Article type: Case Series

Title: Six Cases of Refractory Pruritus and Histologic Dermal Hypersensitivity Reaction Successfully Treated with Dupilumab

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Introduction:

Dermal hypersensitivity reaction (DHR) represents a histopathological finding common to many different clinical diagnoses such as chronic pruritis of unknown origin, drug reactions, arthropod bite reactions, spongiotic dermatitis, bullous pemphigoid, scabies, urticarial erythema multiforme, dermatitis herpetiformis, eosinophilic folliculitis, and urticarial vasculitis.\(^1\) Because DHR is a histological diagnosis rather than a clinical diagnosis, no single treatment regimen has been consistently used and rather treatment has focused on addressing the underlying cause. Chronic pruritis of unknown origin (CPUO) is defined as an itch lasting greater than 6 weeks not better explained by a dermatologic or other medical condition and can be associated with DHR and/or a spongiotic pattern on skin biopsy.\(^2\) Treatment of CPUO with DHR on histology is particularly challenging as there is no primary disease to target. Topical therapy, oral antihistamines, systemic corticosteroids, antidepressants, and anticonvulsants have proven to be minimally effective for the treatment of CPUO.\(^3\) Dupilumab, an IL-4R alpha antagonist approved for the treatment of atopic dermatitis, may be a viable treatment option for CPUO associated with DHR, given its effectiveness treating other T-helper-2 (Th2) mediated diseases,\(^4\) such as idiopathic chronic eczematous eruption of aging, chronic prurigo, allergic contact dermatitis, hyper-eosinophilic syndrome, prurigo nodularis, and bullous pemphigoid. Here we present six cases of CPUO with biopsy findings consistent with DHR successfully treated with dupilumab, a potential novel treatment option for this challenging and poorly understood disease.

Cases:

Additional clinical information summarized in Table 1.

Case 1: A 53-year-old male presented with a pruritic rash on the trunk as well as upper and lower extremities. Examination was notable for lichenified papules throughout the trunk and extremities, most notably on the back. Biopsies of the rash showed mild acanthosis without spongiosis with an underlying superficial and deep perivascular infiltrate (Figure 1). Due to failure of topical halobetasol, topical tacrolimus, oral antihistamines, prednisone and mycophenolate mofetil, dupilumab was initiated at standard dosing. Within 3 months, the patient noticed a dramatic improvement of his rash and pruritis, complaining only of mild pruritis between injections and minimal residual post-inflammatory hyperpigmented macules.
Dupilumab was stopped after one year due to insurance reasons, and the initial pruritic rash returned. After insurance re-approval, dupilumab was restarted with complete resolution of his rash and pruritus.

**Case 2:** A 48-year-old female presented with a 5-year history of intense pruritus and rash significantly impacting her daily life. Examination showed few excoriated papules and subtle lichenification on the upper back, elbows, dorsal forearms, thighs and fingers. Biopsy revealed no significant epidermal changes with a perivascular lymphocytic infiltrate containing rare eosinophils, consistent with dermal hypersensitivity reaction (Figure 2). After failing multiple therapies including topical betamethasone, topical tacrolimus, and oral mycophenolate mofetil (MMF), dupilumab was initiated with improvement in severity and duration of flares within the first six months. Due to blurry vision and headache, the dose was decreased to 200 mg every two weeks with subsequent flaring. On further discussion, her ocular symptoms consisted of a chronic, slowly progressive sensation of pressure and blurry vision more consistent with glaucoma rather than the pain and conjunctivitis which have been reported as side effects of dupilumab. The dose of dupilumab was increased back to 300 mg every two weeks with resolution of her pruritus and rash and no further exacerbation of ocular symptoms.

**Case 3:** A healthy 43-year-old female presented with a one-year history of a pruritic rash affecting her legs and abdomen. On exam, the patient was noted to have erythematous, blanchable papules coalescing into small plaques on her abdomen and lower legs. Biopsy of the rash revealed an unremarkable epidermis and superficial perivascular lymphocytes with abundant interstitial eosinophils consistent with dermal hypersensitivity reaction. Patch testing was performed, which was 2+ positive for nickel sulfate and 1+ positive for p-tert-Butylphenol formaldehyde resin, but the rash was persistent even with allergen avoidance. After failing multiple topical regimens including triamcinolone and clobetasol, as well as oral prednisone, the patient was initiated on MMF therapy, with excellent control but poor gastrointestinal tolerance. Her rash subsequently recurred so dupilumab was started at standard dosing and five months after starting dupilumab the patient’s rash and pruritis had resolved without any side effects.
Case 4: A 68-year-old male presented with a 6-month history of a pruritic rash that began on his back and legs and spread to his knees, elbows, shoulders, and chest. Patch testing showed 1+ positivity for both sodium laurel sulfate and benzaprene #4, which were deemed not clinically relevant. On examination, he had scattered erythematous scaly patches on the upper chest, shoulders, and back with overlying excoriation. Biopsy of the right shoulder showed an unremarkable epidermis and a sparse perivascular and interstitial mixed infiltrate containing scattered interstitial eosinophils, consistent with a dermal hypersensitivity reaction (Figure 3). Oral prednisone initially cleared the rash, but it recurred on discontinuation. The rash was also recalcitrant to trials of topical steroids, oral antihistamines, and topical tacrolimus; therefore, he was transitioned to dupilumab at standard dosing. After three months, the patient reported complete clearing of the rash and pruritus. He did note occasional eye dryness which was well-managed with artificial tears.

Case 5: A 75-year-old male presented with a one-year history of recurrent diffuse, pruritic rash. Examination revealed a generalized eruption of erythematous papules with minimal scale on the extremities and trunk particularly the flanks. Initial differential diagnosis included hypersensitivity dermatitis, contact dermatitis, non-bullous pemphigoid, atopic dermatitis, and Grover’s. A biopsy was performed on the left chest which showed a predominantly perivascular inflammatory infiltrate with occasional eosinophils consistent with dermal hypersensitivity reaction. Direct immunofluorescence was negative. The patient failed multiple therapies including topical triamcinolone, clobetasol, and hydroxyzine. Oral prednisone helped but was discontinued due to steroid induced diabetes. The patient was started on dupilumab 300 mg injections every 14 days and within 4 months, his dermatitis and pruritus resolved. Due to cost, the injections were spaced to every 30 days, and he continued to experience resolution of his symptoms without any side effect from the medication.

Case 6: A 78-year-old male presented with a 5-year history of extreme pruritus. No significant dermatitis was observed aside from faint pink patches on the upper chest and lower back with mild lichenification. Patch testing was performed which revealed 1+ positivity to potassium dichromate, but no culprit allergens were identified. A biopsy taken from the right chest revealed mild acanthosis and minimal spongiosis with a perivascular lymphocytic infiltrate
containing rare eosinophils and negative direct immunofluorescence, consistent with a dermal hypersensitivity reaction. The patient failed multiple therapies including topical corticosteroids, antihistamines, doxepin, narrow-band UVB, doxepin, gabapentin, butorphanol, and aprepitant. Azathioprine was poorly tolerated due to fatigue. The patient was then started on dupilumab with dramatic improvement in his pruritis and 50-60% reduction of the rash within the first 2 months with no associated side effects. His condition remains stable on this medication.

Discussion:

Though DHR presents variably, the most common primary lesions associated with DHR are often papules, papulovesicles, plaques, patches, or erythema. Similarly, CPUO can present with small, pink “micropapules” in a generalized distribution. All six of the cases presented here had a papular component to the dermatitis as well as pruritis and erythema. The location of the rashes varied by case, but spared the face, palms, and soles in all cases.

Extensive work up to exclude alternative underlying etiologies was done in all cases. Laboratory work up was unrevealing, although two of six patients showed peripheral eosinophilia. Patch testing was performed in three cases, notable for 2+ positive nickel sulfate and 1+ p-tert-Butylphenol formaldehyde resin, 1+ positive sodium laurel sulfate and benzaprene #4, and 1+ positive potassium dichromate respectively. No culprit allergens could be identified, however.

All six cases included in this study had evidence of DHR on biopsy with a perivascular inflammatory infiltrate with eosinophils, which was an inclusion criterion for this study. Three of the six cases had mild focal spongiosis noted in the pathology report as well, though not to a degree seen in eczematous dermatitis. Secondary change of acanthosis and lichenification was noted in 1 of the 6 cases.

Side effects have been reported with dupilumab therapy including injection site reaction, conjunctivitis, and upper respiratory tract infections. In this case series, one patient experienced dry eyes and another patient experienced blurry vision, though the blurry vision was ultimately determined to be chronic rather than a side effect of the medication.

Though previously refractory to multiple oral and topical therapies, all six patients in this study experienced significant improvement of their symptoms while using dupilumab, and five experienced complete resolution of their rash and pruritis. Outside of this case series, there is
only one published case report documenting the successful use of dupilumab in a patient with chronic pruritis and DHR on biopsy. Based on these 6 cases and the prior report, dupilumab may be a new treatment approach for patients with treatment refractory chronic pruritis of unknown origin with DHR on biopsy.
Table 1: Patient Characteristics
Table 1 in separate document (page must be set to portrait mode to view)
References:


Abbreviations and Acronyms

288 University of Virginia- UVA

289 Dermal Hypersensitivity Reaction- DHR

290 Chronic Pruritis of Unknown Origin- CPUO

291 T cell helper 2- TH2

292 Interleukin 4 Receptor- IL-4R
<table>
<thead>
<tr>
<th>Age at diagnosis</th>
<th>Gender</th>
<th>Comorbidities</th>
<th>Location of Rash</th>
<th>Morphology of Initial Rash</th>
<th>Clinical Differential Diagnosis</th>
<th>Path Report Comments</th>
<th>Additional Work Up</th>
<th>Previous Therapies</th>
<th>Outcomes</th>
<th>Side Effects-Dupilumab</th>
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<tbody>
<tr>
<td>53 M</td>
<td>hypertension, dyselecteremia, hyperesosinophilic, membranous nephropathy with severe refractory nephrotic syndrome</td>
<td>trunk and extremities</td>
<td>pink/lichenified papules</td>
<td>dermal hypersensitivity reaction, arthropod bite reaction, resolving spongiosis dermatitis, atopic dermatitis, IgG4 disease</td>
<td>Mildly spongiotic epidermis with lymphocytic inflammatory infiltrate with numerous eosinophils surrounding the vessels of the papillary dermis (Figure 1).</td>
<td>PAS negative. WBC with slight neutrophilia. Cr 2.3, BUN 27.</td>
<td>prednisone, mycophenolate mofetil, certirizine, halobetasol, tacrolimus</td>
<td>resolution of rash and pruritis</td>
<td>none</td>
<td>blurry vision (determined to be chronic), headache</td>
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<td>48 F</td>
<td>renal tumor, menorrhagia, acute DVT of left gonadal vein, anxiety, bipolar depression</td>
<td>upper back, elbows, dorsal forearms, thighs, and fingers (especially dorsal MCPs and PIPs)</td>
<td>excoriated papules with subtle lichenification</td>
<td>hypersensitivity dermatitis, latex allergy, irritant dermatitis, contact dermatitis, infectious disease reaction, dermatomyositis</td>
<td>Mild epidermal spongiosis with a scant perivascular lymphocytic infiltrate and rare dermal eosinophils (Figure 2).</td>
<td>No histologic evidence of dermatomyositis. CBC/CMP within normal limits.</td>
<td>mycophenolate mofetil, prednisone, tacrolimus, betamethasone, calcineurin lotions, Neosporin, coconut oil, bleach, mupirocin</td>
<td>resolution of rash and pruritis</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>43 F</td>
<td>hypertension, hyperlipidemia, peripheral artery disease, coronary artery disease, gastrosophageal reflux disease, chronic obstructive pulmonary disease</td>
<td>abdomen and lower legs</td>
<td>erythematos, blanchable papules coalescing into small plaques</td>
<td>hypersensitivity dermatitis, granuloma annulare, mucin deposition disease, contact dermatitis, nummular eczema, atopic dermatitis, drug reaction, infectious process</td>
<td>Unremarkable epidermis and dermis with superficial perivascular lymphocytes and abundant interstitial eosinophils.</td>
<td>Patch testing was minimally positive for nickel sulfate (2+) and p-hydroxybenzyl alcohol (1+). CBC/CMP/TSH within normal limits. Negative Hepatitis B surface antigen, Quantiferon, and HIV antibody</td>
<td>prednisone, mycophenolate mofetil, hydroxyzine, triamcinolone, nystatin-hydrocortisone-zinc oxide, fluconazole, clobetasol, certirizine, cephalaxin</td>
<td>resolution of rash and pruritis</td>
<td>none</td>
<td>eye dryness</td>
</tr>
<tr>
<td>68 M</td>
<td>coronary artery disease, steroid induced diabetes mellitus, asthma, sarcoidosis</td>
<td>Upper chest, shoulder, back</td>
<td>scattered erythematous scaly patches with overlying excoriation</td>
<td>atopic dermatitis, dermatitis herpetiformis, chronic pruritus secondary to other causes, dermal hypersensitivity reaction</td>
<td>Unremarkable epidermis and a dermis containing sparse perivascular lymphocytes as well as scattered interstitial eosinophils, and neutrophils (Figure 3).</td>
<td>Patch testing showed was minimally positivity for sodium laurel sulfate (1+) and benzaprene (1+).</td>
<td>tacrolimus, clobetasol, halobetasol, prednisone, chlorpheniramine</td>
<td>resolution of rash and pruritis</td>
<td>none</td>
<td></td>
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<td>75 M</td>
<td>coronary artery disease, gout, peripheral artery disease, cerebrovascular accident</td>
<td>trunk, particularly the flanks</td>
<td>pink, red dermatitis with mostly broad patches of erythema and slight scale but some more papular components as well</td>
<td>hypersensitivity dermatitis; contact dermatitis, non-buluous pemphigoid, mastocytosis, atopic dermatitis, Griffin’s (with papular component).</td>
<td>Predominantly perivascular inflammatory infiltrate with occasional dermal eosinophils.</td>
<td>Grocott's Methenamine Silver (GMS) stain negative. Direct immunofluorescence studies are negative.</td>
<td>clobetasol, nystatin cream, triamcinolone cream, prednisone, and hydroxyzine</td>
<td>resolution of rash and pruritis</td>
<td>none</td>
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<td>78 M</td>
<td>coronary artery disease, gout, peripheral artery disease, cerebrovascular accident</td>
<td>upper chest, lower back</td>
<td>faint pink patchy dermatitis with slight lichenification, minimal papular component, no scale</td>
<td>dermatitis herpetiformis, bullous pemphigoid, hyper eosinophilic syndrome</td>
<td>Mild acanthosis and spongiosis of epidermis. Superficial perivascular lymphocytes and rare interstitial eosinophils.</td>
<td>Direct immunofluorescence studies negative. Patch testing minimal positivity to potassium dichromate (1+) High low at 12.9. Platelets/WBC normal. CMP normal. Negative Hepatitis B surface antigen and HIV antibody. Immunohistochemistry including serum free kappa/lambda light chain within normal limits.</td>
<td>phototherapy, doxepin, mitracapine, gabapentin, butorphanol, hydroxyzine, aprepitant, clobetasol, tacrolimus, oral prednisone, mycophenolate mofetil, azathioprine</td>
<td>occasional pruritis, 50-60% improvement of rash on physical exam</td>
<td>none</td>
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Figures 2A-C: H&E findings from punch biopsy of the right chest of patient case 2 at (A) 4 x magnification and (B-C) 20 x magnification. Figures A-C demonstrate mild epidermal spongiosis with a scant perivascular lymphocytic infiltrate and rare dermal eosinophils.
Figures 3A-C: H&E findings from punch biopsy of the right shoulder of patient case 4 at (A) 2 x magnification and (B-C) 10 x magnification. Figures A-C demonstrate an unremarkable epidermis and a dermis containing sparse perivascular lymphocytes as well as scattered interstitial eosinophils and neutrophils.
Figures 1A-D: H&E findings from punch biopsy of the left back of patient case 1 at (A) 2 x magnification, (B) 10 x magnification, and (D) 20 x magnification. Figures A-D demonstrate a mildly atypical epidermis with lymphocytic inflammatory infiltrate with numerous eccrine bodies surrounding the vessels of the papillary dermis.