TEN [37].

Treatment :

Early treatment in intensive care unit or burn center reduces the rate of bacteremia and mortality rate in TEN [38].

Avoidance of systemic steroid needs to be stressed in treatment of TEN[39], because of increased mortality with prolonged use of systemic steroids [40,41]. Steroid could be used early as an adjuvant treatment to suppress T.N.F. alpha[42].

Prophylactic antibiotic is not recommended [24]. Sepsis is the cause of death in 50% of cases. It is vital to control infection and it is recommended to do repeated culture from multiple skin sites and from blood daily.

Laboratory investigations are essential for diagnosis, prognosis and monitoring the disease and treatment.

Antiseptic bath and change of intravenous lines and urinary catheters. Antibiotics are only given if infection is proven.

Artificial nutrition[43] and control of hypovolemia is essential and 5-7 liters of fluids are needed in first 24 hours.

Fluids are given by nasogastric tube and intravenous lines. Fluids given are water, electrolytes, plasma, albumin and macromolecular solutions as synthetic colloid.

Patient may need help from other medical disciplines particularly ophthalmology.

Hyperbaric oxygen is given in a pressure chamber with pure oxygen at two atmospheric pressure for 60-120 minutes once daily. This treatment activates dermal metabolism and enhances epidermal regeneration, has antishock and antiseptic effect and is possibly immuno suppressive [44].

One of the first lines of treatment of TEN is exchange plasmapheresis. Alternate day exchange is better than everyday. It is safe, effective and causes immediate relief from pain and rapid cessation of necrolysis [45,46] and reduces mortality rate and it appears that some kind of necrolytic factor is removed by plasmapheresis [47,5, 45, 46]. Plasmapheresis also removes offending drugs and their metabolites and eliminates inflammatory mediators [48].

Intravenous immunoglobulins have been used successfully to treat TEN [49]. Antibodies present in pooled human intravenous immunoglobulins (IVIG) block Fas mediated keratinocyte death and gives rapid favorable results [35].

Cyclosporin A (CSA) has been used successfully to treat TEN. CSA inhibits the main cell population in TEN, lymphocytes, macrophages and keratinocytes. CSA has antiapoptotic effect and apoptosis is the mechanism leading to keratinocyte death in TEN. Tumor necrosis factor alpha is an important cytokine which plays a major role in epidermal destruction in TEN. CSA acts on TNF alpha diminishing its role in TEN [50, 51].

Thalidomide although a potent inhibitor of apoptosis is paradoxically detrimental in TEN as it paradoxically enhances production of TNF alpha [1].

Granulocyte colony stimulating factor is used in neutropenia in TEN [52].

Intravenous cyclophosphamide 300mg/day is very helpful and systemic toxicity in TEN ceases in two days[53]. Cyclophosphamide (Cytoxan) is a derivative of nitrogen mustard : 75% of the drug is absorbed from gastrointestinal tract. It is mainly metabolized in the liver and its alkylating effect is exerted by its metabolites which are 50% protein bound. Fifty percent of the drug is excreted in urine and its half life is 2-10 hours. The recommended dose is 1-5 mg/kg/body weight/day and is best given in the morning with plenty of fluid to avoid cystitis and some prefer to give the drug on 3 divided doses. The side effects of cytoxan are : increased risk of lymphoma 5-40%, increased risk of bladder cancer, cardiomyopathy, pneumonitis, pulmonary fibrosis, haemorrhagic colitis, azospermia, anorexia, nausea, vomiting, stomatitis and anagen alopecia [3]. Monitoring the drug is essential by doing basic CBC weekly, the W.C. should not be less than 3000/cu.mm and the granulocytes must be greater than 1000/ cu.mm. Urine analysis should be done daily and stop cytoxan if RBC appear in urine. Monthly blood boichemistry is recommended. Cytoxan produces dramatic response in TEN as it inhibits the cell mediated cytotoxicity [54].

Biobrane is a biosynthetic skin substitute for early wound covering to avoid repeated dressing and pain[55,56]. Over the last decade several dressings were used such as fresh frozen or cryopreserved cadavar allograft, porcine xengraft and amniotic membrane. Biobrane a biosynthetic dressing has been used successfully to treat burns and TEN. Patient is debreded in operating room and denuded areas were covered with Biobrane within 24-48 hours of admission. Biobrane demonstrate greater than 90% adherence by 48 hours and no sepsis occurs and patients demonstrate epithelialization within 9 days. So Biobrane when used early in patients with TEN provide a reasonable means of wound coverage[57].

Sepsis in TEN may lead to full thickness loss of skin which needs keratinocyte or skin autografting[58].

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The second emergency is Staphylococcal Scalded-Skin Syndrome (SSSS) :

SSSS is a clinical term used to describe an acute blistering skin disorder which affects most of the body surface. It is caused by expholiative toxin (ET) A and B which are extracellular products of staphylococcus aureus phage group II [1, 2]. SSSS usually starts by staphylococcus aureus cutaneous or extracutaneous infections which if not treated early and properly the exotoxins released by the causative microorganism will directly produce an intraepidermal split through the granular layer with widespread expholiation. Clinically SSSS patient within few days of the primary infection become febrile with widespread tender and erythematous rash which rapidly blisters forming large fluid filled bullae that coallesce and rupture on slightest pressure to leave extensive areas of denuded skin that may affect up to 90% of the total body surface [3] (Fig. 2,3,4).

Nikolsky's sign is positive when blistering extends as a result of applying lateral pressure to the border of an intact blister [4]. The blisters are exotoxins mediated and the staphylococcus aureus is not isolated from such lesions but may be isolated from the primary site of bullous impetigo. The peeling of the skin usually begins on the central part of the face, axillae, groin and neck - There is usually crusting around the mouth and nose. Sheets of epidermis peel off leaving a moist erythematous skin underneath that looks scalded. Most patients recover with appropriate antibiotic treatment within a week[5].

The staphylococcus aureus is often isolated from blood cultures of adult patients and rarely from children [6]. SSSS is life threatening in children [7]. They are the prime susceptable patients because they lack immunity to the staphylococcal epidermolytic toxins and because of their renal immaturity there is poor clearance of these exotoxins [8].

The syndrome primarily affects preterm infants[9]; neonates [10]; infants or young children as well as very old subjects [11]. Many cases were reported in adults [12,13,14,15,16,17,18,5]. Adults with SSSS may be suffering from renal failure, immunosuppression, overwhelming sepsis, leukemia [19], oral steroid therapy[20]; NSAID[21,13] and HIV[2, 22, 23]. Experimentally SSSS was reported to fulfil Koch's postulates[28] and the following statements were found -

1- Staphylocossus aureus was isolated from every case

2- Isolated S-aureus can produce the syndrome in experimental animals.

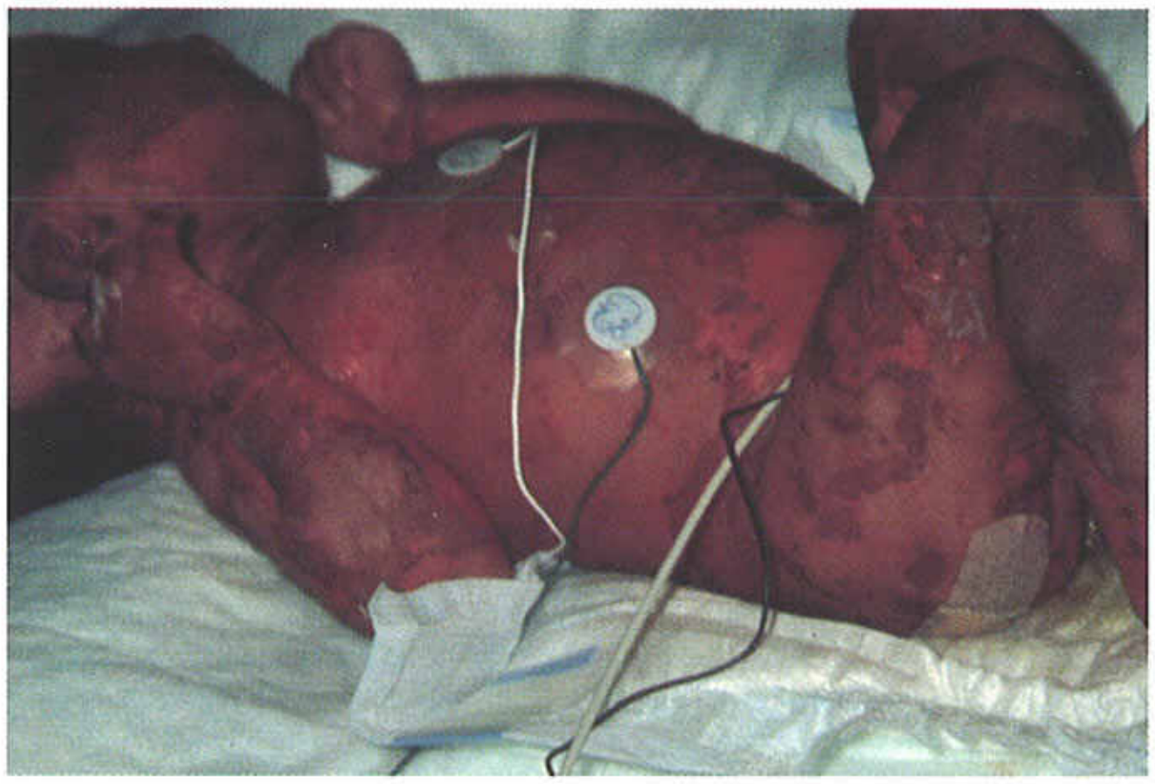

Fig. 9 : Staphylococcal scalded skin syndrane (SSSS)

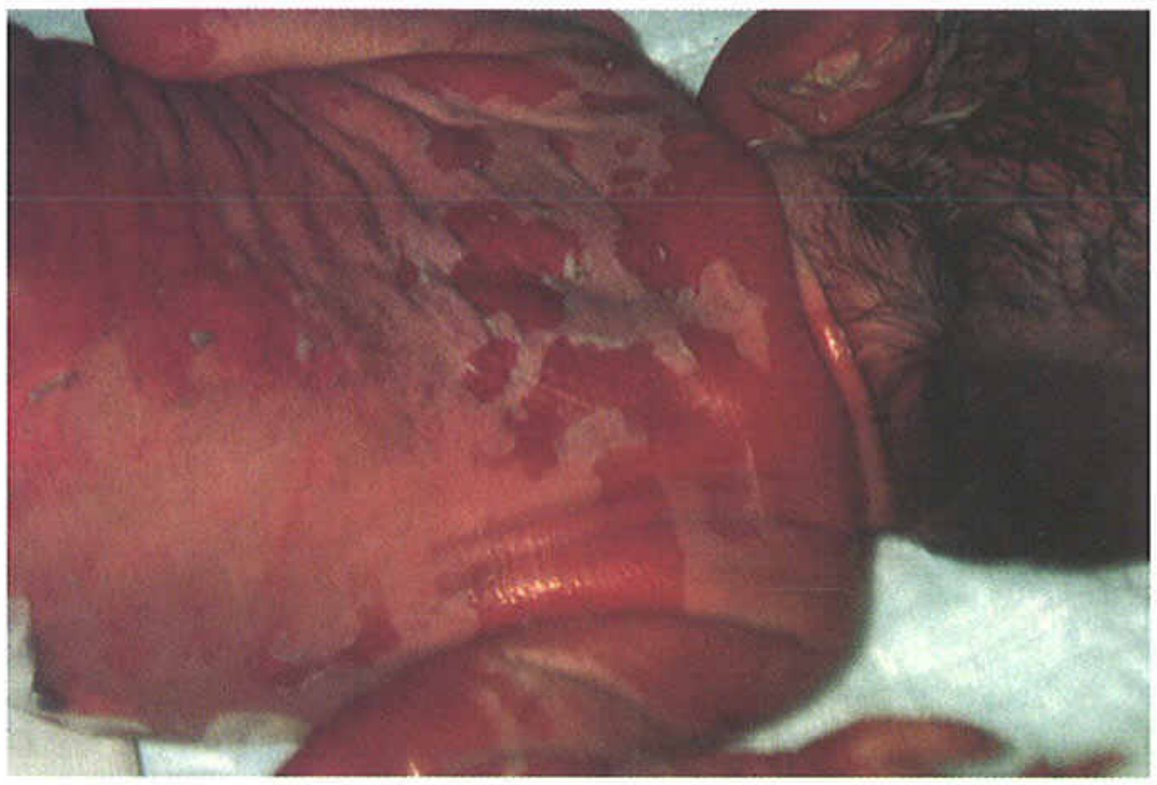

Fig. 3 : (SSSS)

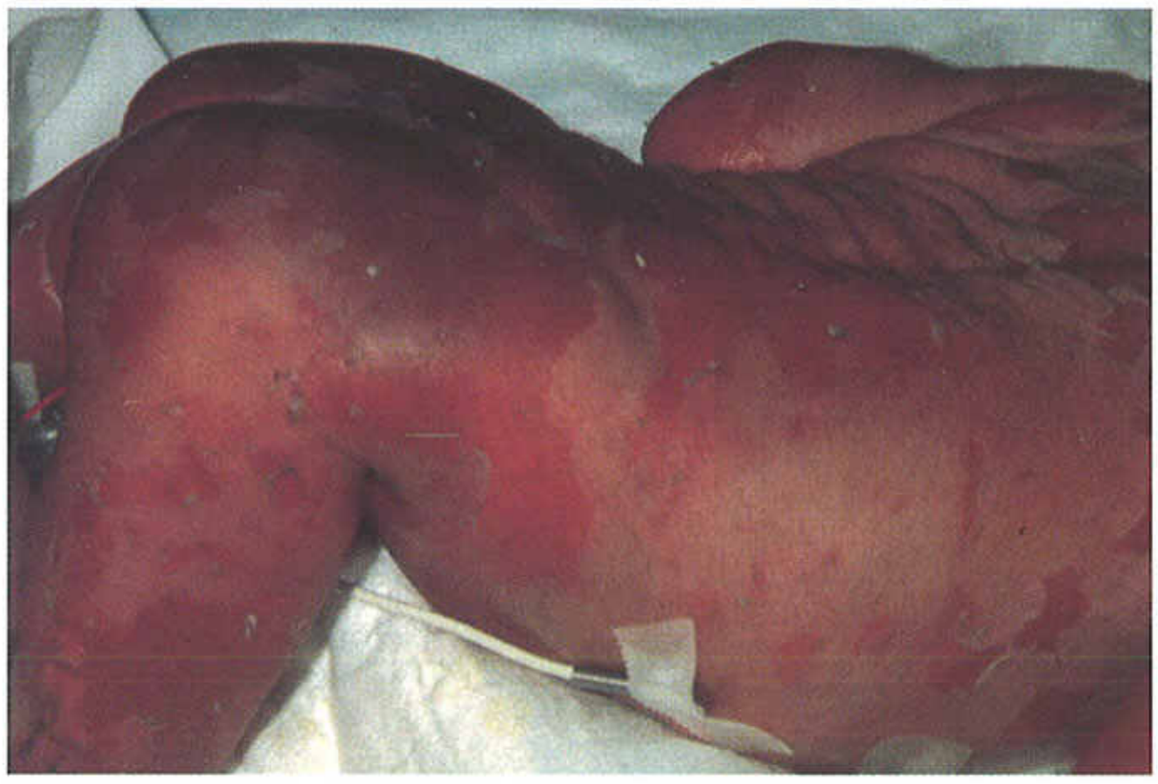

Fig. 4 : (SSSS)

3- A specific extracellular toxin can reproduce the disease.

4- Antibody to toxin can protect experimental animals from SSSS. It was found also that E.T. does not cause the erythema or tenderness but other factors such as delta haemolysins are involved in pathogenesis of these conditions [11].

The diagnosis if SSSS is confirmed by histopathology. Diagnosis can be made by examining frozen sections and conventional skin biopsy [15, 24]. A top of a blister is removed and sent to laboratory on saline moistured gauze to prepare frozen sections by which precise diagnosis is reached within minutes. The histopathology shows in SSSS cleavage plane high in the epidermis being subcorneal in location and consist of stratum corneum and few squamous cells. Tzank smear from the base of the blister shows no inflammatory cells.

Systemic treatment with appropriate antibiotic is mandatory together with replacement of water, colloid and electrolytes lost through the scalded skin which have lost its barrier function. Recovery with treatment is the rule but the disease still carries significant or high mortality rate [17].

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The third emergency is Kaposi's Varicelliform Eruption :

It is a potentially serious disease which necessitates a prompt antiviral treatment. It is a wide spread infection caused by a virus which usually in normal persons leads to a localized vesicular eruption but this wide spread infection occurs in patients who already have a skin disease mainly atopic dermatitis [1]. Other dermatoses reported sometimes to be similarly, affected include Dariers's disease [2], pemphigus foliaceous [3], familial benign chronic pemphigus [Haily and Haily disease] [4], Icthyosiform erythroderma[5,6], mycoses fungoids, Sezary syndrome[7], seborrhoeic dermatitis[6], Wiscott Aldrich[6], Icthyosis vulgaris [8], pityriasis rubra pilaris [9], irritant contact dermatitis [10] and other inflammatory dermatoses [1]. It has been also reported with healing second degree burn [11], traumatic facial abrasion [12], and autologous skin grafting [13].

The majority of such Kaposi's varicellrform Eruption are due to herpes simplex virus infection (eczema herpeticum) and rarely due to vaccinia virus causing eczema vaccinatum. Eczema herpeticum is caused by haematogenous dissemination of herpes simplex virus type I (HSV-1) infection in patient with atopic dermatitis especially those with

severe or erythrodermic variety.

The majority of eczema herpeticum are primary infections with HSV-1. The source of infection is usually a family member with HSV-1 infection or from the use of hot tub together with a person who has "fever blisters" because HSV can survive hot tub environment [14] and in 20% of cases dissemination of infection may occur endogenous following recurrent HSV attack[5]. Recurrence of eczema herpeticum in the same person was reported [5, 15]. Sometimes the recurrence of eczema herpeticum is due to exogenous re-infection [16].

Two genotypes of HSV-1 were identified F1 and F35. The F35 genotype of HSV-1 seemed to be associated more frequently with eczema herpeticum than F1 genotype [17].

The susceptibility of some atopic children to HSV infection is most likely explained by a reduced number of Natural Killer cells (NK) and a decrease in IL-2 receptors and increased activity of IL-4 in atopic dermatitis rather than a HSV immune defect either humaral or cell mediated [18, 19, 20]. The systemic or local use of steroid could not be always associated with the occurrence of eczema herpeticum infection and it is not known whether the use of heavy steroid predispose to herpetic infection or simply reflects the severity of atopic eczema and hence a more susceptibility to eczema herpeticum [1].

Eczema herpeticum affects infants and adults and affected patients may get recurrence once twice or thrice[5].The manifestations of eczema herpeticum appears after an incubation period ranging 5-19 days with an average of 10 days. The patients show widely disseminated vericulopustular eruption with erosions and crusted lesions usually affecting diseased skin but often is generalized affecting face, peri-oral, perioccular, chest, upper arms, lower limb with facial oedema and regional lymphgland enlargement[1] (Fig.5,6). High fever and constitutional symptoms may be severe with secondary bacterial infection of the skin [6].

Occular envolvement with bilateral herpetic keratitis are reported [5, 10, 21] and viral infections of the lungs, brain and adrenal glands can occur [22]. The fever subsides after 4-5 days with treatment and pustules become crusted and heal slowly leaving little scarring. Eczema herpeticum may be potentially fatal [5, 23]. Management of eczema herpeticum should include instruction to atopic patients to avoid close contact with patients who have active HSV-1 infection. Severe cases should receive intravenous acyclovir. Dose of I.V. acyclovir is 10mg/kg 8 hourly. Milder cases are usually self limited [24] and could be treated by oral acyclovir, valacyclovir and famciclovir.

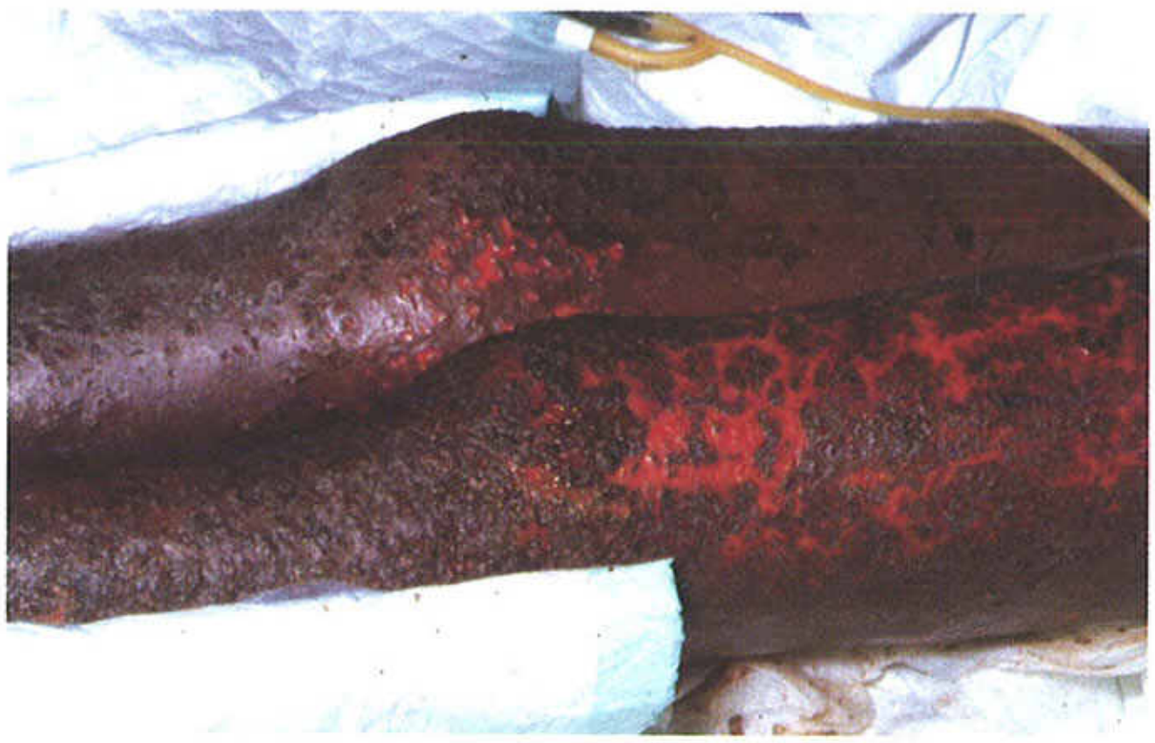

Fig. 5 : Eczema Herpeticum

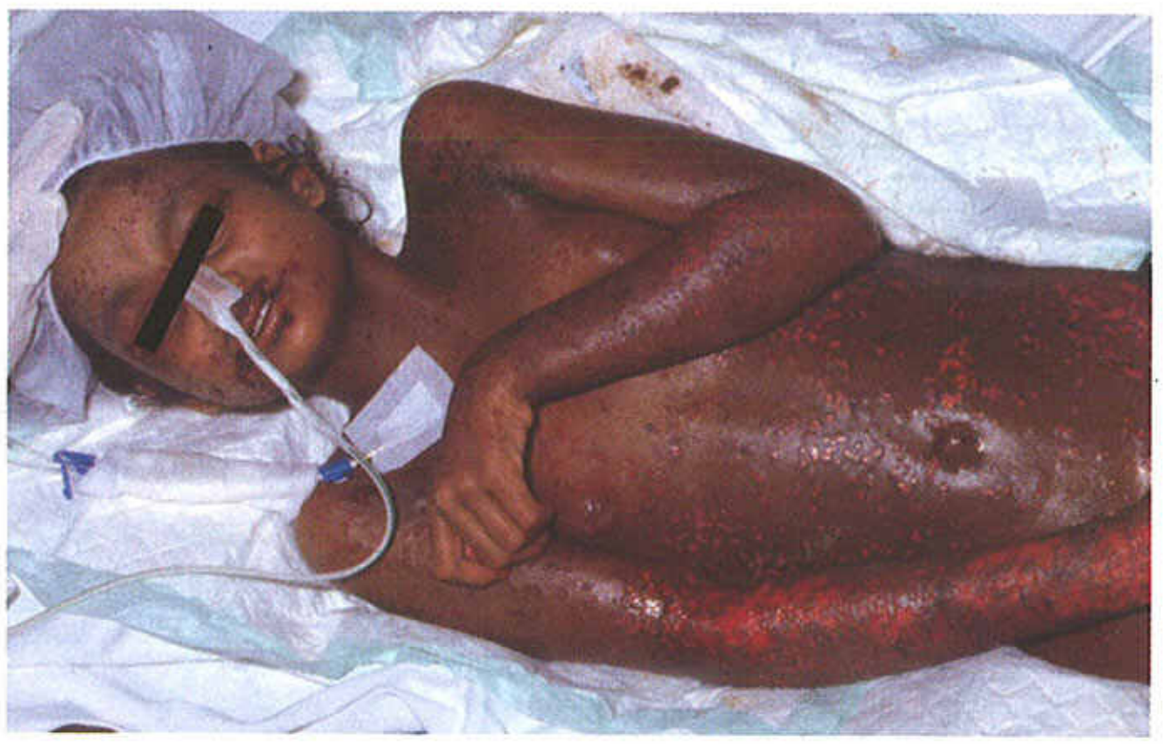

Fig. 6 : Eczema Herpeticum

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The fourth emergency is Purpura Fulminans (PF) :

Disseminated intravascular coagulation (DIC) is manifested clinically as purpura fulminans (PF) with a mortality rate of about 30-40% [1]. It could be severe and rapidly fatal in 2-3 days.

The onset is sudden with high fever and development of progressively enlarging hemorrhagic skin necrosis and varying combinations of bleeding, thromboembolism and hemolytic anemia and septic shock. Clinically there is massive ecchymosis with hemorrhagic necrosis of the skin (Fig.7,8) and acral necrosis which can result in limb amputation[2].

There is thrombocytopenia, decreased fibrinogen and increase in fibrin degradation products. HistologicallyPF shows intravascular thrombi and wide spread extravasation of erythrocytes.

PF in neonates is a marker of proteins C and S deficiency [1, 3]. PF can result from severe herpes simplex infections [4, 5], disseminated herpes simplex in renal transplant recepient [6], severe varicella [7], klebsiella pneumonia sepsis, complicating kawasaki disease [8] and gram negative septicemia. PF also results from acute premyelocytic leukemia [9], snake bite [10], giant hemangiomas [11, 12, 13], pregnancy related adult respiratory distress syndrome [14], tissue damage in juvenile chronic arthritis [15], periarteritis nodosa [16], systemic lupus erythematosus [17], nonsuppurative recurrent febrile panniculitis (Weber Christian syndrome) [18], severe sclerema neonatorum [19] and pyoderma gangrenosum [20].

Meningococcal sepsis can cause PF in adults and in children due to elaboration of endotoxin [21, 22, 23, 24, 25, 26, 27]. The endotoxin disturbes the balance of anticoagulants and procoagulants activities of endothelial cells. This appears to be mediated by cytokins particularly interleukin-12, interferon gamma, tumor necrosis factor alpha and interleukin-1 leading to consumption of protein C and S and antithrombin III [28]. In Intravascular coagulopathy

laboratory tests shows that Prothrombin time (PT) is increased, Partial Thromoplastin time PTT is increased, Factors V, VII, VIII are decreased, Prothrombin is decreased, Fibrinogen is decreased, Fibrin degradation products are increased. Patients with DIC are admitted to intensive care unit for management.

Treatment includes administration of antibiotic, fresh blood transfusion and platelet suspension [11]. Protein C concentrate is given early as replacement therapy in PF to correct the severe acquired protein C deficiency; it is given as a continuous infusion with the dose adjusted daily to keep plasma concentration between 0.8-1.2 I.U/ml. Together with continuous veno-venous hemodiafiltration [29].

Protease inhibitor Contrykal in the dose of 30.000 to 60.000 unit is recommended as treatment of choice in DIC in liver cirrhosis [30]. Adult onset Still's disease may be complicated by DIC and need heparin and steroid therapy [31].

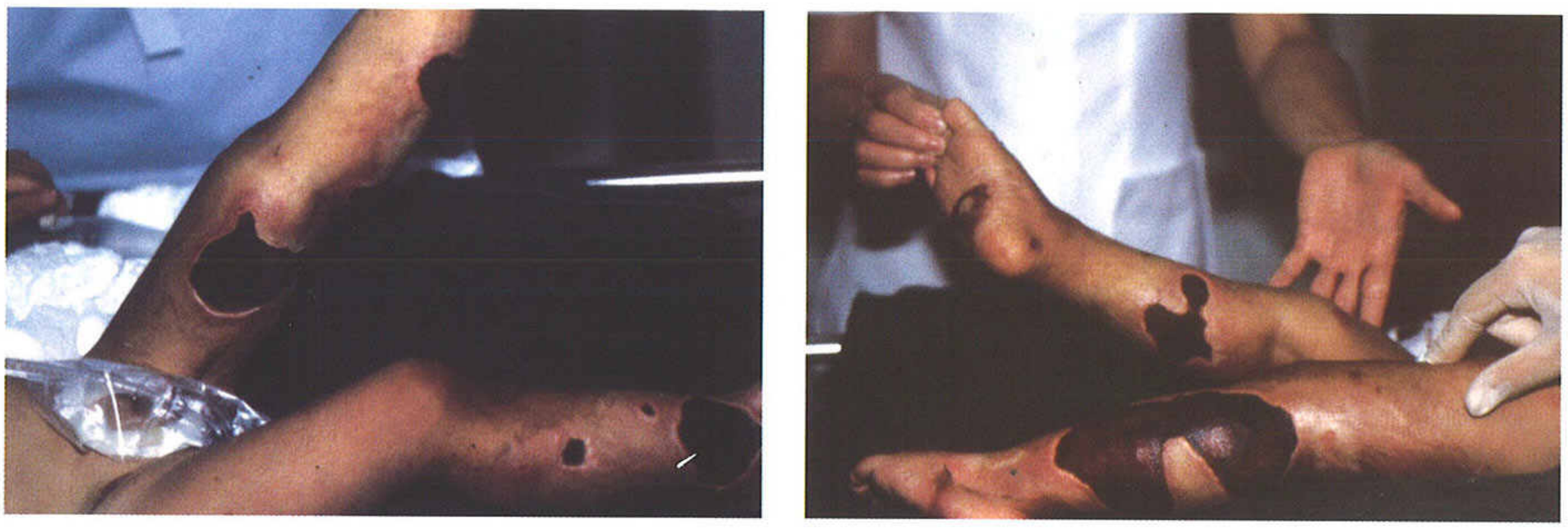

Fig. 7& 8 : Intravascular Coagulopathy

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The fifth emergency is Angio Edema :

Angio Edema (AE) is characterized by oedema of subcutaneous tissue and mucosa and is of sudden onset.

Any part of the body may be affected by AE but the commonest sites are lips, eyelids, genitalia, tongue and pharynx [1]. Before the advent of modern therapy mortality from AE of the larynx and acute airway obstruction reached 20% [1].

AE can be due to a variety of causes [2]. The first cause can be an immediate type one IgE mediated hypersensitivity reaction when the AE is a variant of urticaria in which the subcutaneous tissue rather than the dermis is affected by the oedema (Fig.9). This immediate type one reaction may present clinically with urticaria alone in 40% of cases or AE alone in 11% of cases or mixed urticaria and AE in 49% of cases[1].

These IgE mediated reactions may be induced by drugs, foods, chemicals and is sometimes idiopathic [2]. Both urticaria and AE may be acute or chronic and it is estimated that 50% of cases of chronic urticaria have an autoimmune disorder mediated by autoantibodies to the high affinity IgE receptor on mast cells [3] and may be in some cases associated with thyroid autoimmunity [4] and such cases respond to thyroid hormone therapy.

Mucosal AE in the IgE mediated reaction causes great distress and is life threatening and needs emergency treatment by giving the patient adrenaline 1/1000 in the dose of 0.01/c.c./kg intramuscular or subcutaneous together with intravenous or intramuscular antihistamine and the patient may need intravenous hydrocortisone as well. It is also essential to correct associated hypovolemic shock and tracheostomy may be needed as a life saving measure[1].

The second cause of AE is hereditary AE (HAE) and acquired AE (AAE). HAE is autosomal dominant with the inherited gene on chromosome 11 [1]. HAE represents 1% of all cases of AE and 5% of all

angio-oedemas not associated with urticaria.

HAE and AAE are disorders of C1 esterase inhibitor protein (C1-1NH) caused by deficiency, dysfunctions or exhaustion of the C1-INH molecule [5]. Eighty five percent of HAE patients have reduced C1-1NH to 5 or 30% of the normal value of the C1-INH [6] and in 15% was found to be inactive [1]. The C1-INH is an alpha 2 globulin and is synthetized in the liver. C1-INH is a natural inhibitor of Kallikrin.

In absence of C1-INH there will be activation of C1 leading to uncontrolled CIS activity with break down of C4 and C2 and release of vasoactive peptide kinin leading to vasodilatation of post capillary venules causing oedema [6].

The onset of HAE is sudden and usually starts in childhood but may be delayed till adulthood and the oedema usually lasts 48-72 hours. Patients with HAE get recurrent AE of skin of face (Fig.10), tongue, supraglottis, extrimities and gastrointestinal tract [7]. The patients also suffer from nausea, vomiting, abdominal pain and colic, small bowel AE, urinary symptoms and colorectal interssusception was reported as an unusual gastrointestinal complication of HAE [8]. Laryngeal oedema in HAE is potentially lethal and accounts for mortality rate as high as 30% [9].

Abdominal lesion in HAE may occur without skin manifestations and may cause a great diagnostic difficulty and in a large series 34% of such patients had abdominal surgery [10].

HAE may increase the risk of spontaneous abortion and premature labour [11]. Episodic attacks of HAE occur spontaneously or may be precipitated by vigorous exercise, emotional stress, menses [6] trauma, dental trauma or surgery and HAE may get exacerbated by Helicobacter pylori infection [12].

Acquired C1-INH deficiency give the same clinical picture as in HAE except that it usually has a late onset and was reported to occur in association with B-cell lymphoma, systemic lupus erythematosus, secondary antiphospholipid syndrome, IgM lambda type monoclonal paraproteinemia [13] and chronic hepatitis C [14].

Angiotensin converting enzyme inhibitors (ACEI) can cause angio odema without urticaria (Fig.11). The AE occurs within the first weeks of ACEI treatment and some cases occur after months or years of its use [15].

The late onset AAE is more prevalent among immunosuppressed cardiac and renal transplant patients [16].

Angiotensin II receptor antagonist can rarely induce AE [17]. In HAE the C1-INH level is low (normal values are 15-35mg%) [6] and the levels of C2, C4 are low during, after and in between attacks of HAE (C2 normal level is 1.6-4mg%) [6].

In asymptomatic carriers of HAE, C4 is nearly always low (normal 15-45mg%) [6]. A normal C4 level excludes the diagnosis of HAE[6]. HAE response to treatment with adrenaline, systemic steroid and antihistamine is generally inadequate.

Treatment during an acute attack of HAE or AAE needs replacement therapy with fresh frozen plasma or purified C1-INH. C1-INH concentrate infusion given in HAE was safe and effective leading to relief of oedema twice as fast than if not treated [18].

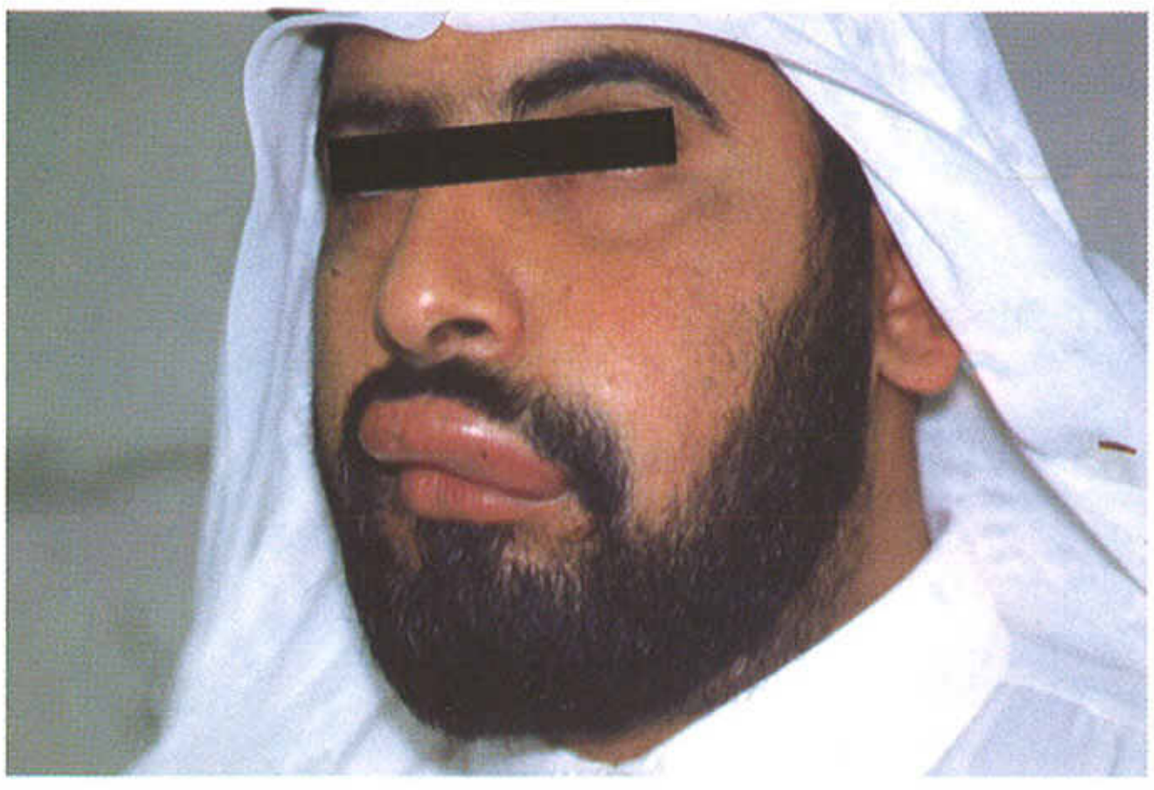

Fig. 9 : Immediate Type one reaction AE

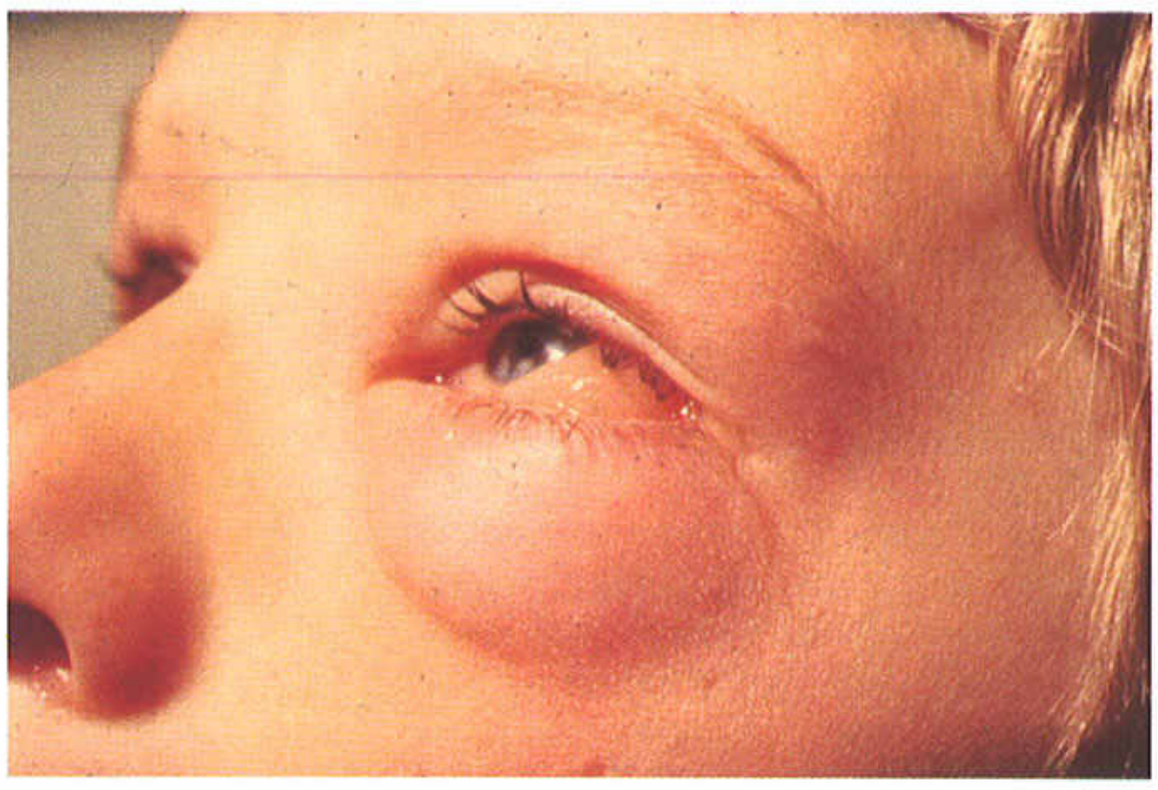

Fig. 10: HAE

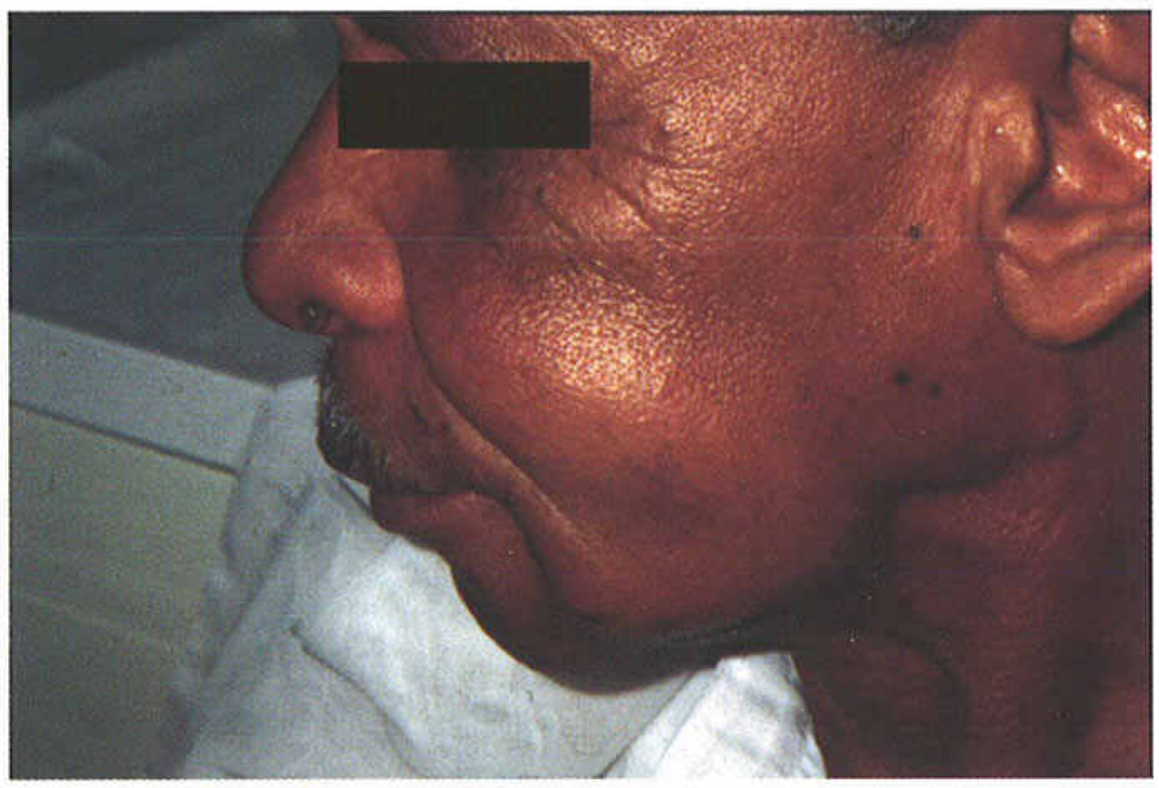

Fig. 11: Angiotensin converting enzyme inhibtor AE

C1-INH transfusion proved to be satisfactory in a dose of more than 100.000 units and the HAE attack was relieved after transfusion by 50± 8 minutes [19]. No side reactions, antibody formation or virus transmission were observed after C1-INH transfusion [20].

C1-INH concentrate after being vapor heated to inactivate hepatitis and human immuno-deficiency viruses was safely and effectively used to treat acute HAE [21].

HAE patients undergoing surgical procedures need short term prophylaxis by danazol [22]. Danazol is an attenuated androgen anabolic drug given in the dose of 200-600 mg per day for 4 days pre/and post operative restores the compliment components to normal levels. C1-INH concentrate was also used for short term prophyloxis before surgery [23].

Epsilon (aminocaproic acid) is also given as prophylaxis in the dose of 12-18 grams daily. Tranexamic acid which is a protease inhibitor is also used for prophylaxis in HAE [20].

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The Sixth emergency is Necrotizing Fasciitis (N. F.) :

Skin Bacterial infections may account for upto 17% of the dermatologic clinic [1]. N.F. is a severe emergency with dermatologic presentation[2] and is one of the most serious infections caused by high inoculum of aggressive bacteria which cause cellulitis and rapidly spreading infection to fascial planes resulting in thrombosis of blood vessels that are running through the fascia leading to necrosis of skin, subcutaneous fat, fascia and even muscle along with bacteremia.

Patient is usually severely ill and toxic and there is high mortality [3] that was reported to reach 45%[4]. In a prospective study of group A streptococcal N.F. 34% of patients who also suffered from hypotension and bacteremia died [5]. Patients usually present with red or dusky red swollen, very indurated hot tender area which rapidly spreads and causes destruction of superficial nerves leading to local cutaneous anesthesia. Sometimes the onset of N.F is indolent and gives rise to a false sense of lack of emergency[6], but pain out of proportion to the clinical findings should make the clinician alert and aware of N.F. The definitive diagnosis is made by biopsy and frozen section obtained at bed side and rapid histologic assessment to establish early diagnosis [7, 8].

The diagnosis may be also helped by MRI which reveals deep fascial involvement [9, 10]. N.F. usually affects lower extrimities, the abdominal and thoracic walls, the perineum and genital area commonly known as Fournier's gangrene. Rarely the face and neck are affected with NF because of its rich vascularity that makes the face and neck less succeptible to infection and development of ischemia[11]. Neck infection is rare but often fatal and is predisposed to by odontogenic infection [12] or peritonsillar abscess[13]. NF may complicate accidental needle prick injury [14], traumas, ulcers and cutaneous infestations[15], pressure ulcers [16, 17], foot infections in diabetics[18,19], surgical wounds[11], liposuction[7], tube gastrostomy [20], trauma with bowel perforation [21], systemic lupus erythematosus [22], lupus nephritis[23], immune suppression [24], HIV [12]. Paronychia was reported to be followed by NF affecting symmetric chest wall [25]. NF affects any age and in infants may follow birth trauma, omphalitis [26], scalp electrodes[27], and circumcision [28]. It has been reported that diclofenac injections may induce greater severity of NF due to delay of therapy as a consequence of the misleading clinical effect of NSAID and not to inhibition of antibacterial defence [29].

Diclofenac intramuscular injection was reported to be followed by streptococcal fasciitis, myositis and toxic shock syndrome and so intramuscular injection of NSAID is no longer needed [30].

A wide variety of bacteria have been isolated with NF. N.F. is caused by aerobic, anaerobic and mixed bacterial flora [31]. An example of the aerobic and anaerobic bacteria is Marganella marganii and Bacteroides species respectively [23]. N.F. in children is caused by polymicrobial anaerobic and aerobic or facultative bacteria.

Group A betahemolytic streptococci are often associated with varicella infection[32]. Group A streptococcal infection is characterized by M protein and Tagglutinin typing and PCR detection of streptococcal pyrogenic exotoxin genes A and C [5].

The facultative organism streptococcus pyogenes was present alone in 25% and mixed aerobic and anaerobic bacteria were isolated in 75% of patients. The predominant isolates were Peptostreptococcus, streptococcus pyogenes, bacteroides fragiles group, Clostridium perfringens, Escherichia coli and Prevotella [33]. Pseudomonas aerogenosa [34] and non group A streptococcus was also found in the mixed infection N.F. [18].

The mixed bacterial infection in NF commonly includes streptococcus pyogenes which is known in the lay press as flesh eating bacteria [35]. N.F. could be exclusively caused by group A streptococci and may have a fulminante course with systemic toxicity and with severe intravascular coagulation or may have a subacute course without systemic toxicity and mild intravascular coagulation [36]. N.F. is reported to be caused also by toxic shock strains of streptococcus [37] and is associated with toxic shock. Culture was positive for staph. aureus [15] and streptococcus pyogenes serotype A. These bacteria produced superantigen TSST-1; enterotoxin A, enterotoxin C (staph. aureus) and erythrogenic toxin C (strept. pyogenes) and the patient also presented with staphylococcal scalded skin syndrome which proved to be an unfavorable prognostic sign in NF [38].

Treatment :

The most important aspect in treatment is early diagnosis and aggressive surgical therapy with immediate incision, open drainage [35], emergency debridement and excision of all necrotic tissue in order to halt disease progression and prevent patient mortality [16] and mitigate exotoxin release [18]. At the same time aggressive medical treatment with antibiotic and hyperbaric oxygen [23] will give the lowest mortality [33]. The main antibiotics used are penicillinase resistant semisynthetic penicillins; first generation cephalosporins, the macrolides and high dose clindamycin [30]; combination antibacterials such as amoxicillin / clavulinate potassium and trimethoprim / sulfamethoxazole [15].

Pristinomycin (pyostacine 500) / is an effective and very active antibiotic on streptococi and staphylococci given 3 grams daily until 10 days after apyrexia [39].

After surgical debridement nursing care is important and essential for wound management which includes packing with aloevera gel and saline soaked sponges [40] and later split thickness skin is grafted[40].

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The Seventh emergency is Cavernous Sinus Thrombosis :

Thrombosis of the Cavernous sinus usually results from direct spread of infection along the venous channels draining the orbit and face. It may complicate nasal carbuncle [1, 2, 3]; nasal vestibule furuncle[4]; furuncles of upper lip, cheek and pyogenic skin infection of the central part of the face in the maxillofacial area [5, 6]; periorbital soft tissue and orbital cellulitis [7, 8] Orbital cellulitis is characterized by acute swelling with protosis and marked oedema of conjunctiva and lids. Orbital cellulitis in children may cause blindness in hours, and is reported also to complicate Behcet's syndrome[9]. The patient presents with septic fever, exophthalmos, periorbital pain and swelling and severe cerebral symptoms, headache, convulsions papilloedema and visual loss. The prognosis is grave and invariably fatal. Culture to isolate causative organism and CT Scan should be performed.

Early diagnosis, urgent admission and aggressive management was reported to reduce mortality from 50% to 26% ([10]).

Early and intensive treatment of acute purulent infections of the maxillofacial area is important and essential to prevent progression of infection. Delay in treatment may cause cavernous sinus thrombosis, brain abscess and meningitis [11].

Full dose heparin or light density heparin (fraxiparine) are used to treat cavernous sinus thrombosis [12, 4] in combination with systemic antibiotic and intravenous fluids and bed rest is imperative.

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