

UC Davis

Dermatology Online Journal

Title

A possible role for dupilumab (Dupixent) in the management of idiopathic chronic eczematous eruption of aging

Permalink

<https://escholarship.org/uc/item/55z1f6xh>

Journal

Dermatology Online Journal, 24(2)

Authors

Brummer, Grace C
Wang, Lawrence T
Sontheimer, Richard D

Publication Date

2018

DOI

10.5070/D3242038109

Copyright Information

Copyright 2018 by the author(s). This work is made available under the terms of a Creative Commons Attribution-NonCommercial-NoDerivatives License, available at <https://creativecommons.org/licenses/by-nc-nd/4.0/>

Peer reviewed

A possible role for dupilumab (Dupixent) in the management of idiopathic chronic eczematous eruption of aging

Grace C Brummer BS, Lawrence T Wang MD, Richard D Sontheimer MD

Affiliations: University of Utah School of Medicine, Salt Lake City, Utah

Corresponding Author: Richard D. Sontheimer MD, Department of Dermatology, University of Utah School of Medicine, 30 North 1900 East #4A 330, Salt Lake City, UT 84132, Tel: 801-581-6465, Fax: 801-581-6484, Email: richard.sontheimer@hsc.utah.edu

Abstract

Aging individuals can develop generalized, exquisitely-pruritic, eczematous eruptions of uncertain etiology that can be therapeutically-refractory and life-altering. Limited information exists in the literature to guide clinicians in the diagnosis and management of such patients. It is suggested that in approximately 40% of such patients a known cause for their chronic pruritic eruptions cannot be identified. In this report we will refer to this subgroup of patients as having idiopathic chronic eczematous eruption of aging (CEEA). Idiopathic CEEA must be distinguished from other established eczematous dermatoses. Idiopathic CEEA patients often require long-term systemic immunosuppressive drugs to make living bearable. Elder-onset atopic dermatitis is the most difficult of the known dermatoses to distinguish from idiopathic CEEA. Because of their clinical similarities we questioned whether dupilumab (Dupixent®), the first FDA-approved biologic for atopic dermatitis, might be valuable in the management of idiopathic CEEA. We report the case of an elderly man with idiopathic CEEA of four-years' duration who had a complete clinical response to the initiation of treatment with dupilumab. This case is presented to stimulate more discussion and systematic study of a possible role for dupilumab in otherwise-refractory idiopathic CEEA patients. We also propose a set of diagnostic criteria for idiopathic CEEA.

Keywords: dermatitis, dupilumab, Dupixent®, eczematous, eruption, aging, atopic dermatitis

Introduction

Aging individuals (i.e., ≥ 50 years) can present with highly-pruritic, potentially disabling, chronic eczematous eruptions that can be challenging to control with conventional topical and systemic anti-inflammatory therapies as well systemic immunomodulatory therapies including corticosteroids, methotrexate, and mycophenolate mofetil (CellCept®). The differential diagnosis of this challenging clinical presentation includes drug-induced hypersensitivity reactions, unrecognized allergic contact dermatitis with autoeczematization, occult inflammatory dermatophyte infection with id reaction, unrecognized scabies, late-onset atopic dermatitis, cutaneous T-cell lymphoma/mycosis fungoides, chronic actinic dermatitis, and prodromal pemphigoid (syn., pre-bullous pemphigoid, non-bullous pemphigoid, pre-bullous pemphigoid, early bullous pemphigoid, pre-pemphigoid, pruritic pemphigoid, pruritic pre-pemphigoid, limited clinical phenotype of bullous pemphigoid). However, no identifiable cause is discovered in about 40% of patients presenting with aging-onset chronic eczematous eruptions [1]. Our work has previously focused on the drug-induced chronic eczematous eruptions in aging [2]. In this report we will use the more specific designation "idiopathic CEEA" when referring to the subgroup of chronic eczematous eruptions in aging that cannot be found to have an underlying known etiology.

This report describes the dramatic clinical efficacy of dupilumab (Dupixent®) in treating a case of

otherwise-refractory idiopathic CEEA of four years duration. This patient is presented with the hope of stimulating systematic studies of a possible role of dupilumab therapy in the management of idiopathic CEEA.

Dupilumab is a fully humanized monoclonal antibody that inhibits inflammatory cytokines IL-4 and IL-13. It gained notoriety when it was designated as the first FDA-approved biologic for treatment of moderate-severe atopic dermatitis [3]. Based on clinical trial data, dupilumab treatment also resulted in less skin infection than placebo, suggesting that, in addition to inhibiting the cytokine signaling that activates T cells and other inflammatory pathways, it might also improve skin barrier function. It is currently approved only to treat atopic dermatitis in adults who have failed topical anti-inflammatory therapy. There are ongoing studies to expand approval to treat other conditions including eosinophilic esophagitis, asthma, nasal polyps, and children with atopic dermatitis.

For the purposes of this discussion we distinguish idiopathic CEEA from aging individuals with isolated pruritus at presentation secondary to internal medical disorders (e.g., liver dysfunction, renal dysfunction, thyroid dysfunction, internal malignancy) who might experience secondary skin changes resulting from scratching/rubbing and/or allergic contact dermatitis from the use of topical over-the-counter (OTC) anti-pruritic products. In addition, we distinguish idiopathic CEEA from the banal pruritic dermatosis experienced by aging individuals such as nummular eczema/asteototic eczema that may become chronic as result of misdiagnosis and/or incorrect treatment.

Case Synopsis:

Methods/Results: Our patient is a 66-year-old man who presented to our clinic in Salt Lake City, Utah in 2016 with a three-year history of an intensely pruritic eczematous eruption. By the patient's history, an itchy rash initially started on his left thigh, but quickly spread to his chest, back, abdomen, and the flexor and extensor surfaces of both upper and lower extremities (**Figure 1**). Notably, the face, neck, and

scalp were spared. He had no prior history of a similar rash nor other dermatologic problems. He denied ever having asthma, seasonal allergic rhinitis, or urticaria. Other medical problems included hypertension, hyperlipidemia, and corticosteroid-induced osteopenia. His only known drug allergy was ciprofloxacin.



Figure 1. Technically acceptable photographic images of our patient's skin changes seen at the time of our initial evaluation were not available for this publication. The clinical photograph shown here is from one of our drug-induced CEEA patients. This representative image can serve to illustrate the clinical appearance of the skin changes we observed at the time of our initial examination of the idiopathic CEEA patient described in this report. (We have been unable to distinguish the skin changes of idiopathic CEEA from those of chronic eczematous eruptions of aging of known cause on clinical examination alone). A version of the clinical image in this figure was published in our earlier work and is reprinted here with permission of the publisher, the American Medical Association.

Our work up was initiated with an H&E lesional biopsy from the right lateral chest wall that showed a psoriasiform spongiotic dermatitis with a few scattered eosinophils in the inflammatory infiltrate (**Figure 2**). An additional perilesional biopsy for direct immunofluorescence exam revealed no evidence of pemphigoid, pemphigus, linear IgA disease, dermatitis herpetiformis, or immune-mediated vasculitis. To address the possibility of late-onset atopic dermatitis we ordered an IgE blood level, which was within normal limits. In addition, a complete serum chemistry screen that included serum creatinine and liver function tests was within normal limits. Also, a complete blood count with

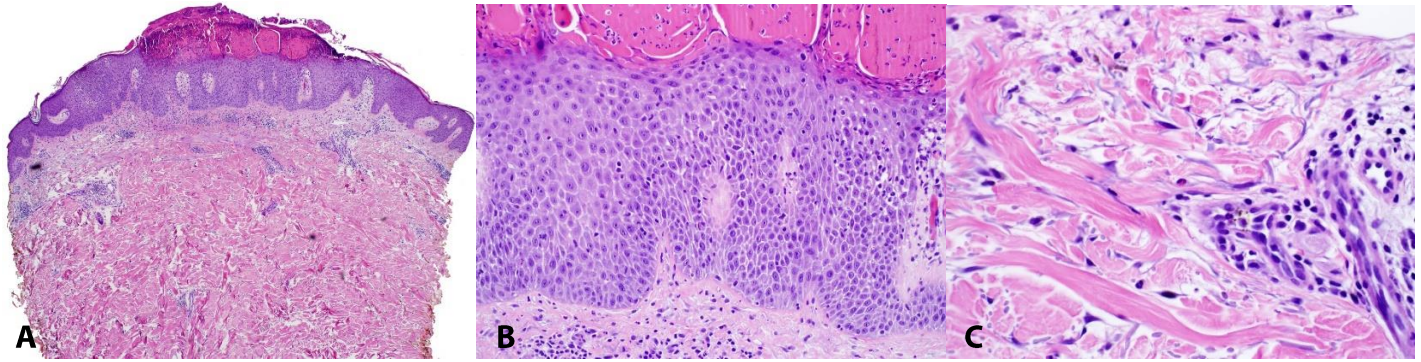


Figure 2. H&E exam of a lesional skin biopsy of the patient described in this report. Panel A - low power overview of biopsy specimen, 40x; Panel B - intermediate power view of epidermis and dermal-epidermal junction, 100x; Panel C - high power view of dermal inflammation, 400x. Our University Dermatopathology Service reported the biopsy as showing a psoriasiform spongiotic dermatitis based on the following findings:

"Multiple leveled sections of this punch biopsy reveal psoriasiform epidermal hyperplasia with spongiosis, spongiotic vesiculation, focal mounded parakeratosis, and a mild superficial perivascular lymphocytic infiltrate with scattered interstitial eosinophils. There are subcorneal collections of neutrophils and neutrophils are present in edematous dermal papillae. The periodic acid-Schiff stain does not reveal hyphae (pathogenic fungal elements), with an appropriately stained control."

Based on these findings the differential diagnosis was thought to include contact or nummular dermatitis, spongiotic drug reaction, "id" reaction, or possibly arthropod assault. The presence of a few eosinophils, so much spongiosis, and wet scale was suggested to argue against a diagnosis of authentic psoriasis.

differential was unremarkable and specifically did not reveal eosinophilia.

Notably, the patient was on lisinopril 10 mg daily for hypertension when he presented to our clinic. As other antihypertensive drug classes are known to be significantly associated with aging-onset chronic eczematous eruptions (e.g., calcium channel blockers, thiazide diuretics), we recommended that the patient be withdrawn from lisinopril and other ACE inhibitors for a minimum of 2 months to test the possibility that he was suffering from a drug-induced chronic eczematous eruption. As with drug-induced subacute cutaneous lupus erythematosus, drug-induced chronic eczematous eruptions tend to remit slowly after discontinuing the triggering agent [2]. The patient's primary care physician discontinued the lisinopril upon our recommendation. However, eight weeks after its discontinuation and avoidance of other ACE inhibitors his skin changes and pruritus were unchanged, making a drug-related hypersensitivity eruption less likely.

The patient had also been taking simvastatin at time of onset of his chronic eczematous eruption. Considering their prevalence of use over the past three decades, HMG-CoA reductase inhibitors have proven to have an extremely low rate of producing

any pattern of cutaneous hypersensitivity reaction. There has been a rare report of generalized eczematous eruptions occurring in association with this drug class thought possibly to result from xerotic skin changes secondary to altered cutaneous cholesterol metabolism rather than an immunologic hypersensitivity [4]. This question is moot in our case as the patient had discontinued the simvastatin therapy three months before starting dupilumab without clinical benefit.

Our patient did not have evidence of inflammatory tinea pedis, other patterns of cutaneous fungal infection, or scabies. In addition, his skin biopsy did not show evidence of cutaneous T-cell lymphoma/mycosis fungoides. Thus, it was our feeling at that time that he was suffering from idiopathic CEEA as per the proposed diagnostic inclusion and exclusion criteria outlined in the accompanying **Table 1**.

Prior to our initial evaluation, the patient had been receiving topical triamcinolone 0.1% ointment and oral prednisone. He reported only transient, modest improvement in the pruritus and appearance of the eruption. The only thing that had given him significant but temporary relief was intermittent intramuscular triamcinolone (Kenalog) injections.

Table 1. Proposed Diagnostic Criteria for Idiopathic CEEA*.**Inclusion criteria**

- 1) A highly-pruritic, patchy or confluent, subacute or chronic eczematous eruption affecting the extremities and trunk with characteristic facial sparing
- 2) Age 50 years or older
- 3) At least two months duration of the eruption
- 4) Skin biopsy histopathology consistent with spongiotic dermatitis with or without eosinophils or spongiotic and interface dermatitis with or without eosinophils.
- 5) Being withdrawn from medications that are known to be capable of inducing an eczematous drug eruption for two months or longer without clinical improvement of pruritus and dermatitis
- 6) Intensity of dermatitic symptoms justifying consideration of intermittent or long term systemic corticosteroid therapy

Exclusion criteria

- 1) History of earlier-life atopic dermatitis or other atopic clinical disorders (asthma, seasonal allergic rhinitis, urticaria)
- 2) Chronic pruritus without a visible inflammatory skin eruption at the time of initial clinical onset
- 3) Other known causes of aging-onset chronic eczematous eruptions based on: histopathology (e.g., cutaneous T-cell lymphoma/mycosis fungoides), direct/indirect immunofluorescence microscopy (e.g., prodromal pemphigoid), elevated IgE blood level (e.g., "extrinsic" aging-onset atopic dermatitis) or patch test results (e.g., allergic contact dermatitis)
- 4) Presence of clinical/microscopic evidence of cutaneous infection/infestation that can produce a generalized, pruritic, eczematous eruption (e.g. inflammatory tinea pedis with id reaction, unrecognized scabies)
- 5) Photosensitive facial skin involvement (i.e., chronic actinic dermatitis)

*Adapted from [2].

However, such long-term oral and parenteral systemic corticosteroid therapy had resulted in osteopenia.

In an attempt to decrease the frequency of systemic corticosteroid treatments, we initially started him on methotrexate 17.5 mg weekly plus folic acid 1 mg daily. After one month he believed that his eruption was worsening. We then discontinued the methotrexate and started mycophenolate mofetil (CellCept) 1000 mg BID plus an oral prednisone burst and taper because of the severity of his skin symptoms. This course of treatment was only partially successful and he subsequently decided to resume his monthly intramuscular corticosteroid injections through his outside private physician.

One of the authors (L.T.W.) provided this patient's subsequent dermatologic care while the patient was in residence in his winter home in San Diego in late 2016 and early 2017. During that timeframe the patient underwent patch testing with 80 contact allergens. He was found to be weakly reactive to only one, fragrance mix, at the 96-hour reading. The patient was counseled on fragrance avoidance but

this did not significantly improve his pruritus or rash. Thus, the weakly-positive, delayed-in-time fragrance patch test reaction was not believed to be clinically relevant. The patient next received narrowband UVB phototherapy without significant clinical benefit.

The patient was next treated with dupilumab injections, which had recently been approved by the FDA for severe atopic dermatitis. With a loading subcutaneous dose of 600 mg of dupilumab, followed by 300 mg every 14 days, his eruption and pruritus cleared rapidly and completely. At his last appointment in our clinic in Salt Lake City two months after starting dupilumab, our patient had no active eczematous skin changes and was without pruritus. However, the patient stated that he had recently been experiencing the return of mild pruritus without rash several days before each semi-monthly maintenance dupilumab injection, supporting the possibility that the dupilumab rather than some other factor was responsible for his dramatic clinical improvement. At the time of our last contact with the patient by telephone four months after starting dupilumab, his dramatic clinical improvement was continuing.

To expedite dupilumab treatment, this man purchased the initial dose of dupilumab with his own personal funds. He later stated that this was the best \$1,200 that he had ever spent in his life, reflecting how debilitating idiopathic CEEA can be even with previously available management strategies (personal communication from patient included here with patient's permission).

Case Discussion

CEEA is a challenging area of geriatric dermatology with which experienced practicing dermatologists are familiar. Such patients suffer from chronic, intensely-pruritic, potentially-disabling eczematous eruptions that when initially seen can be challenging both diagnostically and therapeutically. The differential diagnosis in this clinical setting includes a number of clinical entities as discussed above and summarized in Table 2. Some of these patients cannot be found to fulfill diagnostic criteria for any of these known clinical entities. This can leave the clinician in a quandary concerning the optimal medical management of such patients.

We are proposing a new designation for this latter subgroup of aging individuals – “idiopathic CEEA.” There is always some trepidation when introducing a new name for a previously existing clinical entity. However, as there is currently a dearth of published data concerning this challenging geriatric dermatologic problem, this new designation is offered to provide clinicians and investigators with a framework for further thought and discussion on this subject and to encourage more systemic study in this area.

Aging individuals who develop isolated pruritus (i.e., without rash at the time of pruritus onset) resulting from known internal metabolic and endocrine medical disorders (e.g., renal disease, liver disease, thyroid disease, internal malignancy) or secondary skin changes resulting from the pruritus are not included under the idiopathic CEEA designation.

We believe that the patient described in this report suffered from idiopathic CEEA according to the proposed diagnostic inclusion and exclusion criteria presented in **Table 1**.

Idiopathic CEEA is a pattern of skin inflammation characterized by aging-onset, intensely-pruritic, erythematous papules/papulovesicles (i.e. acute eczematous dermatitis) that coalesce into papulosquamous patches and thin plaques having ill-defined borders (subacute eczematous dermatitis). Such papulosquamous patches and plaques can occur in various sizes and shapes and upon further thickening from rubbing and scratching can present a psoriasiform appearance (i.e., chronic eczematous dermatitis). The skin lesions of idiopathic CEEA are typically bilateral but not mirror image symmetrical. In our experience, such lesions often present on the extensor aspects of the upper extremities and trunk but can then generalize to other skin locations. Although photo-exposed areas of skin can be involved, skin that is constantly exposed to light such as that on the face is characteristically spared. In addition, patients typically do not recognize sun exposure as being a triggering/aggravating factor for their rash and pruritus. As with chronic actinic dermatitis, it has been our experience that idiopathic CEEA has a male preponderance. Unfortunately, we did not obtain clinical images of our patient's skin changes at the time of presentation having a technical quality adequate for publication. A representative clinical image of our patient's skin change that has been presented elsewhere is reproduced here with the publisher's permission [2].

Owing to its extremely severe associated pruritus, idiopathic CEEA can produce a significant decrease in the healthcare quality of life. It is our experience that patients have often been suffering from this condition for several months if not years before being evaluated by a dermatologist who might be familiar with their condition.

Lesional histopathologic exam of idiopathic CEEA demonstrates a spongiotic dermatitis or spongiotic and interface dermatitis. These patterns of inflammation may or may not be associated with eosinophil infiltration. No characteristic immunofluorescence microscopy findings for idiopathic CEEA have been reported to date.

Screening blood tests can exclude the presence of underlying medical problems that can produce

isolated pruritus with secondary skin changes that might be confused with idiopathic CEEA (e.g., obstructive liver disease, chronic renal failure, thyroid dysfunction, lymphoma).

Idiopathic CEEA must be distinguished from other dermatologic conditions that can produce a similar dermatologic illness in aging individuals. Prescription drug use has long been associated with cutaneous eruptions and occurs at higher incidence rates in the aging because medication use increases with age [5]. Over the last decade, elderly-onset, drug-induced chronic eczematous eruptions have been characterized in the literature as being specifically associated with calcium channel blockers (CCB). Joly et al. conducted a case-control study in 2007 showing a statistically significant association between elderly-onset chronic eczematous eruptions and chronic use of CCB [6]. They also performed an ancillary study showing that over 80% of patients healed from their eruptions after CCB withdrawal. A case-control study Summers et al. reported in 2013 confirmed these findings and identified thiazide diuretics as an additional associated drug class [2].

The only medications our patient was taking at the time of his clinical presentation was lisinopril and simvastatin. Angiotensin-converting enzyme (ACE) inhibitors are not a class that has been shown in the literature to have a proven link to eczematous drug eruptions. However, there is one case series published in 2013 by Vena et al. exhibiting 23 patients with an eczematous reaction that was attributed to either ACE inhibitors or angiotensin II receptor blockers [7]. Despite the paucity of evidence linking ACE inhibitors and eczematous eruptions specifically, adverse cutaneous drug reactions to other anti-hypertensive medication classes are widely recognized in clinical practice. Thus, we recommended that our patient be taken off lisinopril for a minimum of eight weeks. However after eight weeks, neither his eczematous skin changes nor his severe pruritus improved, making it unlikely that the etiology of his chronic eczematous eruption was drug-induced. As previously discussed simvastatin also did not appear to be a drug trigger for our patient's chronic eczematous eruption.

When a patient of advancing age presents with a new-onset, persistent, generalized eczematous eruption, allergic contact dermatitis with autoeczematization reaction must also be considered. For example, aging individuals are more likely to suffer from stasis dermatitis of the lower extremities. When using OTC products for the pruritus associated with stasis dermatitis (e.g., topical anti-inflammatories, topical antipruritics, topical antibiotics), older individuals can develop an allergic contact dermatitis to the chemical constituents of such products that becomes superimposed on the underlying stasis dermatitis. With continued use of such products the dermatitic eruption can generalize to the upper extremities and trunk through an autoeczematization mechanism. As previously noted, patch testing did not reveal strong evidence for an allergic contact dermatitis in our patient.

In addition, patients typically have initially used one or more OTC anti-inflammatory and anti-pruritic products for the rash and pruritus of idiopathic CEEA before pursuing professional medical care. This raises the possibility of idiopathic CEEA patients presenting with a superimposed, confounding, allergic contact dermatitis to allergens present in such OTC products.

Another scenario that can simulate the idiopathic CEEA is an unrecognized pruritic infection/infestation that can occur incidentally in the aging. Inflammatory tinea pedis that triggers an id reaction can result in a generalized pruritic eczematous eruption, the underlying etiology of which can be overlooked by healthcare professionals other than dermatologists. The immunologic mechanism of the id reaction is thought to be similar to that of the autoeczematization reaction [8]. Although uncomplicated scabies can occur at any age range, crusted (Norwegian) scabies occurs more commonly in the aging population. All clinical forms of scabies are subject to misdiagnosis. Our patient had no clinical or biopsy evidence of inflammatory tinea pedis, other clinical patterns of dermatophytosis, or scabies.

Late-onset atopic dermatitis is quite rare in aged patients. Only 9% of atopic dermatitis patients are

diagnosed after age 20, with over 85% being diagnosed before age five [9]. A common diagnostic finding in patients with atopic dermatitis is elevated IgE blood levels, although this disorder can occur in the setting with normal IgE blood levels [10]. Our patient's IgE level was within normal limits and he did not have a prior history of other atopic disorders (asthma, seasonal rhinitis, urticaria) making the diagnosis of late-onset atopic dermatitis less likely. As is typical for CEEA, his eczematous dermatitis did not display a predilection for the flexural skin areas. However, atopic dermatitis in adults can also spare the flexures.

Our assumptions in this area could be challenged as there is currently no readily available way for clinicians to distinguish between idiopathic CEEA and the "intrinsic" form of IgE-negative, late-onset atopic dermatitis. The fact that our patient's chronic pruritic eczematous dermatitis responded so rapidly and completely to dupilumab therapy could be taken as evidence for a pathogenetic commonality between idiopathic CEEA and late-onset atopic dermatitis. Dupilumab inhibits IL-4 and IL-13 signaling pathways thereby down-regulating Th2 lymphocyte maturation and function. It would be of interest to know if patients with idiopathic CEEA might share research biomarkers for atopic dermatitis such as antimicrobial peptide dysregulation (e.g. cathelicidin), filaggrin gene mutations, up-regulation of Th2 cytokines and chemokines (IL-4, IL-13, TSLP, IL-31, CCL22), and up-regulation of atopic dermatitis-associated microRNAs including miR-155.

Bullous pemphigoid is a well-known debilitating autoimmune bullous disorder that is seen predominantly in the aging population. All such patients have evidence of IgG and/or complement components deposited in a linear band-like fashion at the dermal-epidermal junction. Less widely recognized is the prodromal, non-bullous phase of bullous pemphigoid that varies in its presentation most commonly from urticarial patches and plaques, to eczema-like lesions to dermatitis herpetiformis-like lesions [11, 12]. The characteristic histopathologic pattern of prodromal pemphigoid is eosinophilic spongiosis. By definition, all prodromal

pemphigoid patients have the same immunofluorescence microscopy findings at the dermal-epidermal junction as do bullous pemphigoid patients.

Prodromal pemphigoid typically matures to the frank bullous phase within 12-18 months after onset [13]. However, some patients may go 10 years or longer before developing blisters at all [14]. As mentioned above, our patient's perilesional skin biopsy examined by direct immunofluorescence microscopy showed no signs of pemphigoid or other autoimmune blistering disorders. Total blood levels of IgE are typically elevated in fully-expressed bullous pemphigoid and eosinophilia is often present. Although not as well studied, there is evidence to suggest that IgE blood levels can also be elevated in prodromal pemphigoid. As previously mentioned, our patient had a normal IgE blood level and did not have eosinophilia. In addition, only rare eosinophils were noted on our patient's skin biopsy. For these reasons we feel that prodromal pemphigoid is not a viable consideration of our patient's dermatologic illness.

During the clinical care of our patient, we did not screen him for circulating antibodies to BP180 and BP230 autoantigens by solid-phase immunoassay, the reason being that such autoantibodies are less specific for bullous pemphigoid than perilesional skin immunofluorescence microscopy studies, which were negative in our patient. Feliciano and coworkers recently reported that 5 of 15 (33%) aging patients with various non-bullous pruritic skin conditions (prurigo-like lesions, pruritic erythema, and pruritus of unknown etiology) were positive for circulating IgG autoantibodies to BP180 and/or BP230 by solid-phase immunoassay utilizing recombinant BP180 and BP230 antigens [15]. Interestingly, none of these aging individuals met diagnostic criteria for classical bullous pemphigoid over a period of 4-31 months of observation. These same workers found that all of a group of 30 classic bullous pemphigoid patients had IgG autoantibodies to BP180 and/or BP230 by this solid-phase immunoassay.

IgG and complement deposited in a linear band-like fashion at the dermal-epidermal junction is a

diagnostic hallmark of classic bullous pemphigoid. However, experimental studies have not been able to fully confirm that IgG class bullous pemphigoid antibodies and associated complement component deposition are the sole pathogenetic cause for the dermal-epidermal junction cleavage observed in classic bullous pemphigoid. More recently, IgE class bullous pemphigoid autoantibodies have been implicated as a pathogenetic factor in the pattern of inflammation observed in experimental animal models of bullous pemphigoid and classic human BP [16].

Freire and co-investigators recently provided additional support for the bullous pemphigoid IgE hypothesis by a showing that more IgE is bound in the skin of patients with bullous pemphigoid compared to that of normal individuals [16]. And, rather than being found at the dermal-epidermal junction, IgE was found to be predominately bound to mast cells and eosinophils within the dermal inflammatory infiltrate of bullous pemphigoid skin lesions. Some of the bound IgE has been shown to be bullous pemphigoid antigen-specific. Thus, it is conceivable that IgE class pemphigoid autoantibodies could be contributing to the inflammatory response seen in bullous pemphigoid lesional skin in a manner different from the IgG bullous pemphigoid antibodies that are bound to the dermal-epidermal junction.

Some have speculated that there might exist an incomplete/partially-expressed/limited form of bullous pemphigoid that never progresses on to classic bullous pemphigoid. It is possible that IgE

pemphigoid antibodies might be playing a major pathogenetic role in such a pemphigoid variant. In the future studies of idiopathic CEEA, it would be of interest to examine blood specimens not only for IgG bullous pemphigoid antibodies but also for IgE bullous pemphigoid antibodies.

Another consideration when an aged patient presents with a chronic pruritic dermatitic eruption is chronic actinic dermatitis (CAD), (syn. persistent light eruption, photosensitive eczema, actinic reticuloid). CAD is suspected when a patient presents with persistent eczematous papules and plaques limited to sun-exposed skin. The other two diagnostic criteria for CAD include histologic findings of spongiotic dermatitis and reduction in minimal erythema dose to UVB [17]. Photopatch testing is typically used for diagnosis. The pathogenesis is unclear but is thought to be either a delayed-type, photo-induced hypersensitivity reaction against an endogenous antigen or a response to an exogenous photosensitizer [17, 18]. In the literature, there are no examples of CAD that spare the face. It affects all sun-exposed areas equivalently, sparing only regions of the body that are protected from sunlight (i.e. skin folds and shadows). Our patient's face was spared from his chronic eczematous eruption, virtually excluding CAD. In addition, he denied that sun exposure was ever an aggravating factor for his dermatologic problems. As such, we did not perform phototesting.

The mycosis fungoides variant of cutaneous T-cell lymphoma can present with a chronic eczematous dermatitis. However, the histopathology of our case excluded this as a possibility.

Table 2. *Differential diagnosis of Idiopathic CEEA.*

	Distinguishing Feature(s)
Chronic actinic dermatitis	Extreme photosensitivity, facial skin involvement, variant biopsy features
Contact dermatitis with autoeczematization	Patch testing
Cutaneous T-cell lymphoma/mycosis fungoides	H&E skin biopsy exam
Drug-induced hypersensitivity reaction	Withdrawal of imputed drug(s) (especially, calcium channel blockers, thiazide diuretics) for 2 months with clinical regression or resolution
Late-onset "extrinsic" atopic dermatitis	Elevated IgE blood level, history of other atopic disorders (asthma, seasonal allergic rhinitis, urticaria)
Occult infection/infestation:	Resolution with diagnostic confirmation & definitive Rx
<ul style="list-style-type: none"> • Inflammatory tinea pedis with id reaction • Scabies 	
Prodromal pemphigoid	Diagnostic biopsy findings by direct immunofluorescence microscopy

An approach to the clinical evaluation of the differential diagnosis of idiopathic CEEA is summarized in **Table 2**.

Conclusion

Idiopathic CEEA can be an extremely severe dermatologic problem that can profoundly impact an aging individual's quality of life. Conventional topical and systemic dermatologic anti-inflammatory and immunosuppressive therapies often fail in this clinical setting. There is a paucity of evidence in the literature discussing treatment strategies for such patients. Our patient's dramatic clinical response to the initiation of dupilumab may

bring a ray of optimism to other similarly affected individuals. It is our hope that this report might stimulate more thought, discussion and systematic study of idiopathic CEEA including the role that dupilumab might play in its management.

Acknowledgements

We thank Scott R. Florell, M.D. for his kind assistance in obtaining the photo micrographs shown in **Figure 1**. We also thank Douglas L. Powell, M.D. and Erika M. Summers, M.D. for their thoughtful review of the manuscript at the draft stage.

References

- Morin C, Joly P, Courville P, et al. Chronic eczematiform eruption in the elderly. *Ann Dermatol Venereol*. 2002;129(1, pt 1):19-22. [PMID: 11937924].
- Summers EM, Bingham CS, Dahle KW, Sweeney C, Ying J, Sontheimer RD. Chronic eczematous eruptions in the aging: further support for an association with exposure to calcium channel blockers. *JAMA Dermatol*. 2013 Jul;149(7):814-8. [PMID: 23636109].
- FDA approves new eczema drug Dupixent. 2017, March 28. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm549078.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery. Accessed on August 21, 2017.
- Krasovec M, Elsner P, Burg G. Generalized eczematous skin rash possibly due to HMG-CoA reductase inhibitors. *Dermatology*. 1993;186(4):248-52. [PMID: 8513188].
- Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. Recent patterns of medication use in the ambulatory adult population of the United States: the Slone survey. *JAMA*. 2002;287(3):337-344. [PMID: 11790213].
- Joly P, Benoit-Corven C, Baricault S, et al. Chronic eczematous eruptions of the elderly are associated with chronic exposure to calcium channel blockers: results from a case-control study. *J Invest Dermatol*. 2007 Dec;127(12):2766-71. [PMID: 17713574].
- Vena GA, Cassano N, Coco V, De Simone C. Eczematous reactions due to angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. *Immunopharmacol Immunotoxicol*. 2013 Jun;35(3):447-50. [PMID: 23672527].
- Fehr BS, Takashima A, Bergstresser PR, Cruz PD Jr. T cells reactive to keratinocyte antigens are generated during induction of contact hypersensitivity in mice. A model for autoeczematization in humans? *Am J Contact Dermat*. 2000 Sep;11(3):145-54. [PMID: 11012002].
- Bannister MJ, Freeman S. Adult-onset atopic dermatitis. *Australas J Dermatol*. 2000 Nov;41(4):225-8. [PMID: 11105366].
- Tanei R, Hasegawa Y. Atopic dermatitis in older adults: A viewpoint from geriatric dermatology. *Geriatr Gerontol Int*. 2016 Mar;16 Suppl 1:75-86. [PMID: 27018286].
- Lamb PM, Abell E, Tharp M, Frye R, Deng JS. Prodromal bullous pemphigoid. *Int J Dermatol*. 2006 Mar;45(3):209-14. [PMID: 16533217].
- Kasperkiewicz M, Zillikens D, Schmidt E. Pemphigoid diseases: pathogenesis, diagnosis, and treatment. *Autoimmunity*. 2012 Feb;45(1):55-70. [PMID: 21923615].
- Zhang Y, Luo Y, Han Y, Tian R, Li W, Yao X. Non-bullous lesions as the first manifestation of bullous pemphigoid: A retrospective analysis of 181 cases. *J Dermatol*. 2017 Jul;44(7):742-746. [PMID: 28256743].
- Ikeda T, Okamoto K, Furukawa F. Case of atypical bullous pemphigoid with generalized pruritus and eczema as the prodrome for 10 years. *J Dermatol*. 2012 Aug;39(8):720-1. [PMID: 22011062].
- Feliciani C, Caldarola G, Kneisel A, Podstawa E, Pfützner M, Pfützner W, Hertl M. IgG autoantibody reactivity against bullous pemphigoid (BP) 180 and BP230 in elderly patients with pruritic dermatoses. *Br J Dermatol*. 2009 Aug;161(2):306-12. [PMID: 19485996].
- Freire PC, Munoz CH, Stingl G. IgE auto-reactivity in pemphigoid: eosinophils and mast cells as major targets of pathogenic immune reactants. *Br J Dermatol*. 2017 177(6):1644-1653. [PMID: 28868796].
- Hawk JLM, Lim HW. *Chronic actinic dermatitis*. In: Photodermatology, Lim HW, Honigsmann H, Hawk JLM. (Eds), Informa Healthcare, New York 2007. p.169.
- Lim HW. Abnormal responses to ultraviolet radiation: photosensitivity induced by exogenous agents. In: Fitzpatrick's Dermatology in General Medicine, 7th, Wolff K, Goldsmith LA, Katz SI, et al. (Eds), McGraw-Hill, New York 2008. Vol 1, p.828.