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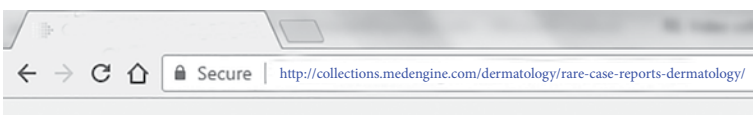

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CASE REPORT

Combined Reduced-Antigen Content Tetanus, Diphtheria, and Acellular Pertussis (Tdap) Vaccine-Related Erythema Nodosum: Case Report and Review of Vaccine-Associated Erythema Nodosum

Philip R. Cohen

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ABSTRACT

Background: Vaccination programs reduce the morbidity and mortality of diphtheria, pertussis, and tetanus. Erythema nodosum is a reactive erythema that can be associated with infections, drugs, and many conditions. The new onset of erythema nodosum after receiving vaccination is uncommon.

Purpose: Combined reduced-antigen content tetanus, diphtheria, and acellular pertussis (Tdap) vaccine-associated erythema nodosum is described and the reports of vaccine-related erythema nodosum are summarized.

Methods: The clinical features of a 39-year-old woman who developed erythema nodosum after receiving Tdap vaccine are reported. Using the PubMed database, an extensive literature search was performed on erythema nodosum, vaccine, and vaccination.

Results: Tdap, the most commonly used booster vaccine against tetanus, diphtheria, and pertussis, is well tolerated in all age groups. Local injection-site reactions are the most common adverse events, whereas headache, fatigue, gastrointestinal symptoms, and fever are the most frequent systemic events. Erythema nodosum has not previously been reported in patients who have received Tdap vaccine. The patient developed erythema nodosum within 48 h after receiving Tdap vaccine; her symptoms cleared and nearly all skin lesions resolved within 2 weeks after initiating oral treatment with ibuprofen, fexofenadine, and prednisone. Vaccine-associated erythema nodosum has previously been reported following vaccination for cholera, hepatitis B, human papillomavirus, malaria, rabies, small pox, tuberculosis, and typhoid.

Conclusion: Vaccine-associated erythema nodosum is uncommon. Erythema nodosum occurring after Tdap vaccination is a rare, yet potential, adverse effect.

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Keywords: Acellular pertussis; Dermatology; Diphtheria; Erythema nodosum; Tdap;

Tetanus; Vaccine; Vaccine-associated; Vaccine-related; Vaccination

INTRODUCTION

The combined reduced-antigen content tetanus, diphtheria, and acellular pertussis (Tdap) vaccine is a single-dose booster vaccine that not only maintains the standard of care for tetanus and diphtheria protection but also reduces pertussis morbidity [1–7]. Erythema nodosum is a reactive erythema that can be associated with infections, drugs, and many conditions [8–12]; however, the new onset of erythema nodosum after receiving a vaccine is rare. A young woman who developed erythema nodosum after receiving Tdap vaccine is reported and vaccinations that have been associated with erythema nodosum have been summarized.

CASE REPORT

A healthy 39-year-old Japanese woman visited her primary care physician for an annual examination. She had received all of her childhood vaccinations without any complications. She did not have any history of preceding infections, sore throat or diarrhea. She also had no prior or current skin or systemic diseases and her laboratory studies were normal. There was no personal or family history of tuberculosis. Her physician recommended prophylactic vaccination with combined tetanus-diphtheria-pertussis (Tdap) vaccine since her booster immunization was due. Informed consent was obtained from the patient for being included in the study and for the publishing of photographs. This article does not contain any studies with human subjects performed by the author.

Within 24 h of receiving Tdap vaccine, she noted several areas of pruritus and swelling on her distal lower extremities. During the next 24 h these areas enlarged and developed into tender red nodules. The painful nodules persisted and she sought dermatologic medical attention.

Cutaneous examination, 7 days after receiving Tdap vaccine, revealed tender erythematous nodules on her legs (Fig. 1). There was a large, 12 by 8 cm, erythematous nodule on distal pretibial left leg (Fig. 1). Multiple, individual and grouped, nodules were present on her right leg; they were located on the distal lateral thigh (4.0 by 2.5 cm), the proximal lateral calf (6.0 by 3.5 cm), the distal lateral calf (2.0 by 2.0 cm), and the distal lateral leg proximal to the ankle (each of 3 lesions measuring 2.5 by 2.5 cm) (Fig. 2).

Correlation of her medical history, clinical symptoms, and lesion morphology were compatible with a diagnosis of Tdap vaccine-

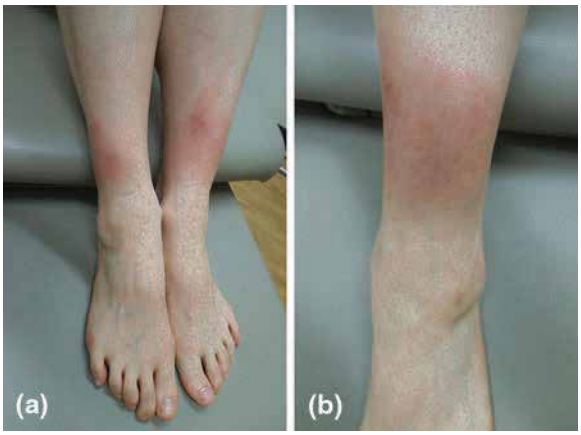

Fig. 1 Distant (**a**) and closer (**b**) frontal views of the anterior lower extremities of a 39-year-old Japanese woman with erythema nodosum developing after she received vaccination with Tdap vaccine. Tender, erythematous, individual (left leg) and grouped (right leg), nodules are present on the distal pretibial legs (**a**). Erythema nodosum appears as a large, 12 by 8 cm, nodule on the distal pretibial left leg (**b**)

Fig. 2 Distant (**a**) and closer (**b**) view of the woman's right leg show multiple individual and grouped nodules of Tdap vaccination-associated erythema nodosum. Lesions of erythema nodosum on the right leg are located on the distal lateral thigh, the proximal lateral calf, the distal lateral calf, and the distal lateral leg proximal to the ankle (**a**). A group of 3 nodules of erythema nodosum are noted on the distal right leg (**b**)

related erythema nodosum; however, the differential diagnosis also included an Arthus-like phenomenon induced by immunization and erythema nodosum secondary to another etiology with immunization being associated by chance. Several circumstances favored Tdap vaccine-related erythema nodosum. Specifically, she had not receiving any topical or systemic medications. Also, she had no recent streptococcal pharyngitis or systemic conditions such as Crohn's disease, sarcoidosis, or tuberculosis. Therefore, the temporal association between her recent Tdap vaccination and the development of the skin lesion suggested that the development of her erythema nodosum was related to her receiving Tdap vaccine.

Symptomatic treatment was initiated: oral ibuprofen 600 mg four times daily. Since a drug-induced etiology was suspected, daily oral systemic therapy with an antihistamine and a corticosteroid was started: 180 mg of fexofenadine and prednisone (60 mg for 4 days, followed by 40 mg for 3 days, and followed by 20 mg for 2 days). Her symptoms began to improve and the nodules started to flatten within 3 days.

Follow-up examination occurred 2 weeks after her initial visit. Her symptoms had completely resolved. One of the nodules proximal to her right ankle was smaller, yet palpable with mild erythema of the skin. All of her other nodules had completely flattened and there was macular hyperpigmentation at the sites.

DISCUSSION

The morbidity and mortality from the bacterial diseases diphtheria, pertussis and, tetanus have been dramatically reduced secondary to vaccination programs beginning in infancy [1–7]. The originally developed infant combined diphtheria-tetanus-whole-cell pertussis (DTwP) vaccine was subsequently supplanted by the infant combined diphtheria-tetanus-acellular pertussis (DTaP) vaccine that is less reactogenic [1, 2]. Booster vaccination of adolescents and adults is still necessary since immunity—either vaccine induced or naturally acquired—to pertussis is not lifelong. However, because of the risk of increased reactogenicity with successive doses, the infant DTaP vaccine is not suitable for use as a booster vaccine in adolescents and adults [1, 2].

The most commonly used booster vaccine against tetanus, diphtheria, and pertussis in adolescents and adults is the three-component pertussis Tdap (Boostrix^{TM}, GlaxoSmithKline, Research Triangle Park, NC, USA) vaccine that contains an aluminum adjuvant [1, 2]. The

quantities of antigens (toxoids) in Tdap vaccine are reduced by 10–50 percent of those in the infantile DTaP vaccine. The three pertussis antigen components are filamentous haemagglutinin, pertactin, and pertussis toxin [1, 2].

Combined reduced-antigen content tetanus, diphtheria, and acellular pertussis vaccine is well tolerated in all age groups [1–7]. The most common adverse events associated with Tdap vaccine administration are local injection-site reactions such as pain, redness, swelling, and increased upper-arm circumference [1–7]. Headache, fatigue, gastrointestinal symptoms and fever are the most frequent systemic events [1–7]. These adverse events occur in up to approximately 20 percent of individuals, are only mild or moderate in intensity, and are typically transient [1–7].

Serious adverse events following Tdap immunization are rare [5]. They include allergic reactions (such as anaphylaxis), cardiac conditions (pericarditis, myocardial infarction, and arrhythmia), exacerbation of pre-existing illnesses, general systemic symptoms, infections, injection site cellulitis, neurologic conditions (Guillain–Barre syndrome, Bell's palsy, seizure, demyelinating diseases, and encephalopathy), syncope, and thrombocytopenia [5]. However, to the best of my knowledge, erythema nodosum has not previously been described following vaccination with Tdap.

Erythema nodosum is clinically characterized by acute onset of painful, warm, red subcutaneous nodules—of 1 to 5 cm in diameter–appearing bilaterally on the pretibial legs. Associated systemic symptoms may include fever, fatigue, malaise, and arthralgias. Microscopic examination of a lesion typically demonstrates a septal panniculitis, with a neutrophilic infiltrate; vasculitis is absent. Within a few days to 2 weeks, the erythematous nodules begin to slowly involute by flattening and developing purple color that subsequently evolves into a bruise-like macular hyperpigmentation that has been referred to as erythema contusiformis [8–12].

Erythema nodosum is most commonly observed in young women—particularly those between 20 and 50 years of age [8–12]. Indeed, erythema nodosum occurs 4–6 times as often in women as compared to men [8–12]. Although the extensor leg below the knee is the most frequent location, lesions may also appear on other sites such as the thighs and extensor arms [8–12].

Erythema nodosum can present as an idiopathic reactive erythema. However, there is an extensive list of infections (such as bacterial, viral, fungal, mycobacterial, and protozoan), drugs (such as antibiotics and oral contraceptives), and conditions (such as inflammatory bowel disease, pregnancy, and sarcoidosis) that have been described in patients with developed erythema nodosum. Some of the erythema nodosum-associated etiologies (such as streptococcal throat infection, oral contraceptives and pregnancy, sulfonamides, Crohn's disease, and sarcoidosis) are more commonly observed whereas other erythema nodosum-related causes have only been noted in a small number of patients or single individuals [8–12].

Erythema nodosum has occurred following vaccination; however, vaccines are an uncommon etiology for this reactive erythema (Table 1) [13–24]. To the best of my knowledge, the currently described woman is the first individual in whom erythema nodosum has been reported following vaccination with Tdap. Her symptoms and lesions began within 48 h after she was vaccinated; she had no conditions that have previously been noted to cause

Table 1 Vaccinations associated with the subsequent development of erythema nodosum

Vaccine	References
Bacille–Calmette–Guerin[a]	[13–15]
Hepatitis B[b]	[16–18]
Human papillomavirus[c]	[19]
Malaria[d]	[20]
Rabies[e]	[21, 22]
Smallpox[f]	[23]
Tetanus, diphtheria, and pertussis[g]	Current report
Typhoid and cholera[h]	[24]

[a] Bacille–Calmette–Guerin (BCG) vaccine, a live attenuated vaccine derived from attenuated strains of Mycobacterium bovis, is used to prevent tuberculosis [13]. A retrospective study of etiologic factors associated with erythema nodosum in children was performed; BCG vaccination was the related etiology in 1 of 45 patients [14]. Another patient developed erythema nodosum 30 days after BCG vaccination; the local inflammatory reaction caused by the vaccine was normal [15]

[b] Erythema nodosum has been associated with administration of hepatitis B vaccine prepared either from human serum (Heptavax B®, Merck & Co., Inc., Whitehouse Station, NJ, USA) [18] or by recombinant-DNA techniques (Engerix B, GlaxoSmithKline, Research Triangle Park, NC, USA [16] and Recombivax HB®, Merck & Co., Inc., Whitehouse Station, NJ, USA [17])

[c] A 16-year-old girl developed erythema nodosum after administration of vaccine against human papillomavirus types 6, 11, 16, and 18 (Gardasil®, Merck & Co., Inc., Whitehouse Station, NJ, USA) [19]

[d] Two of 10 volunteers (a 25-year-old Asian woman and a 26-year-old Caucasian woman—both taking oral contraceptives) developed dermatology consultant-confirmed erythema nodosum after receiving 1 dose of 20 μg Pvs25/ISA 51 vaccine [a vaccine consisting of recombinant Pvs25 (a surface protein of mosquito stage of the malaria parasite Plasmodium vivax) which is formulated with Montanide ISA 51 (a water-in-oil emulsion)] [20]

[e] An 11-year-old girl developed erythema nodosum at the site of a dog bite after receiving a vaccination against rabies [22]. Another patient, 35-year-old woman developed biopsy-confirmed erythema nodosum a few days after receiving the second dose of a rabies vaccine treatment: Rabipur® (Novartis Vaccines and Diagnostics, Cambridge, MA, USA), a purified chick embryo/second generation tissue culture vaccine [21]

[f] Three patients are reported who developed cutaneous eruptions that were essentially varioliform, but ranged from erythema multiforme and erythema nodosum to severe hemorrhagic exanthems, on the 14th, 20th, and 22nd day after primary vaccination [23]

[g] A 39-year-old woman developed erythema nodosum within 48 h after receiving a dose of the combined reduced-antigen content tetanus, diphtheria, and acellular pertussis (Tdap) vaccine [current report]

[h] A 56-year-old woman developed pain and stiffness in both ankles, knees and lower back 24 h after receiving 0.5 ml of typhoid vaccine (to prevent salmonella infection) and 1.0 ml of cholera vaccine (to prevent cholera infection) intramuscularly; the symptoms were followed by the development of classical erythema nodosum on the anterior aspects of both lower legs [24]

erythema nodosum and she was not taking any medication that has previously been associated with the development of erythema nodosum. The lesion-associated tenderness and the nodules both began to resolved within 3 days after initiating oral treatment with a corticosteroid and a long-acting antihistamine daily, and a nonsteroidal anti-inflammatory agent four times each day. During the next 1½ weeks, her symptoms resolved and all but one of the nodules had completely cleared.

The onset of clinical symptoms and skin lesions is variable in patients with vaccine-associated erythema nodosum. Similar to the

rapid onset of Tdap-related erythema nodosum within 48 h, symptoms and skin lesions of erythema nodosum associated with hepatitis B vaccine (prepared by recombinant-DNA techniques) appeared within less than 24 h [16] or after only 4 days [7], in the patients who received either Engerix B (GlaxoSmithKline, Research Triangle Park, NC, USA) [16] or Recombivax® (Merck & Co., Inc., Whitehouse Station, NJ, USA) [17]. In addition, the woman who had previously received a course of typhoid and cholera vaccine more than 5 years earlier, developed symptoms 24 h after her booster vaccination followed by classic appearing erythema nodosum lesions on her anterior lower legs [24]; similar to this patient, erythema nodosum developed within a few days after the second dose of rabies vaccine [21] and 15 days after the second injection of human papillomavirus vaccine (and subsequently 10 days after the third injection of Gardiasil 4 months later) [19]. In contrast, vaccine-related erythema nodosum appeared 18, 14–22, and 30 days after vaccination with malaria [20], small pox [23], or Bacille–Calmette–Guerin [15], respectively.

The pathogenesis of vaccine-related erythema nodosum remains to be established. Many of the investigators favor the development of erythema nodosum being secondary to the antigen of the infectious disease. However, it is impossible to absolutely exclude the possibility of a hypersensitivity reaction to one or more of the adjuvant components used to prepare the vaccine.

CONCLUSION

The new onset of erythema nodosum after receiving vaccination is uncommon, but has been reported following vaccination for cholera, hepatitis B, human papillomavirus, malaria, rabies, small pox, tuberculosis, and typhoid [13–24]. This is the first report of erythema nodosum occurring after Tdap vaccination for the prevention of tetanus, diphtheria, and pertussis. It is important for clinicians to be aware of this rare, yet potential, adverse effect to Tdap vaccine.

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Conflict of interest. Dr Philip R. Cohen declares no conflict of interest.

Compliance with ethical guidelines. Informed consent was obtained from the patient for being included in the study and for the publishing of photographs. This article does not contain any studies with human subjects performed by the author.

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BMC Dermatology

CASE REPORT

Adult autoimmune enteropathy presenting initially with acquired Acrodermatitis Enteropathica: a case report

Erina Lie[1*], Sarah Sung[2] and Steven Hoseong Yang[3]

Abstract

Background: Acrodermatitis enteropathica (AE) is a rare dermatitis secondary to zinc deficiency most commonly seen as an inherited disease in infants. In the last decade, increased number of reports have been published on the acquired form that presents in adulthood. Unlike its inherited counterpart, acquired AE (AAE) is often secondary to underlying pathologic or iatrogenic etiologies that interfere with nutritional absorption, such as inflammatory bowel disease or alcoholism. Various gastrointestinal pathologies have been associated with AAE, but there is currently no report on its association with adult autoimmune enteropathy (AIE), a rare gastrointestinal disorder commonly seen in infants, with limited cases reported in adults. Here we present a case in which AAE was the initial clinical manifestation in an adult patient subsequently diagnosed with AIE.

Case presentation: A 41-year-old African American female presented to our emergency department at the Johns Hopkins Hospital with several months of progressively worsening dermatitis in the legs and acral regions, along with worsening symptoms of diarrhea, alopecia, poor oral intake, lethargy, hematochezia, peripheral edema, and weight loss. Our dermatology team was consulted given a presentation of exquisitely tender, erythematous, and diffusely desquamating skin lesions in the setting of two prior outside hospitalizations in the last 3 months with the same dermatitis that was refractory to topical and oral corticosteroids. Low serum zinc level and positive response to zinc supplementation confirmed the diagnosis of AAE. However, persistent hypovitaminosis and mineral deficiency despite aggressive nutritional supplementation prompted further investigation for an underlying malabsorption etiology. Jejunal biopsy and associated autoantibodies confirmed a diagnosis of adult AIE.

Conclusion: This case highlights the fact that adult AIE can present initially with clinical findings of AE. While proper zinc supplementation can resolve the latter, recognizing this association can trigger earlier diagnosis, minimize unnecessary tests, and establish earlier intervention to improve quality of life and prevent recurrence of AAE. The case also highlights the importance of collaboration between general and subspecialist physicians in identifying a primary etiology to a secondary clinical presentation. This report can be beneficial to general internists and emergency physicians, as much as it can be to dermatologists, rheumatologists, and gastroenterologists.

Keywords: Acrodermatitis enteropathica, Zinc deficiency, Dermatitis, Autoimmune enteropathy, Malnutrition, Case report

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Background

Acrodermatitis enteropathica (AE) is a condition caused by zinc deficiency that classically presents with periorificial and acral papulosquamous eruptions accompanied by diarrhea and alopecia [1]. The inherited form, a rare autosomal recessive trait due to mutations in the gene SCL39A4 on chromosome 8q24.3 [2], is more common and typically seen in infants. However, in the last decade, we have witnessed an increased number of reports on acquired AE affecting adults and the elderlies particularly in association with anorexia nervosa, alcoholism, bariatric surgery, total parenteral nutrition, nephropathy, inflammatory bowel disease (IBD), blind loop syndrome, and celiac disease [3–7]. Here we present a novel case of acquired AE as an initial presentation of autoimmune enteropathy (AIE), itself a rare gastrointestinal disorder characterized by refractory diarrhea and malnutrition that affects less than 1/100,000 infants, with limited case reports in adults [8, 9].

Case presentation

A 41-year-old African American female presented with a 4-month history of progressive, exquisitely tender, non-pruritic leg and acral dermatitis, diarrhea, alopecia, poor oral intake, lethargy, hematochezia, lower extremity edema, and 22lbs of unintentional weight loss. Physical examination revealed erythema and desquamation along the extremities (Fig. 1a), plantar feet (Fig. 1b), and palmar hands (Fig. 1c), paronychia, angular cheilitis with lip fissure, glossitis, ulcerations and satellite erosions in the lumbosacral, perianal, and perineal regions (Fig. 1d), and diffuse alopecia of the scalp.

Her symptoms began initially with dysgeusia, lower extremity edema, along with erythematous cutaneous eruption and desquamation of the lower extremities and acral region that was refractory to topical triamcinolone 0.1% ointment. By the second month, her symptoms persisted with additional blurring of vision, xerostomia, diarrhea, hematochezia, anorexia, and thrombocytopenia that necessitated a 22-day hospitalization. She was diagnosed with immune thrombocytopenic purpura (ITP) and non-alcoholic steatohepatitis, confirmed by positive anti-platelet antibody and liver biopsy, respectively. She was started on prednisone 60 mg and discharged with a 4-week taper.

By the third month, specifically a day after discontinuing prednisone, she noted recurring edema in her lower extremities that progressed rapidly to painful desquamative and vesiculobullous lesions resulting in a second hospitalization. Skin biopsy revealed mild spongiotic dermatitis with alternating hyperparakeratosis and papillary dermal edema without evidence of vasculitis, systemic lupus erythematous, or autoimmune bullous disease on immunofluorescence. She was diagnosed with an eczematous dermatitis and discharged with another 4-week prednisone taper. During this hospitalization, she also developed sacral pressure ulcer. Two weeks after this last hospitalization, persistent edema, a non-healing sacral ulcer, and worsening desquamative plaques eventually brought her to our institution for the first time with the presentation described above.

Repeat skin biopsy of the right medial malleolus demonstrated an unremarkable epidermis, slightly ectatic superficial dermal vessels with surrounding focal rare

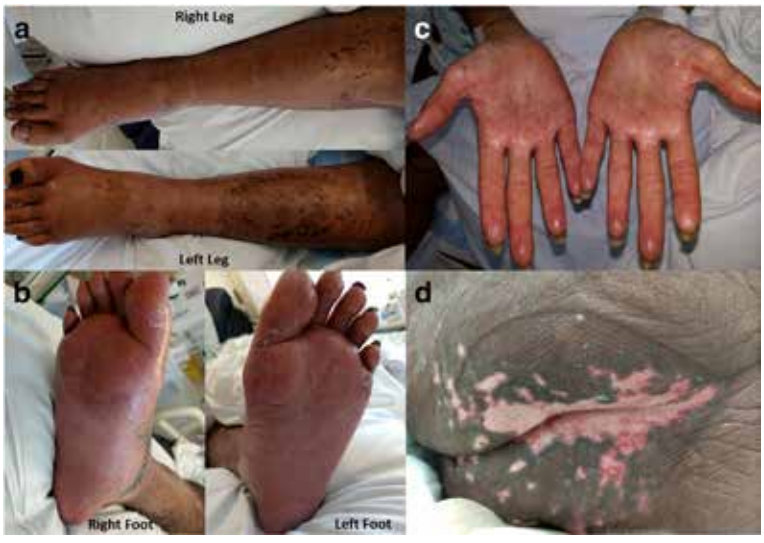

Fig. 1 Acquired acrodermatitis enteropathica – Day 2 of admission. Legend: Desquamative erythematous patches with edema involving bilateral lower extremities (**a**) and plantar feet (**b**). Erythema with subtle desquamation on bilateral palmar hands (**c**). Ulceration and satellite erosions in the lumbosacral, perianal, and perineal region (**d**)

lymphocytes and rare extravasated red blood cells, without evidence of erythema multiforme or Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN). However, her zinc level was found to be 30 μg/dL (normal: 60-130 μg/dL), which improved after 20-days of intravenous supplementation of zinc sulphate 220 mg thrice daily (Table 1). Clinically, her cutaneous findings and gastrointestinal function also showed marked improvements (Fig. 2a-b). Her dermatologic findings and responsiveness to zinc supplement confirmed the diagnosis of acquired AE.

Notably, she had severe hypovitaminosis and mineral deficiencies that improved only minimally despite repletion (Table 1). Given a newly-diagnosed ITP, hematochezia, sicca syndrome, and persistently low pre-albumin level, she underwent an extensive additional work-up to investigate the possibility of an underlying etiology contributing to her nutritional deficiency. Her diagnostic work-up included broad titer analyses (Tables 2 and 3), blood/urine/stool analyses, esophagogastroduodenoscopy with biopsy, and colonoscopy with biopsy. Negative biopsy findings and associated autoantibody, viral, fungal, and bacterial titers ruled out the more common autoimmune and infectious causes of malabsorption, such as IBD and celiac disease (Table 3). Our patient was eventually diagnosed with AIE based on jejunal biopsy findings of mild increase in intraepithelial lymphocytes, crypt apoptosis, reactive epithelial changes, and mild mononuclear and neutrophil expansion of the lamina propria, supported by positive anti-gastric parietal cell and anti-smooth muscle autoantibodies. Other reported associations with AIE, including sicca syndrome, gastritis, nephrotic syndrome, autoimmune hepatitis, and chronic pancreatitis, were also present in this patient, further supporting the diagnosis. She was discharged after 20 days with central parenteral nutrition (CPN), prednisone 15 mg daily, and close outpatient follow-up with markedly improved dermatologic findings. Follow-up visit at our dermatology clinic 15 weeks later was unremarkable with no recurrence of cutaneous findings (Table 4). At the time of manuscript submission, patient has remained stable without further hospitalization nor recurrence of symptoms. She continued to require CPN and oral supplements with weekly nutritionist monitoring and periodic gastroenterology follow-up.

Discussion

Zinc is an essential mineral that plays crucial roles in metabolism, development, tissue repair, and cell proliferation, including proper maturation of basal keratinocytes

Table 1 Serum nutrient levels (values at initial presentation and prior to discharge) and nutrient repletion regimens during the 20 days of hospitalization

Serum Level	Initial Value	Value after 15–20 Days	Reference Range	Repletion
Pre-albumin[ab]	7 mg/dL	7 mg/dL	18–38 mg/dL	-
Albumin[ab]	1.5 g/dL	2.3 g/dL	3.5–5.3 g/dL	-
Ionized Calcium[a]	1.07 mmol/L	1.20 mmol/L	1.13–1.32 mmol/L	-
Copper[ab]	51 μg/dL	67 μg/dL	70–175 μg/dL	2 mg PO daily
Iron[ab]	48 μg/dL	44 μg/dL	50–170 μg/dL	325 mg PO with meals
Magnesium	2.0 mg/dL	1.8 mg/dL	1.6–2.4 mg/dL	-
Phosphorus[a]	2.5 mg/dL	3.0 mg/dL	2.7–4.5 mg/dL	-
Selenium[ab]	44 μg/dL	48 μg/dL	63–160 μg/dL	50mcg PO daily
Zinc[ab]	30 μg/dL	52 μg/dL	60–130 μg/dL	220 mg PO TID[d]
Vit A[ab]	11 μg/dL	14 μg/dL	38–98 μg/dL	200,000 IU PO ×3
Vit B1	109 nmol/L	-	78–185 nmol/L	100 mg PO daily
Vit B3/Niacin	<20 ng/mL	-	Variable	100 mg PO qhs
Vit B6[ab]	<2.0 ng/mL	-	2.1–21.7 ng/mL	100 mg PO daily
Vit B9/Folate	1743 ng/dL	1578 ng/dL	>498 ng/dL	-
Vit B12	1161 pg/mL	1592 pg/mL	211–946 pg/mL	-
Vit D total[ab]	18 ng/mL	8 ng/mL	30–100 ng/mL	Vit D_2: 50,000 IU PO q7d $CaCO_3$: 1300 mg PO TID
Vit E – **α**[abc]	1.1 mg/L	2.5 mg/L	5.7–19.9 mg/L	100 mg PO daily
Vit E – **β**[c]	0.4 mg/L	1.0 mg/L	≤4.3 mg/L	100 mg PO daily
Vit K	84 pg/mL	-	80–1160 pg/mL	-

[a]Initial value is below normal
[b]Latest value prior to discharge is below normal
[c]α = alpha tocopherol; β = beta tocopherol
[d]200 mg zinc sulphate tablet contains 50 mg of elemental zinc

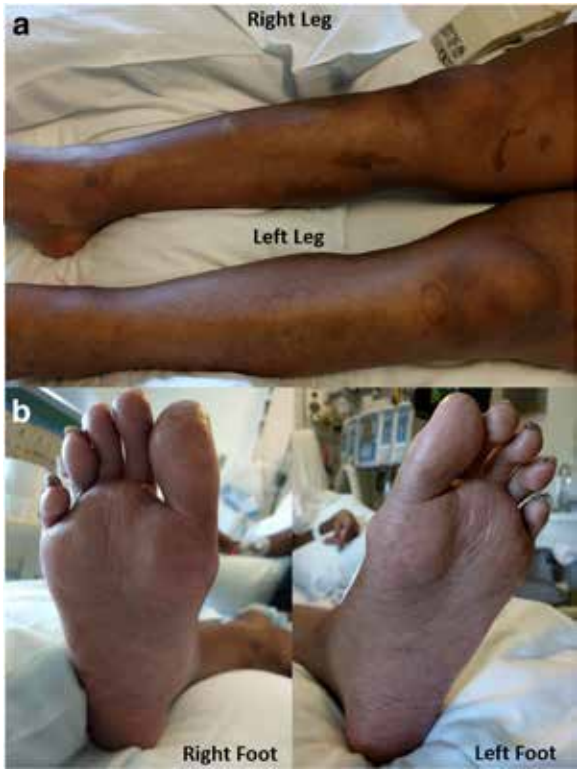

Fig. 2 Acquired acrodermatitis enteropathica – Day 20 of admission. Legend: Resolution of edema, erythema, and desquamation in the bilateral lower extremities (**a**) and plantar feet (**b**)

[1]. Zinc deficiency, manifested in AE, can be acquired through decreased intake (e.g. vegetarianism, alcoholism), increased demand (e.g. pregnancy), intestinal malabsorption (e.g. IBD, gastric bypass), increased urinary loss (e.g. diuretics), or state of hypoalbuminemia since zinc binds albumin in the circulation (e.g. liver damage) [1]. Aside from the triad of dermatitis, diarrhea, and alopecia, symptoms of AE can also include angular cheilitis followed by paronychia, glossitis, ophthalmologic disturbances, poor wound healing, anemia, dysgeusia, dysosmia, and profound lethargy [1, 10]. Differential diagnoses include necrolytic migratory erythema, SJS/TEN, blistering diseases, epidermolysis bullosa, and pellagra [6, 10]. Histopathologic findings are typically indistinguishable from other forms of malnutrition dermatitis. Pathognomonic feature of fully-developed necrolysis has been reported, which involves cytoplasmic pallor, vacuolization, ballooning degeneration, and confluent epidermal parakeratosis [1]. More commonly, however, histopathology is either non-specific, such as found in our patient, or displays upper epidermal pallor with psoriasiform hyperplasia and confluent parakeratosis [1, 11]. Diagnosis is made by clinical findings subsequently responsive to zinc supplementation supported by findings of low plasma or serum zinc concentration and/or suggestive histologicfindings [1, 11].

AIE is a rare cause of intractable diarrhea and malnutrition associated with gut autoantibodies and predisposition to autoimmunity [9, 12]. Histologically, there is partial or complete small bowel villous blunting, deep crypt lymphocytosis, increased crypt apoptosis, and minimal intraepithelial lymphocytosis. Diagnostic criteria necessitate chronic diarrhea (>6 weeks) with malabsorption refractory

Table 2 Abnormal titre results for autoantibodies, viruses, fungi, and bacterial toxins

Titre Names	Results	Reference Range
Abnormal results:		
Anti-Ro (SSA) Ab	Moderate Positive	Negative
Gastric parietal cell Ab	55.5 units	≤20 units = Negative
Smooth muscle Ab	Positive	Negative
C3, serum	71 mg/dL	79–251 mg/dL
CMV viral load	2640 IU/mL	<137 IU/mL

Ab = antibody
CMV = Cytomegalovirus

Table 3 Titre results within normal range for autoantibodies, viruses, fungi, and bacterial toxins

Titre Names		
Alpha-1 anti-trypsin, stool, 24-h	Anti-Jo-1 Ab	Direct anti-globulin test
p-ANCA	Anti-La (SSB) Ab	Glomerular basement membrane Ab
c-ANCA	Anti-nuclear Ab (ANA)	Islet cell Ab
Anti-cardiolipin Ab, IgG	Anti-Scl70 Ab	Liver-kidney microsomal Ab
Anti-cardiolipin Ab, IgM	Anti-Smith Ab	Mitochondrial Ab
Anti-cardiolipin Ab, IgA	Anti-URP Ab	Rheumatoid factor
Anti-dsDNA Ab	Beta-2 glycoprotein Ab, IgG	Thyroglobulin Ab
Anti-enterocyte Ab, IgG	Beta-2 glycoprotein Ab, IgM	Thyroid peroxidase microsomal Ab
Anti-enterocyte Ab, IgM	Beta-2 glycoprotein Ab, IgA	Tissue transglutaminase, IgA
Anti-enterocyte Ab, IgA	Cyclic citrul peptide Ab	TSH receptor Ab
C4, serum	EBV viral load	*C.difficile* toxin B gene NAT
CH50, serum	(1–3)-Beta-D-Glucan	Diphtheria antitoxin Ab
	Galactomannan, serum	

Ab = antibody
p-ANCA = perinuclear anti-neutrophilic cytoplasmic antibody
c-ANCA = cytoplasmic anti-neutrophilic cytoplasmic antibody
ANA = Antinuclear Antibody
EBV = Epstein-Barr Virus
TSH = Thyroid-Stimulating Hormone

Table 4 Case report timeline

Chronology	Timeline Description
T_0–4 months	Clinical presentation: dysgeusia, lower extremity edema, and cutaneous eruption and erythema of the lower extremities and acral region with desquamation Management: refractory to topical triamcinolone 0.1% ointment
T_0–3 months	Clinical presentation: symptoms persisted with additional blurring of vision, xerostomia, diarrhea, hematochezia, anorexia, and thrombocytopenia Diagnosis: immune thrombocytopenic purpura (ITP) and non-alcoholic steatohepatitis Management: 22-day hospitalization, prednisone 60 mg and discharged with a 4-week taper
T_0–2 months	Clinical presentation: recurring edema in the lower extremities progressing rapidly to painful desquamative and vesiculobullous lesions Diagnosis: eczematous dermatitis Diagnostic tests: skin biopsy Management: second hospitalization, discharged with another 4-week prednisone taper Comments: developed sacral pressure ulcer
T_0	Clinical presentation: persistent edema, non-healing sacral ulcer, worsening desquamative plaques Diagnosis: acquired acrodermatitis enteropathica and severe nutrition deficiency Diagnostic tests: skin biopsy of the right medial malleolus, broad titre analyses, esophagogastroduodenoscopy and colonoscopy with biopsy Management: broad nutrition repletion
T_0 + 3 weeks	Clinical presentation: marked improvements of cutaneous findings and gastrointestinal function Diagnosis: adult autoimmune enteropathy Management: discharged with central parenteral nutrition (CPN), prednisone 15 mg daily, and close outpatient follow-up
T_0 + 4 months	Clinical presentation: outpatient follow-up with unremarkable cutaneous findings Management: continue CPN and oral supplements, close outpatient follow-up with gastroenterology and nutrition

to dietary modification, presence of autoantibodies, no known immunodeficiency, and histologic findings that exclude other causes of villous atrophy [9]. Autoantibodies associated with AIE include antibodies against enterocytes, goblet cells, pancreatic islets, DNA, thyroglobulin, smooth muscle, and gastric parietal cell, the latter two of which were present in our patient [9].

Zinc, and other nutritional, deficiencies in adults are often a manifestation of an underlying malabsorptive etiology. With the rise of chronic diseases in adults, it has become increasingly difficult to determine the main cause of malabsorption in a patient with multiple chronic illnesses that individually predisposes to malnutrition. Clinical history and continuity of care become critical for establishing a clear timeline of symptoms onset and associations. Our patient had a 10-year history of Roux-en-Y gastric bypass with concurrent vegetarianism, pregnancy complicated by gestational hypertension and opioid dependence 2 years prior, and chronic hypertension treated with diuretics, each individual risk factors for zinc deficiency. However, zinc is not stored in large amount in the body [13], so given the chronicity of these medical issues and no history of acquired AE, they were unlikely to be the cause of her current presentation. The timing of hematochezia, sicca syndrome, and ITP closely following the onset of AE symptoms 4 months ago suggested that she likely developed AIE that presented initially with cutaneous findings of zinc deficiency secondary to gastrointestinal dysfunction.

Acquired AE has a very good prognosis with prompt intravenous supplementation starting at 3 mg/kg/day of elemental zinc. Recurrence is likely with untreated underlying conditions, so serum/plasma zinc levels and zinc-dependent enzyme levels should be monitored every 3 to 6 months. It is likewise advisable to monitor copper level and supplement if necessary since zinc can interfere with copper absorption [1, 14]. Reports have shown dramatic clinical improvements within the first few days to weeks of zinc supplementation, often ahead of normalization in serum zinc level [1, 3–7, 10], as illustrated in our patient.

Conclusion

In summary, clinicians should maintain a low threshold of suspicion for acquired AE and check for zinc deficiency in adult patients with associated risk factors for malnutrition who presents with a confluence of relevant dermatologic findings that are refractory to standard therapy. Additionally, clinicians should also consider the possibility of a broader nutritional deficiency and an underlying primary malabsorption etiology. In investigating the latter for a patient with acquired AE, recognition of the association with adult AIE can benefit patient care by triggering earlier diagnosis, minimizing unnecessary tests, and establishing earlier interventions that can improve a patient's quality of life and prevent the recurrence of acquired AE.

Abbreviations

AE: Acrodermatitis enteropathica; AIE: Autoimmune enteropathy; CPN: Central parenteral nutrition; IBD: Inflammatory bowel disease; ITP: Immune thrombocytopenic purpura; SJS: Stevens-Johnson Syndrome; TEN: Toxic epidermal necrolysis

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Availability of data and materials

All laboratory, imaging, and study data relevant to this case report can be found in the "Case presentation" section of this article.

Authors' contributions
EL performed data collection, photography of clinical images, and was the main contributor in drafting and revising the manuscript. SS was the primary dermatology resident physician during the patient's hospitalization, served as interdisciplinary liaison with the patient's other care teams (e.g. internal medicine, rheumatology), and was a key contributor to the revisions of the manuscript. SHY was the attending-in-charge of the care of the patient and a key contributor to the revisions of the manuscript. All authors read and approved the final manuscript.

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Competing interests
The authors declare that they have no competing interests.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of written consent is available for review by the Editor-in-Chief of this journal.

Ethics approval and consent to participate
Not applicable.

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A Rare Benign Bump on a Child's Digit

Case

Clinical Data

A 4-month-old male, presented with a single firm, non-tender, erythematous nodule on the right middle finger (Figs. 94.1 and 94.2). The nodule appeared shortly after birth and progressively increased in size. The child had no systemic symptoms, and there was no functional impairment or deformity. His medical history was unremarkable and there was no history of trauma.

Differential Diagnosis

- **Dermatofibroma:**
  - It has a different distribution.
  - Lesions are not usually nodular.
- **Keloid:**
  - Often, there is a history of trauma.
  - It does not appear soon after birth.
- **Reticulohistiocytoma:**
  - Rare at this age.
  - Lesions are usually multiple.
- **Fibrosarcoma:**
  - Rare at this age.
  - Rare on this location.
- **Congenital self-healing reticulohistiocytosis:**
  - Rare on this location.
- **Infantile digital fibromatosis:**
  - Typically occur on the digit of an infant.
  - Clinically present as an erythematous or skin-colored nodule.

Biopsy Findings

Biopsy of the nodule revealed epidermal hyperplasia, thickened dermis showing thick collagen fibers intermingled with interlacing fascicles of spindle-shaped cells. Higher power further revealed the interlacing fascicles of spindle-shaped cells and collagen bundles. There were unique perinuclear eosinophilic bodies (Figs. 94.3, 94.4, and 94.5).

Investigations

- None.

M.A. El-Darouti, *Challenging Cases in Dermatology*,
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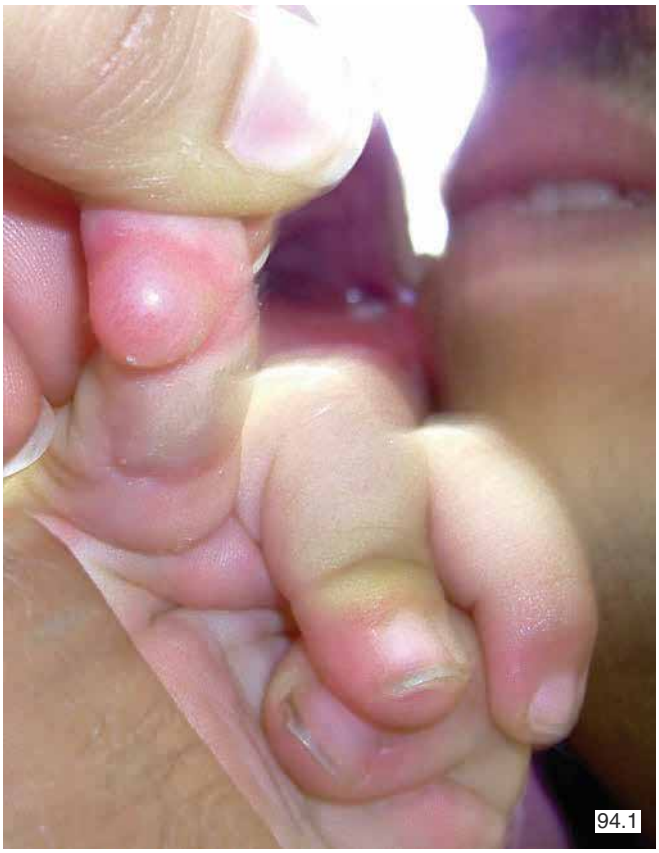

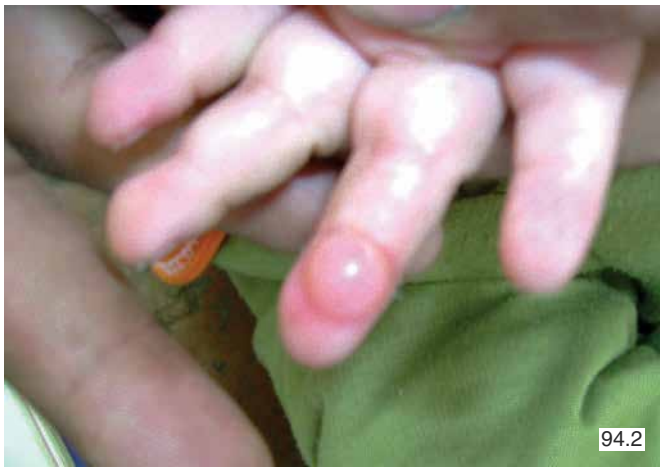

Figs. 94.1 and 94.2 A child's hand with a single, erythematous, smooth, dome-shaped nodule located on the distal phalanges of the middle finger

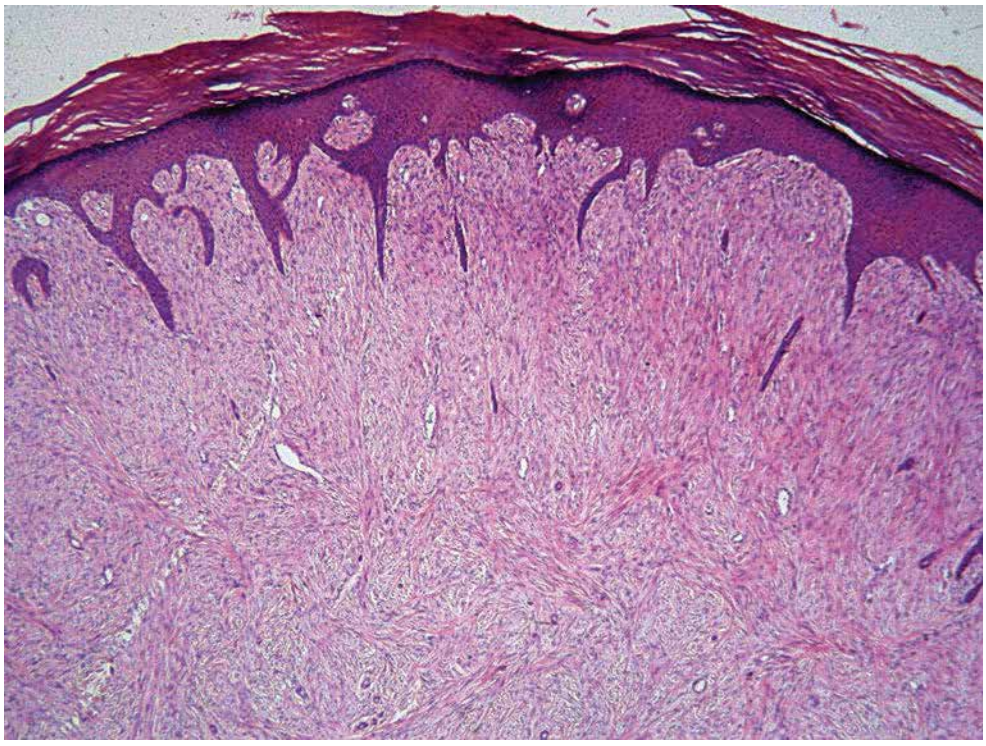

Fig. 94.3 Epidermal Hyperplasia, thickened dermis showing thick collagen fibers intermingled with interlacing fascicles of spindle-shaped cells

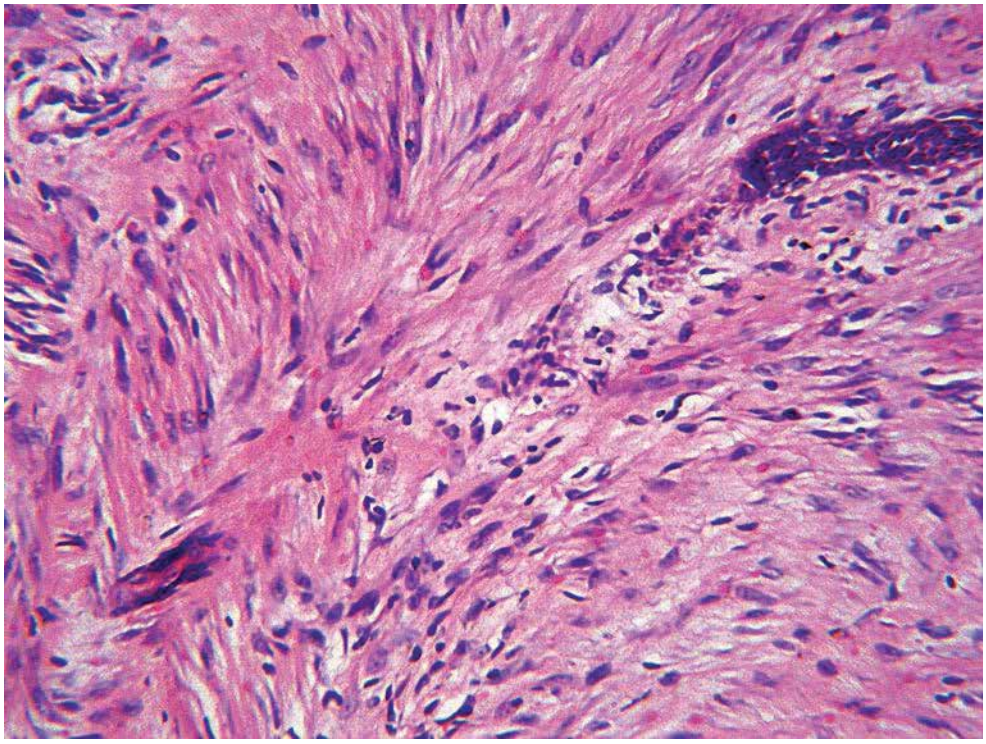

Fig. 94.4 Interlacing fascicles of spindle-shaped cells and collagen bundles

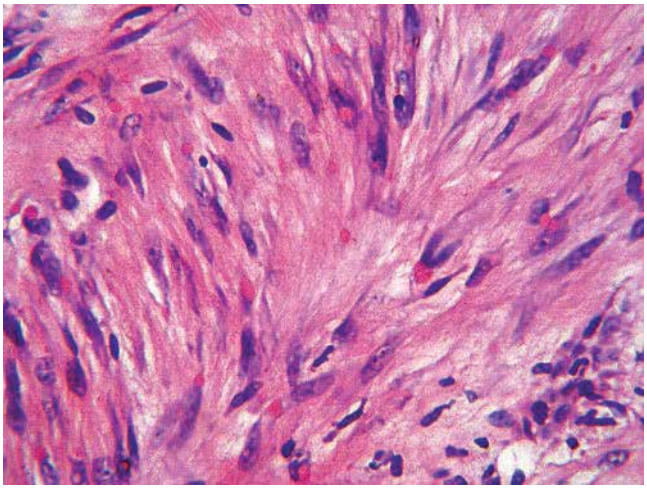

Fig. 94.5 Higher power showing interlacing fascicles of spindle-shaped cells and collagen bundles. Note the perinuclear eosinophilic bodies

Based on the Following Findings

- The clinical picture of a digital nodule in an infant.
- The histopathological features of spindle cell interlacing fascicles with unique perinuclear eosinophilic inclusions.

The Final Diagnosis was Infantile Digital Fibromatosis (IDF).

About the Diagnosis

Definition

- Infantile Digital Fibromatosis (IDF) is a rare, benign, and asymptomatic nodular proliferation of fibrous tissue.
- Numerous synonyms describe IDF, including Reye's tumor, multiple hyaline fibromatosis, infantile dermal fibromatosis, subdermal fibromatous tumor of infancy, fibroma durum multiplex, recurrent digital fibroma, and juvenile dermatofibroma.
- It occurs almost exclusively on the dorsal and lateral aspects of the digits.
- It was first described by Reye in 1965.

Epidemiology

- Approximately; 250 cases of IDF have been reported worldwide.
- IDF typically develops during the first year of life, and the majority of cases are sporadic.
- 30 % of cases are congenital.
- Reports of IDF developing in older children and adults are rare.
- Males and females are equally affected.

Pathogenesis and Etiology

- The cause of IDF is unknown.
- It has been suggested that possible deregulation of the normal bone morphogenetic protein (a member of the transforming growth factor-β superfamily) mediated apoptotic pathway may explain the location of these lesions at the sites of digital septation.
- Transforming growth factor-β1 (TGF-β1) also mediates myofibroblast differentiation from fibroblasts. Myofibroblasts are the primary cell type in this disorder.
- The intracellular inclusions suggest a viral origin. However, this aetiopathogenic hypothesis was invalidated by PCR and electron-microscope studies.

Clinical Features

- IDF presents as single or multiple asymptomatic papules or nodules.
- The nodules are smooth, round, indurated, and confluent.
- The size of a nodule may reach up to 2 cm in diameter.
- Predilection sites include the lateral and dorsal aspects of the fingers and toes; usually on the distal phalanx.
- Rare extradigital sites may include the hands, feet, nose, breast and tongue.
- Ulceration may occur. Functional impairments or deformities are rare.

Histological Features

- Characteristic perinuclear eosinophilic inclusion bodies are revealed within proliferating spindle-shaped cells.
- Mitotic figures are rare.
- Electron microscopy shows that perinuclear inclusions represent an abnormal accumulation of contractile protein in the cytoplasm of the tumor cells.
- Immunohistochemical stains are positive for vimentin, cytokeratin, desmin, calponin, and alpha-smooth muscle actin.

Investigations

- Not required.

Differential Diagnosis

- Dermatofibroma.
- Keloid and Hypertrophic Scar.
- Reticulohistiocytoma.
- Fibrosarcoma.
- Juvenile aponeurotic fibroma.

Definite Diagnosis

- The diagnosis of IDF is based on the unique clinical features in correlation with the histopathological finding of perinuclear eosinophilic inclusion bodies.

Prognosis

- Several case reports of spontaneous regression suggest a benign biological behavior of IDF.
- 60 % of cases recur after surgical excision.
- Malignant transformation and metastases have never been reported. http://www.ncbi.nlm.nih.gov/pubmed/18830128.

Treatment

- Currently; conservative treatment is recommended due to the following reasons:
  - The benign nature of IDF.
  - The tendency to spontaneous regression.
  - The frequent recurrences after surgery (>60 %).
- Surgery is recommended only if the digits are impaired or deformed.
- Mohs micrographic excision has been successful in a few cases that required surgery.
- Topical/intralesional steroids were not effective.
- Intralesional 5-FU may prove beneficial as it decreases TGF-β (see pathogenesis).

Management of This Case

- Patient's parents decided not to interfere with the lesion.
- Follow-up was unattainable.

Message

- Infantile Digital Fibromatosis (IDF) is a distinctive tumor both clinically and morphologically.
- It is important to recognize IDF to avoid unnecessary surgery unless serious functional concerns intervene.
- Parents should be informed of the benign nature of IDF and encouraged for a conservative approach until spontaneous involution occurs.

- As IDF has been reported in adults and in extradigital sites; a better term is 'inclusion body fibromatosis'.

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A Rare Violaceous and Reticulate Lichenoid Eruption with Greasy Scales on the Face

Case

Clinical Data

A 47-year-old male presented with generalized keratotic plaques and papules showing a reticulate pattern for several years (Figs. 73.1, 73.2, and 73.3). Examination revealed erythematous papules with greasy scales and scattered papulopustules on the face. The hair, mucous membranes, and nails were normal. His past medical history was unremarkable.

N.B.
The patient refused to take photos of his face.

Differential Diagnosis

- Parapsoriasis lichenoides.
- Keratoses lichenoides chronica (KLC).
- KLC-like mycosis fungoides with vasculitis.
- Lichen planus (atypical).

Biopsy Findings

Biopsy of a papule showed hyperkeratotic horny layer, hypertrophic epidermis, follicular plugging and upper dermal band like infiltrate encroaching upon the lower border of the epidermis (Figs. 73.4, 73.5, 73.6, and 73.7).

Investigations

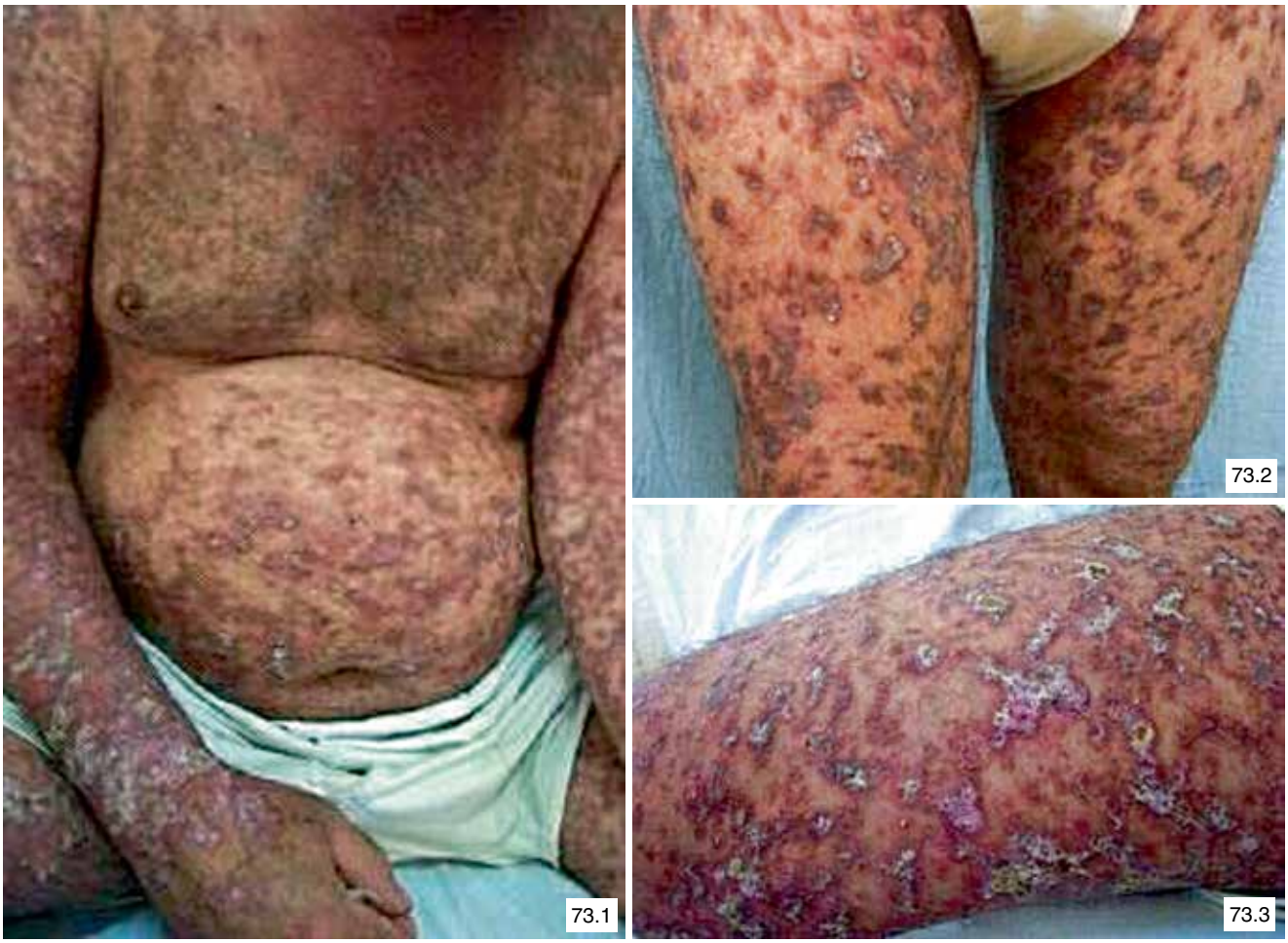
- Routine lab investigations were within normal.

Based on the Following Findings

- The clinical features of chronic reticulate violaceous keratotic papules and plaques, in addition to seborrheic dermatitis-like facial eruption.
- The histopathological feature of lichenoid dermatitis.

The Final Diagnosis was Keratosis Lichenoides Chronica (KLC).

M.A. El-Darouti, *Challenging Cases in Dermatology*,
DOI 10.1007/978-1-4471-4249-2_73, © Springer-Verlag London 2013



Figs. 73.1, 73.2, and 73.3 Pictures of different parts of the patient's body, showing generalized keratotic plaques and papules that are violaceous in color and covered with a scaly layer. Some areas show a reticulate pattern

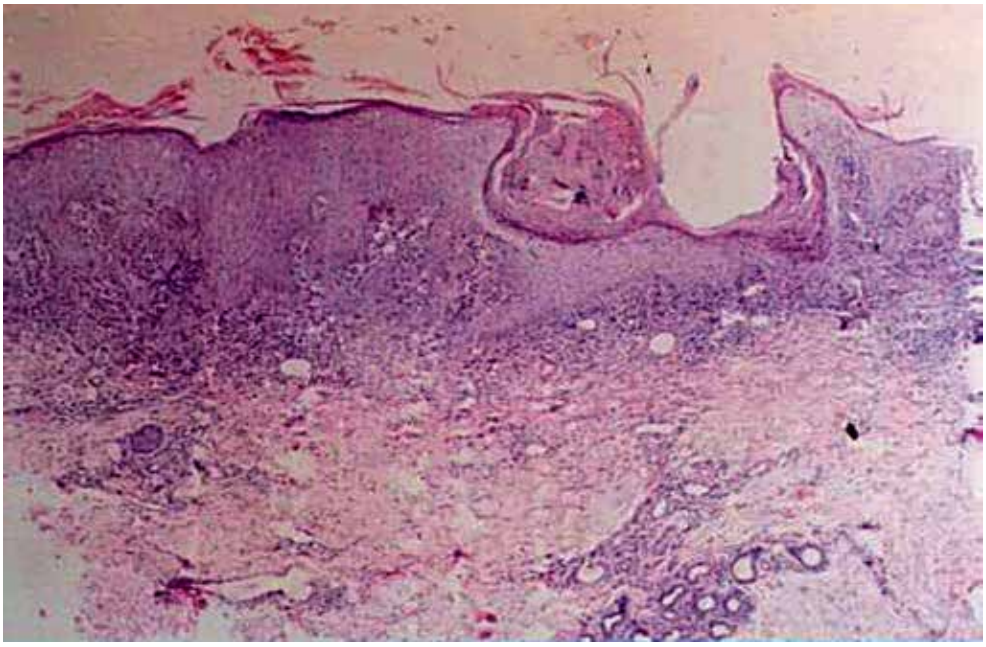


Fig. 73.4 Hyperkeratotic horny layer, hypertrophic epidermis and upper dermal band like infiltrate

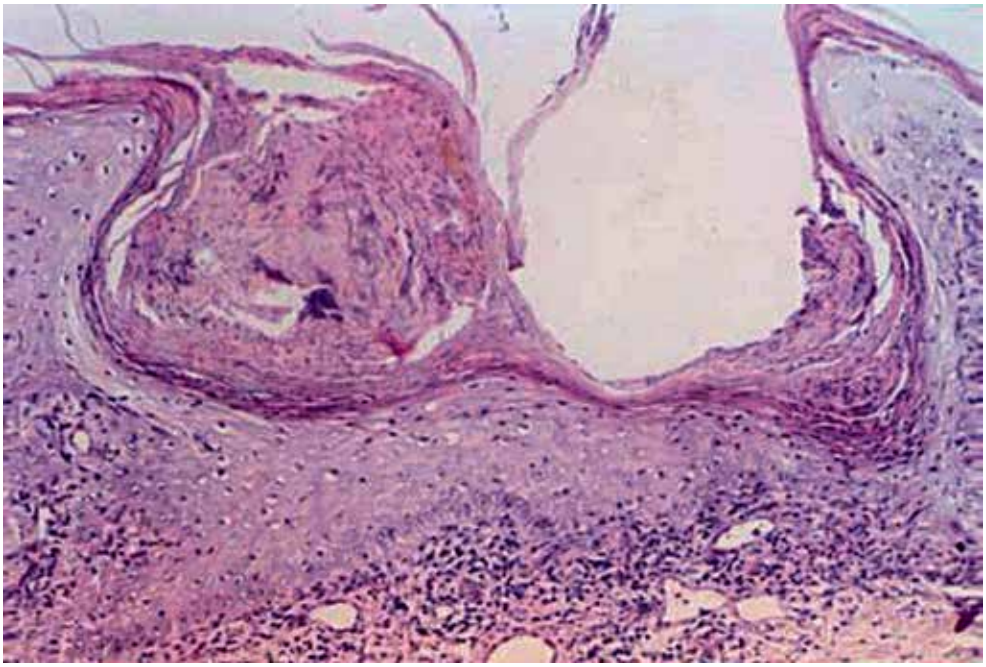


Fig. 73.5 Cup-shaped depression containing keratinous plug, epidermal hyperplasia, and a band like upper dermal infiltrate encroaching upon the lower border of the epidermis

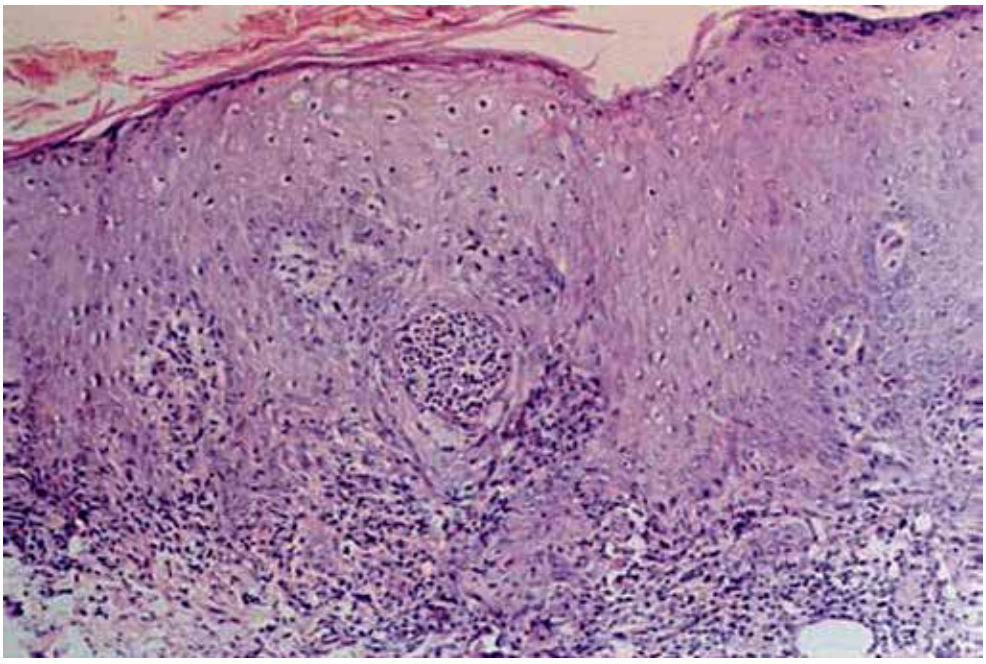


Fig. 73.6 Hyperkeratosis, epidermal hyperplasia, and a band like upper dermal infiltrate encroaching upon the lower border of the epidermis

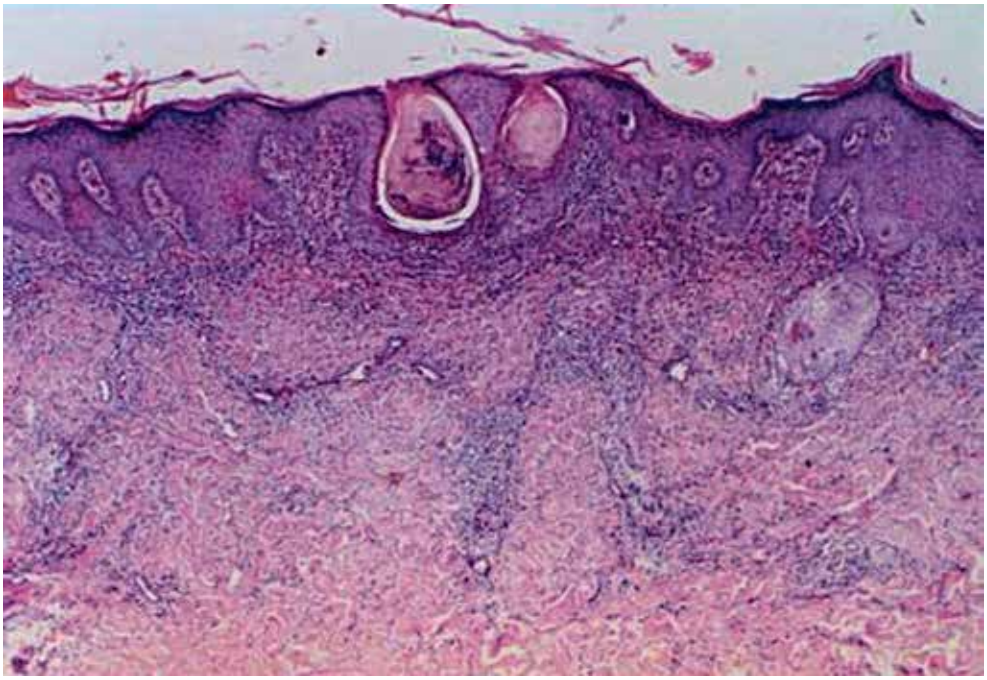


Fig. 73.7 Follicular plugging, Irregular epidermal hyperplasia, and a band like upper dermal infiltrate encroaching upon the lower border of the epidermis

About the Diagnosis

Definition

- Keratosis Lichenoides Chronica (KLC) is a rare disorder characterized by a distinctive seborrheic dermatitis-like facial eruption together with development of asymptomatic violaceous papules, and plaques on the limbs and the trunk, with a partially linear and reticular distribution.
- The term keratosis lichenoides chronica was proposed by Margolis in 1972 to define this disorder, which was first described at the end of the nineteenth century.
- The disease is generally thought to represent a special form of lichen planus.
- Other nomenclatures used to describe this entity include lichen verrucosus et reticularis, porokeratosis striata lichenoides, and Nékam's disease.

Epidemiology

- KLC is extremely rare.
- About 70 cases reported in literature until 2010.
- The great majorities of cases are adults between the ages of 20 and 40 years, although children are occasionally affected.

Pathogenesis and Etiology

- Its physiopathology remains elusive, and the etiology is unknown.
- It is possibly related to lichen planus.
- Lesions of KLC have been reported to develop following trauma and erythroderma.

Clinical Features

- KLC is characterized by asymptomatic violaceous plaques and papular lesions, often arranged in a linear and reticulate pattern. Individual lesions are covered by hyperkeratotic plugs that can only be removed with difficulty.
- Distribution of the papules is mostly on the extremities and buttocks. Face involvement is rare.
- Another typical feature is seborrheic dermatitis-like scaling and telangiectasias of the scalp, face, and neck.
- Systemic complaints are absent as a rule. However, there have been case reports of association with glomerulonephritis, lymphoproliferative disorders, amyloid deposition, and hypoparathyroidism.
- Other reported features are:
  - Vascular variant.
  - Panniculitis-like lesions.
  - Palmoplantar keratoderma.
  - Sclerodactyly.

  - Nail involvement (thickening and longitudinal ridging).
  - Involvement of the mucous membranes (Oral, ocular, genital).

Histological Features

- Histologically, changes are often non-specific and consistent with a chronic dermatitis, but lichenoid features can be seen.
- The horny layer is thickened and may show foci of parakeratosis with alternating orthokeratosis and compact hyperkeratosis.
- There is irregular epidermal hyperplasia that may contain extensive necrosis of keratinocytes and collections of exocytosed lymphocytes.
- The upper dermis is occupied by a band-like lymphohistiocytic infiltrate, with distinct lower limits.
- There are no significant differences in immunofluorescence or immunopathologic findings between KLC and idiopathic lichen planus, suggesting that it may be an unusual variant of lichen planus or an unusual isomorphic response.

Investigations

- Not required.

Differential Diagnosis

- **Clinical differential diagnosis:**
  - Parapsoriasis lichenoides.
  - Lichen planus (atypical).
- **Pathological differential diagnosis:**
  - Lichen planus.
  - Mycosis fungoides.
  - Lichenoid eruptions.
    - Lichenoid drug eruption.
    - Lichen striatus.
    - Graft-versus-host disease.
    - Lichenoid lupus erythematosus.
    - Pityriasis lichenoides chronica.

Definite Diagnosis

- KLC is diagnosed based on the followings:
  - The clinical feature of distinctive seborrheic dermatitis-like facial eruption together with asymptomatic violaceous papules, and plaques on the limbs and the trunk, with a partially linear and reticular distribution.
  - The histopathological picture of lichenoid dermatitis.
  - Exclusion of other differential diagnoses.
- Some authors believe that KLC is an unusual variant of lichen planus, while others consider that it is a distinct entity.

Prognosis

- The course of KLC is chronic and progressive, extending over many years.
- It is very resistant to many therapeutic approaches.
- Some lesions may disappear spontaneously, leaving no scar or leaving residual pigmented atrophy.
- Several publications reported KLC with a visceral pathology such as hepatitis, chronic lymphoid leukemia or nephropathy, but it has not been possible to establish a link between KLC and any particular visceral disorder.

Treatment

- The treatment is usually unsatisfactory.
- The following treatments have been tried, but with little success:
  - Topical and systemic corticosteroids.
  - Topical calcipotriol (Vitamin D3).
  - Methotrexate.
  - Cyclosporine.
  - Etretinate.
  - Antimalarial agents.
  - Sulfones.
  - Gold.
  - Photochemotherapy (PUVA).
- Beneficial effect from etretinate plus PUVA has been reported.
- Photodynamic therapy has been reported to be helpful.

Management of This Case

- Steroid pulse therapy 100 mg dexamethasone daily for 3 days every 2 weeks until recovery then once every 4 weeks as a maintenance for 6 months.
- Etretinate 1 mg/kg/day for 6 months (Figs. 73.8, 73.9, and 73.10). show the results of the treatment.

Message

- Keratosis Lichenoides Chronica (KLC) is a diagnostic and therapeutic challenge.
- It is unique in its resistance to available therapeutic modalities, although its inflammatory features closely resemble those of lichen planus.

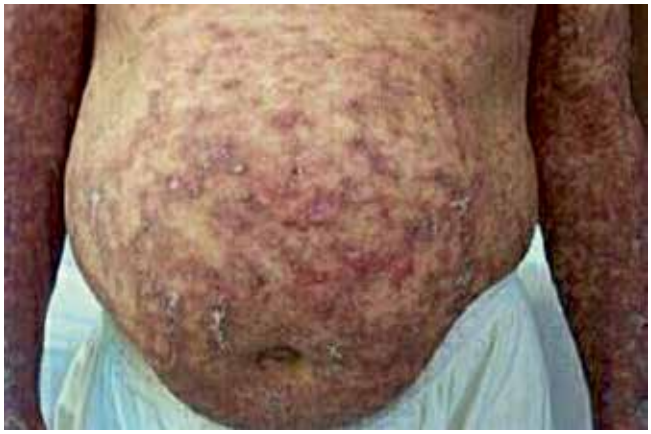


Fig. 73.8 Case of keratosis lichenoides chronica, abdomen, before treatment

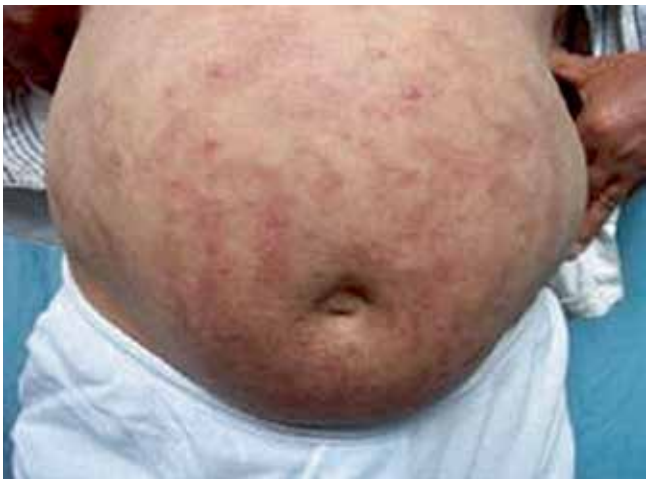


Fig. 73.9 Case of keratosis lichenoides chronica, abdomen, 3 months after treatment

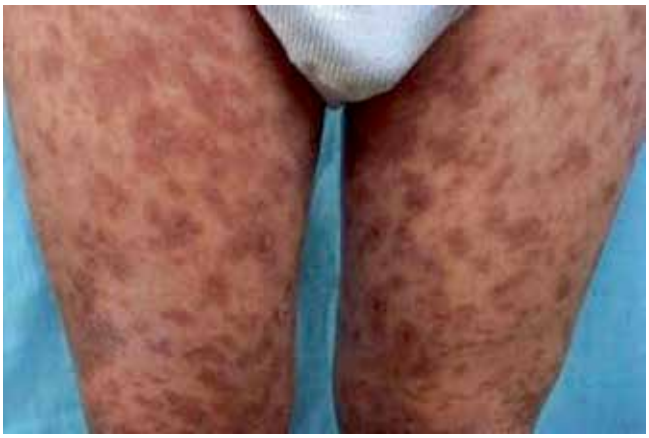


Fig. 73.10 Case of keratosis lichenoides chronica, thighs, 3 months after treatment (compare with Fig 73.2)

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An Extremely Rare Cause of Erythroderma

Case

Clinical Data

A 16-year-old male presented with erythema and scaling over the whole body (Figs. 52.1, 52.2, 52.3, 52.4, and 52.5), associated with palmar and plantar keratoderma and nail thickening (Figs. 52.6, 52.7, 52.8, and 52.9). There was no history of drug intake and no history of skin diseases. Clinical examination revealed no lymphadenopathy and no hepatosplenomegaly.

Differential Diagnosis

Differential diagnosis of erythroderma is shown in Table 52.1.

Biopsy Findings

Skin biopsy revealed thick horny layer, moderate epidermal hyperplasia, and dense upper dermal lymphohistiocytic infiltrate admixed with few plasma cells and eosinophils (Fig. 52.10). Close-up view showed numerous hyphae in the horny layer (Fig. 52.11).

Investigations

- Lab investigations:
  - Complete blood count (CBC): Normal.
  - Erythrocyte sedimentation rate (ESR): Normal.
  - Liver function tests (LFT): Normal.
  - Urea/electrolytes: Normal.
  - Occult blood in stool.
  - Scraping and culture of scales: *Trichophyton violaceum.*
- Immunological profile:
  - IgG: High.
  - IgM: Normal.
  - C3: Low.
  - T and B lymphocytes: Both reduced.
- Radiological investigations:
  - Chest X-ray: Normal.
  - Abdominal sonography: Normal.

Based on the Following Findings

- The clinical presentation of exfoliative dermatitis.
- The positive fungal culture of *Trichophyton violaceum.*
- The histopathological findings of skin biopsy.

The Final Diagnosis was Erythrodermic Trichophyton Violaceum (Trichophyton-induced erythroderma).

M.A. El-Darouti, *Challenging Cases in Dermatology*,
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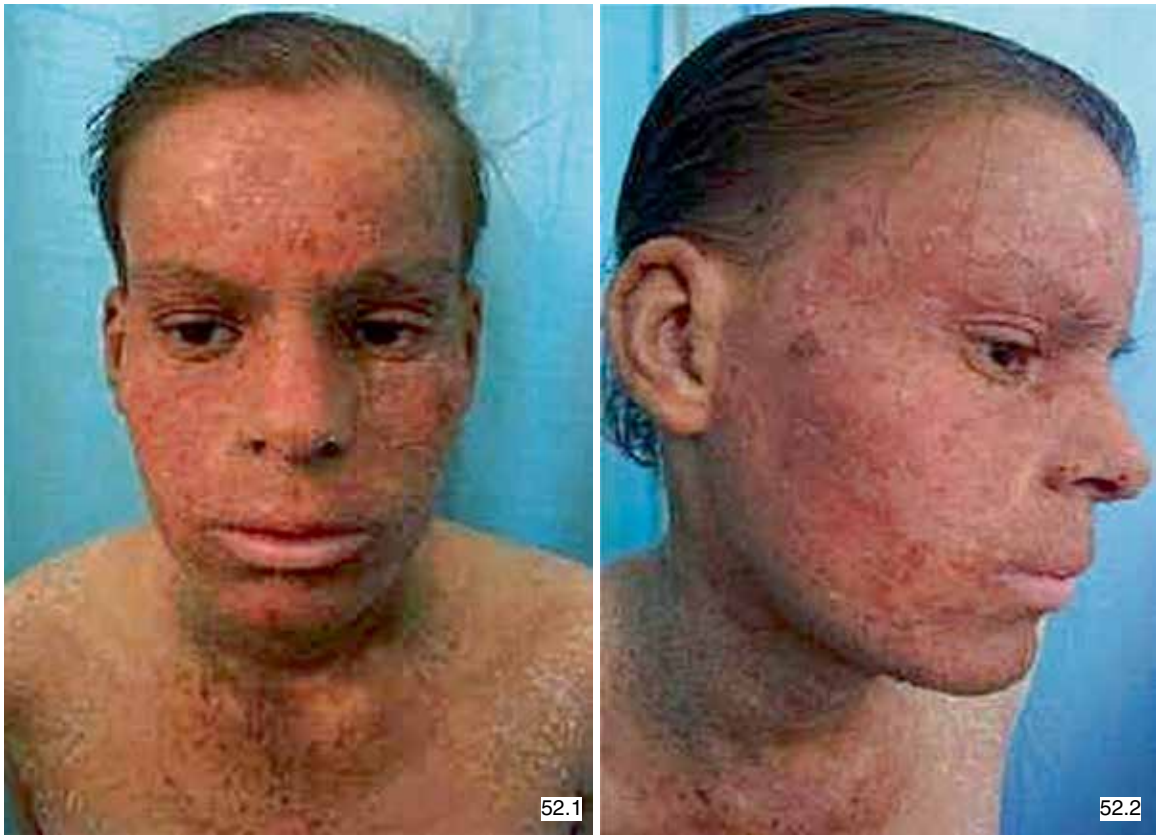
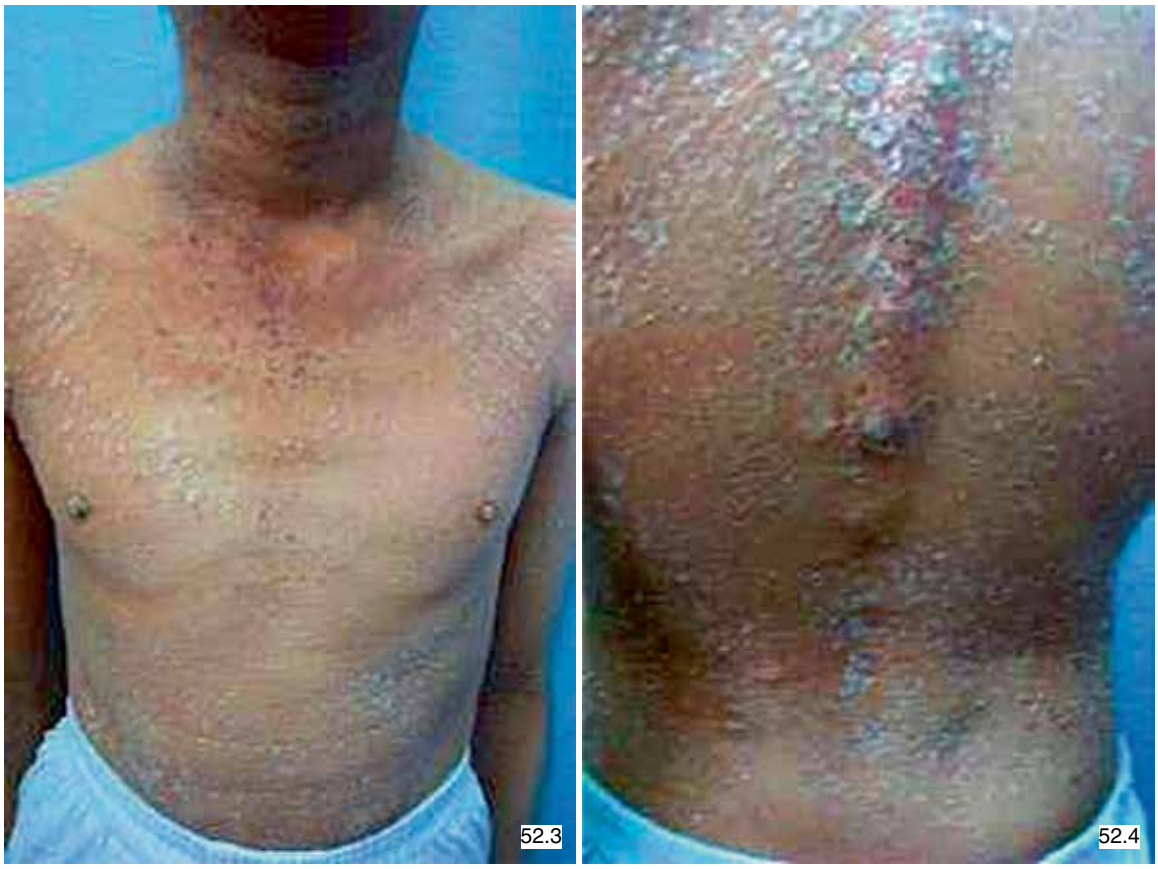


Figs. 52.1 and 52.2 Facial involvement of erythema and scaliness. Mild ectropion is seen



Figs. 52.3 and 52.4 Erythema and scaliness, involving the trunk

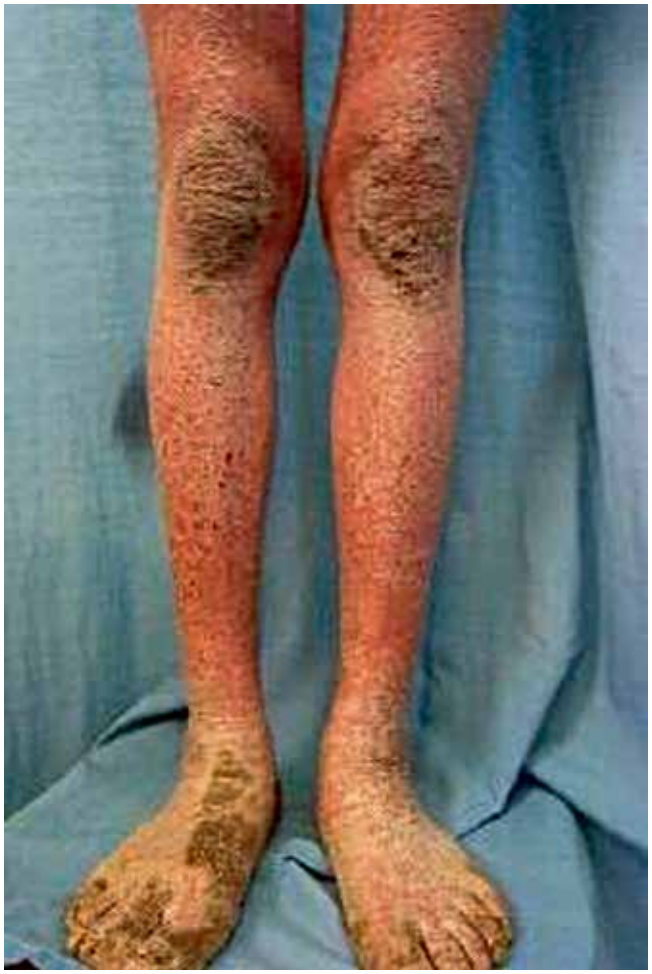


Fig. 52.5 Erythema and thickening of the lower extremities

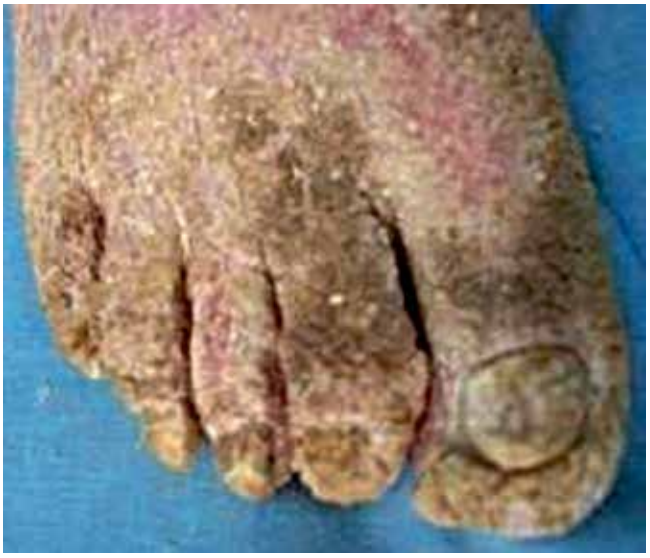
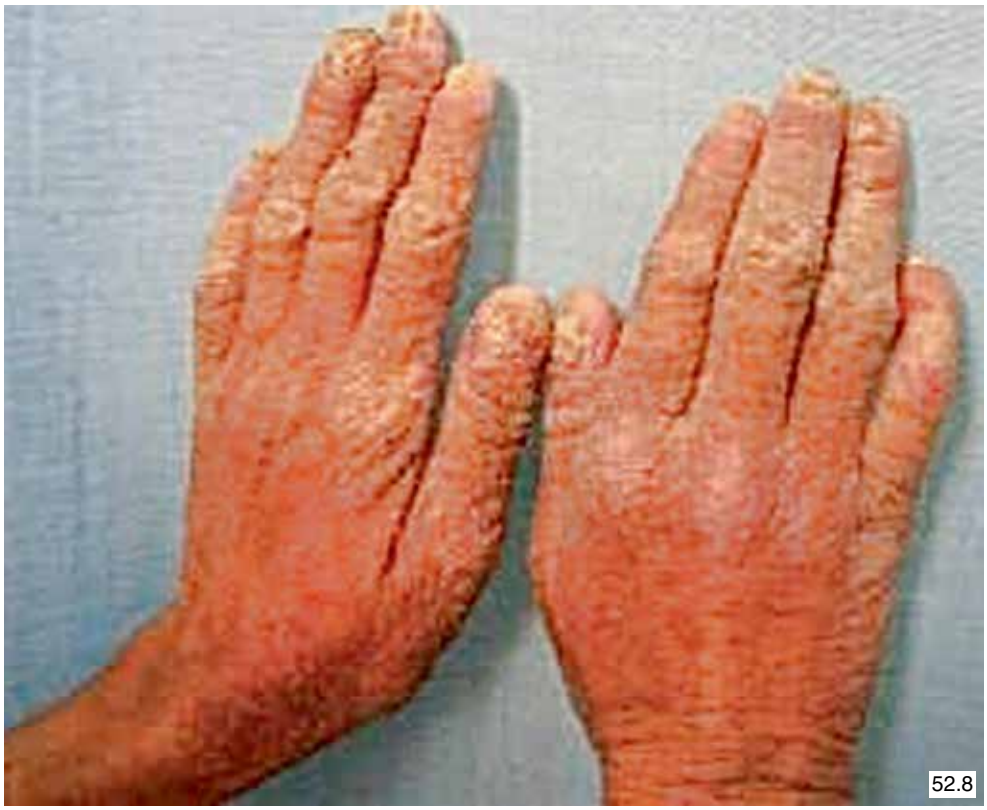


Fig. 52.6 Excessive thickening of the dorsum of the foot with thickened toe nails

Fig. 52.7 Excessive plantar keratoderma

Figs. 52.8 and 52.9 Palmar keratoderma with thickening of fingernails



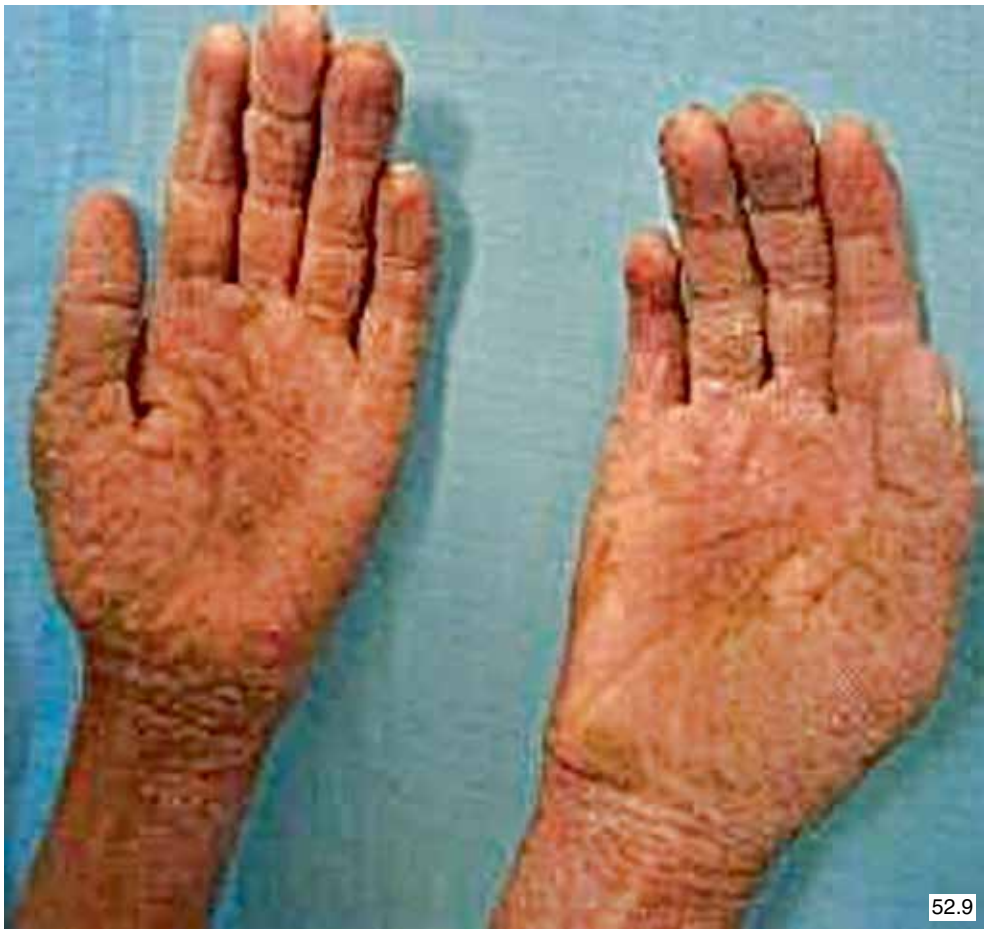


Table 52.1 Causes/differential diagnosis of erythroderma

Common	Less common	Rare
Psoriasis	Eczema	Cutaneous T-cell lymphoma
Atopic dermatitis	Seborrheic dermatitis	Sezary syndrome
Drug reaction	Internal malignancy	Pityriasis rubrapilaris
Idiopathic		Mastocytosis
		Trichophyton-induced erythroderma
		Icthyosiform erythroderma
		Papuloerythroderma of Ofuji
		Lichen planus
		Norwegian scabies

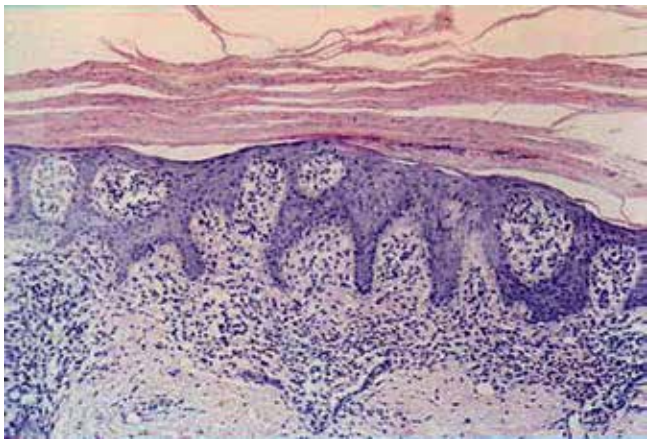


Fig. 52.10 Thick horny layer, moderate epidermal hyperplasia, and dense upper dermal lymphohistiocytic infiltrate admixed with few plasma cells and eosinophils

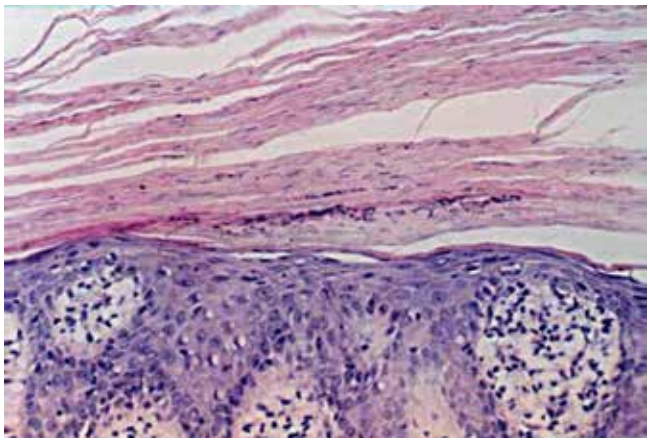


Fig. 52.11 Close up view showing thick horny layer containing numerous hyphae

About the Diagnosis

Definition

- The term 'erythroderma' or 'exfoliative dermatitis' describes any inflammatory skin condition with erythema and scaling, which affects more than 90 % of the body surface.
- There are various causes of erythroderma (see Table 52.1). Rarely, dermatophytosis may present as erythroderma.
- Trichophyton-induced erythroderma is a rare entity that usually occurs in immunocompromised patients (e.g. HIV, organ transplant recipients, patients on immunosuppressive therapy). However, it may occur without obvious underlying immunological abnormalities.

Epidemiology

- There are only few case reports of erythrodermic fungus infection in literature.
- Two reported cases by Shelley et al. were due to *Trichophyton violaceum*.
- Some cases developed in patients with congenital ichthyosiform erythroderma.
- Other cases occurred in patients receiving immunosuppressive therapy.

Pathogenesis and Etiology

- Erythroderma in general, has multiple etiologies (see Table 52.1).
- The pathways involved in the de novo genesis of erythroderma or the generalization of pre-existing skin lesions are not well understood.
- The number of germinative cells as well as their mitotic rate is increased in erythrodermic skin, and the transit time of cells through the epidermis is shortened. Consequently, scales consist of material normally retained by the skin (nucleic acids, amino acids, soluble protein), and the daily loss of scales increases from 500–1,000 mg to 20–30 g.
- An increased skin blood perfusion occurs in exfoliative dermatitis that results in temperature dysregulation (resulting in heat loss and hypothermia) and possible high-output cardiac failure.

Clinical Features

Despite the varied causes, erythrodermas have several common clinical features:

- Pruritus.
- Malaise, fever, and chills.
- Generalized erythema followed by scaling.
- Generalized lymphadenopathy.
- Bilateral ectropion.
- Ankle edema.
- Palmoplantar keratoderma.
- In chronic cases: Lichenification of skin, diffuse non-scarring alopecia, and nail dystrophy.
- Colonization of the skin with *S. aureus* leading to secondary infections.
- Tachycardia and thermoregulatory disturbances.

Histological Features

- Although sometimes subtle, histopathologic features of the underlying disease are present in about two-thirds of patients.
- In erythrodermic-trichophyton violaceum, the following features can be seen:
  - Neutrophils in the stratum corneum and parakeratosis.
  - Sandwich sign (orthokeratosis or parakeratosis alternated in layers with basket-weave stratum corneum) hyphae are seen within the parakeratotic and orthokeratotic areas.
  - Fungal hyphae in the stratum corneum, sometimes visible with H&E stain, are best seen with PAS or GMS stains.

Investigations

- Generally in erythroderma, there will be increased erythrocyte sedimentation rate, anemia, hypoalbuminemia, and hyperglobulinemia.
- Scraping and culture of scales are positive in trichophyton-induced erythroderma.
- Immunological profile may show evidence of low immunity in case of trichophyton-induced erythroderma.
- In a report by Griffiths et al., decreased CD4+ T-cell count was observed in patients with exfoliative dermatitis in the absence of HIV disease.

Differential Diagnosis

- See Table 52.1.

Definite Diagnosis

- The recognition of erythroderma is easy, but the diagnosis of the underlying cause is challenging.
- Establishing the correct diagnosis requires consideration of initial sites of involvement, additional clinical findings, histologic and molecular features, and associated systemic abnormalities, as well as a complete medical history.
- Trichophyton-induced erythroderma can be detected histopathological findings and confirmed by scraping and fungal cultures.

Prognosis

- The prognosis of exfoliative dermatitis depends largely on underlying etiology.
- The overall mortality is in the range of 20–40 %; It is particularly dangerous in elderly people.
- The metabolic disturbances involve a serious risk of hypothermia, cardiac decompensation, peripheral circulatory failure and thrombophlebitis.
- Cutaneous, subcutaneous and respiratory infections are common, and the majority of patients who die; do so from pneumonia.
- The treatment can also be hazardous, especially when systemic steroids and immunosuppressants are required.

Treatment

- Treatment strategies should address the dermatologic disease as well as the underlying etiology and the systemic complications of the erythroderma.
- In acute erythroderma, patients require admission and close monitoring.
- Regardless of the underlying disease, the initial management consists of nutritional assessment, correction of fluid and electrolyte imbalances, prevention of hypothermia, and treatment of secondary infections.
- Sedating oral antihistamines may ease the often severe pruritus.
- In case of trichophyton-induced erythroderma, topical and systemic antifungal therapy must be administered.

Fig. 52.12 Case of trichophyton-induced erythroderma, face, after treatment (compare with Fig. 52.1)

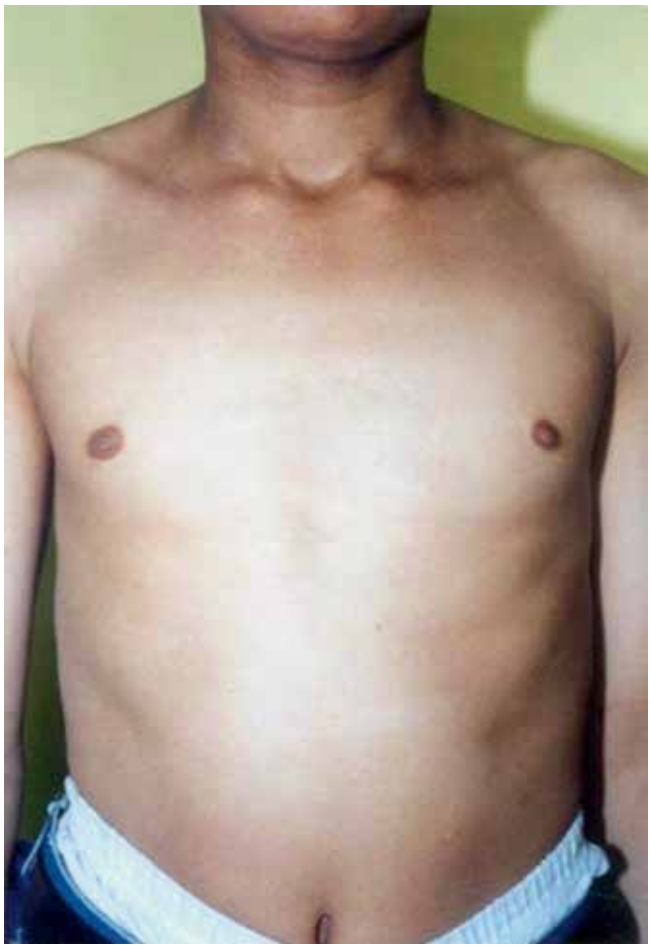


Fig. 52.13 Case of trichophyton-induced erythroderma, trunk, after treatment (compare with Fig. 52.3)

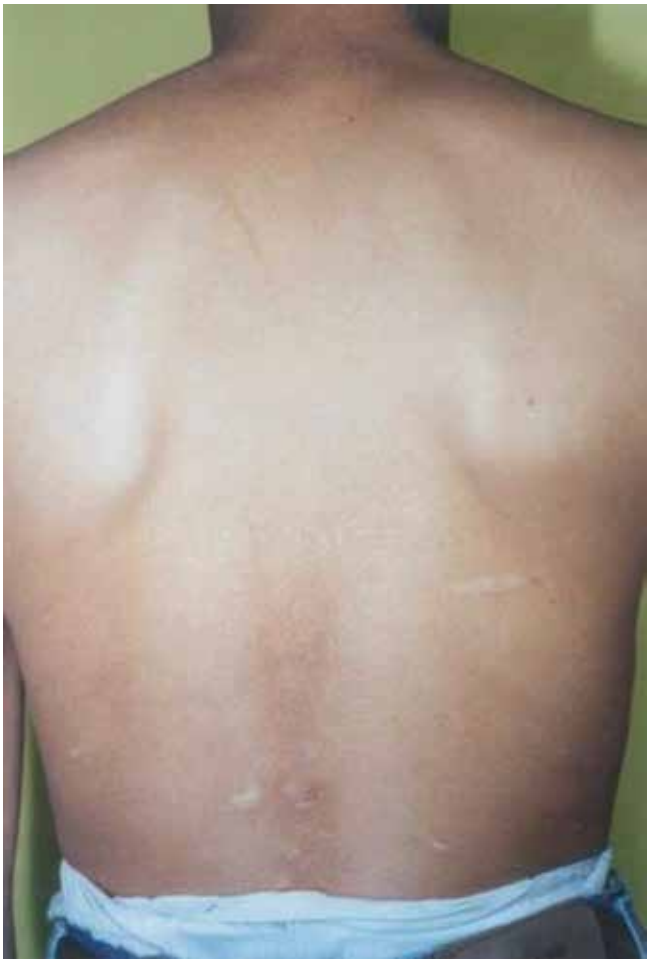


Fig. 52.14 Case of trichophyton-induced erythroderma, back, after treatment

Management of This Case

- The patient was treated with griseofulvin and itraconazole (150 mg b.i.d.), with marked improvement within 5 days and virtual clearing of the erythroderma after 1 month.
- There was no recurrence of the lesion during the next 2 years of follow-up.

(Figs. 52.12, 52.13, 52.14, 52.15, 52.16, and 52.17) show the results of treatment.

Message

- Patients with unexplained exacerbation of ichthyosis or erythroderma must be evaluated for superimposed fungal infection.
- Trichophyton erythroderma may be the only manifestation of an underlying immune disorder.

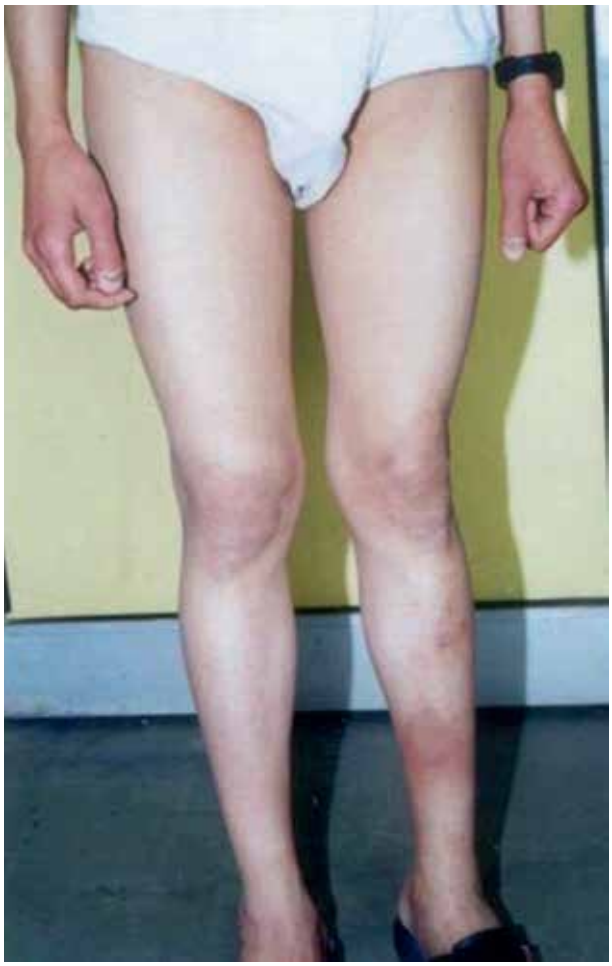


Fig. 52.15 Case of trichophyton-induced erythroderma, legs, after treatment (compare with Fig. 52.5)

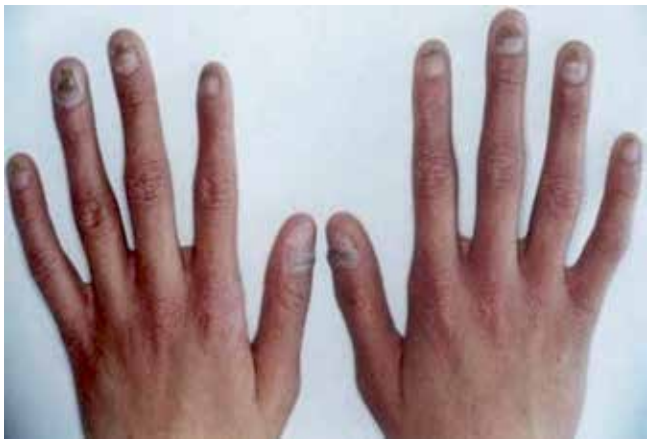


Fig. 52.16 Case of trichophyton-induced erythroderma, hands, after treatment (compare with Fig. 52.8)

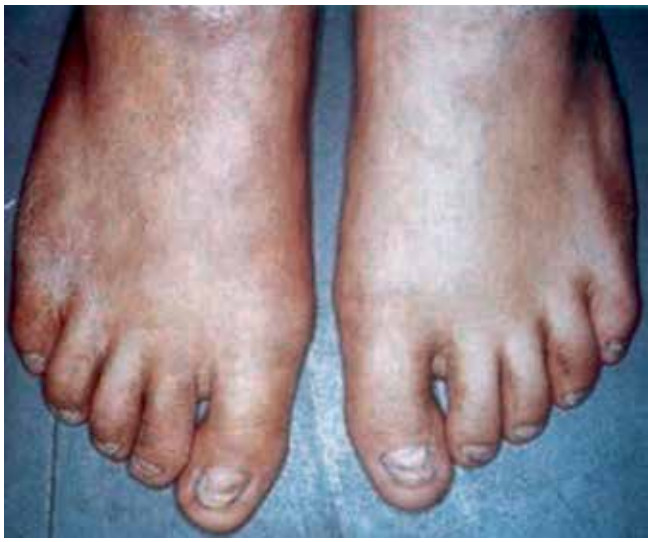


Fig. 52.17 Case of trichophyton-induced erythroderma, feet, after treatment

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Source: Mohammad Ali El-Darouti (ed). An Extremely Rare Cause of Erythroderma. Challenging Cases in Dermatology. 1st ed. London: Springer-Verlag; 2012, pp 371-378. DOI 10.1007/978-1-4471-4249-2_52.

A Rare Cause of Mucocutaneous Ulceration

Case

Clinical Data

A 27-years-old male presented with an ulcerated large tumour on the nose, for duration of 7 months (Fig. 55.1). He also had several ulcerated nodules on the neck, chest and back (Figs. 55.2 and 55.3). The ulcerated nodules involved the hard palate (Fig. 55.4). The patient worked in the western desert of Egypt, near Alexandria. He gave history of receiving treatment for leishmaniasis (glucantime); without any response. Clinical examination revealed no lymphadenopathy and no hepatomegaly.

Differential Diagnosis

- **Cutaneous leishmaniasis:**
  - Oral lesions do not occur in cutaneous leishmaniasis.
  - The patient had no history of residence in an endemic area and there was no response to glucantime.
  - This diagnosis was unlikely.
- **Natural killer cell lymphoma (NKL); nasal type:**
  - Oral and nasal lesions in this case are consistent with NKL.
  - Cutaneous lesions do occur in nasal type NKL.
  - This was a possible diagnosis.
- **Atypical mycobacteria:**
  - Oral lesions in this patient make this diagnosis unlikely.
- **Wegner's granulomatosis:**
  - It may present with oral as well as facial ulcerated plaques.
  - This was a possible diagnosis.

Biopsy Findings

- Biopsy of the lesion revealed suppurative, mixed cell granuloma, with numerous intracellular and extracellular encapsulated bodies. The bodies were surrounded, in some foci, by clear halos. (Figs. 55.5, 55.6, 55.7, and 55.8).
- Giemsa stain: Positive.
- Periodic acid-Schiff (PAS) stain: Positive (substantiating the diagnosis of histoplasmosis).
- Tissue culture: Histoplasma Capsulatum (growth in the form of trabeculate macroconidia, at 25 °C).

Investigations

- Human immunodeficiency virus (HIV): Negative.
- Chest X-ray: Normal.

Based on the Following Findings

- The progressive cutaneous and oral ulcerated nodules.
- The intracellular and extracellular rounded bodies surrounded by clear halos.
- Positive staining with both Giemsa and PAS.
- The result of tissue culture.

The Final Diagnosis was Primary Cutaneous Histoplasmosis.

M.A. El-Darouti, *Challenging Cases in Dermatology*,
DOI 10.1007/978-1-4471-4249-2_55, © Springer-Verlag London 2013

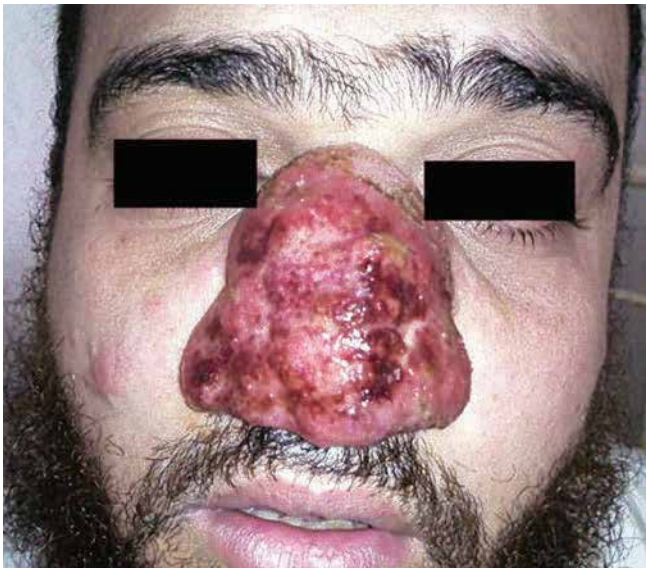

Fig. 55.1 A large ulcerating tumor covering the entire surface of the nose

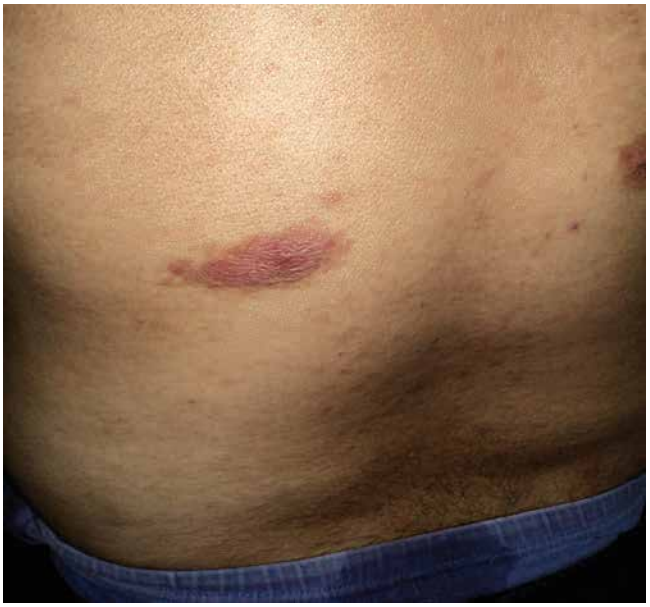

Fig. 55.2 A nodule on the back

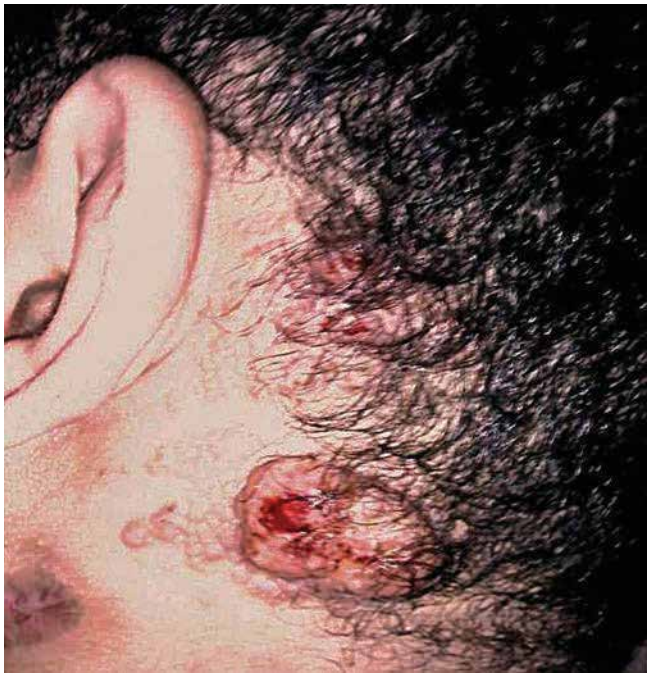

Fig. 55.3 An ulcerating nodule behind the ear, surrounded by multiple erythematous papules and nodules

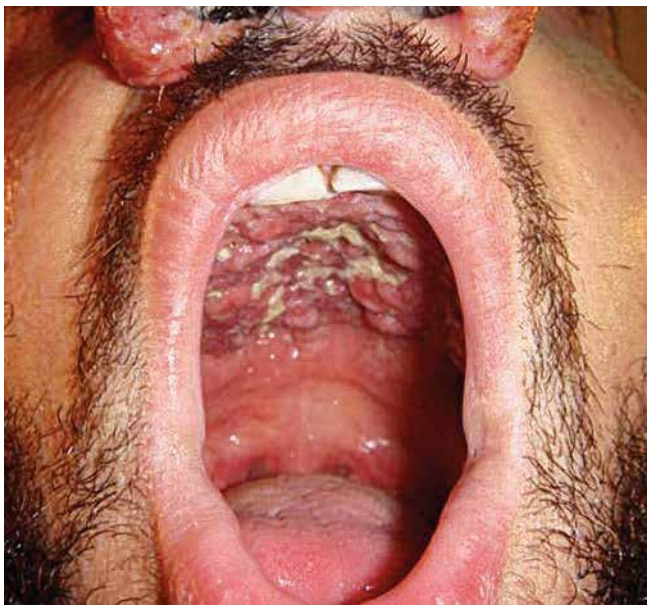

Fig. 55.4 Multiple ulcerating nodules on the hard palate

About the Diagnosis

Definition

- Histoplasmosis (also known as Darling's disease, Cave disease, or Ohio Valley fever) is an opportunistic mycosis caused by the dimorphic fungus Histoplasma *capsulatum.*
- It was originally identified as a rare, life-threatening disease, but, in 1945, was more accurately described by Christie & Peterson as a largely asymptomatic, primary pulmonary infection that occasionally disseminates.

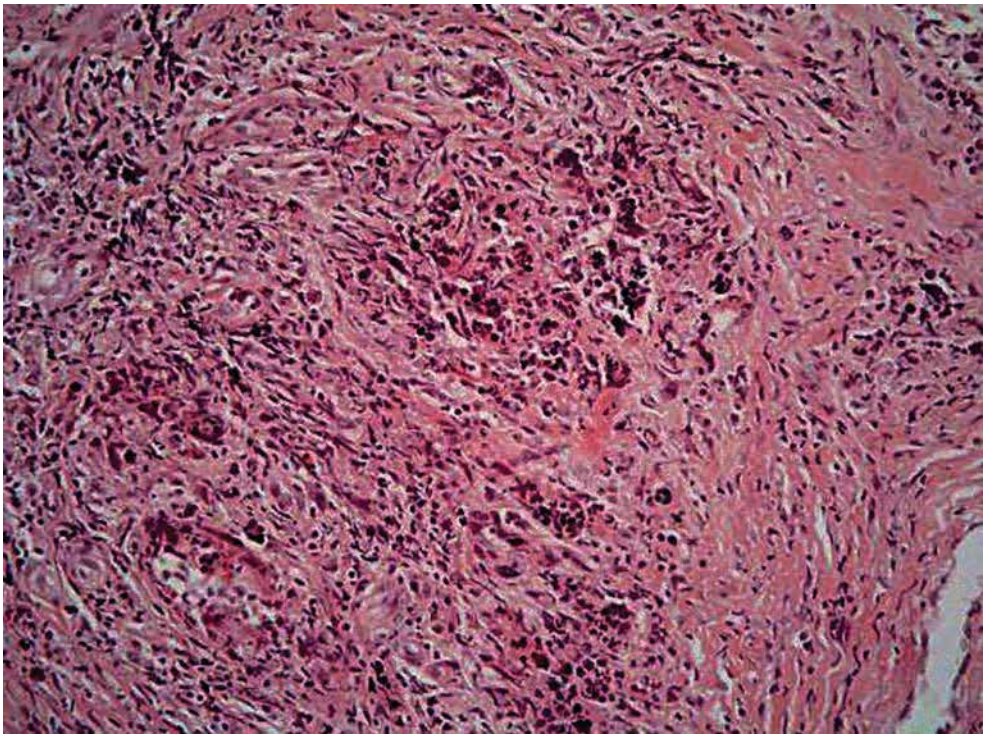

Fig. 55.5 Suppurative (mixed cell) granuloma

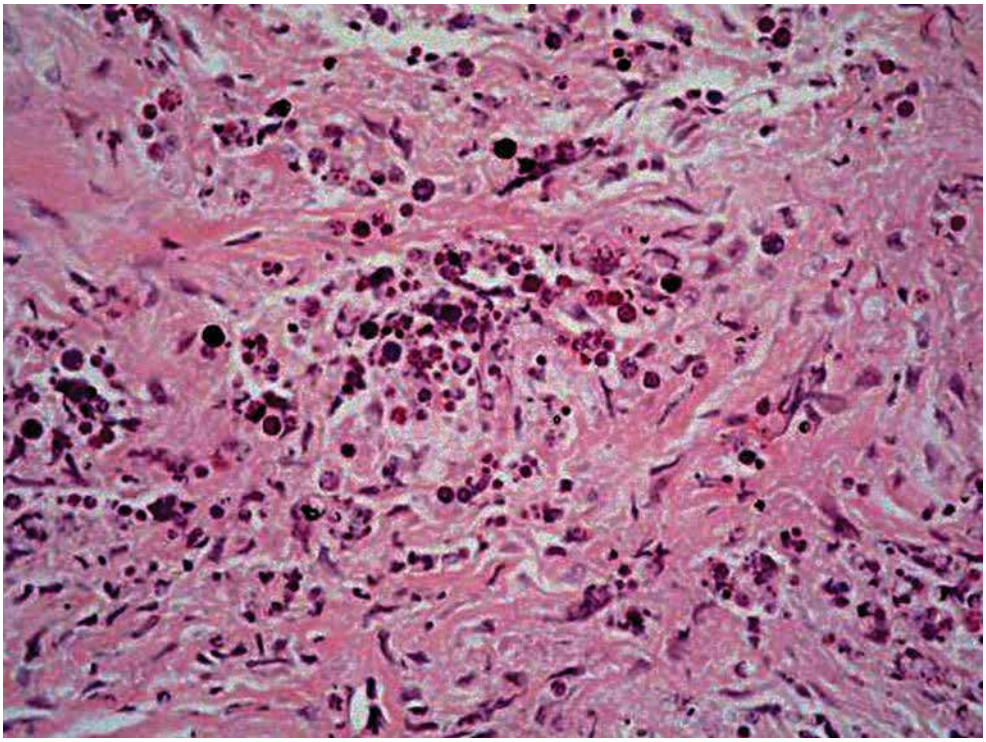

Fig. 55.6 Numerous intracellular and extracellular encapsulated bodies. The bodies are surrounded, in some foci, by clear halos

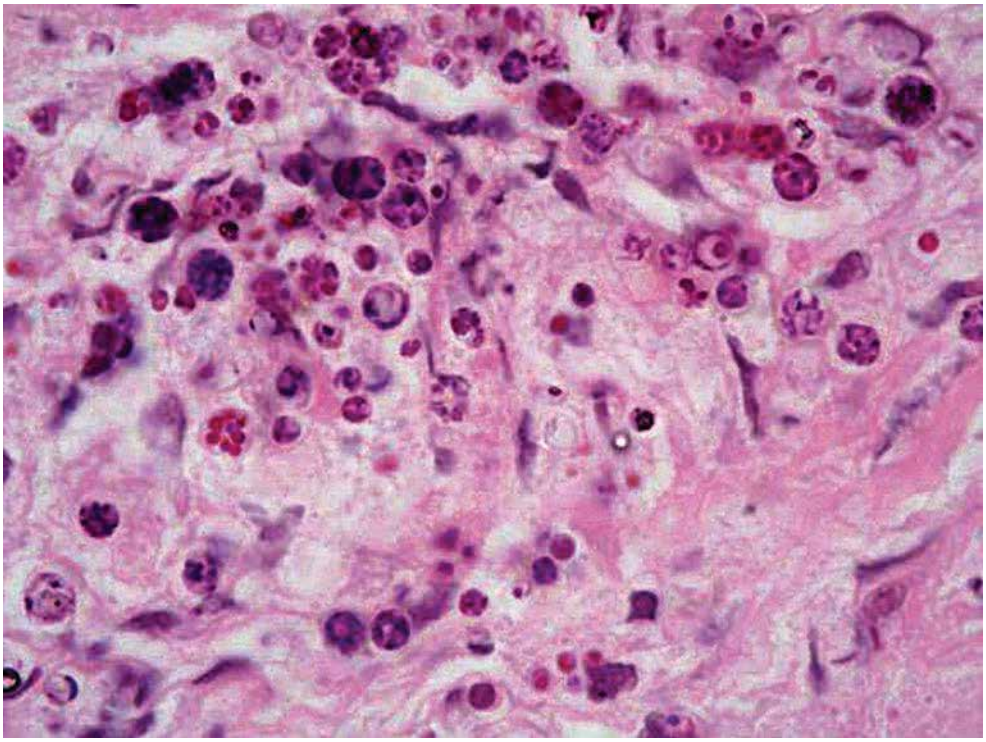

Fig. 55.7 Higher view of the rounded encapsulated bodies occurring both intra and extracellularly raising the possibility of histoplasmosis

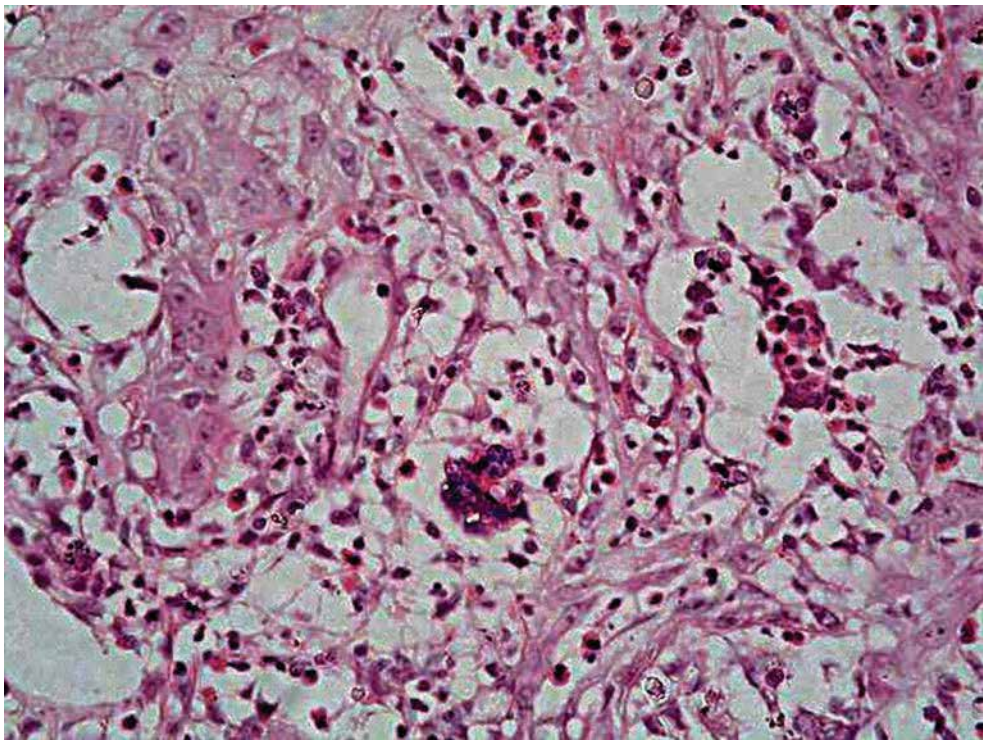

Fig. 55.8 Intracellular and extracellular rounded to oval bodies surrounded by clear halos

- Histoplasmosis is caused by either Histoplasma capsulatum var. capsulatum, which is found in America and the tropics, or Histoplasma capsulatum var. duboisii, which is found in Africa. The African form differs from the classical American form in its clinical and pathological features:
  - In the African form, lesions of skin and bones predominate in contrast to the American form, in which pulmonary changes dominate the clinical picture.
  - The histopathology of the African form characteristically shows a giant cell granuloma containing yeast cells 10–15 μm in diameter, whereas in the American form smaller (3–4 μm) yeast cells are embedded in histiocytes.

Epidemiology

- *Histoplasma capsulatum* var. capsulatum is endemic in USA, Latin America, the Far East and Australia. Whereas *H. capsulatum* var. duboisii have been reported only from Africa.
- Over 80 % of persons from endemic areas exhibit positive histoplasm in skin testing.
- Cases reported in non-endemic areas occur in the setting of previous exposure in an endemic area or endemic microfoci of Histoplasma.
- Infants and children are frequently infected, and among adults, the rate is highest in male agricultural workers.
- *H. capsulatum* is an environmental saprophyte that can be isolated from soil, particularly when it is contaminated with bird or bat excreta.
- The disease is acquired by inhalation of spores, and epidemics of respiratory infection may occur in persons exposed to a spore-laden environment when exploring caves or cleaning sites heavily contaminated with bird droppings.
- Risk areas are caves, schoolyards, construction sites, unoccupied buildings, chicken coops, bird roosts or barns.

Pathogenesis and Etiology

- Histoplasmosis results from inhalation of the dimorphic fungus; *H. capsulatum* or, rarely, by direct cutaneous inoculation of the fungus.
- The host defense includes neutrophils and macrophages. T lymphocytes are crucial in limiting the extent of infection. Susceptibility to dissemination is increased markedly with impaired cellular host defenses (such as AIDS or lymphoma).
- Immunocompromised hosts have a high risk of dissemination. Immunocompetent hosts may acquire the disease if the inoculum is significant. This is why *H. capsulatum* is considered a 'true' pathogen.
- As the host immunity response develops, yeast growth ceases within 1–2 weeks after exposure. Cytokines systemically activate the fungistatic activity of macrophages against intracellular yeasts. With further maturation of the cell-mediated response, delayed-type hypersensitivity to histoplasmal antigens occurs (3–6 weeks after exposure).
- Over weeks to months, the inflammatory response produces calcified fibrinous granulomas with areas of caseous necrosis.

Clinical Features

- Histoplasmosis runs the spectrum from asymptomatic to progressive dissemination with a hematogenous spread to multiple organs.
- Clinical presentations include:
  - Primary pulmonary histoplasmosis.
    - It can be acute, subacute, or chronic.
  - Disseminated histoplasmosis.
    - Common sites of involvement (after the lung) are the spleen, lymph nodes, bone marrow and liver, (hepatosplenomegaly, mediastinal syndrome).
    - Disseminated histoplasmosis in immunocompromised hosts can present with mucocutaneous erosions or ulcers as well as multiple erythematous papules or nodules, molluscum-like, and cellulitis-like lesions.
  - Primary cutaneous histoplasmosis.
    - Most commonly result from dissemination. Very rarely, from direct inoculation (in which it presents as a chancre and lymphadenopathy).
    - Lesions are non-specific. Papules, ulcers, nodules, abscesses, fistulae, scars and pigmentary changes may be seen, and there may be secondary involvement of the bone with osteomyelitis.
    - Oral ulcers, nodules or vegetations are highly characteristic.
- In African histoplasmosis most patients present with mucocutaneous, subcutaneous and bone lesions.
- Asymptomatic forms of histoplasmosis, indicated by the presence of positive skin-test reactivity without evidence of infection, are common in endemic areas.

Histological Features

- Diffuse mixed dermal infiltrate of neutrophils, lymphocytes, histiocytes, and few giant cells. Necrosis is common.
- Numerous small 2–4 μm spores surrounded by a clear halo (pseudo-capsule) can be seen within histiocytes and giant cells.
- They can be seen with H&E stains. However, they are seen more readily with PAS, GMS, Giemsa, or Gram stain.

Tip

Organisms that are engulfed by macrophages (parasitized organisms) are:

- *Histoplasmosis.*
- *Granuloma Inguinale.*
- *Rhinoscleroma.*
- *Leishmaniasis.*
- *Penicilliosis.*
- *Leprosy.*

Investigations

- Lab investigations:
  - CBC (anemia, pancytopenia).
  - Alkaline phosphatase: Elevated.
  - Lactate dehydrogenase: Marked elevations may be seen in AIDS.
  - Bone marrow culture.
  - Blood culture at 25 and 37 °C (the diagnostic tuberculate macroconidia develop at 25 °C).
  - Sputum and body fluid's culture.
  - Polysaccharide antigen testing of blood and urine (useful in detecting disseminated disease).
- Radiological investigations:
  - Chest X-ray.
  - CT scanning of the chest.
- Other tests:
  - Histoplasmin skin testing (indicated only in non-endemic areas).
  - Serologic assays to measure antibody responses (complement fixation, immunodiffusion).
  - Highly sensitive and specific nested PCR can be used to identify histoplasmosis in blood and tissue.

Differential Diagnosis

- Cutaneous histoplasmosis has a wide spectrum of clinical presentations. Diseases in the differential diagnosis include other deep fungal infections, mucocutaneous tuberculosis, wegner's granulomatosis, natural-killer-cell lymphoma nasal type and oral squamous-cell carcinoma.
- Umbilicated lesions can be seen in cryptococcosis, penicilliosis, coccidioidomycosis, in addition to histoplasmosis when accompanied with immunosuppression.
- Histological differential diagnosis:
  - Leishmania (Very similar to histoplasmosis, however, stains negative with PAS and GMS).
  - Rhinosclerema (Characterized be Miculiks cells and Russel bodies; stains negative with PAS and GMS).
  - Granuloma inguinale (There is no clear halo around the cells, stains negative with PAS).
  - Leprosy (There is no suppurative granuloma; stains negative with PAS).

Definite Diagnosis

- Biopsy and special stains: The diagnosis of histoplasmosis is established by identifying the small intracellular yeast cells (2–5 μm) of Histoplasma in sputum, peripheral blood, bone marrow or in biopsy specimens. Lymph node aspiration may also be employed.
- Culture: The identity of the organism should be confirmed by culture.
- Antibody detection tests: like complement fixation, DNA probes and radioimmunoassays.

Prognosis

- Acute pulmonary histoplasmosis is associated with a good outcome. Spontaneous resolution may occur in immunocompetent patients.
- Chronic progressive disseminated histoplasmosis has a long-term protracted course, lasting up to years, with long asymptomatic periods.
- If untreated, subacute progressive disseminated histoplasmosis results in death within 2–24 months. (Dissemination is the rule in immunosuppressed patients).
- Disorders of the interferon-gamma/interleukin-12 pathway may result in progressive disease.
- A relapse rate of 50 % is associated with acute progressive disseminated histoplasmosis, if treated. The rate decreases to 10–20 % with life-long antifungal maintenance. Death is imminent without treatment.

Treatment

- Most acute forms of histoplasmosis in immunocompetent hosts resolve without specific treatment.
- Systemic antifungal treatment is indicated for severe acute pulmonary histoplasmosis, chronic pulmonary

histoplasmosis, progressive disseminated histoplasmosis and any manifestation in an immunocompromised patient.

- Amphotericin B, is currently the most effective therapy and should be used initially for severe disease, followed by itraconazole.
- In immunocompetent hosts with mild to moderate or stable disease, itraconazole is the treatment of choice. Ketoconazole can also be used.
- HIV-infected patients with disseminated histoplasmosis require lifelong maintenance therapy with itraconazole after initial treatment with amphotericin B. It appears that the use of Highly Active Antiretroviral Therapy (HAART) may reduce the requirement for maintenance therapy in some cases.
- Voriconazole, which has demonstrated good in vitro activity against Histoplasma, may also prove effective.
- Some patients with solitary skin lesions may simply respond to excision without chemotherapy, although antifungals should be given where possible.

Management of This Case

- Amphotericin B; given by infusion (1 mg/kg every other day for 2 months).
- Itraconazole (300 mg daily for 6 months).
- Improvement started to show after 2 weeks and was evident in 2 months.
- Maintenance therapy with itraconazole was continued for 1 year.
- No recurrence was seen in a period of 1-year-follow up after stopping the treatment (Figs. 55.9, 55.10, and 55.11) show the results of the treatment.

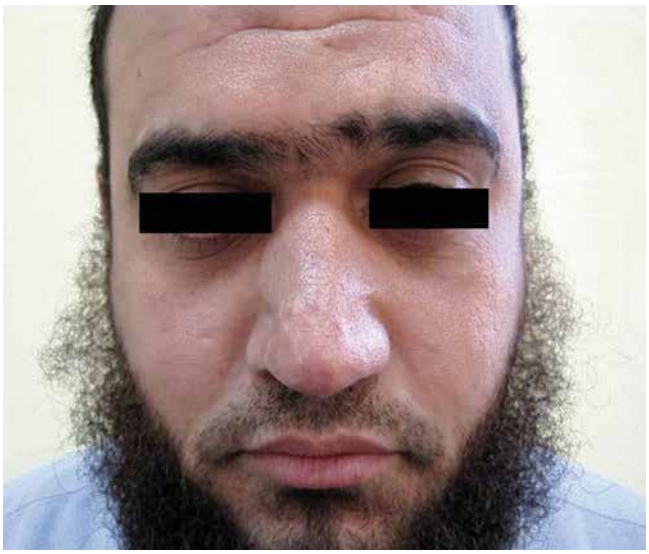

Fig. 55.9 Case of primary cutaneous histoplasmosis, nose, after treatment (compare with Fig. 55.1)

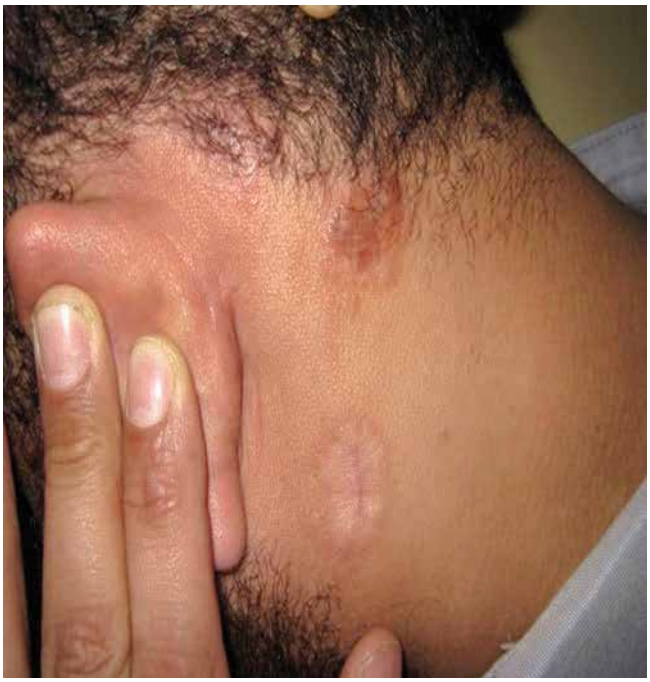

Fig. 55.10 Case of primary cutaneous histoplasmosis, behind ear, after treatment (compare with Fig. 55.3)

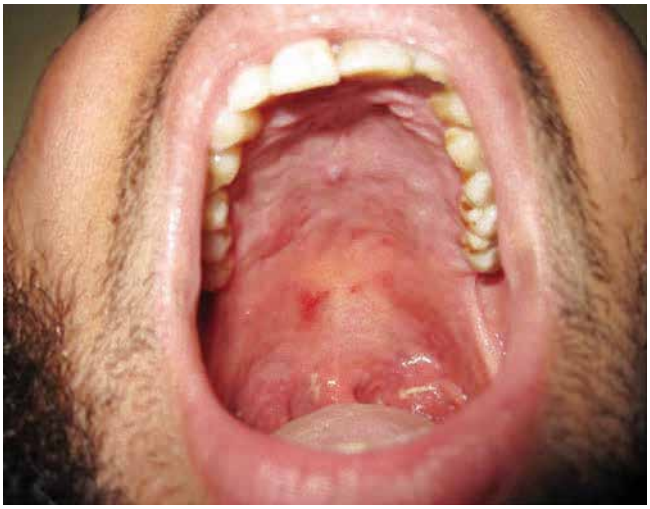

Fig. 55.11 Case of primary cutaneous histoplasmosis, hard palate, after treatment (compare with Fig. 55.4)

Message

- Histoplasmosis is extremely rare in Egypt and North Africa.
- Incidence in this patient can be explained by previous exposure in an endemic area or exposure in a microendemic area.
- Histoplasmosis should be included in the differential diagnosis of ulcerative cutaneous and oral lesions.

- Skin lesions are usually the manifestations of disseminated histoplasmosis. Primary cutaneous histoplasmosis as this case is very rare.

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A Rare and Severe Variant of a Common Disease

Case

Clinical Data

A 37-year-old male presented with recurrent and persistent folliculitis associated with suppurative nodules and pyoderma gangrenosum-like ulcers, for duration of 20 years. Lesions were most extensive on the trunk (Fig. 56.1). Other involved areas were the face, upper arms, and the root of the penis (Figs. 56.2, 56.3, and 56.4). Lesions were associated with fever, bone pain, weight loss. He had renal failure 5 years prior to presentation and there was a history of severe nodulocystic acne.

Differential Diagnosis

- Unusual pyoderma gangrenosum (PG) (this diagnosis does not explain the systemic symptoms and the associated renal failure).
- Wegener's granulomatosis (may present with PG-like lesions and renal failure).
- PG-like lymphoma (This will not have such a long-standing signs and symptoms).

Biopsy Findings

Skin biopsy showed dilated infundibulum and ruptured follicular wall surrounded with necrotic collagen (Fig. 56.5). There was dense perifollicular infiltrate composed of neutrophils, lymphocytes, plasma cells, and giant cells (Fig. 56.6).

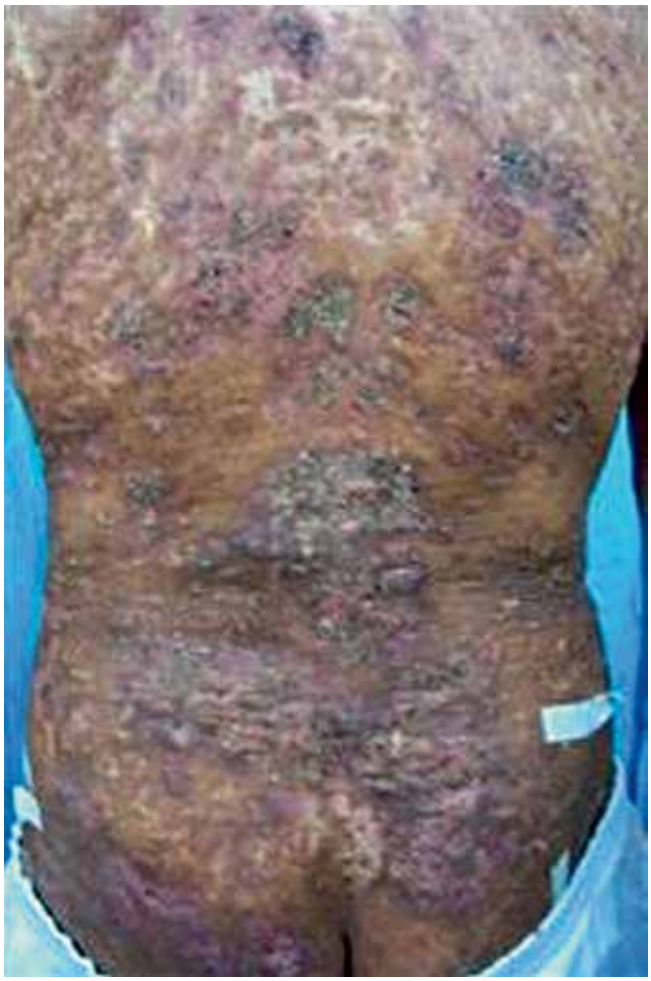

Fig. 56.1 Widespread confluent hemorrhagic plaques with ulceration, necrosis and crustation

M.A. El-Darouti, *Challenging Cases in Dermatology*,
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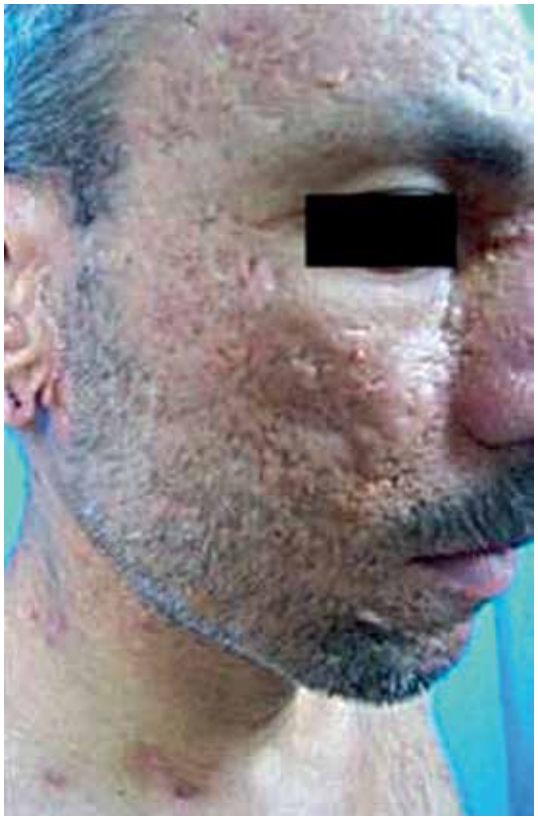


Fig. 56.2 Nodulocystic lesions on the face with areas of scarring

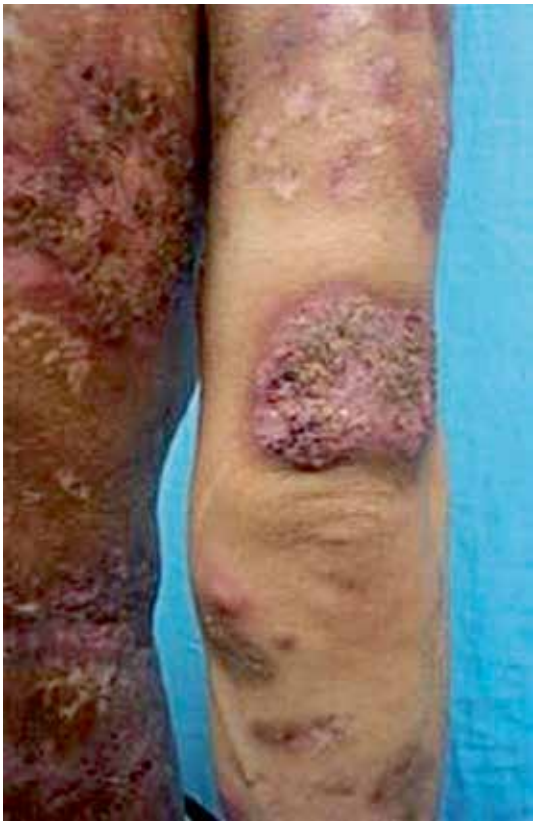


Fig. 56.3 Close-up picture showing hemorrhagic plaques involving the forearm

Investigations

- Elevated ESR.
- Leucocytosis.
- Increased serum immunoglobulins.
- Markedly elevated urea and creatinine.

Based on the Following Findings

- History of severe nodulocystic acne.
- History of severe bone pain, recurrent fever and weight loss.
- History of renal failure.
- Pyoderma gangrenosum-like skin lesions.
- Histopathological features of folliculitis with ruptured follicular wall.

The Final Diagnosis was Acne Fulminans.

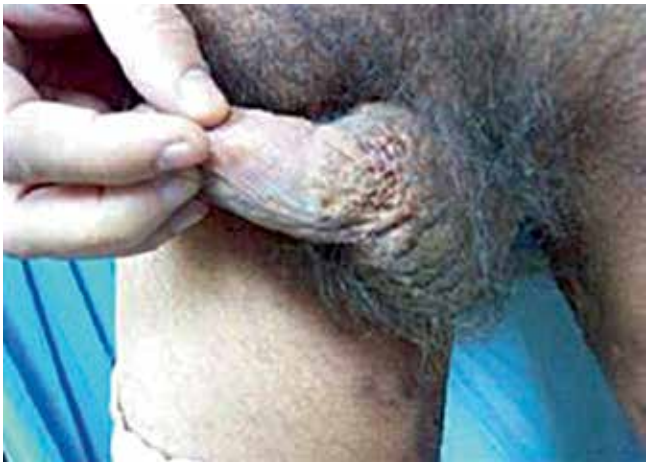


Fig. 56.4 Lesions involved the root of the penis

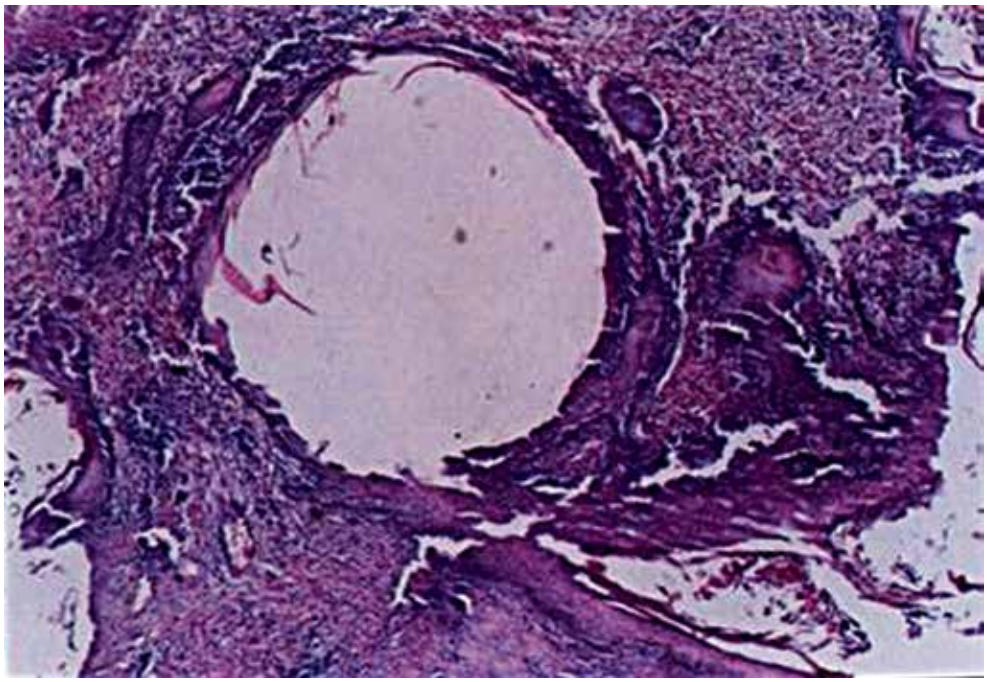
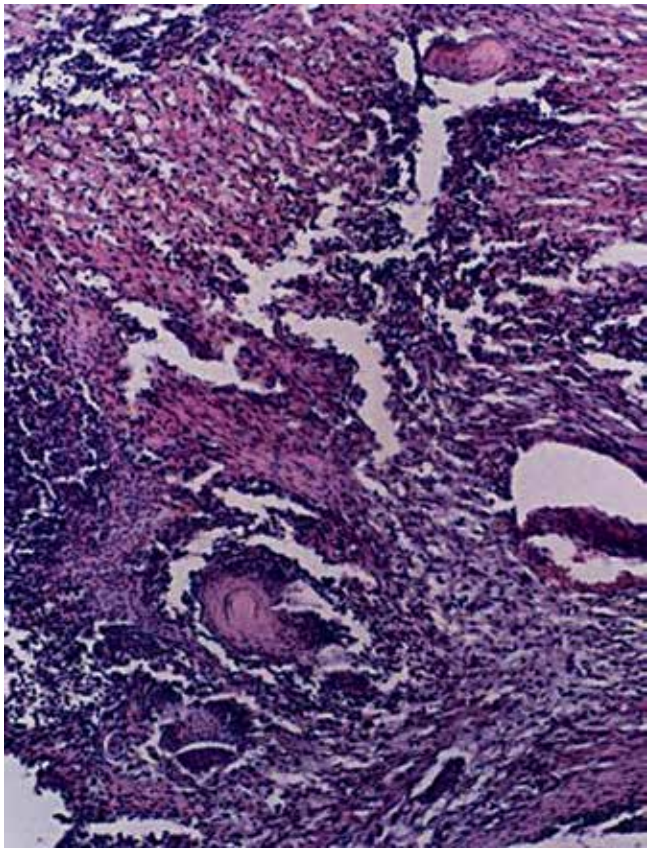
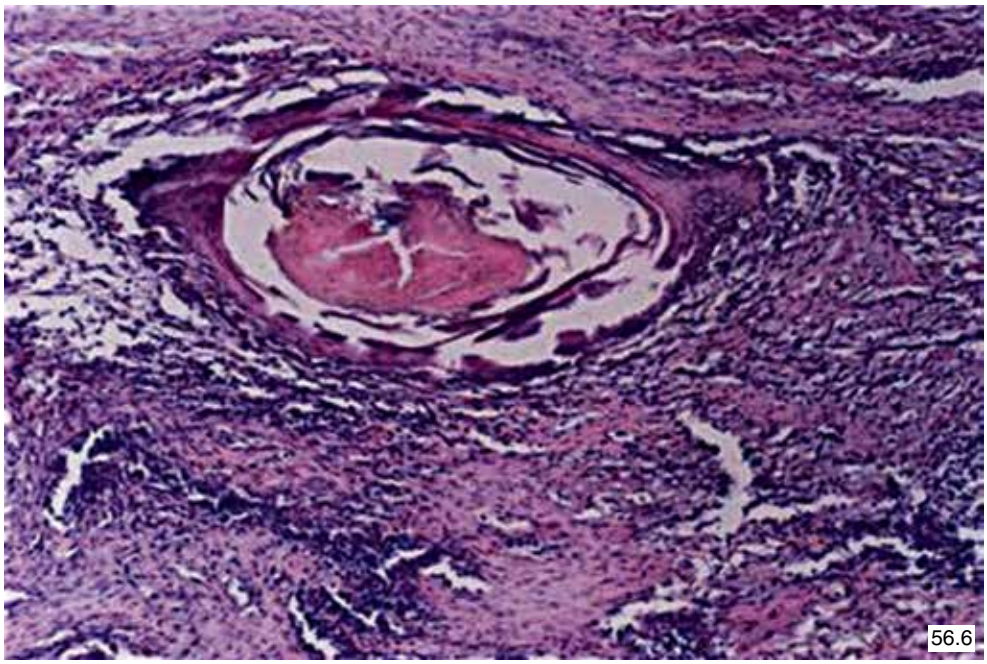
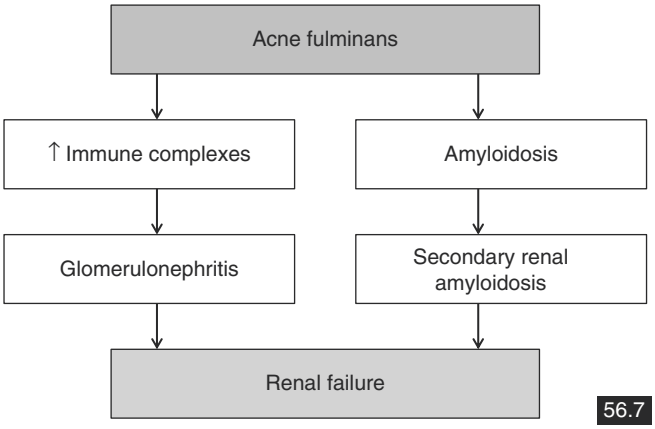


Fig. 56.5 Dilated infundibulum and ruptured follicular wall surrounded with necrotic collagen





Figs. 56.6 and 56.7 Dense perifollicular infiltrate composed of neutrophils, lymphocytes, plasma cells, and giant cells



Figs. 56.6 and 56.7 (continued)

About the Diagnosis

Definition

- Acne fulminans (also known as acute febrile ulcerative acne) is the most severe form of acne and is characterized by the abrupt onset of nodular, suppurative, and necrotizing acne in association with variable systemic manifestations and laboratory abnormalities.
- It was originally described as an acute form of febrile ulcerative acne conglobata.
- It can be the dermatologic manifestation of the Synovitis Acne-Pustulosis-Hyperostosis-Osteitis (SAPHO) syndrome.

Epidemiology

- Acne fulminans is extremely rare. Approximately, 100 patients with acne fulminans have been described.
- It predominantly affects young males aged 13–22 years with a history of acne.
- Over the past several years, incidence of this disease became even rarer, possibly because of earlier and better treatment of acne.

Pathogenesis and Etiology

- Acne fulminans is thought to be an immunologically induced, systemic disease in which the triggering antigen is believed to be from *Propionibacterium acnes* (See Fig. 56.7). The followings findings in some patients were supportive of this theory:
  - Erythema nodosum.
  - Increased response to *P. acnes* antigen on skin tests (immediate and delayed reaction, revealing type III or type IV hypersensitivity reaction).
  - Depressed response to intradermal purified protein.
  - Circulating immune complexes.
  - Isotretinoin may precipitate acne fulminans, possibly due to highly increased levels of *P. acnes* antigens after high doses of isotretinoin.
- High levels of testosterone and anabolic steroids can cause long standing induction of androgen receptors leading to an increase in sebum excretion and in the population density of *P. acnes*.
- One case has been reported in a young man with late-onset congenital adrenal hyperplasia.
- An acne fulminans-like picture has been reported in association with Epstein–Barr virus infection. Thus, patients with a sudden exacerbation of previously relatively mild acne should be checked for infectious mononucleosis.
- Acne fulminans has also been observed in patients with measles infection.
- Genetic factors may play an important role in some patients; four sets of identical twins who developed an identical pattern of acne fulminans have been documented.
- Bone pain is related to aseptic osteolysis (increased degeneration of collagen type-1 leading to bone destruction).

Tip

Renal Failure and Acne:

- Acne may be associated with renal failure.
- Types of acne associated with renal failure are:
  1. Acne Fulminans:
     - It develops long time before renal failure.
     - It is not associated with pruritus.
     - The course of acne is not altered by hemodialysis.
  2. Pruriginous Acne of Hemodialysis:
     - It develops for the first time during hemodialysis.
     - It is severe, and is associated with intractable pruritus, prurigo and hyperpigmented acne scars.
     - There is no response to antipruritic measures.
     - There is a marked response to systemic retinoids.
- The pathogenesis of renal failure in acne fulminans is illustrated in Fig. 56.8.

Clinical Features

- Affected individuals are usually young males who often have a history of previous mild to moderate acne.

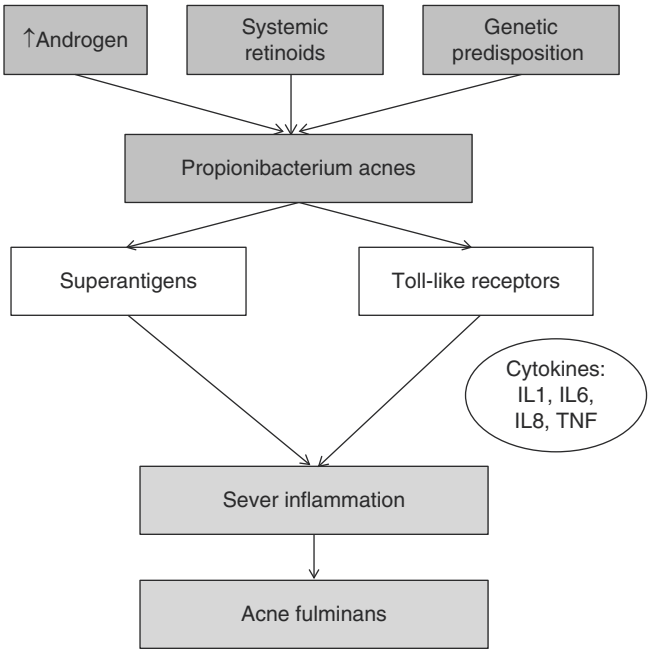


Fig. 56.8 Pathogenesis of acne fulminans. *IL* Interleukin, *TNF* tumor necrosis factors

- It presents as a very sudden eruption of large nodules that become ulcerates with overhanging borders. The surrounding plaques coalesce into painful and oozing friable necrotic lesions covered with hemorrhagic crusts.
- The ulcerated lesions often heal with significant scarring.
- The lesions predominate on the back and chest. The face is often not involved.
- Systemic manifestations include fever, polyarthritis, weight loss, anorexia and general malaise and hepatosplenomegaly.
- Bone pain is common. The clavicle and sternum are predominantly affected.
- Bone pain related to aseptic osteolysis may be present. Gordon et al. reported a case of a 13-year-old boy with severe acne and multiple osteolytic bone lesions who presented to pediatric oncologists; the patient avoided unnecessary painful diagnostic procedures when it was recognized, he had acne fulminans.
- Painful splenomegaly and erythema nodosum may be present.

Histological Features

- Non specific.
- Features of aggressive folliculitis:
  - Dilated infundibulae.
  - Ruptured follicular wall.
  - Dense perifollicular infiltrate composed of neutrophils, lymphocytes, plasma cells, and giant cells.
  - Variable necrosis of the epidermis and dermis.
  - Extensive dermal fibrosis (occurs later).

Investigations

- Lab investigations:
  - CBC (anemia, leukocytosis, even a leukaemoid reaction).
  - Increased percentage of polymorphonuclear leukocytes.
  - Elevated ESR.
  - Proteinuria.
  - Blood cultures from the pustular lesions are universally sterile.
  - Circulating immune complexes.
- Radiologic investigations:
  - Osteolytic cysts can be detected on a radiograph or as hot spots by technetium scintillography.
  - Destructive lesions resembling osteomyelitis are demonstrated on radiographs.

Differential Diagnosis

- Possible differential diagnoses are:
  - Acne conglobata.
  - Pyoderma gangrenosum.
- Although acne fulminans is often classified with acne conglobata, there are basic differences. The onset of acne fulminans is more explosive, nodules and polymorphous comedones are less common. The face is not involved as frequently and the neck is usually spared. Ulcerative and crusted lesions are unique, and systemic symptoms are more common.

Definite Diagnosis

- The diagnosis is mainly clinical, based on several features, including the following:
  - Sudden onset, with history of acne.
  - Severe and often ulcerating nodular lesions.
  - Fever, polyarthritis and bone pains.
  - Failure to respond to antibacterial therapy.
  - Good response to oral steroid therapy.
- Laboratory studies are not helpful in establishing the diagnosis, but may be predictive of therapeutic response, i.e. normalization of previously abnormal values corresponding to clinical improvement.

Prognosis

- The cutaneous lesions of acne fulminans often heal with scarring and fibrosis.
- The prognosis for bone lesions is good, and chronic sequelae, if any, are mild, leading to sclerosis and hyperostosis.
- Renal failure is rare but serious.

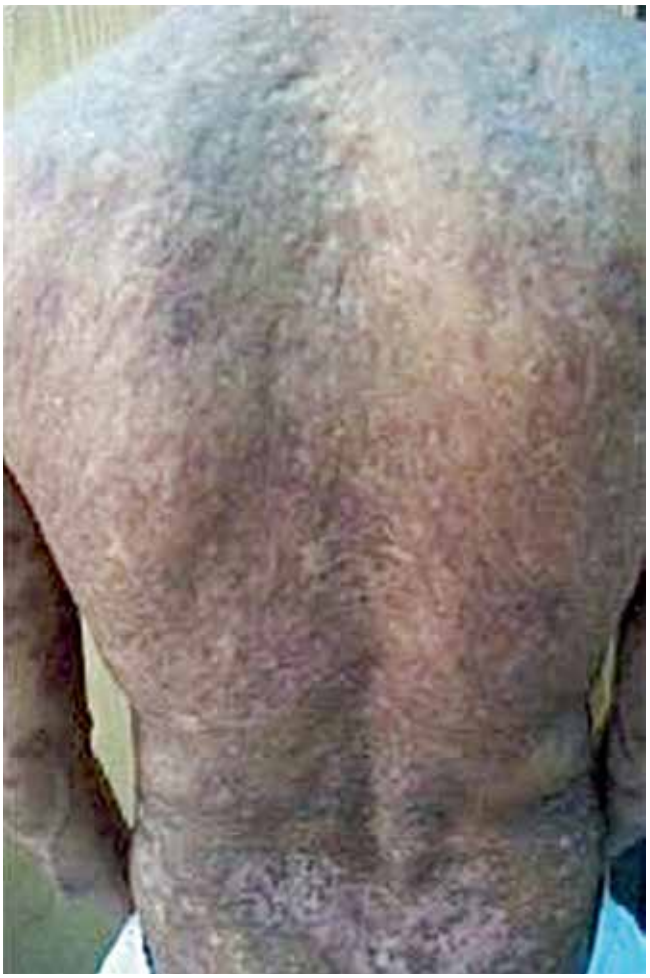


Fig. 56.9 Acne fulminans, back, after treatment (compare with Fig. 56.1)

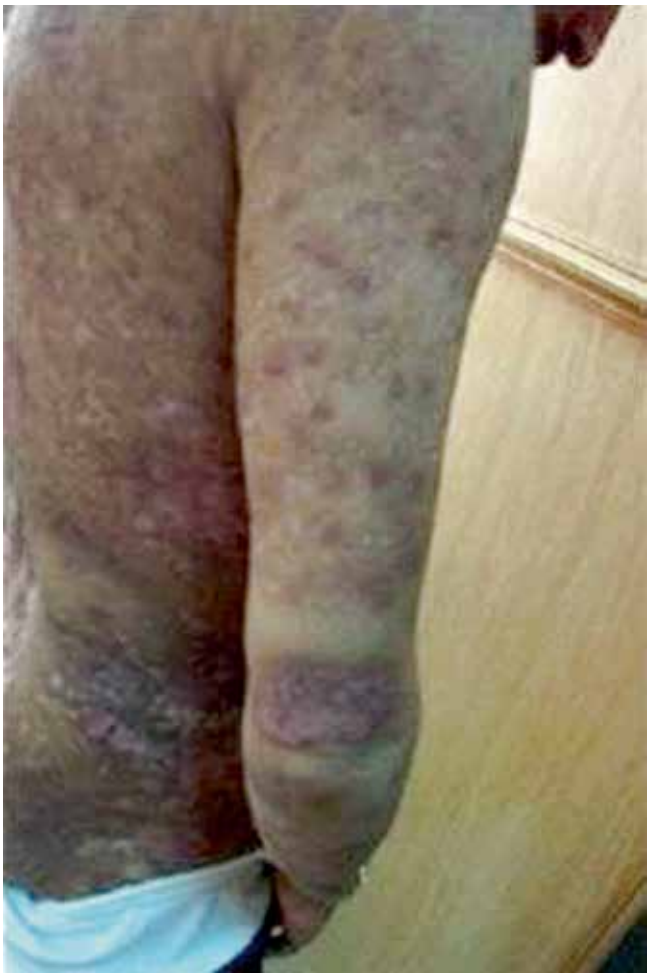


Fig. 56.10 Acne fulminans, forearm, after treatment (compare with Fig. 56.3)

Treatment

- Oral prednisolone therapy should be commenced as a first-line (0.5–1.0 mg/kg day, decreased slowly over 2–3 months, or in the form of pulse therapy).
- Oral salicylates or non-steroidal anti-inflammatory drugs for acute myalgia, arthralgia and fever.
- Oral isotretinoin (should be used with caution as paradoxically, it may induce acne fulminans). To avoid this, a combination of oral steroids and isotretinoin is recommended.
- Some authors add intralesional glucocorticoids to the above therapy.
- The response to broad-spectrum antibiotic treatment is poor.
- Topically, crusts need to be removed by soaking the skin with emollient oil, followed by the use of a potent steroid/antimicrobial cream for 2–3 weeks.
- Dapsone in conjunction with isotretinoin was reportedly beneficial in the treatment of acne fulminans associated with erythema nodosum.
- Infliximab may be a treatment option for patients who are unresponsive to conventional therapies.

Management of This Case

- Pulse steroid therapy (500 mg methyl prednisone/day × 3 days) every 2 weeks.
- Isotretinoin daily 20 mg daily (higher doses may increase acne fulminans).
- Zithromax 500 mg/day (it has anti-inflammatory as well as antibiotic effects).
- Treatment was continued for 6 months.
- Thereafter, pulse steroid was tapered to once every 4 weeks.
- Isotretinoin dose was reduced to 20 mg three times per week for another 6 months.
- Zithromax dose was reduced to 500 mg three times/week. Figs. 56.9 and 56.10 show the results of the treatment.

Message

- The association of severe nodulocystic acne and pyoderma gangrenosum-like lesions with severe bone pain should prompt the diagnosis of acne fulminans.
- Acne may be associated with other disorders such as:
  - Severe bone pain.
  - Pyoderma gangrenosum-like lesions.
  - Renal failure.

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