10 Differential Diagnosis of Atopic Eczema

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10.1 Introduction

Several studies demonstrate our difficulties in establishing the diagnosis of atopic eczema (AE). Its unknown aetiology, the wide range in symptomatology, and the fluctuating course, including the many eliciting factors, form the background for these difficulties [1].

During the past few decades, several proposals have been made to establish diagnostic criteria for AE [2–5]. The main problem of most criteria is that they are not applicable to both adults and children and do not discriminate between the allergic IgE-mediated and the nonallergic type of AE [6, 7].

The differential diagnosis of AE is closely related to the age of the patient. It includes other forms of eczema, immunodeficiencies associated with eczematoid rashes, infectious diseases and infestations, metabolic diseases, neoplastic diseases and other chronic inflammatory skin conditions (Table 10.1).

10.2 Chronic Inflammatory Skin Diseases

"Eczema" is a nonspecific term often confounding the clinical and histopathologic description of various unrelated inflammatory diseases. All eczemas are histologically spongiotic, but not all spongiotic dermatoses are clinically eczematous. The histology is mainly noncontributive to the diagnosis, as there are no definite features allowing us to distinguish between AE and other forms of eczema. The eczematous eruptions all manifest T-cell proinflammatory mediator involvement, yet may be quite different clinically [8].

Differentiating seborrhoeic dermatitis from AE may be difficult in an infant less than 6 months old. The dif-

Table 10.1. Differential diagnosis of atopic eczema

Chronic inflammatory skin diseases
Contact (allergic, irritant)
Seborrhoeic dermatitis
Psoriasis
Lichen simplex chronicus
Infectious agents
Candida
Dermatophytes
Herpes simplex
Staphylococcus aureus
Sarcoptes scabiei
HIV-associated dermatitis
Immunologic disorders
Dermatitis herpetiformis
Pemphigus foliaceus
Graft-versus-host disease
Dermatomyositis
Malignant Diseases
Cutaneous T-cell lymphoma (mycosis fungoides, Sézary syndrome)
Histiocytosis X (Letterer-Siwe disease)
Congenital disorders
Netherton's syndrome
Dubowitz syndrome
Erythrokeratodermia variabilis
Immunodeficiencies
Wiskott-Aldrich syndrome (immunodeficiency with thrombocytopenia and eczema)
Thymic hypoplasia (DiGeorge syndrome)
Hyper-IgE syndrome
Severe combined immunodeficiency (SCID)
Ataxia teleangiectasia
Metabolic Diseases
Phenylketonuria
Tyrosinemia
Histidinemia
Zinc deficiency
Pyridoxine (vitamin B6) and niacin deficiency
Multiple carboxylase deficiency
Nonallergic reaction to medication
Infliximab

ferential diagnosis of AE and seborrheic dermatitis is most often complicated by the seemingly definite seborrheic dermatitis developing into the later condition. Seborrheic dermatitis is characterized by onset during the 1st days or weeks of life, absence of pruritus, and presence of greasy scaling on a yellow-red base. Involvement of the top of the scalp (cradle cap), axilla, and diaper area makes it more likely the patient has seborrheic dermatitis, whereas excoriated dermatitis involving the extensor surfaces, face, and trunk favour AE.

In patients with well-established AE who become resistant to therapy, the possibility of contact dermatitis to the topical therapy, including allergy to corticosteroid or a preservative, should be considered [9, 10]. In these patients patch testing should exclude allergic contact dermatitis, particularly in the case of localized lesions. Interestingly, in an Australian contact dermatitis clinic, approximately 20 % of total cases consisted of AE without patch test positivity [11]. Three distribution patterns predominated in this study: generalized dermatitis and dermatitis involving only the hands or face.

10.3 Infection and Infestation

Scabies may be misdiagnosed at any age with AE in presence of highly pruritic, erythematous papular lesions. In most cases, the typical burrows can be found on the flexor wrists, finger webs and genitalia. Similar symptoms in other family members may point to the diagnosis scabies. Otherwise there is an enhanced susceptibility to infection with *Sarcoptes scabiei* in atopic patients.

In addition, dermatophytosis and candidiasis as well as infection with *Herpes simplex* and *Staphylococcus aureus* may be confused with skin lesions of AE. Complicating the differential diagnosis, patients suffering from AE are predisposed to these infections and infestations [10, 12, 13].

Diseases of the skin are important signs of HIV infection in which dermatitis and eczema present mostly as seborrheic dermatitis. In children with paediatric AIDS, AE has been described in up to 50 % of cases [14]. HIV-infected adults commonly develop a condition that strongly resembles AE and is sometimes called atopic-like dermatitis [15]. Conditions such as sinusitis, asthma, and hyper-IgE syndrome, and laboratory abnormalities such as elevated IgE levels, eosinophilia, and possible TH1-TH2 imbalances, suggest a predilection for atopic disorders in these patients.

10.4 Immunologic Disorders

Dermatitis herpetiformis Duhring (DHD) is an IgA-mediated blistering skin disease characterized by the presence of granular deposits of IgA in papillary dermis. The skin rash may resemble AE lesions and is gluten-dependent. Less than 10 % of patients with DHD have gastrointestinal symptoms suggestive of coeliac disease, yet they all have gluten-sensitive enteropathy [16].

Pemphigus foliaceus is an acquired superficial blistering skin disease in which IgG autoantibodies target the extracellular region of desmoglein 1, a member of the desmosomal cadherin family, responsible for adhesive function [17]. Due to superficial blistering, intact bullae are rarely found. Therefore, the skin lesions that are often distributed in seborrheic areas can mimic acute/subacute eczema.

The skin symptoms of graft-versus-host disease (GvHD) may resemble AE.

Acute GvHD occurs during the first 100 days after transplantation in up to 50 % of graft recipients, while chronic GvHD develops in about 30 % – 50 %, usually within 100 – 500 days following allogeneic stem cell transplantation [18]. It can involve the skin, liver, gastrointestinal tract, and less frequently the lungs, eyes and neuromuscular system. Initial symptoms of acute GvHD may be pruritus and dysaesthesia or pain of the palms, soles and ears. Maculopapular exanthemas of the face, palms and soles are frequently seen. Acral and perifollicular papules and involvement are typical. In addition, xerostomia and nail manifestations can be seen.

Initial symptoms of chronic GvHD may be a persistent erythema of the face with pigmentation. Chronic GvHD may be limited or extensive, localized (about 20 %) or generalized (about 80 %). Progressive chronic GvHD immediately follows acute GvHD (about 32 %); delayed chronic GvHD occurs after a disease-free interval (about 36 %) and de novo chronic GvHD occurs without prior acute GvHD [18].

Localized chronic GvHD resembles lichen ruber planus, in about 3% a morphea or lichen sclerosus et atrophicus. The generalized form is characterized by scaly erythemas, telangiectasias and pigment anomalies. Chronic disseminated GvHD may be lichenoid or sclerodermiform. Most cases show Wickham's striae of the buccal mucosa. In about 40% of cases, the nails are involved.

The skin findings in dermatomyositis are characteristic, but initially they may be confused with atopic eczema. Dermatomyositis is an immune-mediated disease of the muscle and the surrounding connective tissue which is more common in female patients. It is associated with an increased risk of cancer.

The skin findings in dermatomyositis are characterized by a lilac discoloration of the eyelids (heliotrope rash), often with periorbital edema, and erythematous papules over knuckles (Gottron sign), elbows, knees, and upper chest and back. These lesions are frequently photosensitive. Dilated nail-fold capillary loops can be found at the base of the fingernails. Although proximal and symmetrical muscle weakness is typical, skin lesions may exist without inflammatory myopathy (amyopathic dermatomyositis) [19]. Interestingly, in children the heliotrope rash and Gottron papules classically associated with dermatomyositis appeared less commonly than a rash on the extremities and periungual erythema [20].

Myositis-specific autoantibodies such as Anti-Jo-1, anti-SRP and anti-Mi-2 may be present as antinuclear antibodies, increased levels of immunoglobulins. Creatinine kinase and aldolase levels may not be elevated on initial presentation.

10.5 Malignant Diseases

Unexplained eczema of adult onset may be associated with an underlying lymphoproliferative malignancy. When a readily identifiable cause (e.g. atopy, contactants, drugs) is not found, a systematic evaluation should be pursued. Patients should be evaluated with a careful physical examination, complete blood counts, peripheral blood smears, chest roentgenography, computed tomography of the chest and abdomen, and serum protein electrophoresis.

Cutaneous T-cell lymphoma (mycosis fungoides, Sézary syndrome) mimics several benign skin disorders including eczema. It can present clinically as patches, plaques, tumors or generalized erythroderma [21, 22]. Even though the prognosis is good in most patients with patch-stage disease, extracutaneous spread involving any organ is possible and may eventually lead to death. Sézary syndrome is a systemic variant and manifests as erythroderma with generalized bright red, scaling skin and associated leukemia and lymphadenopathy. Multiple biopsies may be necessary to confirm the diagnosis. Immunophenotyping and T-cell receptor gene arrangement analysis confirming a malignant clone are sometimes helpful in diagnosis. Moreover, in preexisting nonclassified chronic palmoplantar eczema that responds poorly to standard therapies, differential diagnosis of mycosis fungoides-type cutaneous T cell lymphoma of the hands and soles should be considered [23].

Histiocytosis X (Letterer-Siwe Disease). Though principally a paediatric disease, Langerhans cell histiocytosis can affect any age group. It can be unifocal (skeletal) or multifocal (skeletal and/or visceral). Head and neck manifestation may mimic eczema and can thus be misdiagnosed as AE. Typical skin symptoms are crusted purpuric papules and a scaly seborrhoeic-like eruption in the scalp and groin. The disease can vary from a mild cutaneous-only eruption to a severe, life-threatening systemic disease.

10.6 Congenital Disorders

Netherton's syndrome is defined by a triad consisting of congenital ichthyosiform dermatitis with defective cornification, trichorrhexis invaginata (bamboo hair) and severe atopic diathesis with high serum IgE levels and hypereosinophilia. It was originally described by Dr. E.W. Netherton in 1958 [24].

Life-threatening complications during infancy include temperature and electrolyte imbalance, recurrent infections, and failure to thrive. Genetic linkage of the autosomal recessive disorder has been established to the SPINK5 gene locus on chromosome 5q32 encoding the serine protease inhibitor LEKTI (lymphoepithelial Kazal-type-related inhibitor), which is involved in T-cell differentiation [25].

The true incidence of Netherton's syndrome might be as high as 1/50,000, often unrecognized due to chal-

lenging diagnostic problems during infancy and early childhood and overlapping features with AE and other recessive ichthyoses [25].

Skin symptoms are present at birth or develop within the first postpartum days or weeks and can range from ichthyosis linearis circumflexa Comel (ILC) in milder cases to congenital ichthyosiform erythroderma (CIE), which may resemble acrodermatitis enteropathica or Leiner's disease [26]. The skin lesions are often pruritic, resemble atopic eczema, but do not respond to topical corticosteroid treatment and show an unstable, undulating course. ILC appears as erythematous migratory patches surrounded by serpiginous double-edged scales which are usually found in flexural areas. Patients also have skin findings suggestive of AE, such as lichenification and scaling. The scalp is usually quite scaly, but nails and teeth are usually not involved. White dermographism is not present [26].

Skin lesions are usually accompanied by hair shaft abnormalities that develop during early childhood and may result in diffuse alopecia. The hallmark is trichorrhexis invaginata (bamboo hair), but other abnormalities, including pili torti (twisted hair) and trichorrhexis nodosa (hair of varying diameter), have been observed.

However, there can be several similarities to AE, i.e. frequent eczematoid appearance, onset in infancy, frequent pyogenic superinfection, elevated total serum IgE levels, concomitant food allergies, anaphylactoid reactions, and respiratory allergy, including asthma. T-cell numbers are reduced and the T-cell response is impaired, whereas peripheral eosinophilia is common [26].

Clearly excluding the differential diagnoses may also be of importance with respect to treatment. For example, it has been shown that children with Netherton's syndrome who responded to treatment with 0.1 % tacrolimus ointment had substantial percutaneous absorption of the drug, with serum concentrations well above the therapeutic range [27]. Therefore, it has been recommended that the diagnosis of Netherton's syndrome should be considered in any infant or child with extensive erythroderma resistant to treatment and these patients should be monitored for blood tacrolimus concentrations [28].

Dubowitz syndrome is an autosomal recessive disorder defined by a syndrome phenotype on the basis of clinical descriptions. The facial appearance is characteristic and present in most patients. The phenotypic spectrum is quite variable and ranges from normal growth and head circumference with mild psychomotor retardation and lack of eczema to a condition of severe intrauterine growth retardation, mental retardation, microcephaly, and uncharacterized eczematous skin lesions in 40 % [29].

10.7 Immunodeficiencies

Any patient presenting with an eczematoid skin rash dating from the 1st month of life should be carefully followed for the possibility of an immunodeficiency disorder, particularly if recurrent infections and failure to thrive complicate the clinical course. Most of these conditions could be diagnosed by means of screening for lymphopenia or for T-cell deficiency in cord blood at birth. Long-term prognosis is poor; few patients survive beyond their teens.

Wiskott-Aldrich syndrome is a condition with variable expression characterized by a mixed humoural and cellular immune disorder associated with a flexural rash indistinguishable from AE. The diagnosis is usually suggested by haemorrhagic diathesis associated with small platelets and commonly includes immunoglobulin M deficiency. It represents an X-linked (Xp11.22) recessive syndrome, thus found almost exclusively in boys, characterized by eczema, thrombocytopenic purpura with normal-appearing megakaryocytes but small defective platelets, and undue susceptibility to infection [30]. Atopic symptoms are frequently present, and eczema develops in 81 % of patients. Atopic dermatitis and recurrent infections usually also develop during the 1st year of life. The eczema may improve as the patient gets older, although serious complications such as secondary infection (e.g. cellulitis, abscess) or erythroderma can occur. Infections, vasculitis, and bleeding are major causes of death, but the most common cause currently is EBV-induced lymphoreticular malignancy [30]. The genetic basis of the disease is a mutation in the gene for the Wiskott-Aldrich syndrome protein (WASP), which is found only in blood cells and is involved in the organization of the actin cytoskeleton [31]. Interestingly, in Wiskott-Aldrich syndrome, there is a defective expression of CD43 in blood mononuclear cells, which appears to be rather increased in atopic eczema [32]. In classic Wiskott-Aldrich syndrome, IgM levels are low and IgG levels are relatively normal, but IgA and IgE levels may be elevated.

Thymic hypoplasia (DiGeorge anomaly) is a congenital immunodeficiency that is usually diagnosed shortly after birth because of abnormal facies, hypocalcaemia or cardiac manifestation. However, it may be confused with AE because severe eczema can be present [33]. DiGeorge anomaly is associated with microdeletions from chromosome 22q11.2 and leads to hypoplasia or aplasia of the thymus and parathyroid glands, often associated with anomalies of the great vessels, oesophageal atresia, bifid uvula, upper limb malformations, congenital heart disease, a short philtrum of the upper lip, hypertelorism, an antimongoloid slant to the eyes, mandibular hypoplasia, and low-set, often notched ears [30]. Phenotypically similar syndromes are collectively grouped under the acronym CATCH-22 (cardiac defects, abnormal facies, thymic hypoplasia, cleft palate, and hypocalcaemia resulting from 22q11 deletions). DiGeorge anomaly is the most frequent contiguous gene deletion syndrome in humans occurring in about one case per 3,000 persons.

Depending on T-cell proliferative response to mitogens, DiGeorge anomaly can be classified as partial or complete. Patients are usually only mildly lymphopenic, but the percentage of CD3+ T cells is variably decreased. Immunoglobulin concentrations are usually normal, although IgE may be elevated.

Total serum IgE levels up to several thousand units per millilitre give a differential diagnosis with the hyper-IgE syndrome, which is characterized by scalp and face eruptions with fine papular and sometimes pustular skin lesions and chronic eczematoid dermatitis usually manifesting itself early in life, and is often complicated by deep tissue infections such as skin and respiratory staphylococcal abscesses, sometimes associated with candidiasis [34,35]. The bacterial infections generally commence in infancy or early childhood involving the skin and sinopulmonary tract. The "cold" abscesses (large fluctuant mass, that is neither hot nor tender and is not associated with fever or signs of inflammation) are occasionally seen and are pathognomic but not essential to the diagnosis. There is typically an absence of atopic symptoms, wheeze or family history of atopy.

Coarse facies, mild eosinophilia, lymphomas, cryptococcal meningitis, neutrophil chemotactic dysfunction, and mucocutaneous or systemic fungal disease are variable features [35].

The importance of clinical differentiation of hyper-IgE syndrome from AE is important because treatment and prognosis are different. Hyper-IgE syndrome should be considered in children with staphylococcal pneumonias or recurrent abscesses complicating chronic eczema. The rash is typically pruritic, often lichenified, and in a distribution atypical for true AE. The dermatitis will often improve with prophylactic antibiotics alone, unlike atopic dermatitis [36].

Severe combined immunodeficiency (SCID) is a fatal syndrome of diverse genetic cause characterized by profound deficiencies of T- and B-cell (and sometimes NK-cell) function [30]. During the first few months of life, infants present with frequent periods of diarrhoea, pneumonia, otitis, sepsis, and cutaneous infections. X-linked SCID is the most common form, although mutated genes have been demonstrated on several autosomal chromosomes [30].

10.8 Metabolic Diseases

Eczematous skin lesions have been described in a variety of hereditary or nutritional metabolic disorders. However, in rare diseases, e.g. histidinaemia, prolidase deficiency, Hartnup's disease (hereditary aminoaciduria), and multiple carboxylase deficiency, precise data with respect to AE and/or atopy are lacking.

In up to 50 % of cases with phenylketonuria, eczematous lesions indistinguishable from AE lesions occur during the 1st year of life and clear with appropriate diet avoiding phenylalanine. The disease is caused by mutations in the phenylalanine hydroxylase (PAH) gene, resulting in elevated concentrations of phenylalanine and phenylalanine metabolites (phenylketones) in the body fluids. This autosomal recessive disorder demonstrates extensive genetic and clinical variability, occurs in one of 15,000 births and is most common among persons of Western European background [37]. Untreated, affected individuals develop severe to profound mental disabilities, behavioural difficulties, seizures, rashes, pigment dilution, and an unusual body odor.

Acrodermatitis enteropathica is a rare autosomal recessive disorder caused by impaired absorption of zinc from the gastrointestinal tract. It is characterized by acral and periorificial dermatitis, alopecia and diarrhoea, although the complete presentation is seen in only 20 % of patients [38]. Retardation of growth and secondary infections are frequently observed. Morphologically, erythematous scaly plaques and eczematous or vesiculobullous lesions can be found. Nail

Table 10.2. Synopsis of some differential diagnoses of atopic eczema in early infancy

Feature	Atopic eczema	Seborrheic dermatitis	Netherton's syndrome	Dubowitz syndrome	Hyper-IgE syndrome	Wiskott-Aldrich syndrome	DiGeorge syndrome	Phenylketonuria	Scabies
Age of onset	>2 months	First days or weeks	At birth or first days to weeks	At birth or first years	1–8 weeks	At birth or first years, rare cases are first detected in adults	At birth	First year of life	Any age
Sex	Male = female	Male = female	Male = female	Male = female	Male = female	Almost exclusively males	Male = female	male = female	Male = female
Prevalence	Common	Common	Rare 1/50,000 births	Rare	Very rare	4/1 million live male births	1/3,000, most frequent gene deletion syndrome in humans	1/15,000 births; most common in Western Europe	Middle
Genetic abnormality	Unknown	None	Chromosome 5q32, SPINK5 gene mutation of LEKTI	Unknown	Chromosome 4q deletions	Chromosome Xp11.22–23, WASp gene mutations	Chromosome 22q11 deletions	Chromosome 12q24.1, PAH gene mutations, extensive genetic variability	None
IgE level	Normal to very high	Normal	Very high	May be elevated	Extremely high	May be elevated	May be elevated	Normal	Normal to high
Eosinophilia	Frequent	Uncommon	Frequent	Possible	Frequent		Uncommon	Uncommon	Frequent
Other laboratory findings					Neutrophil chemotactic defect	IgM deficiency, small platelets, reduced CD43 on lymphocytes	Defective T-cell function, hypocalcaemia in 60%	Phenylalanine and metabolites are elevated in body fluids	
Eczema	Typical morphology and distribution (age-dependent), pruritic, excoriated	Axillae, diaper area, often not pruritic and not excoriated	Resistant to topical corticosteroids	Uncharacterized	Atypical, scalp and face eruptions, chronic eczema typically pruritic, often lichenified	In 81% of patients, responsive to topical steroids	Atypical, may be severe	Indistinguishable from AE lesions, clears with diet avoiding phenylalanine	Atypical, flexor wrists, finger webs, genitalia
White dermographism	Common	Uncommon	Absent	Uncommon	Uncommon		Uncommon		Uncommon
S. aureus infection	Superficial (skin)		Superficial (skin)		Deep-seated (sepsis)	Common	Common		Rare
Other infection	Rare	Rare			Common, serious	Common, serious	Common, serious		Rare
Respiratory allergy	Common	Uncommon	Common		Absent	Common	Uncommon	About 50%	Rare
Food allergy	Common	Uncommon	Common		Absent		Uncommon		Rare
Coarse facies	None	None		Common	Common	None	Common	None	None
Other findings			Hair shaft anomalies	Mental retardation, growth retardation	"Cold" abscesses	Bleeding	Congenital heart disease, thymus hypoplasia, hypo-parathyroidism	Mental disabilities, seizures, pigment dilution, unusual body odor	Similar symptoms in family members

changes such as onychodystrophy, onycholysis, and paronychia, and oral and ocular manifestations such as stomatitis, perlèche, blepharitis, conjunctivitis, and photophobia may occur.

Very recently, nonallergic reactions to medication resulting in AE-like eruption have been published. Two cases were reported in which successful treatment with infliximab for rheumatoid arthritis precipitated AE-like skin lesions [39]. In both cases the skin reaction was nonallergic. Infliximab's mechanism of action involves alteration of the cytokine pattern with suppression of type 1 T-cell response and thus infliximab therapy may result in a type 2 T-cell pattern which is characteristic for AE.

A synopsis of the most important differential diagnoses in infancy and adulthood is given in Table 10.2 and Table 10.3, respectively.

10.9 Conclusion

More than 20 years have passed since the publication of Hanifin and Rajka's criteria for the diagnosis of AE, but there is still no objective laboratory or genetic test for establishing the diagnosis of AE, which continues to be based on the presence or absence of a constellation of signs and symptoms. Several other proposals to optimize clinical criteria have been made but have failed to be applicable in every clinical setting. Clinical criteria are imprecise and no amount of mathematical, statistical manipulation or validation will make them precise. This may explain our difficulties in the differential diagnosis of AE.

We have clearly gained new insights into the immunologic pathophysiology of AE, i.e. the role of T lymphocytes, particularly CD4+ and CD8+, eosinophils and antigen-presenting cells, and we now know that the role of specific sensitization is more and more questionable in the manifestation and course of AE. Thus, perhaps future diagnostic strategies may be based upon immunologic changes found in both the nonallergic as well as the allergic type of AE, but not in other eczematous conditions such as immunodeficiencies associated with eczematoid rashes, infectious diseases and infestations, metabolic diseases, neoplastic diseases and other chronic inflammatory skin conditions.

Table 10.3. Synopsis of some differential diagnoses of atopic eczema in adults

Feature	Atopic eczema	Seborrhoeic dermatitis	T-cell lymphoma	Contact dermatitis	Scabies	Pemphigus foliaceus	GvHD
Age of onset	Any age	Any age	50 – 60 years	Any age, mostly adults	Any age	Middle age	Any age
IgE level	Normal to very high	Usually normal	Usually high	Usually normal	May be elevated	Usually normal	Usually normal
Eosinophilia	Common	Rare	Rare	Rare	Common	Rare	Uncommon
Eczema	Typical morphology and distribution, pruritic, often excoriated	Atypical, seborrheic areas, often not excoriated and not pruritic	Atypical, persistent scaly patches poorly responding to topical steroids	Often localized	Involvement of flexor wrists, finger webs and genitalia, typical burrows	Atypical, in seborrheic areas, superficial	Atypical, papulosquamous eruptions, lichenoid
White dermographism	Common	Rare	Rare	Rare	Rare	Rare	Rare
Pruritus	Typical	Rare	Common	Possible	Typical	Uncommon	Common
Respiratory allergy	Common	Uncommon	Uncommon	Uncommon	Uncommon	Uncommon	Uncommon
Food allergy	Common	Uncommon	Uncommon	Uncommon	Uncommon	Uncommon	Uncommon
Other findings			T-cell receptor rearrangement	Positive patch test	Similar symptoms in family members	IgG autoantibodies to desmoglein 1	

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