Case Report

Extensive Scalp Angioedema Following High-Dose Diphenylcyclopropenone for Alopecia Areata

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Abstract

Objective: To describe a case of an unusual adverse drug reaction to diphenylcyclopropenone for the treatment of alopecia areata.

Case summary: A 31-year-old Caucasian male presented with extensive angioedema to the head with neck involvement 10 days following treatment with diphenylcyclopropenone 2% solution in acetone topically on his scalp to treat alopecia areata. Findings on patient presentation included edema of the soft tissues (deeper dermis and subcutaneous tissue) of the head and face with mild neck involvement, acute inflammatory changes from chemical-induced irritation, scalp erythema, and serous fluid drainage from inflamed and fissured edematous scalp. Acute treatments used for control of the reaction included intravenous steroids and antihistamines during hospitalization followed by oral steroids and antihistamines for maintenance during outpatient treatment of the resolving condition.

Discussion: The role of topical diphenylcyclopropenone in this case of alopecia areata is probable according to the Naranjo criteria, with a score of 8. Diphenylcyclopropenone is not approved by the US Food and Drug Administration, but it has been used by many clinicians for the treatment of alopecia areata. Diphenylcyclopropenone causes an allergic contact dermatitis in the area of hair loss. In general, diphenylcyclopropenone is applied at a high concentration of 2% once and then at lower concentrations once weekly after the sensitization dose. This patient applied the 2% concentration on multiple consecutive days.

Conclusion: Frequent use of topical diphenylcyclopropenone 2% applied to the scalp may cause scalp angioedema.

Key Words—alopecia areata, diphenylcyclopropenone, scalp angioedema

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Alopecia areata is characterized by chronic loss of hair due to an autoimmune disease.¹ Alopecia areata is present in 4.5 million Americans in all age groups, although it is most commonly seen in persons younger than 30.² Clinical presentation of alopecia areata includes patches of hair loss most commonly on the scalp, but hair loss is also seen facially and less commonly over the whole body. Despite attempts to find curative therapy, multiple treatment options have been explored and implemented by clinicians to regain hair growth that is lost due to the disease. Studies that have been conducted to find an efficacious way of regaining hair growth have not

yielded strong evidence for using specific pharmacological interventions. Commonly used drugs for the treatment of alopecia areata, such as topical steroids and minoxidil, lack studies to show long-term efficacy.³ Other therapy options include intralesional corticosteroids, photochemotherapy, photodynamic therapy, systemic corticosteroids, and systemic cyclosporine. Currently, clinicians use topical immunosuppressive therapy, such as triamcinolone, or topical immunotherapy, such as diphenylcyclopropenone.

Diphenylcyclopropenone is currently not approved by the US Food and Drug Administration (FDA), although it is used by many clinicians for the treatment

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of patients with alopecia areata. Diphenylcyclopropenone has been used for more than 30 years with the intent to cause an allergic contact dermatitis to the area of hair loss. The exact mechanism of action is unknown, but it has been theorized to increase clearance of follicular antigens through recruitment of new T cells, antigenic competition, and excessive production of proinflammatory cytokines by the follicular keratinocytes.⁴ Recommended treatment with diphenylcyclopropenone includes sensitizing a patient with a higher dose of the medication, such as 2%, followed by lower concentrations of the medication applied once weekly. Only observational studies have been conducted to show the efficacy of diphenylcyclopropenone using this recommended treatment regimen.⁵ A published review study found that 58% of patients treated with diphenylcyclopropenone had hair growth of at least 30% in areas of previous hair loss.³ The most commonly used dosing regimen seen in the literature includes sensitization of the patient with diphenylcyclopropenone 2% once, followed 2 weeks later by 0.001% to 0.1% once weekly then titrating up the concentration every week. After erythema or pruritis results, signifying an appropriate allergic response to the medication and proper therapeutic concentration, the patient is maintained on this concentration for 6 to 12 months. Side effects include eczematous reactions that blister and spread, sleep disturbances, urticarial reactions, and dermographism. Other side effects may include lymph-node enlargement, headache, itching, and pigmentary disorders.⁴ After conducting a full medical literature search, we found no reports of diphenylcyclopropenone causing scalp angioedema. With no proven long-term, yet efficacious, therapy for the treatment of alopecia areata, we found it relevant to highlight a risk of using diphenylcyclopropenone, most specifically at high doses.

CASE REPORT

A 31-year-old Caucasian male electrician with a past medical history significant for hair loss presented to the emergency department (ED) with a 2-day history of extensive edema of his head with mild neck involvement that was increasing in severity following a 10-day administration of diphenylcyclopropenone to his scalp for alopecia areata. Except for alopecia areata, the patient had no known medical problems or remarkable past medical history. The patient stated that he had visited his dermatologist regarding the alopecia and was prescribed the topical medication diphenylcyclopropenone 2% along with a less concentrated version of the same medication. The patient started administering the medication to affected regions

of his scalp 10 days prior to presenting to the emergency department. The prescription label of the medication stated to administer the diphenylcyclopropenone 2% topically once daily to the scalp for 2 weeks. The patient followed these directions; after 5 doses of the medication, he reported that his skin started to feel irritated. During his course of therapy, the patient stopped the medication due to the irritation and the new onset of scalp drainage. Upon resolution of the drainage, he rechallenged himself with the medication, which resulted in a more severe adverse reaction. His head started to swell, and the onset of edema in his face and neck bilaterally prompted the ED visit (Figure 1). At the ED, the patient's scalp was edematous and had serous fluid drainage and fissures. He reported sensations of tightening of the skin around his head (Figure 2). The superficial layer of his scalp was erythemic and flaky from a chemically induced inflammatory response and localized urticarial reaction in addition to the angioedema of the head and neck (Figure 3). Review of systems was unremarkable except for pruritis affecting his scalp.

Laboratory workup was performed and treatment was initiated in the ED with steroids and antihistamines for suspected IgE-induced reaction to his medication, as eosinophilia was discovered on further testing. The patient did not exhibit airway symptoms. He was subsequently admitted to the hospital for

Figure 1. Swelling of the patient's head along with onset of edema in his face and neck bilaterally prompting the emergency department visit.

Figure 2. The patient's scalp was edematous accompanied with serous fluid drainage and fissures of the scalp. He reported sensations of tightening of the skin around his head.

treatment and monitoring of his condition. He developed generalized pruritis with dermatographism induced by scratching, most noticeable over his anterior chest wall and upper extremities bilaterally during the first few days of his hospital stay. The dermatographism and angioedema improved by day 3 of his hospitalization after optimum control was achieved via an antihistamine regimen supplemented by steroids.

Figure 3. Patient was admitted to the hospital due to the adverse drug reaction. The superficial layer of his scalp was erythemic and flaky from the chemical induced inflammatory response

Upon presentation, a basic metabolic panel and a complete blood count with differential were performed. Abnormal lab results included a white blood cell count of $15.7 \times 10^3/\mu\text{L}$ (reference range, $3.6\text{--}11.1 \times 10^3/\mu\text{L}$) with 77% neutrophils (reference range, 43.2%–71.5%), 7% eosinophils (reference range, 0.7%–7.8%), and an elevated blood urine nitrogen at 25 (reference range, 6–20 mg/dL). All other labs were within normal limits. The patient also had dermatographism, signaling an increase in histamine levels. The patient was subsequently diagnosed with scalp angioedema secondary to acute allergic reaction from diphenylcyclopropenone.

Due to the patient's clinically elevated levels of histamine and a heightened immune reaction to diphenylcyclopropenone 2%, his mainstays of therapy were antihistamines and steroids. To reduce his heightened immune response, the patient was treated with methylprednisolone 125 mg intravenous for one dose and then 60 mg intravenous every 6 hours thereafter. Doxepin 10 mg was given orally at bedtime as well as hydroxyzine 25 mg orally every 6 hours. For gastrointestinal prophylaxis and potentiation of histamine blockade, famotidine 20 mg orally twice daily was administered. During the patient's admission, his condition improved, and the edema and erythema decreased. After 3 days of inpatient therapy, the patient was stable and was discharged for follow-up as an outpatient. Outpatient medications prescribed were doxepin 25 mg orally at bedtime as needed, hydroxyzine 50 mg orally every 6 hours as needed, and prednisone 40 mg orally daily for 3 days, then 20 mg daily for 3 days, 10 mg daily for 3 days, and then 5 mg daily for a total of 14 days. Additionally, the patient was told to discontinue use of diphenylcyclopropenone 2%. The patient was scheduled for a follow-up appointment 5 days after discharge.

DISCUSSION

According to the Naranjo probability scale, the patient's score was 8 with diphenylcyclopropenone as the probable cause of alopecia areata, because (a) irritation began after administration, (b) the patient rechallenged himself with the medication resulting in an increased adverse reaction, (c) the reaction improved after discontinuation along with administration of antihistamines and steroids, and (d) no alternative causes were identified.⁶ Currently, there are no published cases of scalp angioedema resulting from use of diphenylcyclopropenone 2%. A literature search regarding adverse effects of diphenylcyclopropenone highlights known adverse effects of the medication,

such as urticaria.^{7,8} This specific patient case offers insight into another adverse event not previously seen with high-dose diphenylcyclopropenone. Because the patient had no significant past medical history and did not take any other home medications, there were no confounding variables for his scalp angioedema. Unique to this case is the high dose of diphenylcyclopropenone used. In the majority of published literature, the 2% dose is only used once for sensitization purposes and is followed by application of a lower dose once weekly. The patient's prescription label from the pharmacy directed that the diphenylcyclopropenone 2% be used daily instead of as a one-time sensitization dose. Scalp angioedema may occur with daily topical application of diphenylcyclopropenone 2% and is treated successfully with steroids and antihistamines.

The use of diphenylcyclopropenone 2% for alopecia areata may result in scalp angioedema. Prescribers and users of diphenylcyclopropenone should be aware of this adverse reaction. This case has been reported to the FDA via the MEDWATCH program.

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