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Online Supplement

Guidelines for diagnostic testing in adults with presumed atopic dermatitis refractory to treatment

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Supplemental Table 1. Summary of indirect evidence

Summary of review findings	Studies (participants)	Supporting evidence details
Misdiagnosis of adults with presumed AD unresponsive to standard therapy(-ies)		
Misdiagnosis is a concern for adults diagnosed with AD that does not respond to conventional therapy. **Adults with misdiagnosed AD may experience initial improvement with TCS and/or dupilumab use followed by a subsequent worsening of skin symptoms** **Misdiagnosis resulted in delay of diagnosis & appropriate treatment of between 1 month and 7 years.** **Diagnostic testing including skin biopsy, scrapping & patch testing was required in all cases to arrive at an appropriate diagnosis**	3 case series[1-3] (n= 183) 40 case reports[4-43] (n= 75)	Three case series consistently demonstrate that the rate of misdiagnosis of adults treated for presumed AD that is resistant to conventional therapy may be between **20 and 47%**. **60/183 (32.8%)** participants initially diagnosed with AD were subsequently diagnosed with a different condition via diagnostic testing including biopsies, skin scraping, and patch testing, following incomplete/no response to conventional AD therapies. 75 adults were diagnosed & treated for AD that was subsequently diagnosed as another condition including: ACD (n=2) Autoimmune conditions (n=2) CTCL (n=32) Cutaneous lupus (n=1) Eosinophilic pustular folliculitis (n=1) Familial benign chronic pemphigus (n=1) Infection (n=1) Hairy cell leukemia (n=1) Adenocarcinoma (n=1) BCC (n=1) Multisystem Langerhans cell histiocytosis (n=1) Non-Hodgkin lymphoma (n=1) Pityriasis rubra pilaris (n=2) Scabies (n=25)
Concomitant allergic contact dermatitis in adults with atopic dermatitis		
Adults with AD may also develop concomitant ACD resulting in residual or new localized dermatitis. **Residual facial dermatitis is especially common in cases of concomitant ACD** **Studies including adult AD patients with recalcitrant AD report a concomitant ACD rate of 7.0% to 69.6%.**	11 case series/cohort studies[44-54] (n=83,980) 3 case reports[55-57] (n=5)	-5 adults with AD and residual facial/head/neck dermatitis following dupilumab were diagnosed with ACD following patch testing. -One study reported an increased likelihood of ACD in adults with AD: OR 12.7 - Studies report a wide range of rates of concomitant ACD in adult AD from 7% in a population of AD patients treated with dupilumab but experiencing persistent localized dermatitis or eczema flares to 91.4% in a study of patch-tested AD patients on dupilumab.
Concomitant conditions, other than ACD, affecting the skin in adults with AD		
Adults with AD may develop concomitant conditions resulting in residual or new localized dermatitis.	3 case reports[41, 58, 59] (n=5)	5 adults with a diagnosis of AD were subsequently diagnosed with a concurrent condition affecting their skin: -Malassezia hypersensitivity (n=2) -Rosacea, dermatophytosis, and actinic keratosis (n=1) -Varicella zoster infection (n=1) -Pityriasis rubra pilaris Type II (n=1) -Patch testing or biopsy was required in all cases to confirm concomitant conditions.
Change in clinical management		

In adults with presumed AD, diagnostic testing due to refractory dermatitis and/or the development of other skin symptoms can lead to a change in management due to confirmation of concurrent conditions or alternative diagnoses. **Diagnostic testing in presumed AD is prompted by refractory dermatitis and/or the development of other skin symptoms during AD treatment.**	8 case series[2, 3, 44, 54, 56, 60-62] & 40 case reports[5, 6, 8-11, 13-17, 19-29, 31-43, 55, 57-59, 63] (n=218)	For 218 patients with presumed AD a change in clinical management was initiated following diagnostic testing.
Clinical improvement following diagnostic testing in adults with presumed AD		
Diagnostic testing in adults with presumed AD refractory to therapy generally results in clinical improvement due to management changes initiated by the results of the diagnostic testing. **Diagnostic delay may result in worsening of clinical condition due to advanced progression of the underlying condition.**	8 case series[2, 44, 54, 56, 60-62] & 36 case reports[5, 6, 8-10, 13-17, 19-29, 33-35, 37-43, 55, 57-59, 63] (n=173)	-Across 173 patients, diagnostic testing prompted by refractory skin symptoms in adults with presumed AD led to management changes resulting in improvement or cure of skin symptoms in 142/173. -One case demonstrates the diagnostic delay of scabies resulted in the need for surgery & development of a MRSA infection. -Several cases (n=6) of initially misdiagnosed CTCL resulted in rapid progression of disease after management change, and in one case death, due to the delay in appropriate therapy.

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Supplemental Table 2. Duration of symptoms, delay in best management, and time on systemic therapy for atopic dermatitis

Study	Duration of symptoms*	Delay in best management	Time on systemic therapy for AD
Allergic contact dermatitis			
Ashbaugh 2022 (n=14)	-	Mean 3 months	-
de Beer 2019 (n=2)	-	-	3 months (Dupi) 6 months (Dupi)
Deschamps 2019	-	72 months	-
Navarro-Trivino 2021	-	-	12 months (Dupi)
Suresh 2018 (n=3)	-	-	6 months (Dupi) 9 months (Dupi) 3 months (Dupi)
Average time on dupilumab before change in diagnosis: 6.5 months ; Median 6 months (range 3-12 months)			
Autoimmune conditions			
George 2006	120 months	-	-
Zhang 2021	60 months	-	-
Average duration of symptoms: 90 months			
Cutaneous T-cell lymphoma			
Ayasse 2021	48 months	36 months	23 months (MTX) 13 months (Dupi)
Chiba 2019	132 months		1 month (Dupi)
Espinosa 2020 (n=4)	24 months 240 months “several years” 84 months	24 months NR NR 84 months	8 months (Dupi) 4 months (Dupi) 27 months (Dupi) 15 months (Dupi)
Fletcher 2004	84 months	84 months	-
Foo 2016	24 months	-	-
Kawamoto 2024	12 months	12 months	8 months (oral prednisone)
Krishan 2004	18 months	18 months	-
Lazaridou 2020	228 months	-	3 months (cyclosporine) 2 months (Dupi)
Miyashiro 2020	12 months	12 months	2 months (AZA) 4 months (Dupi)
Moguel 2006	-	24 months	12 months (cyclosporine)

Newsome 2021 (n=2)	72 months 60 months	72 months 60 months	5 months (Dupi) 6 months (Dupi)
O'Neil 2023	-	12 months	12 months (Dupi)
Poyner 2019	-	-	1 month (Dupi)
Russomanno 2020	12 months	12 months	2 months (Dupi)
Sokolowska-Wojdylo 2011 (n=4)	48 months 156 months 240 months 144 months	- - - 144 months	3 months (prednisone/CSA) 8 months (MTX/CSA/mycophenolate) 6 months (CSA) 96 months (CSA)
Toker 2023	10 months	8 months	6 months (Dupi)
Tran 2020	60 months	60 months	5 months (Dupi)
Umemoto 2020	24 months	24 months	2 months (Dupi)
Zhou 2018	192 months	-	-
Average duration of symptoms: 87.5 months; Median 60 months (range 10-240 months) Average delay in best management: 42.9 months; Median 24 months (range 8-144 months) Average time on systemic therapy for AD: 12.5 months; Median 6 months (range 1-96 months)			
Eosinophilic pustular folliculitis			
Li 2024	120 months	-	-
Familial benign chronic pemphigus			
Chen 2023	240 months	-	-
Infection			
Liu 2023	12 months	12 months	-
Malignancies (other than cutaneous T-cell lymphoma)			
Chuang 2012	8 months	3 months	-
Natsuga 2007	36 months	36 months	
Average duration of symptoms: 22 months Average delay in best management: 19.5 months			
Multisystem Langerhans cell histiocytosis			
Cheng 2024	24 months	24 months	7 months (Dupi)
Pityriasis rubra pilaris			
Al Khalifa 2023	-	36 months	-
Scabies			
Lewin 2010	12 months	12 months	-
Wu 2024 (n=23)	Range 0.5 to 7 months		-

*Cutaneous symptoms in adulthood

Supplemental Table 3. Cases of atopic dermatitis misdiagnosis

Cases of presumed atopic dermatitis in adults refractory to conventional therapies and subsequently diagnosed as an alternative condition. All cases are identified as misdiagnosed adult atopic dermatitis by investigators (may include adults with a previous history of AD, whose current condition was mistaken as a continuation of AD).

Study	Patient(s) (age, gender) AD History	Initial treatments	Factors leading to diagnostic testing (body distribution & symptoms)	Subsequent diagnosis	Time to subsequent diagnosis/diagnostic delay	Initial method of subsequent diagnosis (include # of biopsies performed)	Management change	Outcome of management change
Allergic contact dermatitis								
Deschamps 2019[1]	51 years, F of Hx childhood AD with 6-year hx "evolving" dermatitis dx as adult AD	Emollients & TCS	Hospitalization for treatment of AD flare -pruritic eczermatiform dermatosis with flares affecting the face, neck, forearms, elbow folds, and back -No skin atrophy, mucosal or extra-cutaneous involvement	ACD caused by methylisothiazolinone	6 years (disease had been evolving since February 2011, with dx in May 2017)	Skin biopsy (n=1), blood test, allergological work up	Allergen avoidance	"excellent skin condition" with disappearance of eczema at 8 wks
Mohamoud 2017[2]	39 years, M Hx of AD since childhood	"intensive topical therapy"	Uncontrolled dermatitis on chest, arms, thighs, head & neck but easily controlled on hands	ACD caused by textile dyes	NR	Patch test	Allergen avoidance (undyed clothing)	"Significant improvement" in dermatitis at follow-up
Autoimmune conditions								
George 2006[3]	67 years, M 10-year hx of pruritic skin lesions, dx of AD	TCS; triamcinolone 0.1% ointment	Occasional "water blisters" on elbows and knees that cleared with TCS use -excoriated erosions on buttock -Constipation	Dermatitis herpetiformis	10-year hx of dermatitis	Skin biopsy (presumed n= 1); serology testing	NR	NR
Zhang 2021[4]	61 years, F 5-year hx of generalized dermatitis dx as AD	NR	Progression of dermatitis with blister formation -generalized erythema, papules, and severe itching	Bullous pemphigoid	5-year hx of generalized dermatitis	Skin biopsy (n=1)	Started methylprednisolone (0.5 mg/kg/day) taper; CS; Azathioprine 100mg daily and dupilumab	Clinical remission at 5-month follow-up

Cutaneous lupus								
Joseph 2025	42 years, M Dx of adult onset AD	Dexamethasone injection, oral prednisone, famotidine, loratadine; dupilumab	Pruritic rash on on extremities & trunk recurring when TCS discontinued -Fever -Diarrhea	Cutaneous lupus	5 months	Skin punch biopsy (n=2); *Initial biopsy led to misdx of drug eruption	hydroxychloroquine 200 mg daily for two weeks, then 200 mg twice daily	Complete skin remission after 9 months
Cutaneous T-cell lymphoma								
Akouaouach 2005[5]	87 years, F "years" of skin disease treated as eczema	TCS; antihistamines	-Development of buccal pain -Febrile -Ulcerations inside of lower lip -generalized erythema limbs, abdomen, hyperkeratosis on soles -No palpable lymph nodes	Sezary syndrome	NR ("years")	Skin biopsy (n=2), blood test, bone marrow	NR	NR
Alghamdi 2024[6]	38 years, F Dx of severe AD 7 years prior to presentation	TCS for 4 years & emollients with worsening; Cyclosporine for 1 year with no improvement	-generalized itching, -melanoerythroderma -fine scaling - alopecia 80% of scalp -weight loss -generalized hyperpigmentation -severe diffuse palmoplantar keratoderma with fissuring -Palpable lymph nodes	folliculotropic mycosis fungoides stage T4 N1 M0 B0	7-year hx of AD misdiagnosis & treatment	Skin biopsy (n=1) *Initial biopsy 7 years prior misclassified as AD	Referred to oncology for "extensive therapy"	Deceased
Ayasse 2021[7]	40 years, F Hx childhood AD, recurred/worsening dermatitis at 36 years with dx of AD recurrence	methotrexate, multiple prescription topical therapies, and dupilumab (13 months)	Skin signs/symptoms initially improved on dupi but flared at 5 months -Lesion progression to widespread well-demarcated, circular and annular erythematous patches/plaques on 80% body including face/neck	Mycosis fungoides staged IIB, CD4 folliculotropic with large cell transformation	13 month dx delay; 4 year duration of symptoms	Skin biopsies (n=3), blood and tissue T-cell rearrangement, and flow cytometry	Discontinuation of dupilumab	NR

Chiba 2019[8]	58 years, M Hx childhood AD, recurrence at 47 years dx as recurrent AD	TCS; dupilumab (1 month)	During dupi & TCS treatment face/trunk lesions became more prominent, minor EASI and DLQI decrease but no improvement in itch -Intense itch -Erythematous lesions on face and trunk	Mycosis fungoides	11-year hx of "eczema"	Skin biopsy (n=1); Laboratory testing	Discontinuation of dupilumab, TCS and NBUVB therapy started	NR
Espinosa 2020[9]	A. 64 years, M 2-year hx presumed AD B. 72 years, M 20-year hx of eczema C. 59 years, F Hx childhood AD, persistent dermatitis D. 40 years, F 7-year hx of presumed AD	Various combinations of: azathioprine, diphenhydramine, gabapentin, TCS, systemic steroids, methotrexate, montelukast, mirabegron, dupilumab	A. Initial improvement on dupi followed by worsening of BSA involvement and pruritis; new plaques at 8 months & "skin burning"; -erythroderma BSA 95% sparing upper face/scalp B. Initial improvement on dupi at 6 weeks but persistent and worsening back plaques; -developed superimposed papules (60% BSA) C. Almost complete resolution of skin lesions and itch on dupi for 8 months but persistent facial plaque; At 2 years on dupi weight loss, fatigue, night sweats for 1 year with facial & thigh plaques; -plaque on cheek and right thigh; lymphadenopathy D. Initial improvement at 4 months on dupi but worsening at 15 months with 90% BSA & worsening itch	A. CTCL-NOS stage 1B B. Mycosis fungoides IA C. Mycosis fungoides IB D. Mycosis fungoides IIIA	A. 8 months on dupi (2 year hx presumed AD) B. 4 months on dupi C. 27 months on dupi D. 15 months in dupi	A. Skin biopsies (multiple) B. Skin biopsies (n=2), blood test, imaging C. Skin biopsies (n=2), blood test D. Skin biopsies (n=2), blood test	A. Dupilumab & azathioprine discontinued; acitretin & NBUVB started; bexarotene, TCS, radiation B. Discontinued dupi; Started NBUVB & clobetasol C. Continued dupi against medical advice D. Discontinued dupi; a 5-week prednisone taper & topical triamcinolone ointment	A. "Improvement" B. Near resolution of skin lesions at 5months C. NR D. NR
Fletcher 2004[10]	35 years, F Hx childhood AD	Oral prednisolone & PUVA	Limited control with AD therapies & development of lesions over face and upper back	primary cutaneous CD30+ T-cell lymphoma	7-year hx of adult dermatitis symptoms	Skin biopsy (n= 1)	CHOP chemotherapy, local radiotherapy,	Symptom-free with no clinical evidence of AD or lymphoma at 2 years

	controlled until age 28 dx as recurrence of AD		-Extensive lichenified eczema on limbs -Plaques & nodular lesions on face & upper back				autologous bone marrow transplant	
Foo 2016[11]	**6 adults** aged 40-61 years with a hx of childhood (n=3) or adult-onset (n=3) presumed AD	*Various combinations of:* cyclosporine, mycophenolate, AZA, MTX, and phototherapy	Skin symptoms "no longer respond[ed] to conventional treatment"	MF stage IB (n=3) MF stage IIIA SS stage IVA2 SS stage IVAI	2-50 year hx of dermatoses	Skin biopsy (n=NR), blood test	Started bexarotene, allogenic BMT, mogamulizumab, or MTX	Stable (n=3) at 20, 26 and 144 months Alive at 26 months Progression (n=2) at 4 and 8 months
Frischhut 2024[12]	75 years, F Dx of severe AD at age 67	Systemic steroids, omalizumab, anti-immunoglobulin E with no response; ECP, dupilumab for 5 months with no response	-Severe pruritus	Mycosis fungoides stage IIIB T4 N1 M0 B1	4 years	Skin biopsy (n=4) Initial skin biopsy supported AD; Second skin biopsy did not lead to new diagnosis; Third biopsy led to reconfirmation of AD	Mogamulizumab for 1 year	Complete skin response at 4 months; complete clinical response in skin and blood at 1 year
Kawamoto 2024[13]	40 years, M Recent hx of body dermatitis & heel blisters dx eczema	TCS	Worsening skin eruptions & blisters after 2 months of TCS, prescribed oral prednisolone 20 mg with no improvement and progression at 10 months -Recurring blisters on right heel, palms, soles -Erythematous lesions on limbs -erythema on trunk & limbs -Edema on arms/legs -Enlarged lymph nodes	Mycosis fungoides stage T4NXM0B2	1 year (from presentation to dx)	Skin biopsies (n=2), imaging, lymph node biopsy	Started cyclophosphamide/doxorubicin/prednisone with brentuximab vedotin (A-CHP) therapy	"Partial response"

Krishan 2024[14]	79 years, M New onset pruritic rash managed as AD for 1.5 years	TCS	No significant skin improvement with TCS for 1.5 years -Erythematous macular rash on predominately chest, trunk, lower limbs -Itch	Sezary syndrome	1.5 years	Skin biopsy (n=1), blood test, bone marrow	Started systemic bexarotene	Stable without disease progression at 5 months
Lazaridou 2020[15]	37 years, F 19-year hx of dermatitis dx as AD	PUVA, TCS, tacrolimus, methotrexate, cyclosporine, dupilumab (2 months)	No clinical response to dupilumab at 2 months and worsening of skin symptoms with "intense pruritic" -Pruritic dermatosis of trunk -Intense itch -Skin plaques & palmoplantar keratosis	Sezary syndrome	2 months on dupi after presentation/19-year hx dermatosis	Skin biopsies (n=2), blood test	Started mogamulizumab	Partial remission at 4 months
Martinez-Escala 2018[16]	66 years, M Hx of childhood AD	Methotrexate, NB-UVB, PUVA, infliximab	NR	Mycosis fungoides stage IIIA	Median time from the start of anti-TNF therapy to diagnosis 6 months	Skin biopsy (presumed n=1)	Started TSEBT, HDAC, acitretin, GM, erlotinib, DXA, capecitabine	"Alive with disease" at 7 months follow-up
Miyashiro 2020[17]	51 years, F 1-year hx of pruritic cutaneous lesions dx as AD	TCS, systemic steroids, azathioprine, dupilumab	No response to 2 months of AZA; 8 cycles of dupi resulted in mild pruritic relief but lesions worsened and tumors developed -Lesions on hands, trunk, limbs -Tumors developed	Mycosis fungoides tumoral-stage	1 yr hx dermatosis/ 4 months on dupi	Repeat skin biopsies (multiple), imaging	Started acitretin and PUVA	"Partial response"
Mougel 2006[18]	37 years, M Hx childhood AD with flares in adulthood, interpreted as steroid-resistant AD	TCS, cyclosporine, tacrolimus,	No improvement on 1 year of cyclosporine; -developed atypical lesions on trunk and erythematous and pruriginous popular lesions on the ears & eyebrows; stopped CsA and started tacrolimus will lesions spreading on body and	CD30+ CTCL	2 years from presentation	Skin biopsy (n=1), blood tests,	Sted cyclophosphamide, doxorubicin, vincristine, and prednisone multiagent chemotherapy; allogeneic hematopoietic stem cell transplant	Complete remission of lymphoma with severe cutaneous manifestations of graft-versus-host disease

			development of 10 cm purple tumor on hip					
Newsome 2021[19]	A. 48 years, F 6-year hx of pruritic cutaneous lesions dx of severe AD B. 55 years, M 5-year hx of AD	TCS, methotrexate, UV light therapy, dupilumab	A. No response after 5 months of dupi and MTX -Diffuse pruritic cutaneous eruption B. No response to 6 months of dupi -Widespread hyper and hypopigmented patches	A. Mycosis fungoides patch stage 1 B. Mycosis fungoides stage 1B	A. 6 yr hx dermatoses; 5 months on dupi B. 5 yr hx dermatoses; 6 months on dupi	A. Skin biopsies (n=2) B. Skin biopsy (n=1)	NR	NR
O'Neill 2023[20]	46 years, F Hx of pseudoxanthoma elasticum and development of presumed adult AD	TCS, tacrolimus, calcitriol, phototherapy, excimer laser, dupilumab	AD refractory to all topicals; Dupilumab resolved most cutaneous symptoms at 1 year but erythematous plaques remained on the shin and forearm	Mycosis fungoides	1 year	Skin biopsies (n=2)	Dupilumab was discontinued; mechlorethamine gel started	NR
Poyner 2019[21]	60 years, M Hx severe lifelong AD	Methotrexate, cyclosporine, dupilumab (9 weeks)	-Developed widespread rash and lymphadenopathy at 9 weeks on dupilumab; initial improvement with TCS followed by rapid progression of cutaneous symptoms -Erythematous plaques on face & widespread nodules with bilateral ulcerated nodules in groin	MF with large cell transformation	9 weeks on dupi	Skin biopsies (n=2); retrospective review of clinical photographs	Discontinued dupilumab; started gemcitabine chemotherapy	NR
Russomanno 2020[22]	43 years, M Hx AD in childhood,	Triamcinolone, dupilumab (2 months)	Improved itch at 2 months on dupi but worsening skin lesions,	mycosis fungoides T2bN3M0B1b (stage IVA2)	1 yr hx worsening dermatoses	Repeat punch biopsies (n=4)	Started brentuximab	Stable condition

	worsening of dermatitis over last 12 months		weight loss and lymphadenopathy at 4 months -Diffuse hyperpigmented plaques -Painful fissures on hands/feet -Thinning of hair -Lymphadenopathy -weightloss				and pralatrexate	
Sokolowska-Wojdylo 2011[23]	A. 26 years, F B. 53 years, M C. 64 years, M D. 75 years, F Adult-onset dermatitis dx as AD (n=3) Hx of childhood AD and recurrent adult dermatitis managed as severe AD (n=1)	A.oral prednisone & cyclosporine (3 months) B.-D. TCS, UV light therapy, systemic methotrexate, azathioprine, mycophenolate mofetil, cyclosporine (3 to 8 months)	A. Condition refractory to treatment at 3 months of CsA -widespread eczematous dermatitis -Lymphadenopathy B. Initial improvement but worsening after 8 months on CsA -severe erythroderma and lymphadenopathy C. Initial improvement but recurrence of skin symptoms after 6 months on CsA -Erythroderma D. Year history of progressively poorer disease control on CsA -development of erythroderma & lymphadenopathy -Widespread itchy dermatitis involving head and neck	Sezary syndrome	A. 4 yr hx dermatitis B. 13 yr hx dermatitis C. 20 yr hx dermatitis D. 12 yr hx of progressive dermatitis	A. Skin biopsies (n=2), blood test, lymph node biopsy, imaging, bone marrow B. Skin biopsies (n=2), blood test, lymph node biopsy, imaging, bone marrow C. Skin biopsies (n=4+), blood test, lymph node biopsy, imaging, bone marrow D. Skin biopsy (n=1), blood test, lymph node biopsy, imaging, bone marrow	E. 2 chlordeoxyadenosine for 5; acyclovir, co-trimoxazole, allopurinol & chemotherapy F. Extracorporeal photopheresis G. Discontinued CsA, started systemic steroids & extracorporeal photopheresis H. Discontinued CsA, started extracorporeal photopheresis	A. Clinically stable with moderate pruritic skin lesions in flexural & peri orbicular regions at 6 months B. Partial remission at 4 months C. No response D. No response

Toker 2023[24]	65 years, M 2-month hx of pruritus & dermatitis dx as AD	Dupilumab (6 months)	Initial improvement on dupi but new rash at 6 months -Diffuse scaly plaques -Development of rash	Mycosis fungoides CD30+	8 months	Repeat skin biopsies (n=3)	Discontinued dupi, started TCS then skin electron radiotherapy	Rapid disease progression
Tran 2020[25]	64 years, M 5 yr Hx adult-onset AD	TCS, UV light therapy, dupilumab (5 months)	Continual progression of dermatitis with development of erythrodermic rash (95% BSA) after 2 weeks on dupi with progression of erythroderma at 5 months on dupi -3 month hx of erythroderma -Erythrodermic rash 95% BSA -Lymphadenopathy	Sezary syndrome (after another misdiagnosis of psoriasis)	5 yr hx of dermatitis dx as AD dermatitis; 5 months on dupi	Skin biopsies (n=2), blood test	Started bexarotene & extracorporeal photopheresis	NR
Umemoto 2020[26]	48, F Hx childhood AD, erythroderma for past 2 years dx of adult severe AD	Dupilumab (2 months)	No clinical response on 2 months of dupi -Generalized severe exfoliative erythroderma -Intense pruritus	Sezary syndrome	2yr hx erythroderma	Skin biopsy (n=1), blood test, lymph node biopsy	Started TCS, NBUVB, vorinostat, planned hematopoietic stem cell transplant	"Improved condition"; anticipate radical cure with pending transplant
Zhou 2018[27]	28 years, F 16-year hx of pruritic dry lesions dx of AD	Not reported	"recalcitrant" dermatitis -Pruritic dry lesions spreading from forehead -Skin xerosis -Erythematous plaques covering 50% BSA -Total hair loss -Lymphadenopathy	Folliculotropic mycosis fungoides stage T2N1M0B0 stage IIa	16 yr hx dermatitis	Skin biopsies (n=2+)	Started prednisone, interferon alpha-2b, MTX, topical nitrogen mustard	"Mild improvement" at 18 months follow up
Eosinophilic Pustular Folliculitis								
Li 2024[28]	35 years, M 10-year hx erythematous patches with recent	TCS; oral doxycycline (10 years); Tripterygium wifordii	Temporary symptomatic relief with relapses on long-term medications; No improvement with	Eosinophilic Pustular Folliculitis	10 year hx dermatitis; 1 month hx of exacerbation	Skin biopsy (n=1), fungal microscopy, blood test	Started indomethacin	Skin lesions "mostly disappear[ed]" at 10 days follow up; Symptoms resolved at 1 month; no

	onset, dx of AD w/skin infection	glycosides, levocetirizine, ketotifen, glycyrrhizin (1 week)	systemic medications leading to hospitalization -Erythematous patches with bumps & mild itching on face, trunk, hands, feet -Facial swelling					recurrence at 3 months
Familial benign chronic pemphigus								
Chen 2023[29]	42 years, M 20-year hx erythema & blisters dx as AD and tinea cruris	Topical hormones; antifungals	Gradual symptom resolution followed by recurrence -Erythema & small blisters in armpits and groin -Yellow crusting	Familial benign chronic pemphigus	20 yr hx dermatitis;	Skin biopsy (n=1)	Started methylprednisolone & mupirocin ointment	"lesions gradually subsided"
Infection								
Liu 2023[30]	68 years, F 1-year hx plaques on hands dx of AD	TCS	No improvement with TCS -Painless red plaques on hands Yellow crusting	*Mycobacterium marinum* infection	1 yr hx treatment for AD	Skin biopsy (n=1)	Started doxycycline & clarithromycin	Complete resolution at 5 months with no recurrence at 6 months
Malignancies (other than cutaneous T-cell lymphoma)								
Arai 1988[31]	68 years, M "several year" hx of chronic dermatitis on upper limbs & buttocks dx as AD	"treated by several dermatologists"	No improvement -Chronic itchy eczema of upper limbs & buttock -Enlarged spleen	Hairy cell leukemia	"several years" of dermatitis	Skin biopsy (presumed n=1), blood test, bone marrow	Started antihistamines & TCS; patient initially refused HCL-specific therapy but started interferon	Skin lesions improved "substantially" & after 8 weeks of interferon therapy complete remission of skin lesions & a "drastic" reduction of splenomegaly
Chuang 2012[32]	76 years, M 8-month hx skin lesions on forearms dx as AD	Potent TCS	No improvement of lesions on TCS development of cervical lymph node enlargement -Infiltrative plaques on forearms -No pain, itch, or discharge -Lymph node enlargement	Skin metastasis of adenocarcinoma	3 months of ineffective treatment of AD	Skin biopsy (n=1)	NR	NR

Florin 1994[33]	70 years, M "Several year" hx of pruritic, scaly patch on neck dx as AD	TCS	No response to TCS; lesions became larger and more irritated -Mildly erythematous, scaly, well-demarcated patch on neck with small nodule	Basal cell carcinoma	"several years"	Skin biopsy (n=1)	Mohs microsurgery	Cured
Natsuga 2007[34]	34 years, F 3-year hx of severe eczema	TCS	Skin lesions refractory to TCS & development of fever, malaise, weight loss -Diffuse bright brown excoriated papules & edematous blackish erythema -Fever, malaise, weight loss - enlarged lymph nodes	Non-Hodgkin lymphoma	3 year hx of dermatitis	Imaging, lymph node biopsy	Started rituximab, cyclophosphamide, Adriamycin, vincristine and prednisone chemotherapy, then high-dose chemotherapy & autologous peripheral blood stem cell transplantation	Partial lymphoma remission with complete resolution of skin lesions and no recurrence
Multisystem Langerhans cell histiocytosis								
Cheng 2024[35]	62 years, F 2-year hx diffuse erythematous, pruritic skin lesions dx as AD	"Various traditional therapeutic regimens for AD"; dupilumab	"Poor efficacy" on standard AD therapies; "pruritic slightly improved" on 7 months of dupi but no overall relief of skin lesions culminating in hospitalization for fever, systemic erythema and scale and increased itching -Generalized severe rash with recurrent fever -Diffuse erythematous pruritic lesions and nodules on face, trunk, and limbs -enlarged lymph nodes	Multisystem Langerhans cell histiocytosis	2 yr hx of dermatitis treated as AD; 7 months on dupi	Skin biopsies (n=5), blood test, bone marrow, lymph node biopsy	Started vincristine & prednisone chemotherapy	Initial significant resolution of skin lesions
Pityriasis rubra pilaris								

Al Khalifa 2023[36]	A. 16 years, M Dx of AD with persistent lesions B. 21 years, M Dx of severe AD with recurrent flares and acne	A. TCS; antihistamines B. TCS; antihistamines; acne therapy	A. Partial symptom relief -Itchy eczematous lesions on face, trunk, upper limbs -Generalized follicular hyperkeratosis & lichenfied plaques on elbows B. No resolution of dermatitis or acne & new facial swelling and boils on body -Generalized skin xerosis, follicular keratoses & lichenified dermatitis patches on elbows/knees -Cheek and scalp swelling -Axillae boils	Pityriasis rubra pilaris	A. NR B. 3 yrs post-presentation	A. Skin biopsy (n=1), dermoscopy, imaging, blood test	B. Started isotretinoin C. Started isotretinoin, added prednisolone	A. Significant improvement in skin condition & no pruritic at 6 weeks B. Complete resolution of skin symptoms at 3 months; recurrence of residual skin lesions at 6 months
Scabies								
Chan 2000[37]	66 years, F "few weeks" hx of skin rashes dx of AD	Multiple topical therapies	No improvement in skin symptoms with increased scaling on hands/feet -Widespread scaly crusts on hands/feet	Crusted (Norwegian) scabies	"few weeks"	Skin scrapping	Started benzyl benzoate emulsion, salicylic acid ointment, crotamiton cream, chlorpheniramine maleate, and erythromycin	Skin lesions mostly resolved at 2 weeks follow up, residual periungual hyperkeratosis still identifiable requiring further antiscabietic treatment
Lewin 2010[38]	68 years, F 1-year hx of "skin rash" treated as AD	TCS	Progressive worsening of "intensely pruritic rash" despite TCS over 1 year; development of fever, swelling and tender left arm and vulva leading to hospitalization for necrotizing soft-tissue infection	Scabies (*Sarcoptes Scabiei*)	1 year	Skin scrapping	Hospital admission, intraoperative debridement & 2 does of ivermectin and permethrin cream	Improved after surgery but required treatment for MRSA infection and postscabietic itch

Wu 2024[39]	**23 patients** aged 40-90 years, 52% M 0.5 to 7 months hx of skin rash and itch dx as AD	TCS, systemic steroids, antihistamines, CAM (average duration 3.2 months)	No clinical improvement and worsening with AD treatment -Rash on trunk/extremities -erythema, papules, nodules	Scabies	Range 0.5 to 7 months	Skin scrapping, dermoscopy, RCM	Started sulphur ointment	All patients cured after 3 treatment cycles with no recurrence 2 weeks post treatment

TCS: Topical corticosteroids

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Supplemental Table 4. Concomitant conditions in adult atopic dermatitis

Study	Population	Concurrent ACD rate	Method of diagnosis
Ashbaugh 2022[1]	35 Adult AD patients taking dupilumab with residual facial dermatitis	13/35 (37.1%) Adults with AD taking dupilumab and experiencing residual facial dermatitis had a diagnosis of comorbid ACD following expanded series patch testing. 60/80 (75%) adults with AD taking dupilumab had a comorbid diagnosis of ACD before initiating treatment.	Expanded series patch testing
Chicharro 2024[2]	1168 adults (99%) with a diagnosis of AD	196/1168 (16.8%) adults with a history or current diagnosis of AD had a relevant positive patch test.	Patch testing
Docampo-Simon 2023[3]	54 AD patients treated with dupilumab	2/21(9.5%) patients with persistent localized dermatitis & 1/22 (4.5%) patients with eczema flare-ups were diagnosed with ACD: 3/43 (7.0%)	Patch testing
Guin 2002[4]	23 patients with AD including persistent eyelid dermatitis	16/23 (69.6%) individuals with AD and persistent eyelid dermatitis had concomitant ACD	Patch testing
Lee 2018[5]	281 individuals with AD	71/281 (25.3%) individuals with AD had concurrent ACD	Patch testing
Lopez-Jimenez 2019[6]	37 individuals with t-resistant AD	12/37 (32.4%) patients had ACD (clinically relevant patch test results)	Patch testing
Qian 2023[7]	5,641 adults with AD	3,092/5,641 (54.8%) adults with AD had concurrent ACD	Patch testing
Raffi 2019[8]	35 patch tested adult AD patients on dupilumab	32/35 (91.4%) patch-test patients with AD had comorbid ACD	Patch testing
Roh 2021[9]	39,779 adult patients with AD and 353,743 controls	Adults with AD had an increased likelihood of ACD: OR 12.7	Presumed patch test
Silverberg 2021[10]	36,834 patch tested adults	39.8% of adults with AD had concomitant ACD	Patch test
Trimeche 2024[11]	93 AD patients (median age 20 years)	40/93 (43%) patients had concomitant ACD	Patch test
Case Reports/Series: Atopic dermatitis & concomitant skin conditions			

Study	Patient(s) (age, gender)	Initial treatments & outcomes	Concurrent diagnosis	Initial method of concurrent diagnosis	Diagnostic delay	Management change	Outcome of management change
Almoqati 2024[12]	43 years, F Hx mild AD,	6-month history of persistent itchy skin lesions on her Extremities that did not respond to medium potency TCS -well-demarcated, fine, scaly erythematous patches with areas of spared skin on all four extremities associated with palmoplantar keratoderma	Adult pityriasis rubra pilaris (type II)	Skin biopsy	6 months	NBUVB treatment for 2 months	"complete resolution of skin lesions" ; remission maintained for 2 years
Ashbaugh 2022[1]	14 adults with AD	Dupilumab resulting in an average of 79.1% improvement at 11.7 weeks but experienced residual facial dermatitis -Residual facial dermatitis	ACD 13/14 No relevant patch test results 1/14	Expanded series patch testing	Mean 11.7 weeks	Allergen avoidance	Complete resolution 3/14 Mostly clear 6/14 Somewhat clear 3/14 No improvement 2/14
de Beer 2019[13]	A. 39 years, M B. 29 years, M Hx childhood AD	A. Dupilumab for **11 weeks** with worsening facial & neck dermatitis w/itch & pain B. Dupilumab for **6 months** with development of facial dermatitis w/ itch & pain unresponsive to TCS	Malassezia hypersensitivity resulting in head and neck dermatitis	A. Biopsy, blood test B. Patch test, biopsy, blood test	A. 11 weeks B. 6 months	Started itraconazole	A. Significant improvement in signs & symptoms at 1 week & complete clearance at 3 weeks B. Significant improvement in signs & symptoms
Navarro-Trivino 2021[14]	43 years, M Hx adult AD	TCS & dupilumab for **12 months**- improved body AD but refractory head, neck & eyelid AD	ACD to decyl glucoside 5%	Patch tests	12 months	Allergen avoidance	Complete improvement of head & neck dermatitis at 2 months
Suresh 2018[15]	A. 52 years, F Hx lifelong severe AD B. 54 years, F Hx lifelong mild-to-moderate AD C. 54 years, F Hx lifelong mild AD	Multiple therapies & dupilumab: A. improved AD but residual dermatitis on forearms, neck & face B. improved AD but residual facial dermatitis	A. ACD to perfume mix & fragrance mix B. ACD to limonene C. ACD to Sweet Baby shampoo	Patch test	A. 6 months B. 9 months C. 3 months	Allergen avoidance	A. 75% improvement in residual dermatitis at 2.5 months B. Residual dermatitis cleared month 2 C. Clear by month 2

		C. residual facial dermatitis					
Vilela 2025[16]	44 years, M "longstanding" hx severe AD	Dupilumab with response until month 5, then new head, neck, and eyelid lesions with no response to standard therapies	ACD to shampoo	Patch test	5 months	Allergen avoidance	"improvement of lesions"
Zhu 2019[17]	A. 50-60 years, M B. 50-60 years, M Hx childhood AD	A. Conventional treatment including dupilumab- improved body AD but new facial dermatosis B. Conventional treatment including dupilumab- new body dermatosis "eruptions"	A. rosacea, dermatophytosis, and actinic keratosis B. Varicella zoster infection	Biopsy	NR	A. Started terbinafine	A. "Improvement"

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Supplemental Table 5. Number of biopsies required for subsequent diagnosis in presumed adult atopic dermatitis

Study	***# of biopsies before best management***
Autoimmune conditions	
George 2006	1
Zhange 2021	1
Joseph 2025	2
Cutaneous T-cell Lymphoma	
Akouaouach 2005	2
Alghamdi 2024	1
Ayasse 2021	3
Chiba 2019	1
Espinosa 2020 (n=3)	2 2 2
Fletcher 2004	1
Frischhut 2024	4
Kawamoto 2024	2
Krishan 2024	1
Lazaridou 2020	2
Martinez-Escala 2018	1
Miyashiro 2020	“multiple”
Mougel 2006	1
Newsome 2021 (n=2)	2 1
O’Neill 2023	2
Poyner 2019	2
Russomanno 2020	4
Sokolowska-Wojdylo 2011 (n=4)	2 2 4 1
Toker 2023	3
Tran 2020	2
Umemoto 2020	1
Zhou 2018	2
Average # of biopsies: 1.9 Median # of biopsies: 2 (range 1-4)	

Supplemental Table 6. Trends in clinical presentation prior to differential diagnosis

Allergic contact dermatitis (Total n=82)
Development of new, worsening, or residual facial dermatitis (n=80
Autoimmune conditions (total n=2)
Blister formation (n=2)
Cutaneous T-cell Lymphoma (Total n=33)
Skin rash consisting of plaques, patches, papules and tumors (n=11) Diffuse/generalized pruritic erythema BSA 50-95% (n=17) Enlarged lymph nodes (n=9)
Scabies (n=25)
Pruritic rash (n=25)