Complications and Diseases Associated with Atopic Eczema

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12.1 Introduction

Numerous factors lead to great difficulties in assessing the possible complications and diseases associated with atopic eczema (AE) [134, 281]. A major problem is correct diagnosis of AE, which has only recently been subjected to a certain standardization [31, 76, 124, 133, 135, 136, 138, 140, 183, 236, 309, 347, 393]. A survey of the innumerable case reports and review articles dealing with this topic is hampered by the variable definition of AE and by imprecise description of skin lesions, particularly in the nondermatological literature, making proper classification impossible. Exact epidemiological data concerning the prevalence of atopic diseases are rare. Thus, it is even more difficult to assess the frequency of diseases associated with AE, and to answer the question whether the association is incidental, rare, frequent, or constant. In addition, epidemiological studies and case reports mostly do not address the question of the causal relation between the underlying AE and the reported association. Despite these shortcomings, we will attempt to review diseases associated with AE and, if possible, discuss current ideas on causes and pathogenesis. We will omit from this review disorders dealt with in other chapters of this book (e.g., allergic contact eczema, food hypersensitivity, psychosomatic abnormalities, severe immunodeficiency syndromes, side effects of glucocorticoids).

12.2 Infections in Atopic Eczema: General Remarks

As yet, it is still controversial whether the increased susceptibility to and severity of different viral, mycotic, and bacterial skin infections in AE is a direct consequence of defective cell-mediated immunity and/or other immunological abnormalities [31, 125, 133, 135, 159, 189, 244, 287, 301, 303, 309] or is due to a defective barrier function of the skin. In addition, eczematous skin with crusted erosions and excoriations may provide a favorable milieu for the growth and multiplication of infectious agents [143, 215]. Finally, prolonged topical or systemic glucocorticoid treatment may enhance the susceptibility of the skin to specific viral or bacterial infections due to its immunosuppressive effects. Prolonged antibiotic treatment is likely to favor the emergence of pathogenic microbial agents [65, 215, 287].

12.3 Bacterial Infections

The skin of atopic patients shows a high rate of colonization with coagulase-positive *Staphylococcus aureus* even in the absence of skin lesions [8, 9, 27, 65, 68, 135, 139, 143, 148, 153, 154, 160, 211, 212, 215, 221, 254, 293, 309, 334, 384].This is predominantly seen on lesional skin with excoriations and fissures in infants and children [123]. In one study, the prevalence of *Staphylococcus aureus* has been reported five times higher in the anterior nares and ten times higher in the subungual spaces of patients with AE compared to patients with other skin diseases or in healthy adult controls [258].

Extensive serous weeping and/or honey-colored crusting, especially in the presence of lymphadenopathy, indicate infection with *Staphylococcus aureus* [68, 137, 160, 254, 334]. Though bullous impetigo may also occur in atopic children [334] (Fig. 12.1), staphylococcal scalded skin syndrome (SSSS) is exceedingly rare, despite the regular colonization with staphylococci. This is due to the absence of epidermolytic toxin-producing strains [8, 9]. Other clinical manifestations besides impetiginization may include folliculitis [384] and small pruritic pustules that are not always confined to follicles, which may precede exacerbations of AE [40, 65, 136, 143, 160, 287, 334, 384]. Staphylococcal infection may provoke intense pruritus and scratching, hence crusted erosions are more frequently encountered than pustular lesions [143, 160]. Deeper tissue involvement such as furuncles, carbuncles, abscesses, erysipelas and systemic signs of infection such as fever and leukocytosis are rather uncommon [136, 143, 204, 254, 287]. Their occurrence should alert one to the possibility of a hyper-IgE syndrome. The presence of crusted vesicles should initiate the search for viral, particularly herpetic, superinfection [137, 212]. Superinfection of eczematous skin lesions with β-hemolytic streptococci is a rare event [65, 143, 160, 212, 254, 263, 287], as is secondary infection with *Escherichia coli*, anaerobes, predominantly *Peptostreptococcus* species, pigmented *Prevotella*, *Porphyromonas* species, and *Fusobacterium* species in AE lesions, most frequently found in lesions of the finger, scalp, face, and neck, enteric Gram-negative rods and *Bacteroides fragilis* in lesions of the legs and buttocks [42].

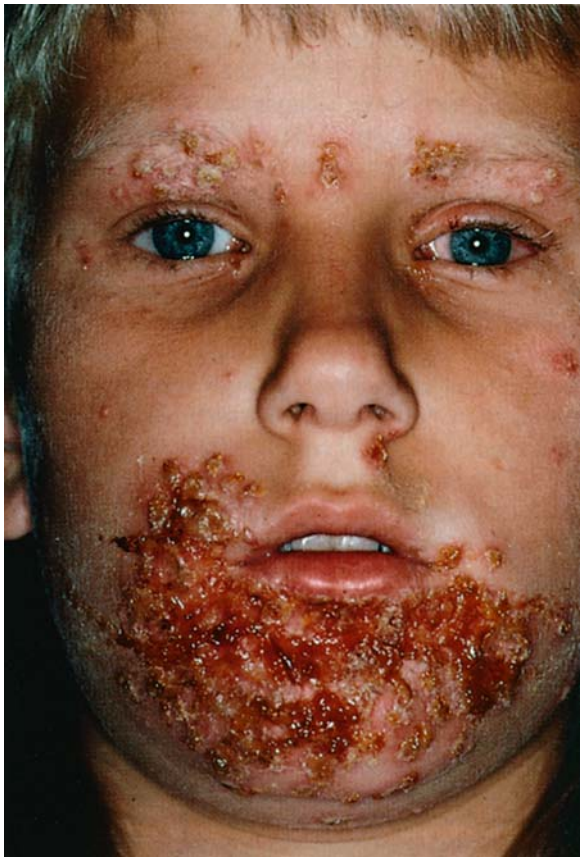

Fig. 12.1. Bullous impetigo in a child with atopic eczema

Adachi et al. [5] report a dramatic increase of streptococcal impetigo associated with AE from 1989 to 1994. The most frequent causative agents were group A streptococci (70.7 %) followed by group G (19.5 %) and group B (9.8 %), in 71.8 % concomitant with *S. aureus*. Impetigo was usually associated with severe eczematous lesions. Recurrence of impetigo and fever occurred at least in one-third of the patients.

However, patients with atopy do not only suffer from bacterial infections of the skin, a higher incidence of infections in the ear, nose, and throat area such as otitis media and sinusitis has been observed [246]. Furthermore, two case reports have recently been described, one of a 4-year-old boy with cutaneous colonization with *S. aureus* and osteomyelitis [328] and one of three children with severe AE and osteomyelitis of the distal phalanges [33]. Another case of olecranon bursitis has been mentioned in the literature [33], as well as other deep infections such as septic arthritis of the hip in a 15-year-old female [193], septic sacroiliitis in children [17], staphylococcal septicemia [163] and acute bacterial endocarditis [265, 278] associated with AE.

12.4 Mycotic Infections

Dermatophytic infections of the skin, hair, or nails show a variety of clinical manifestations ranging from acute discrete or intensely inflammatory skin lesions to chronic recalcitrant ones [342]. In the general population, dermatophytoses are among the most frequently occurring skin disorders (USA: 3.8 % of the population, with 35 % – 45 % of all clinical manifestations

comprising tinea pedis) [343]. Males are more often affected (6.8 %) than females (1.1 %). Infections in children are rare (0.04 % – 1.4 %, males more than females) [344].

The susceptibility to dermatophyte infections is probably influenced by sex, age, and a variety of local factors such as skin disorders accompanied by increased keratinization (e.g., ichthyoses), dryness of the skin, defects of the epidermal barrier function, humidity, and maceration facilitating the colonization by the fungus [342]. In addition to these individual factors, environmental circumstances are also of importance (footwear, profession, sports, etc.) [342, 344]. Atopy, defined as AE, allergic rhinitis, or exogenous allergic bronchial asthma, or as a familial predisposition to these disorders, has been shown in several studies to be associated with a predisposition to acquiring persistent, extensive, usually superficial infections with *Trichophyton rubrum,* predominantly on feet, hands, and nails. Recent epidemiological studies have confirmed the increased susceptibility to infections with *Trichophyton rubrum* and enhanced risk for persistent infections in atopic individuals [142, 180 – 182, 342 – 344, 355].

In the atopic population, intradermal tests have shown diminished delayed-type skin reactivity to *Trichophyton* antigens (especially *T. rubrum* antigens). Most patients with AE showed a lack of delayed response, despite the frequent occurrence of immediate-type reactions to trichophytin [142, 156, 180 – 182, 288, 342, 344, 345]. This may be a sign of cross-reactivity to mold antigens [288]. Atopic respiratory disease seemed to be a more important predisposing factor than AE [180, 182]. The lack of a pronounced inflammatory component is a regular conspicuous finding in chronic dermatophyte infections in atopic individuals. Despite the frequency of superficial mycoses, widespread or severe infection rarely occurs [342, 344, 345].

12.4.1 Atopic Eczema, Pityrosporum Infection, and Head, Neck, and Shoulder Dermatitis

Pityrosporum orbiculare (*Malassezia*) is a saprophytic lipophilic yeast belonging to the normal microbial flora of human skin. Under certain circumstances, it may become pathogenic and cause skin disorders such as Pityriasis versicolor, *Pityrosporum* folliculitis, confluent and reticulate papillomatosis, etc. [37, 57, 306, 373].

Malassezia species may be involved in the so-called head, neck, and shoulder dermatitis (HNS dermatitis). Patients show highly pruritic, intensely inflammatory eczematous skin lesions localized to head, neck, and shoulders. In these patients, *Pityrosporum* species have been isolated from skin lesions. Most interestingly, strong immediate skin reactivity, positive radioallergosorbent tests (RAST), and histamine release could be demonstrated using *Pityrosporum* extracts. It is assumed that in atopic individuals colonization of the skin with *Pityrosporum* species causes IgE-mediated sensitization, leading to flare-up of AE. An additional hint to the causal relationship between HNS dermatitis and *Pityrosporum* species is the response to local or systemic antimycotic treatment with imidazole derivatives, but relapses occur after weeks to months [57, 305, 351, 373, 395].

Newer studies show that HNS dermatitis can be aggravated by *Pityrosporum* species but also by environmental factors such as sweating (81 %), heat (71 %), dryness (70 %), psychological stress (67 %), and sun exposure (50 %). Furthermore, long-term use of topical glucocorticoids might be associated with the development of diffuse erythematous lesions with telangiectasia on the head and neck areas [192].

Other yeasts such as *Candida albicans* have been discussed as flare factors in AE [235], but conclusive scientific evidence for their pathogenetic importance is lacking.

12.5 Viral Infections

Ever since the description of Kaposi's varicelliform eruption (pustulosis vacciniformis acuta) in 1887 [184], numerous publications have underlined the increased susceptibility of AE patients to unusually severe cutaneous infections with vaccinia and, later on, Herpes simplex virus (HSV) [32, 35, 37, 52, 60, 119, 140, 152, 160, 201, 212, 214, 243, 254, 287, 383]. Although Kaposi is generally accepted as the first describer of the varicelliform eruption in eczema vaccinatum, it was Martin in 1882, who attributed this disease to smallpox vaccination [60].

That HSV could cause a clinically similar eruption and illness in patients with AE was not recognized until Esser and Seidenberg isolated and identified it during a small epidemic of such cases in an infants' ward in 1941

[60]. Kaposi's varicelliform eruption due to Coxsackie virus A16 is a rarity [35].

Viral infections in AE may range from harmless problems such as increased incidence of warts and mollusca contagiosa to potentially life-threatening disseminated infections such as eczema herpeticum or vaccinatum. Although exact epidemiological data are lacking, available evidence suggests a slightly higher incidence of HSV 1 and 2 infections, mollusca contagiosa, and, to a lesser degree, common warts in the atopic population compared with nonatopics [35, 64, 70, 119, 140, 263, 287, 317, 332].

12.5.1 Eczema Herpeticum

Eczema herpeticum is a form of disseminated cutaneous HSV type 1 or 2 infection [157]. HSV is a karyotropic DNA virus belonging, together with zoster, Epstein-Barr and cytomegalovirus, to the herpesvirus group. The severity of HSV-induced infections varies from localized and mild transient mucocutaneous lesions to widespread and fulminant, potentially life-threatening, disease [32, 37, 69, 70, 152, 201, 212, 214, 243, 287, 292, 306, 317, 382, 390, 391].

Eczema herpeticum complicates AE mostly in children and young adults [35, 37, 70, 201, 212, 287, 306, 317, 382, 391]. It is characterized by the appearance of initially discrete localized clusters of tiny pruritic superficial vesicles and vesiculopustules that may disseminate over a large skin surface area (Fig. 12.2a–c). They often erupt in crops on erythematous and edematous skin. Individual lesions pass almost simultaneously through developmental stages characterized by vesicles with or without umbilication, pustulation, and crust formation. In severe cases, hemorrhagic and eroded lesions can be observed. Typical locations include face, neck, shoulders, upper trunk, and abdomen, with a symmetrical distribution. The eruption is often accompanied by constitutional symptoms such as fever, headaches, malaise, regional or generalized lymphadenopathy, and, often, exacerbation of AE. Secondary bacterial infection may occur. New crops of lesions may continue to appear for several days, but usually the disease subsides after an average duration of 16 days [35, 37, 98, 135, 177, 201, 212, 214, 243, 254, 287, 306, 383].

The diagnosis of eczema herpeticum is frequently delayed because lesions initially may resemble acute exacerbation of AE or bacterial superinfection with *S. aureus* and occasionally β-hemolytic streptococci; they are frequently excoriated due to pruritus and scratching [37, 70, 177, 201, 212, 254, 287, 306, 383].

Usually eczema herpeticum occurs in patients with active severe and persistent AE, often after prolonged topical or systemic glucocorticoid use. Sometimes, however, even patients in clinical remission or exhibiting minimal atopic skin manifestations such as keratosis follicularis may develop eczema herpeticum [35, 37, 69, 70, 201, 212, 214, 306, 365, 391].

The infection route in eczema herpeticum is often via heteroinoculation from a close contact with a herpes infection such as herpes simplex labialis, but a contact source of HSV cannot be traced in all cases. Incubation time is estimated at 2 – 7 days. Alternatively, reactivation of latent endogenous HSV infection and spread via autoinoculation may lead to disseminated cutaneous disease. In young children, eczema herpeticum may occur as a consequence of primary HSV infection such as gingivostomatitis herpetica. Male children are more often affected than females. Dissemination of the virus may occur cutaneously or systematically via viremia [35, 37, 201, 212, 214, 254, 306, 383].

Eczema herpeticum, particularly if it occurs in the setting of a primary herpetic infection, may occasionally run a serious or even lethal course with internal organ involvement, leading to meningoencephalitis or bronchopneumonia, less frequently to herpes sepsis, hepatitis, colitis, etc. Morbidity and mortality depend upon the extent of internal organ and skin involvement, secondary bacterial infection, and the age and immune status of the patient (prognosis is poorer in young children and immunocompromised individuals). Further complications may include gingivostomatitis herpetica and dendritic keratitis with ulcerations. A careful ophthalmologic examination should be initiated in patients with eczema herpeticum to exclude herpetic keratoconjunctivitis. Recurrent disease may occur and tends to be milder and of shorter duration. Recurrences are frequently limited to areas of eczema and usually lack internal organ involvement [35, 52, 69, 70, 152, 214, 254, 292, 382, 383].

Diagnosis of eczema herpeticum is based upon the clinical picture of an explosive development of a vesiculopustular eruption at the same stage of development occurring in the setting of AE. Diagnosis can be strengthened by cytological examination of a Tzanck

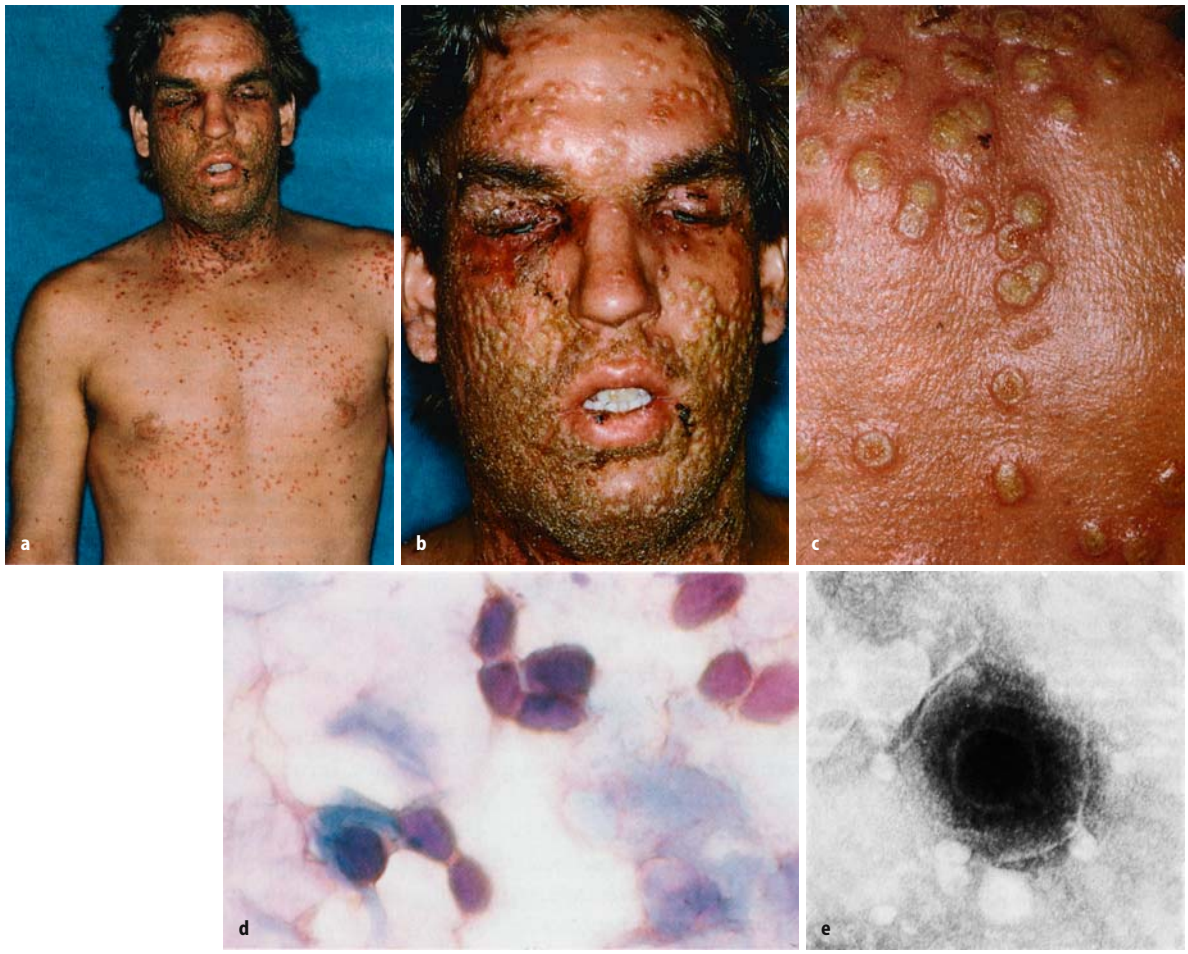

Fig. 12.2. a Eczema herpeticum with widespread monomorphous dissemination of crusted vesicles in a patient with atopic eczema. **b** Detail of **a**. **c** Close-up view of umbilicated vesicles. **d** Tzanck smear of vesicle fluid (courtesy of Dr. B. Gizycki-Nienhaus, Department of Dermatology, University of Munich). **e** Electron-microscopic detection (negative staining technique) of herpes simplex virus in vesicle fluid (courtesy of Dr. W. Stolz, Department of Dermatology, University of Munich)

smear (Fig. 12.2d), showing ballooning degeneration, multinucleate giant cells, and intranuclear inclusion bodies. Rapid diagnosis is possible with electron-microscopic (negative staining) (Fig. 12.2e) or immunofluorescent demonstration of HSV. There is no HSV-specific immune defect found in AE so far, either cell-mediated or humoral [122].

The prognosis of eczema herpeticum has improved dramatically since the advent of effective antiviral agents. Fever and general symptoms rapidly disappear after initiation of intravenous acyclovir therapy [69, 70, 95, 177, 348, 352, 353, 391]. In addition to antiviral therapy, avoidance of secondary bacterial infections should be achieved by adequate local treatment with antiseptic wet compresses or lotions with, for example, quinolone derivatives. In the case of bacterial superinfection, topical and systemic antibiotic treatment should be instituted. Parenteral administration of γ-globulins may be useful in selected cases. Intravenous foscarnet can be used in acyclovir-resistant infection occurring often in immunosuppressed patients [382].

12.5.2 Eczema Vaccinatum

Until recently, poxvirus officinalis vaccination has been required by law in most countries of the world in children and travelers. The first vaccination had to be performed during the 1st year of life, the second by the age of 12. AE, even quiescent, is considered to be an absolute contraindication to vaccination due to the risk of eczema vaccinatum. Exceptionally, vaccinations were given after contact with a known or suspected case of smallpox or to people traveling to endemic smallpox areas. Under these circumstances, vaccination was recommended to be carried out under concomitant protection with antivaccinal hyperimmunoglobulin.

Epidemiological data estimating the risk of eczema vaccinatum in atopic individuals vary according to patient selection [60, 89, 280, 372]. Data from Great Britain suggested that one in 20,000 individuals developed eczema vaccinatum after primary vaccination, with a mortality rate of 6 % [60]. Following an outbreak of smallpox in Stockholm in 1963, 309 persons with AE were vaccinated. In these individuals there was an exacerbation of skin disease in 36 cases and satellite or secondary vaccinial lesions in 27 cases [89]. Patients with severe and persistent AE and those requiring topical or systemic glucocorticoid treatment were at particular risk of developing eczema vaccinatum, but sometimes even individuals with mild disease or in clinical remission were affected [37, 60, 89, 201, 212, 243, 306].

Besides autoinoculation, mostly after the first vaccination, heteroinoculation from a vaccinated family member or close contact with other vaccinated individuals could also cause eczema vaccinatum. Thus, children with AE had to be kept isolated from recently vaccinated persons. In patients with AE, poxvirus officinalis may disseminate either via the cutaneous route or systemically via a viremia phase. The incubation time of eczema vaccinatum is 5 – 12 days. The disease affects males more frequently than females (ratio 2:1) [60, 254]. The severity of eczema vaccinatum varies from localized and mild to fulminant, generalized, potentially life-threatening disease. The clinical picture may be indistinguishable from eczema herpeticum, though vesicles and pustules tend to be larger with thicker walls, show a more pronounced umbilication, and are multilocular. High fever, occurring 2 – 3 days after eruption of vesicles, secondary bacterial infection, prominent regional and sometimes general lymphadenopathy, and flare-up of the eczema may be observed. In uncomplicated cases, defervescence occurred within about 10 days, and the sometimes hemorrhagic vesicles dried up and healed, partly with scarring (Fig. 12.3). Dissemination of virus with organ involvement could lead to a fatal outcome [37, 60, 201, 212, 254, 306].

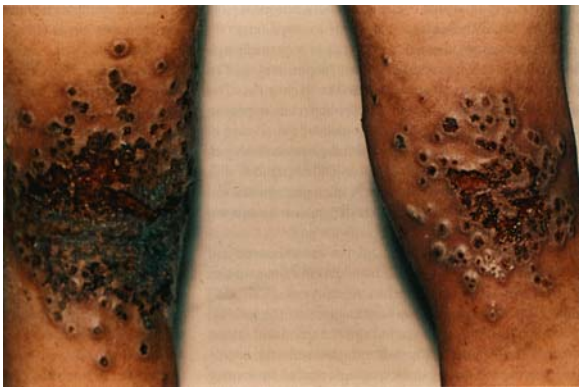

Fig. 12.3. Eczema vaccinatum

Eczema vaccinatum may be clinically indistinguishable from eczema herpeticum; further differential diagnostic considerations include variola vera, modified smallpox, and varicella, as well as disseminated coxsackie virus A16 infection. Initial lesions of eczema vaccinatum may be difficult to distinguish from acute vesicular exacerbation of AE or bacterial superinfection.

Diagnosis and differentiation from eczema herpeticum can easily be achieved by the typical history of vaccination or contact with a vaccinated person and electron-microscopic examination of vesicle fluid. Tzanck smears and histological examination may also aid in diagnosis.

12.5.3 Molluscum Contagiosum

Mollusca contagiosa are a common viral infection, especially in children with AE. Predilection sites are the flexures, most commonly the axillae, neck, and lateral aspects of the trunk. Rarely, dissemination occurs with development of eczema molluscum, an unsightly but rather harmless complication of AE (Fig. 12.4). The risk for developing dissemination of mollusca contagi-

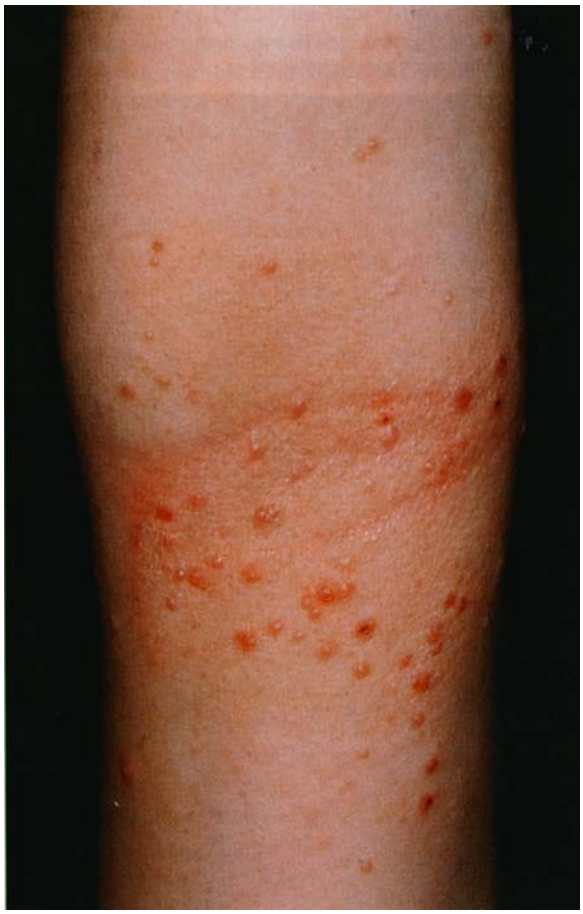

Fig. 12.4. Eczema molluscatum: dissemination of mollusca contagiosa on preexisting flexural eczema

Fig. 12.5. Mollusca contagiosa gigantea

osa increases with long-lasting use of glucocorticoids [119, 254, 272, 218, 232, 389].

The molluscum contagiosum virus is a strongly epidermotropic DNA poxvirus that is 240 × 320 nm in size. The incubation period ranges from weeks to months. The spread of infection occurs directly from person to person or indirectly via bedding, clothes, towels, etc.

The typical skin lesions are shining, whitish to yellowish or pink, hemispherical, umbilicated papules with a smooth, dome-shaped surface. A thick greasy material can be expressed from the central depression by squeezing the papules.

Initial mollusca contagiosa lack the central porus and may be difficult to distinguish from eczematous papules or milia. In atopic children, mollusca contagiosa may cause pruritus and a patchy eczema around the lesions. Mollusca contagiosa tend to be superinfected and after a variable duration (mostly 6–9 months, sometimes persisting for up to 5 years), they show spontaneous inflammatory changes resulting in suppuration, crusting, and eventual destruction of the lesion [37, 201, 212, 243, 306]. Rarely, pediculated tumors or mollusca contagiosa gigantea may occur (Fig. 12.5) [318, 389].

Due to the viral infection, an increased epidermal proliferation occurs, producing lobulated tumors with fibrous septa. The infected epidermal cells undergo necrobiotic changes and appear as so-called molluscum bodies (hyaline bodies up to 25 μm in diameter) containing masses of viral material in the cytoplasm (Fig. 12.6). Numerous molluscum bodies are present near the surface at the center of the lesion [201, 243, 306].

The treatment of choice is mechanical expression of the contents by squeezing the papules with specially formed tweezers and subsequent application of anti-

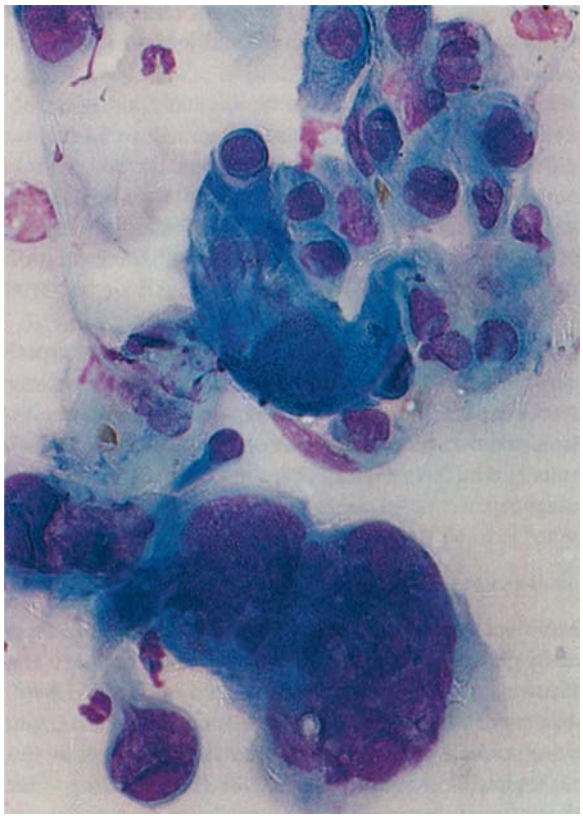

Fig. 12.6. Molluscum bodies in exprimate of a molluscum contagiosum (courtesy of Dr. B. Gizycki-Nienhaus, Department of Dermatology, University of Munich)

septics. If, in children, the number of lesions is very large, e.g., in eczema molluscatum, local anesthetic creams or general anesthesia may be necessary. Alternatively, several treatments with cryotherapy at intervals of 2 – 3 weeks may lead to involution of lesions.

Especially in young children, for whom the recommended treatment modalities may be painful or frightening, application of salicylic acid-containing plaster or local antiseptics may represent alternative treatment choices.

12.5.4 Common Warts

Common clinical experience suggests that viral warts are encountered more frequently and in higher numbers in atopic individuals, particularly children. Patients with AE have an increased susceptibility to spreading

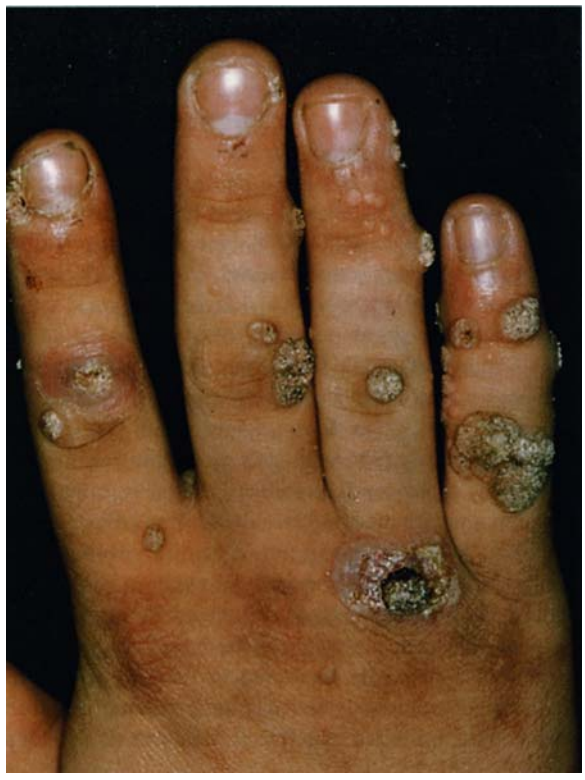

Fig. 12.7. Disseminated warts in a child with mild atopic eczema

recalcitrant infections with human papilloma virus, which are prone to be more resistant to therapy than usual [35, 119, 254, 287]. However, most recent reviews and standard texts (e.g., Jablonska, Rook) provide no information on atopy as a predisposing factor for common and genital warts [161, 175, 306, 323]. Epidemiological studies of warts in the atopic population and of atopy in wart patients are rare. The data of Bonifazi et al. [35] suggest a slight correlation between warts and atopy in children. Gianetti [119] reports an incidence of atopic disease of 13.2 % in children with warts, which does not differ from that in healthy children. Among children with AE, a slightly increased incidence of warts was found (17 %) [35]. Currie et al. [64] also reported an increased incidence of warts among children with AE. In rare cases, a massive dissemination of warts can occur in AE patients (Fig. 12.7), leading to the picture of eczema verrucosum [217, 389]. Clearly, further epidemiological studies are needed to clarify the correlation between atopic eczema and viral warts.

12.5.5 Other Cutaneous Viral Diseases

Bowenoid papulosis of the genitalia associated with HPV type 16 occurred in a 2-year-old boy with extensive AE. The mother gave a history of genital warts prior to delivery. The child's skin lesions resolved spontaneously [39].

A 16-month-old child with generalized AE developed a disseminated orf infection after close contact with infected lambs. The lesions developed particularly in eczematous excoriated skin pretreated with glucocorticoids and resembled clinically granuloma pyogenicum with multiple satellite lesions [82].

Although Strannegard et al. recently reported on a significantly increased frequency of zoster in individuals with AE as compared to nonatopic controls, the incidence of varicella zoster virus infections does not seem to be markedly increased in patients with AE. However, the course of varicella or zoster may be more severe in the presence of active eczematous skin lesions [201, 254, 306, 364].

12.5.6 Extracutaneous Viral Diseases

Reports of an increased frequency of extracutaneous viral diseases support the assumption of a general immune dysfunction as one of the causes of the enhanced susceptibility to infections in AE [106, 311–313, 339, 340]. In a retrospective study of almost 1,000 patients, Strannegard et al. showed that recurrent upper respiratory tract infections were more common in children with past or present history of AE, particularly in those with severe AE, than in nonatopic controls [312, 340]. In a further study, a remarkable correlation between the activity and severity of AE and the incidence of recurrent viral infections of the respiratory tract was found. However, even patients with AE in remission for more than 1 year reported a higher incidence of recurrent viral infections [312, 340].

Serological studies revealed a higher prevalence of elevated Epstein-Barr virus antibodies in AE patients, irrespective of age, and simultaneous bronchial asthma or hay fever than in nonatopic controls. Epstein-Barr virus, a polyclonal B-cell activator, may also play a pathogenetic role in the development of atopic diseases in genetically predisposed individuals. In the early phase of mononucleosis, raised IgE levels may be found [261, 311, 312, 339, 340].

An increased subclinical activation of latent CMV infection was found in patients with aggravated moderate to severe AE [77], but also parainfluenza and respiratory syncytial virus may lead to provocation of atopic diseases, including eczema [313]. Of interest are recent observations of AE in adults infected with the human immunodeficiency virus (HIV) [216, 306]. In children with AIDS [321], as well as in HIV-seropositive haemophiliacs [19], HIV infection led to exacerbation of atopic manifestations in genetically predisposed patients, whereas patients without a prior history of atopic disease did not develop atopic symptoms [123]. One of our patients developed severe AE with eczema herpeticum for the first time at the age of 23, 2 years after contracting HIV-1 infection as a result of intravenous drug abuse. Another patient with previously mild AE and hemophilia showed severe aggravation of his disease after HIV infection from factor VIII concentrate. The question of whether atopic individuals are more susceptible to HIV infection than nonatopic ones should be of great interest in further investigations.

By contrast, improvement or healing of skin lesions in patients with AE about 3 weeks after measles infection has been reported by Boner et al. The improvement paralleled the short-term suppression of cell-mediated immunity, as evident by tuberculin anergy [34]. Nephrosis [34], sometimes possibly associated with atopic disease, hyper-IgE syndrome [41], and alopecia areata [266] have also been reported to improve following measles vaccination and natural measles infection.

12.6 Parasitic Disorders

Infestation with *Acarus siro* var. *hominis* may provoke juvenile AE. Children with AE infected with scabies mites often develop severe pruritus with exacerbation of eczema and secondary skin infections that often persist despite eradication of the mites. In addition, even short-term treatment with antiparasitic preparations may cause irritation of atopic skin and contribute to the aggravation of AE.

A high incidence of atopy was found among patients with scabies, raising the possibility of enhanced susceptibility to infection with *A. siro* in this population. The patients exhibited immediate-type reactivity to

scabies mite antigens on skin and serological testing, which may be caused by cross allergy to pyroglyphid mite species (e.g., *Dermatophagoides pteronyssinus* and *D. farinae).* Atopic individuals were found to develop more serious scabies infections than nonatopic ones [90, 94, 95, 160].

12.7 Exfoliative Erythroderma

Exfoliative erythroderma is characterized by generalized redness, infiltration, and scaling of skin accompanied by systemic toxicity, lymphadenopathy, and fever (Fig. 12.8). Prominent blood eosinophilia may be observed. It often results from exacerbation of a preexisting dermatosis, in 4 % – 14 % of cases from AE. Exfoliative erythroderma in patients with AE may be related to withdrawal of systemic corticosteroids used to control severe disease, to widespread superinfection, or to generalized contact irritant or allergic reactions. The disease may be life-threatening due to cardiac failure, systemic infection, heat loss, protein depletion, etc. [3, 149, 201, 212, 255].

12.8 Associated Ocular Diseases

Depending on selection criteria, up to 40 % of patients [114] with AE may show conjunctival or ocular diseases such as blepharoconjunctivitis, atopic or vernal keratoconjunctivitis, ocular herpes simplex infections, keratoconus, cataracts, or retinal detachment [73, 107].

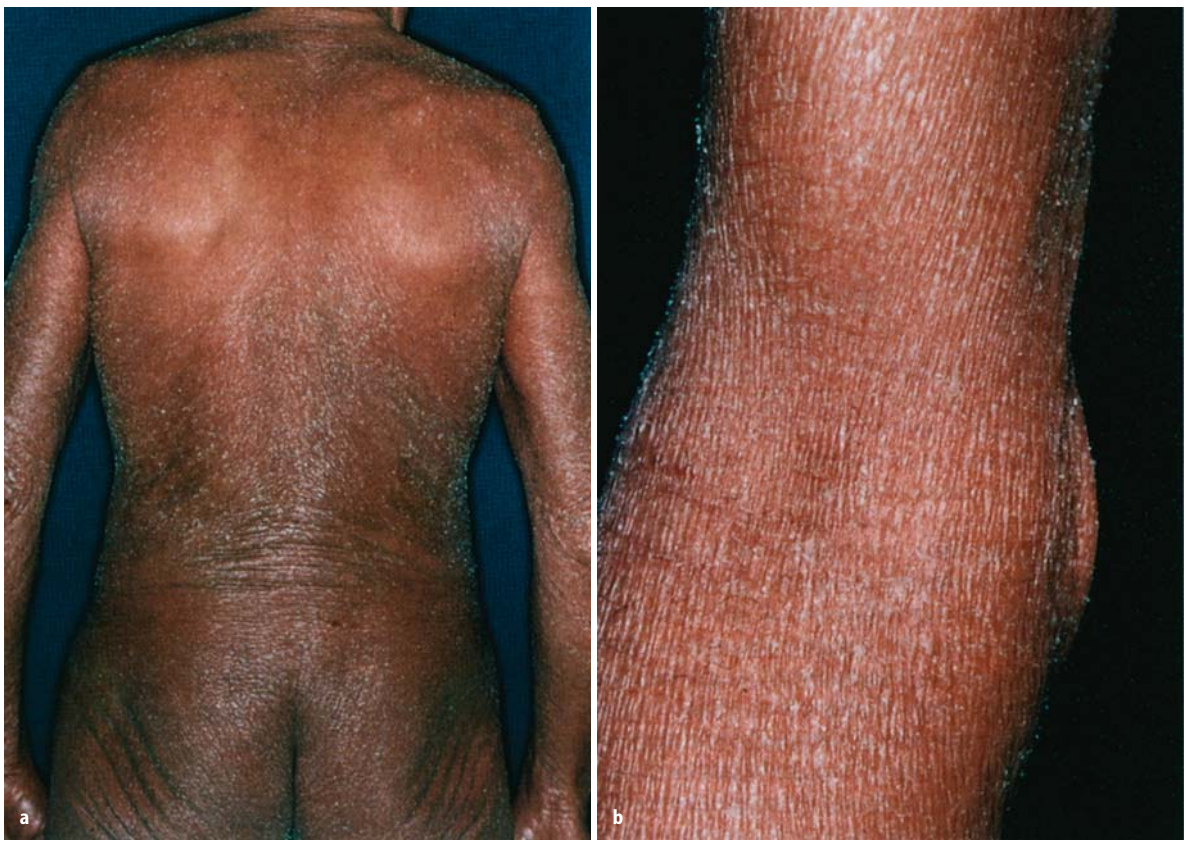

Fig. 12.8a, b. Exfoliative erythroderma with lymphadenopathy in a patient with atopic eczema with massive hyperimmunoglobulinemia E. No unequivocal evidence of Sézary's syndrome was found

Atopic eczema may be associated with seasonal or perennial allergic conjunctivitis or rhinoconjunctivitis as well as with atopic keratoconjunctivitis [107].

In blepharoconjunctivitis, the periorbital skin and the eyelids may show mild dryness and scaling, erythematous, edematous, and exudative or crusted lesions, sometimes associated with severe lichenification (Fig. 12.9) [346]. Secondary staphylococcal impetiginization may occur. There may be hyperemia, chemosis, filamentous exudate, thickening of the bulbar and palpebral conjunctiva, or a giant papillary hypertrophy on the palpebral conjunctiva. The tarsal conjunctiva is thickened, hypertrophic, and milky opaque and causes burning, prickling, and itching sensations [107, 114]. While allergic conjunctivitis is a common association of AE, atopic or vernal keratoconjunctivitis represent rare but more serious ocular disorders and are difficult to treat. Atopic keratoconjunctivitis may persist for months to years and in severe cases the patients show extreme photophobia and lacrimation as well as conjunctival redness accompanied by ocular irritation, itching, and discharge. In rare cases, additional conjunctival scarring or lichenification of the skin of the eyelids may lead to ectropion and constant tearing by shortening of the inferior fornix with symblepharon formation, punctal eversion, and stenosis (Fig. 12.10). In severe cases of atopic and vernal keratoconjunctivitis, corneal scarring, vascularization, and loss of vision have been described. Conjunctival changes may parallel flare-up of eczema. Short-term treatment with topical glucocorticoids and cromolyn eyedrops is useful [107, 114, 126, 164, 178, 185, 206, 269, 299, 302].

Vernal keratoconjunctivitis occurs mainly in children (in males more often than females) and young adults (peak incidence, 11 – 13 years) and is rare after the age of 30 (male to female ratio 1:1 after the age of 20). The patients frequently have a personal or family history of atopic diseases [7, 103, 107, 114, 126, 164, 178, 185, 206, 269, 299, 302]. Vernal keratoconjunctivitis is characterized by a granular appearance, bilaterally and mainly of the upper palpebral conjunctiva with giant polygonal papillae, resulting in a cobblestone-like surface, or by gelatinous swellings at the limbus (more common among dark-skinned patients). Secondary corneal findings are superficial erosions or ulcers and plaque-like deposits in the anterior cornea [7, 107, 114, 315]. Patients' complaints include burning, extreme itching, photophobia, lacrimation, and mucous discharge. Climatic factors may play a role in the pathogenesis of vernal keratoconjunctivitis, since the disease seems to be more common in warm climates than in temperate or cold zones. Allergic (sensitivity to pollen, house dust mites, cat dander) or physical factors may also contribute to the pathogenesis of the disease [7, 20, 24, 103, 107, 315]. Vernal keratoconjunctivitis is usually a self-limited disorder, disappearing after 5 – 10 years. Short-term topical and sometimes systemic administration of glucocorticoids may help influence the inflammatory changes. In addition, topical cromolyn, vasoconstrictors, cold compresses, ice packs, and climatotherapy may be indicated in selected cases [85, 103, 107, 114, 169, 190, 349].

Keratoconus is an unusual cone-shaped ectasia of the cornea that is sometimes associated with AE and was first described by Hilgartner et al. [25, 107, 115].

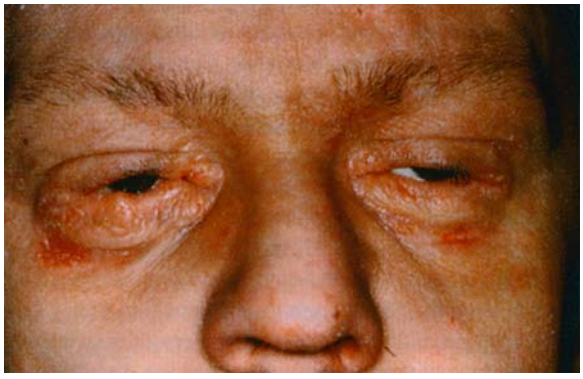

Fig. 12.9. *Lichénification géante* of the eyelids in chronic atopic blepharitis

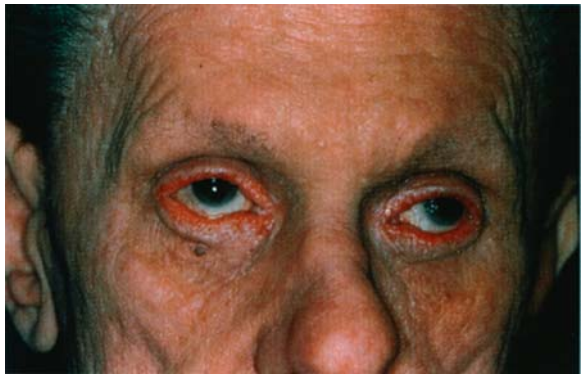

Fig. 12.10. Blepharoconjunctivitis with ectropion formation

Copeman reported that AE was present in 16% of patients with keratoconus [59]. Gasset reported on a significant increase in the prevalence of keratoconus in patients with asthma and/or hay fever, but there was no difference in the incidence of AE compared to the control group [115]. Other studies revealed only rare or no cases of keratoconus associated with AE [10, 44, 200, 209]. It has been suggested that excessive eye rubbing in combination with a thinned and weakened cornea may lead to the development of keratoconus [107, 116]. Keratoconus may occur in severe cases of AE and is rarely apparent before puberty [44, 84, 112, 114, 115, 185, 209, 219, 269, 285, 291, 333].

Itch-induced rubbing of the eyes has also been reported to be responsible for some cases of retinal detachment, but its association with AE is uncertain [10, 58, 61, 150, 168, 171, 185, 187, 194, 247, 252, 269, 368].

The association between cataracts and AE was first described by Andogsky in 1914 [14]. He reported the bilateral development of cataracts accompanying dermatitis in a youth. In 1921, Davis reported a 15-year-old patient suffering from neurodermatitis and asthma who rapidly developed bilateral cataracts. Further publications appearing before the introduction of glucocorticoids in the 1950s supported the possible relationship between cataract in young patients and eczema [23, 43, 58, 62]. AE is the most common skin disease associated with cataracts. On the other hand, the incidence of cataracts among patients with AE is not precisely known, but the disease is uncommon. In selected populations with widespread severe AE involving mainly facial skin, the incidence of atopic cataracts has been reported to range between 0.4% and 33% [44, 262, 269, 319, 361]. In a recent study of 51 AE patients, however, not a single case was identified [54]. Atopic cataracts may appear in early childhood or before the age of 30, with the peak incidence between 15 and 25 years after an average duration of AE of 5–10 years. In most cases, cataracts are subclinical and cause no visual disturbance [10, 23, 44, 48, 54, 61, 90, 114, 116, 185, 186, 219, 247, 248, 262, 269, 314, 319, 368].

In slit lamp studies two types of cataracts associated with AE have been discerned: anterior and posterior subcapsular cataracts. The cataracts are frequently bilateral (50%–70%) and the posterior subcapsular cataract is more frequent than the anterior. While the anterior subcapsular cataract seems to be specific to AE, it is well known that posterior subcapsular cataracts in AE are indistinguishable from those induced by glucocorticoids [81, 269, 302]. Anterior and posterior subcapsular cataracts are probably both the result of similar pathological mechanisms. The ectodermal origin of the skin and the lens invites speculations that there may be common factors in the pathogenesis of skin and lens changes [61, 90, 120]. A significant use of glucocorticoids has been noted in both types of atopic cataracts. This, however, was probably related to the severity of the skin disease rather than the use of glucocorticoids. No correlation was made between the use of glucocorticoids and the development or type of cataract [114, 262, 269, 319]. On the other hand, extensive use of systemic and potent topical glucocorticoids, especially in the periorbital region, has been implicated in increasing the risk of formation of posterior subcapsular cataracts and increased ocular pressure [48, 114, 257, 262, 269, 307, 319, 326, 399]. In a further study, it appeared questionable whether the use of glucocorticoids contributed to the development of the posterior subcapsular cataracts in AE. The complication appeared to be associated with but not necessarily caused by glucocorticoids [114, 262]. Furthermore, enhanced susceptibility to HSV infections such as keratoconjunctivitis may cause scarring of the cornea [84]. No strict dose–effect relation has been found, and individual susceptibility appears to be the most important factor in the development of glucocorticoid-induced posterior subcapsular cataract [48, 319, 330]. Not only psoralen and ultraviolet A (PUVA) therapy has been reported in association with cataract development [63, 129, 132, 336, 392], but more frequently rubbing of the eyes in patients with facial AE, contact lenses, or both seem to be associated with an increased risk of cataract progression [253].

Maruyama et al. [228] reported a moderate to dense pigmentation on the anterior chamber angle in patients with AE, which seemed to be a sign of breaks in the retina or ciliary epithelium, and suggest that the fundus of these patients should be examined carefully for signs of retinal detachment.

12.9 Associated Gastrointestinal Disorders

In up to 20% of patients with gluten-sensitive enteropathy (GSE), scaly skin lesions on the hands, forearms, legs, and face resembling AE have been described. The intensity of the skin disease varies with the severity of

GSE. It may show an improvement on a gluten-free diet and a relapse after reinstitution of gluten-containing food [108, 124, 162]. Other changes or no changes of the mucosa of the small bowel in AE have been reported by different authors [28, 36, 80, 91, 158, 197, 227, 230, 274, 362]. A higher than expected association between dermatitis herpetiformis Duhring, GSE, and AE has been reported by Davies and Buckley and coworkers [45, 72]. However, Leroy et al. reported about the association of AE with bullous linear IgA dermatosis with normal gastrointestinal function [210].

In eosinophilic gastroenteritis, predominantly in patients with primary mucosal involvement, allergic factors have been demonstrated. The exact incidence of AE in this disorder is not known. Associated histories and features of atopic diseases such as bronchial asthma, allergic rhinitis, and AE, as well as elevated total or food antigen-specific serum IgE and food hypersensitivity reactions suggest an atopic nature to this disorder in at least a subgroup of patients. Disruption of the integrity of the lamina propria with a slight villous atrophy or loss of villi, eosinophilic infiltration, and edema of the lamina propria may cause malabsorption, protein-losing enteropathy, gastrointestinal blood loss, and possibly growth retardation and nutritional deficiencies. Small intestinal permeability to potential dietary allergens (e.g., with large molecular weight) may be increased in some patients with AE as compared to noneczematous subjects [16, 26, 28, 36, 49, 80, 91, 96, 111, 158, 176, 188, 197, 226, 227, 230, 274, 279, 375, 376, 396].

An increased incidence of atopy has been found by some authors in inflammatory bowel disease, but this has not been confirmed by others [234, 242, 304]. In some patients with ulcerative colitis or ileitis terminalis, atopy and hypersensitivity reactions may be of possible pathogenic significance. However, in a study of 39 patients with ulcerative colitis and 35 patients with Crohn's disease, no AE and no differences in the frequency of personal or family history of atopy or in serum IgE levels were found. The parents, however, showed significantly more positive prick test reactions to food allergens [234]. Recently, another study showed an association between AE and ulcerative colitis, but not between AE and Crohn's disease [259]. The assumption that hypersensitivity reactions may play a role in the pathogenesis of inflammatory bowel disease is based on three clinical studies showing that sodium cromoglycate was of some benefit to patients with colitis and on reports of increased numbers of eosinophils and plasma cells staining for IgE and elevated histamine content in rectal mucosa [234, 304].

Another study showed that a history of asthma, hay fever, and flexural eczema was significantly more common in adults and children with coeliac disease than in normal controls. In addition, first-degree relatives of patients with adult coeliac disease had an increased incidence of atopic disorders [162, 367].

Gastric hyposecretion and epithelial degeneration in the 1st year of life have been observed in atopic patients, and it has been suggested that this may promote the passage of unchanged food or bacterial antigens through the jejunal mucosa [197].

Two case reports discussed a possible relationship between AE and lymphangiectasia of the small intestine [86, 298]. Dent and Garrets found eczema in six patients with hypocalcemia, steatorrhea, and hypothyroidism [75]. In patients with various widespread skin diseases, including AE, a so-called dermatogenic enteropathy has been described, which is assumed to be secondary to the dermatosis. The enteropathy resulting in steatorrhea rapidly disappears after successful treatment of the underlying skin disease (110, 124, 176, 225, 227, 229, 329].

The reported possible association of AE with intestinal abnormalities (malabsorption, gluten-sensitive enteropathy, subtotal villous atrophy, etc.) and the success of specific therapeutic interventions are interesting features justifying further investigations of intestinal function in patients with severe AE.

12.10 Cystic Fibrosis

Since the report by Lowe in 1949 on the increased prevalence of atopic diseases in patients with cystic fibrosis (CF), a number of publications have confirmed this association although others have disputed it [165, 350, 357, 378, 380]. The occurrence of allergies and atopic diseases is increased in homozygotes as well as heterozygotes for CF [45, 378]. The reason for the increased prevalence of atopy, especially respiratory allergy, in CF is unknown. Increased antigen access and genetic linkage between atopy and CF have been discussed. It is obvious that abnormal mucosal permeability, defective secretory IgA, or failure of antigen clearance at mucosal surfaces may be responsible for this relationship.

Representative figures in patients with CF range from 11% to 49% for the incidence of respiratory allergy or other atopic diseases (AE 8% – 13%) and from 26% to 62% for a positive family history of atopic diseases (significantly increased compared to controls). Immediate skin reactivity to various aeroallergens (especially molds and house dust mites) was present in 43%–88% of patients with CF. No relationship has been found between atopy and severity of CF [165, 349, 357, 378, 380].

12.11 Steroid-Responsive Nephrotic Syndrome

In some atopic patients with steroid-responsive (sensitive) nephrotic syndrome (SRNS; minimal change nephrosis, polycyclic or recurrent nephrotic syndrome), proteinuria and edema appeared to be exacerbated by allergic reactions to aeroallergens (such as pollen and house dust mites) [147, 296, 356, 386, 388] or food antigens (predominantly cow's milk proteins) [101, 316, 379]. The incidence of atopic diseases (40% – 70%) and increased total and allergen-specific serum IgE levels (70% – 100%) is greater in children with SRNS and their first-degree relatives than in controls [101, 128, 233, 264, 269, 359, 379]. The association was stronger in HLA-B12-positive patients [359]. The relative risk of developing SRNS in patients with HLA-B12 and atopy has been reported to be 13 as compared to controls with neither factor [356]. Mouzon-Cambon reported a correlation between SRNS and HLA-DR7, predominantly in patients with associated allergic disorders [245]. Relapses of SRNS may follow allergen exposure and infections, particularly of the upper respiratory tract [147, 233, 296, 316, 379, 386, 388]. The beneficial effects of antiallergic therapy (such as allergen avoidance, specific immunotherapy, etc.) on the course of SRNS are uncertain (233, 300, 316]. However, Sandberg et al. found a decrease in proteinuria in four of six patients with SRNS and cow's milk allergy while on an elimination diet and exacerbation of the disease after oral challenge with cow's milk [316]. In atopic patients with seasonal SRNS, remission may be induced by steroids or measles infection [233, 356]. Trompeter et al. reported a greater tendency to relapse in patients with a history of eczema than in those with other atopic diseases [359].

Poststreptococcal glomerulonephritis may be a rare consequence of superinfection of AE with β-hemolytic streptococci [281]. However, Steiner reported an uncertain coincidence of various types of glomerulonephritis and AE [335]. Kay found only one case of glomerulonephritis in 137 adult patients with long-lasting AE [189].

12.12 Metabolic Disorders

Eczematous skin lesions have been described in a variety of hereditary or nutritional metabolic disorders. Differentiation of the dermatitis from AE has to be considered. Coincidence of AE and metabolic disorders is possible, but due to the rarity of these disorders, the causal relationship remains doubtful [172, 201, 212, 308, 385].

In biotin-responsive multiple carboxylase deficiency, skin lesions have been classified as localized or widespread, atopic eczema-like erythematous dermatitis, frequently superinfected with *Candida albicans*. There is also some similarity in appearance to the periorificial dermatitis of acrodermatitis enteropathica [172, 385].

In 19% – 50% of cases, patients with phenylketonuria show eczematous skin lesions indistinguishable from AE (clinically, histologically, and immunologically) during the 1st year of life [99]. The intensity of skin lesions paralleled the serum level of phenylalanine. The skin lesions clear with appropriate dietary therapy. The proportion of patients with AE having phenylketonuria is unknown but seems to be very low. However, almost half of 21 patients with phenylketonuria showed positive prick test reactions to common allergens [99, 100, 172, 179, 358, 369, 385].

Three of 22 patients with Hurler's syndrome (a hereditary defect in mucopolysaccharide metabolism) seen by Peterson had typical AE, but it is doubtful from the small number of observations whether the incidence is higher than expected for the general population [131, 276]. An eczematous pellagra-like dermatitis (with erythema and scaling), which may be aggravated by exposure to sunlight, is one of the early symptoms of Hartnup's disease (a hereditary aminoaciduria) [172, 213, 385]. Infants with essential fatty acid deficiency are usually quite ill and show a periorificial dermatitis and a scaly dermatosis [145, 385]. Prolidase deficiency is a rare autosomal recessive disorder characterized, among other things, by chronic dermatitis with ery-

thematous and crusted lesions on the face, palms, and soles, ecchymoses, or a fine purpuric rash [172, 322, 385].

Snyderman et al. [331] found in five of six infants below 3 months of age that a diet deficient in histidine resulted in a papular and scaly nonpruritic dermatitis within 3 – 4 days. Lesions were localized predominantly on the face. Any relation to AE was not studied. Reintroduction of histidine led to rapid clearing of lesions after 24 – 48 h. In older infants, skin lesions could not be provoked by this deficiency [331]. On the other hand, histidinemia may also be associated with atopy or AE, although exact data are lacking [118, 173, 238]. Finally, in a study by Zaslow, all 12 patients with atopy showed normal histidine serum levels [398].

12.13 Cutaneous Lymphomas

Mycosis fungoides, Sézary's syndrome, and Hodgkin's disease may initially present with eczematous skin lesions and develop thickening and lichenification of the skin as well as pruritic papules and plaques. Differentiation from AE may be difficult. Some reports suggest that cutaneous T-cell lymphomas can be associated with an atopic diathesis and some authors discuss a possible relationship between AE and Sézary's syndrome or mycosis fungoides. This assumption is based on preexisting AE in some patients with cutaneous lymphomas, the progression of generalized atopic erythroderma into Sézary's syndrome, and the high IgE levels in patients with cutaneous T-cell lymphomas and Hodgkin's disease, with or without a personal or family history of atopy [12, 83, 241, 286, 290, 374, 387]. Regarding other hematological malignancies, no association with atopy was seen in the study of 229 patients with chronic leukemia reported by McCormack [231]. The incidence of atopy in patients with Hodgkin's disease and other lymphomas did not differ from controls in a study by Amlot [11]. However, anecdotal reports hint at possible relations between atopy and cutaneous lymphomas. For example, Zarafonetis reported a single case of reticulum cell sarcoma complicating severe AE [397].

Lange-Vejlsgaard reported on a 13-year-old child with AE who developed a fatal cutaneous T-cell lymphoma [207]. A patient seen by Abel et al. [1], who had received long-term glucocorticoid therapy, showed an association between adult-onset asthma and AE-like skin lesions, markedly elevated IgE, and the development of tumor-stage mycosis fungoides. The eczematous skin lesions may have been initial, specific infiltration of mycosis fungoides in which the diagnosis was overlooked due to topical or systemic treatment with glucocorticoids [1].

12.14 Anhidrotic Congenital Ectodermal Dysplasia

In seven patients with anhidrotic congenital ectodermal dysplasia (ACED), Vanselow et al. found an increased prevalence of atopic diseases and positive prick test reactions to common aeroallergens: bronchial asthma in four patients, allergic rhinitis in three, and AE in three [363]. In addition, other publications have reported an association of ACED with AE, asthma, and a positive family history of atopy [88, 295].

12.15 Growth Impairment

In a recent study in Manchester [67, 203] concerning growth in 89 children aged 1 – 16 years with severe or intractable AE (chronic AE for at least 1 year, more than 5 % of skin surface affected), standing height was compared to national standards. Short stature, defined as a standing height below the third centile when corrected for mid-parenteral height, was found in 22 % of these children. Significantly reduced sitting height and delayed skeletal maturity scores were also found in both boys and girls [67]. Impaired growth was particularly associated with widespread eczema but also with bronchial asthma (which is a known cause of impaired growth) and the use of potent topical glucocorticoids [50, 67, 97, 155, 177, 203, 251]. The cause of growth impairment in AE is not known in most cases, but treatment with potent topical or systemic glucocorticoids, coexisting bronchial asthma, gastrointestinal abnormalities such as malabsorption, or inappropriate dietary restrictions causing malnutrition may contribute to growth impairment [66, 67, 71, 203]. In a 10-month-old infant suffering from extensive AE, large amounts of albumin were lost through the skin, leading to a failure to thrive, hypoalbuminemia, and edema. Treatment with glucocorticoids resulted in a dramatic clearing of

dermatitis and subsequent correction of his hypoalbuminemia, edema, and anemia [2, 354]. Lack of sleep and vitamin D deficiency (perhaps due to avoidance of sun exposure) may be further factors. Growth impairment seems to be a temporary growth delay, but if the short stature is caused by glucocorticoid treatment or if severe AE persists, permanent growth failure may occur [67, 203]. Longitudinal studies will provide further information concerning growth impairment in AE.

12.16 Sleep Disturbances

It is generally acknowledged that sleep disturbance and the ensuing daytime psychological problems of children with AE commonly complicate AE, but the nature of this disturbance, including its physiologic aspects, has been little studied, especially in children. Controversial data are found in the literature. While Stores et al. [338] found out that the 20 school-age children examined in their study suffered from disruption of sleep by both brief and longer awakenings associated with scratching episodes, Reuveni et al. [297] characterized the sleep pattern of 14 children with AE in clinical remission and observed that the AE group suffered more often from arousals and awakenings, but only 15% were related to scratching.

The prevalence and factors associated with snoring and habitual snoring in children are largely unknown, but atopy has been observed as one of the strongest risk factors for habitual snoring, especially allergic rhinitis and AE [53].

12.17 Psoriasis

The coincidence of the common skin diseases AE and psoriasis is not a rare event. Among 1,065 patients with psoriasis, Welp et al. found 18 with simultaneous AE, which is in keeping with the statistical probability [381]. A similar frequency (nine cases of AE in 390 psoriatic patients, 2.3%) was determined by Geyer et al. [117]. Studies by Cristophers and Henseler [55] and Knopf et al. [195], however, showed that the coincidence is rather below the expected frequency [195]. Garofalo showed that the incidence of atopy is significantly higher in inverted psoriasis than in stable plaque-type psoriasis and four times higher than in the psoriatic group as a whole and in healthy children. In this study, no patient showed both skin diseases simultaneously [113].

12.18 Photosensitivity

Although sunlight and therapeutic UV irradiation improve AE in many patients [13, 92, 144, 293], in a proportion of them, estimated at about 10%, AE may deteriorate. The UVB portion of the spectrum may be responsible for aggravation of eczema [277]. Although sunlight may improve or provoke AE [95, 102, 146, 237, 287, 337], the importance of UV irradiation in this effect is unclear, since improvement or aggravation may be explained by a host of unrelated circumstantial factors (relative humidity, scratching, infrared irradiation, pollen exposure, psychological factors, skin care, associated polymorphous light eruption, photoallergy, etc.) [78, 212, 287].

12.19 Drug Sensitivity

The relationship between atopy and drug sensitivity is a highly controversial field. The clinical expression of adverse drug reactions like drug allergy appears to be influenced by several different individual risk factors, and also by genetic factors including atopy [341]. Among atopic individuals, those with bronchial asthma may be at particular risk [15]. It has therefore been discussed by some authors [6, 289, 341] that drug reactions of the anaphylactic type may possibly be more common and more severe in atopic patients due to their increased propensity to produce antibodies on exposure to antigens. Others have not accepted this [130]. In addition, it was reported that atopic persons may also be at increased risk of developing severe, anaphylactoid, IgE-independent reactions to radiocontrast media [15]. An explanation may be the enhanced releasability of inflammatory mediators in atopic subjects. Although the assumption is made by many authors that the allergic/atopic diathesis predisposes individuals to allergic reaction to drugs, the contested association between atopy and drug reactions must be clarified in systematic epidemiological investigations.

12.20 Insect Venom Allergy

Atopic individuals were presumed to be at particular risk of developing Hymenoptera venom allergy [167, 325]. Some recent comprehensive studies, however, have shown that the incidence of atopy or atopic diseases was about the same in subjects with insect venom allergy as in the normal population, whereas others support a certain correlation between venom allergy and atopy. Investigations by Przybilla et al. [282] on the relation of atopy and insect venom allergy showed that atopic patients with positive prick test reactions to common aeroallergens *(Dermatophagoides pteronyssinus*, cat dander, grass pollen) more often had lower Hymenoptera venom prick test thresholds than patients without skin reactivity to these aeroallergens. Furthermore, atopic patients with high total serum IgE levels may have higher Hymenoptera venom-specific IgE concentrations than patients with normal or slightly elevated total serum IgE. These observations have to be taken into consideration in judging diagnostic criteria for insect venom allergy in atopic patients [283, 284]. Miyauchi et al. reported that 47 % of bee keepers with honeybee venom allergy are atopic as compared to 13 % of other subjects allergic to bee venom [239]. Atopic bee keepers may become sensitized more easily via inhalation of bee antigens or frequent stings. Müller reported that atopic individuals develop insect venom allergy earlier and need fewer stings to become sensitized than normal ones [239]. Overall, the data suggest that insect venom allergy occurs, if at all, only somewhat more often in atopic than in nonatopic populations.

12.21 Congenital Perceptive Hearing Loss

Hearing loss has been associated with atopy in some families [15, 198, 209]. A familial aggregation of atypical AE (atypical in age of onset and distribution) and congenital perceptive hearing loss has been described in three of four siblings [198]. In another family, two brothers suffered from bilateral perceptive cochlear hearing loss, AE, and mild palmoplantar keratoderma. There was a predisposition to atopic diseases in the maternal family and palmoplantar keratoderma as a dominant trait in the paternal family [105]. In addition, Seinedari et al. reported an association of Waardenburg-Klein syndrome and AE [324].

12.22 Vitiligo

It is a common clinical impression that an atopic diathesis, though not necessarily AE, is often present in patients presenting with vitiligo [104, 223, 268]. Kierland asserted that vitiligo is seen more frequently in patients with AE [191], but the correlation between the two diseases is not substantiated by epidemiological investigations. In most vitiligo series, the occurrence of AE and other atopic manifestations have not specifically been assessed [51, 199, 267]. When they do coincide, AE often involves not the vitiliginous but the surrounding skin [223].

12.23 Hair Anomalies

Alopecia areata seems to be associated with atopy, particularly in childhood. There are, however, only few recent comprehensive statistical studies comparing these patients to a normal population with regard to the possible link between alopecia areata and AE. Furthermore, there is some evidence that in atopic patients with alopecia areata the prognosis with regard to hair regrowth is worse than in nonatopic patients (Fig. 12.11). In a large North American series, eczema

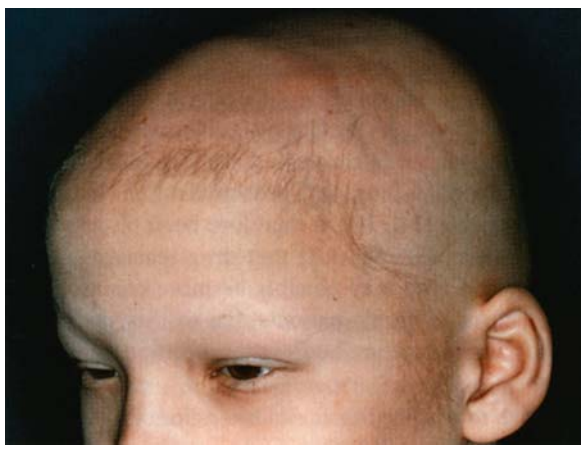

Fig. 12.11. Alopecia areata totalis in an atopic child

and/or asthma were present in 18 % of children and 9 % of adults with alopecia areata; in children with alopecia areata totalis, the incidence reached 23 % [249]. Ikeda (Japan 1965) found 10 % of patients with alopecia areata to be atopic [170] and Penders (Holland 1968) found 52.4 % [273]. In a Danish study, the incidence of AE in patients with alopecia areata was only 1 % [121]. The discrepancies may be due to differences in diagnostic criteria and patient selection [74, 109, 121, 170, 249, 273, 275, 320].

Braun-Falco et al. reported on the coincidence of uncombable hair with hair shaft changes (longitudinal grooves, angular or kidney-shaped cross sections) and pili torti, progressive alopecia areata, and AE in six members of one family [38]. A further report mentions uncombable hair and teeth anomalies in association with ichthyosis vulgaris and AE [205].

12.24 Netherton's Syndrome

AE-like skin changes are also present in Netherton's syndrome, an autosomal recessive disorder characterized by trichorrhexis invaginata, bamboo hairs, ichthyosis linearis circumflexa, and eczematous lesions [46, 127, 202, 204]. The association of Siemens syndrome (keratosis follicularis decalvans) with atopy has also been described in one patient [281].

12.25 Down's Syndrome

Trisomy 21 or Down's syndrome, frequently exhibiting cellular immunodeficiency, may be associated in 25 %–56 % of cases with atopy. Less frequently, autoimmune phenomena such as alopecia areata, vitiligo, and Hashimoto thyroiditis with antithyroidal antibodies occur [47, 276]. During a course of treatment with a topical immunomodulator, rapid regrowth of hair following an attack of measles was reported in an 11-year-old child suffering from Down's syndrome and alopecia areata totalis [266].

12.26 Sudden Infant Death Syndrome

In rare cases of sudden infant death syndrome (SIDS), atopy has been implicated as a possible cause [270]. The assumption is supported by a strong family history of atopic disease in a retrospective study of SIDS and by the high incidence of specific IgE antibodies to *Dermatophagoides pteronyssinus*, *Aspergillus fumigatus*, and bovine β-lactoglobulin [250, 360]. Another study failed to support the interrelation of atopy and SIDS [377]. A further explanation may be allergy to environmental antigens such as cow's milk. A hypothetical mechanism postulates an anaphylactoid reaction to the inhalation of cow's milk proteins regurgitated from the stomach during sleep [270].

12.27 Dubowitz Syndrome

Since the first description by Dubowitz in 1965 [79], the association of low birth weight dwarfism, distinct facial dysplasia, and other associated anomalies as well eczematous skin lesions have been frequently described. In one of our own cases, a 2-year-old boy with Dubowitz syndrome showed features of classical AE [370]. Mohrenschlager et al. [240] report another case of a pair of monozygotic twins with clear-cut AE.

12.28 Eczematous Skin Lesions in X-Linked Immunodeficiency with Hyperimmunoglobulinemia M Syndrome

AE-like skin lesions are common and nonspecific skin manifestations of many primary immunodeficiency syndromes. Other symptoms of atopy such as rhinitis or bronchial asthma are usually absent. Immunodeficiency with hyperimmunoglobulinemia M is a defined primary immunodeficiency syndrome characterized by the absence of or low serum levels of IgG and IgA together with normal to elevated IgM levels and normal T-cell functions. We reported a 3.5-year-old boy with a typical hyper-IgM syndrome associated with AE but in most cases of hyper-IgM syndrome, hitherto described, skin involvement has not been analyzed in detail [371].

12.29 Cutaneous Amyloidosis

Several reports, mostly from Japan, attest to the association of AE and macular amyloidosis of the skin. In some series, up to 25% of patients with amyloidosis showed evidence of AE [30, 24]. Rippled pigmentation of the neck is a special manifestation usually reported as a characteristic of macular amyloidosis in Japan [166, 224, 232]. Manabe et al. [232] showed, however, that in a certain proportion of adults, ripple pigmentation was associated with AE. Amyloid deposits in primary cutaneous amyloidosis may be derived from epidermal keratin [151]. Long-term irritation of the skin such as the chronic scratching in AE may result in amyloid formation in predisposed individuals [224]. Therefore, AE may be one of the underlying disorders causing cutaneous amyloidosis [310]. Shanon [327] analyzed 13 patients with papular amyloidosis and identified AE as the cause in nine of them. In our experience [310], in adult patients of European origin, amyloidosis may complicate chronic AE (Fig. 12.12). More frequently, however, patients with macular amyloidosis of the upper back were misdiagnosed as AE and treated for long periods of time, until the correct diagnosis was established by biopsy with specific histological staining methods.

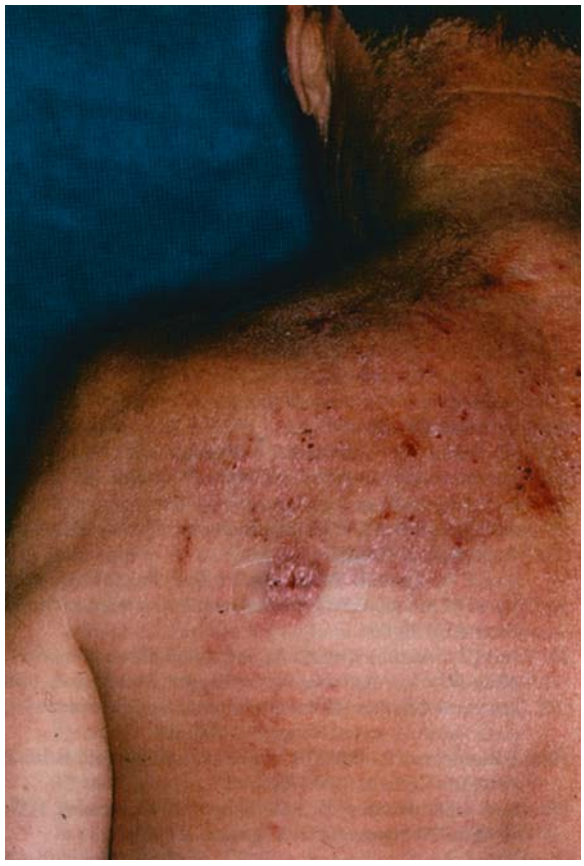

Fig. 12.12. Macular amyloidosis developing on the basis of chronic atopic eczema

12.30 Gynecological Diseases

Nichols et al. [256] reported an increased incidence of atopic diseases in patients with endometriosis. Two other publications reported the association of atopy and persistent lactation [222, 366].

12.31 Neurological Disorders

A neurologic clinical examination and MRI study frequently showed hyperreflexia in the legs and sensory and motor disturbances in the limbs of AE patients. Moreover, a potential association between AE and spondylosis such as intervertebral disc degeneration and bulging/protrusion is described [174].

Eishi et al. [87] detected an impaired sweat response in AE patients attributable to an abnormal sudomotor axon reflex, which was reversed by topical glucocorticoid administration.

12.32 Autoimmune Disorders

Subjects with AE and autoimmune diseases share some similar immune response disorders. Kokkonen et al. [196] showed a significantly increased incidence of autoimmune disorders in atopic patients, especially in patients with early-onset dermatitis who reported recurrent abdominal pains and milk-induced gastrointestinal symptoms.

12.33 Hypoproteinemia

A further complication of AE is hypoproteinemia. The incidence is increased particularly among infants with severe AE. It can be a life-threatening condition owing to hypovolemic shock as a result of hypoproteinemia and vascular infarction as a result of thrombocythemia. However, the pathophysiology of this condition remains unclear. The main route of protein loss is believed to be through the damaged skin. It is of vital importance to diagnose hypoproteinemia at an early stage and start appropriate therapy to prevent hypovolemic shock, vascular occlusion, and growth retardation [260].

12.34 Pityriasis Rosea

Chuang et al. [56] and Björnberg et al. [29] reported an increased incidence of atopy in patients with pityriasis rosea.

12.35 Palmar-Plantar Keratoderma of Unna-Thost

Loh et al. [218] found a high frequency of AE in a cohort of patients with diffuse palmar-plantar keratoderma and suggest that the association between the two skin conditions is much more common than previously recognized.

12.36 Multiple Dermatofibrosarcomata

A few reports on multiple dermatofibrosarcomata have described the disease as a complication of autoimmune diseases or in patients with a history of immunosuppressive treatment or HIV infection. In addition, Yagami et al. [394] recently reported a case of multiple dermatofibrosarcomatas in a patient with AE.

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