

Effective Use of Dupilumab in Managing Systemic Allergic Contact Dermatitis

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Allergic contact dermatitis to metals has become increasingly recognized in patients with endovascular implants. The ACD can lead to in-stent restenosis as well as a prominent eczematous reaction overlying the implant, often necessitating its removal. We present a case of refractory allergic contact dermatitis to nickel in a 44-year-old man with numerous endovascular stents and vascular clips. He developed numerous adverse effects of systemic therapy to manage his symptoms including recurrent infections leading to frequent hospitalizations. He was effectively transitioned to dupilumab, a monoclonal antibody against the IL-4 α subunit currently approved by the Food and Drug Administration in the management of atopic dermatitis, with an improvement in symptoms and a reduction in infection rate.

Metal hypersensitivity reactions to implants have become increasingly recognized for the past 2 decades with prevalence rates ranging from 0% to 5%.¹ Allergic contact dermatitis (ACD) is the most common form of hypersensitivity, which predominantly manifests as an eczematous reaction directly overlying the metallic implant. Stainless steel and nitinol, which both contain nickel, remain the most commonly used metal alloys for endovascular implants. Studies evaluating the risk of in-stent restenosis (ISR) in metal-allergic patients have been inconsistent, but a recent meta-analysis of 1223 patients shows an increased odds ratio of 2.65 of developing ISR.²

The major diagnostic criteria of ACD to metallic implants initially proposed by Schalock and Thyssen³ and more recently adopted by the American Contact Dermatitis Society⁴ include chronic dermatitis beginning weeks to months after metallic implantation overlying the implant, a positive patch test reaction to a metal in the implant, and complete recovery after removal of the implant. Although removal of the offending agent is the preferred management option for ACD, this is not always possible. Immunomodulating therapies have been used in severe refractory cases of ACD in these unique situations.^{5,6}

Dupilumab is a fully human monoclonal antibody, which was recently approved in the United States by the Food and Drug Administration for the management of atopic dermatitis. It binds to the IL-4 α subunit on both the IL-4 and IL-13 receptors, blocking

Th2-mediated signaling. Although it is also being evaluated as a treatment option for allergic asthma, its role in ACD has not been explored. We present a case where dupilumab was used successfully in a patient with severe systemic ACD from vascular clips.

CASE PRESENTATION

A 44-year-old white man with a history of hypercoagulability with positive lupus anticoagulant and anticardiolipin antibody presented to the clinic with a new pruritic rash. He had no personal or family history of atopic dermatitis. Six months before his initial evaluation, he was given diagnoses of stroke and a left lower-extremity arterial thrombus for which he underwent left popliteal artery stent placement at an outside hospital. Within 2 to 4 weeks after the stent was inserted, he developed a generalized eczematous rash with severe pruritus over his entire body, which was more prominent on his left leg (Figs. 1A–C). He was treated with topical steroids without any improvement, and he was eventually given multiple courses of systemic steroids with only a transient benefit. He unfortunately had multiple episodes of ISR requiring 6 stent replacement procedures. Eventually, he underwent femoral arterial bypass surgery, which improved his vascular complaints, but his eczematous rash persisted.

In our dermatology clinic, skin biopsies at various locations revealed spongiotic dermatitis, and he underwent patch testing to several series commonly used at our institution including our standard, plastics, acrylates, and textile trays. These returned positive for nickel, 2-hydroxyethyl acrylate, orange 34, blue 153, and red 46. Of these, nickel was thought to be the most relevant because of his known stents in his left leg, which correlated to the site of his most severe eczematous disease. Although the exact alloy composition of the stent was unknown because of unavailable records, most stents used at that time were stainless steel or nitinol, which are both at least partially composed of nickel.⁴

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Figure 1. Images of the patient before and after therapy with dupilumab. Images A to C represent the patient's initial presentation while on systemic prednisone 40 mg daily and topical clobetasol 0.05% ointment. Image A is of the bilateral palmar surfaces of his hands, whereas images B and C are of his left leg. Images D and E are of the bilateral palmar surfaces of his hands and left leg, respectively, after 12 weeks of dupilumab therapy.

His ACD remained refractory despite adequate trials of high-potency topical steroids with the use of an occlusion suit and high-dose antihistamines, and he was eventually maintained on prednisone 40 to 60 mg daily. In an attempt to reduce his steroid dependence, mycophenolate mofetil was started and titrated up to 1500 mg twice daily. However, his systemic steroid requirement did not improve, and he subsequently developed cellulitis of his left leg likely secondary to his multiple immunosuppressive therapies (Fig. 2). With a hope that the removal of the stent would resolve his dermatitis, vascular surgery was consulted, and removal of the implant only resulted in a nominal improvement of his symptoms. Repeat imaging showed the presence of innumerable stainless steel vascular clips throughout his left leg, from his previous procedures, which were unable to be removed because of their location (Fig. 3).

For the subsequent 6 years, he continued to necessitate prednisone 40 mg and mycophenolate mofetil with only moderate control of his symptoms. He reported multiple adverse events from his therapy including recurrent infections often leading to hospitalizations

from his immunosuppression (Fig. 2). In addition, his chronic steroid use led to bilateral cataracts requiring a surgical intervention, multiple vertebral compression fractures due to osteoporosis, significant weight gain, and severe depression resulting in unemployment.

He was ultimately referred to the allergy and immunology clinic for an evaluation of ACD and secondary immunodeficiency. Laboratory work at that time revealed severe T-cell lymphopenia with a total CD3 count of 479 cells/ μ L and CD4 count of 108 cells/ μ L. His immunoglobulin levels were notable for mild IgG hypogammaglobulinemia (645 mg/dL) and an elevated IgE level of 1257 mg/dL. His eosinophil count was also notably elevated at 1250 cells/dL. Because he had no history of atopic disease, his elevated IgE level and eosinophilia were attributed to a possible Th2 response from his ACD. Because dupilumab had just become commercially available, it was considered as a possible off-label therapy because it has been shown to modulate the Th2 pathway and not cause significant immunosuppression.⁷

Within 8 weeks after starting dupilumab therapy, his dermatitis drastically improved (Figs. 1D, E). He was able to quickly wean off

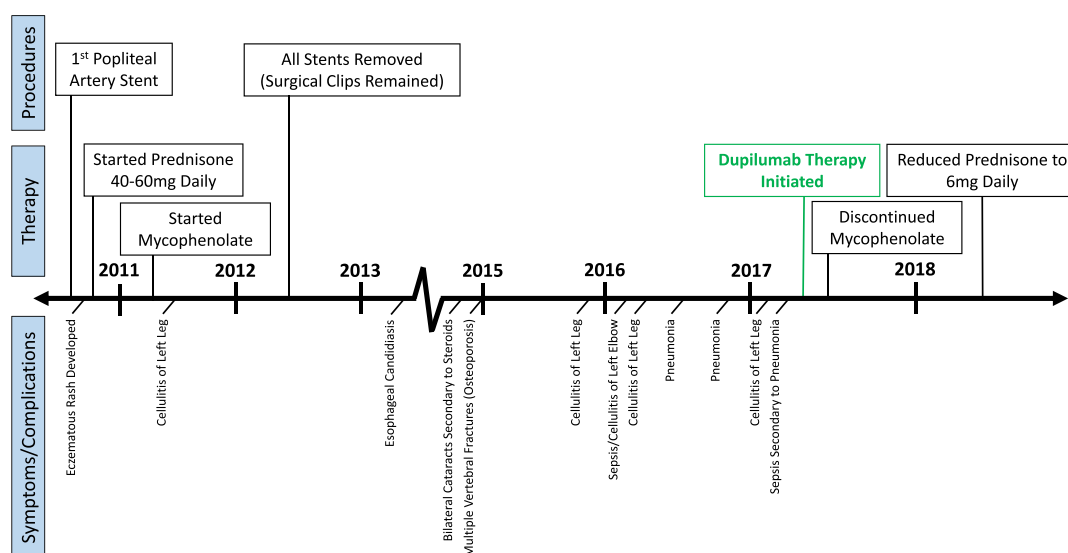


Figure 2. Timeline of symptoms, procedures, interventions, and complications.



Figure 3. Plain x-ray of the patient's left leg revealing numerous surgical clips.

of mycophenolate mofetil and taper his prednisone down to 6 mg daily for the following year. After 4 months of follow-up on dupilumab, he has no longer required his occlusion suit and has returned to the workforce. He did not develop any subsequent infections with an improvement of his markers of Th2 inflammation.

DISCUSSION

Our patient developed a severe eczematous rash predominantly on his left lower extremity within months after the placement of vascular stents due to an arterial popliteal thrombus. His patch testing revealed sensitization to nickel, which was likely present in his stent as well as the numerous vascular clips placed during surgery. He met 3 major criteria of the American Contact Dermatitis Society diagnostic guidelines for ACD to metallic implants.⁴ Allergic contact dermatitis to nickel likely led to the recurrent ISR requiring multiple stent revisions.

His continuous exposure to the offending allergen likely led to his refractory disease making management exceedingly difficult. After stent removal, his symptoms did not significantly improve, likely because of the persistence of many stainless steel vascular clips present throughout his left lower extremity. Although he did show a nominal response to the combination of prednisone and mycophenolate mofetil, the significant immunosuppression led to severe recurrent infections, which limited its effectiveness.

Allergic contact dermatitis has traditionally been considered a Th1-mediated process; however, more recent studies have shown that certain contact allergens can preferentially demonstrate a Th2 response.^{8,9} Because our patient had signs of Th2-related inflammation with an elevated IgE and eosinophilia and no atopic history, it suggested a preferential Th2-mediated ACD, sharing some similarities to the pathophysiology of atopic dermatitis.

Dupilumab was selected because of its ability to disrupt the Th2 pathway as well as having no known immunosuppressive activity.⁷ It has been extensively evaluated in patients with conditions known to have an underlying Th2 inflammatory mechanism including atopic dermatitis, eosinophilic asthma, and rhinosinusitis with nasal polyps.^{7,10,11} To the best of our knowledge, this is the first reported case of dupilumab successfully being used in the management of ACD.

The patient has since been diagnosed with non-Hodgkin lymphoma in 2018, which we do not believe is related to his dermatitis based on the duration of the rash before lymphoma diagnosis and negative skin biopsy results.

Dupilumab could be considered in selective cases of ACD that have a Th2 predominance when removal of the allergen is not possible and immunosuppressive therapy is not tolerated.

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