allergies

Review

Itchy Toxicodendron Plant Dermatitis

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Abstract: Plants such as the Toxicodendron species, consisting of poison ivy, poison oak, and poison sumac, largely contribute to allergic contact dermatitis with itch as a predominate symptom. Many individuals are affected by this skin condition, with approximately 50% to 70% of adults in North America demonstrating a degree of clinical sensitivity to this species of plants. In this review, we discuss the prevalence, pathophysiology, and clinical features of this contact dermatitis, as well as both treatment and prevention directed towards alleviation of itch. Updated research is emphasized throughout this review, although it is evident that this field is evolving, and more research is necessary to enhance treatment.

Keywords: allergic contact dermatitis; itch; Toxicodendron species; poison ivy; poison oak; poison sumac

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1. Introduction

The most common cause of allergic contact dermatitis in the US is exposure to plants, specifically the Toxicodendron species, which include poison ivy, poison oak, and poison sumac. Contact with this species of plants causes a weeping rash that is largely characterized by significant pruritus. Allergic contact dermatitis is a common skin condition that affects millions of people per year, with anywhere between 10 to 50 million cases yearly, and it is a significant medical condition that occurs frequently [1]. Urushiol is the major allergen that elicits the response in the Toxicodendron species and it is dispersed throughout the plant including the leaves, stems, and roots [2]. The reaction occurs via direct contact with any part of the plant, as well as from indirect exposure to contaminated sources, such as clothing, shoes, and pets.

Pruritus is a significant manifestation of rash; other characteristics include an eruption of delineated erythematous vesicles, papules, and edema. For many years, the treatment of allergic contact dermatitis has not changed but recent understanding of the underlying mechanism of itch can contribute to both the treatment and prevention. In this review, we will discuss the prevalence, pathophysiology, clinical features, and treatment of allergic contact dermatitis to the Toxicodendron plant species, highlighting the advancements made in understanding the underlying mechanism of itch and its potential in therapeutic relief.

2. Prevalence

Toxicodendron dermatitis affects millions of individuals yearly. In the US adult population, it has been reported that approximately 50% to 75% of people demonstrate a reaction to urushiol, the allergenic component of oleoresin [3]. Most geographical locations in the US contain the plant species and subsequent allergic contact dermatitis affects individuals of all ages, ethnicities, and skin types [4]. Studies have shown that sensitization to urushiol typically occurs in early adolescence, between the ages of 8 and 14, with findings suggesting that infants are not as susceptible to sensitization [5]. In 2012, the US Centers for Disease Control and Prevention reported that emergency department visits for allergic contact dermatitis due to poison ivy was 929,290, compared to 472,000 visits in 2002 [6]. As

a result, dermatitis from the Toxicodendron species contributes greatly to medical morbidity and these figures are increasing.

Outdoor activities in the wilderness, rural areas, and sub-rural areas, as well as occupational exposure from farming, construction, landscaping, and forest firefighting increase susceptibility. For instance, the US Forest Services reported that dermatitis from Toxicodendron resulted in 10% of lost time due to injury related to rash [7]. Additionally, in areas with dense forestry, such as California, Oregon, and Washington, one third of firefighters are disabled with dermatitis from poison ivy and related species each fire season [8]. The medical burden is significant in these occupations, with the cost of treatment accounting for 1% of the budget of yearly workers' compensation in California, for which the total was 11.4 billion dollars in 2014 [8].

3. Pathophysiology

The allergenicity of poison ivy, poison oak, and poison sumac is due to urushiol, a catechol ring [9]. The composition of the catechol ring with variations in unsaturated to saturated bond ratios in the side chain components distinguishes urushiol found in poison ivy, poison oak, and poison sumac [3]. The antigenicity of urushiol can be attributed to changes in the aliphatic chain composition. Although slight variations occur in the chemical structure of urushiol found amongst the Toxicodendron species, cross reactivity is common and sensitization to one often yields susceptibility to an allergic reaction to other plants in the species [3].

When the epidermis encounters an antigen, the antigen-presenting cells found within the epidermis, Langerhans cells, will uptake the antigen, travel to the nearest lymph node, and present it to T lymphocytes [10,11]. A similar process occurs once exposure to urushiol occurs, and following the migration of Langerhans cells, T lymphocytes are activated and travel to the site of exposure. Several cytokines are released at the site of exposure that propogate the inflammatory response.

Additionally, Langerhans cells have CD1a molecules expressed on their surface. CD1a is a class I major histocompatibility complex molecule that is sensitive to lipids that presents antigens to T lymphocytes and is strongly associated with the reaction to urushiol breakdown molecules, specifically [12,13]. These antigen-presenting cells bind the substrate and present them to CD4 T-helper lymphocytes found in draining lymph nodes, initiating the immunological pathway. The activated CD4 T-helper lymphocytes activate both T-effector cells and T-memory lymphocytes, propogating the cytotoxic immune response against urushiol.

In addition to the adaptive immunological response, local cells found in the epidermis and dermis also contribute to the inflammatory response and subsequent itch. Keratinocytes and monocytes secrete cytokines, prostaglandins, leukotrienes, and other immunomodulators that mediate additional immunochemical responses to urushiol [10,14]. Studies have found that keratinocytes initiate the release of interferon-γ and tumor necrosis factor α (TNF-α) as an early response [3,15]. The delayed response by keratinocytes produces the release of cytokines interleukin 1, interleukin 6, interleukin 8, and granulocyte-macrophage colony stimulating factor, continuing the immune response [3,13].

The immunological pathway of allergic contact dermatitis to the Toxicodendron species has been largely studied; however, the mechanism of its itch has rarely been investigated until recently. New developments have suggested that IL-33 plays a major role in plant itch. Liu et al. employed the use of transcriptome microarray analysis and found that the cytokine IL-33 was upregulated in mice exposed to urushiol [16]. Cytokine IL-33 binds to receptor ST2, an Interleukin 1R receptor that is most commonly expressed in small, dorsal root ganglia. The binding of IL-33 to ST2 leads to the influx of Ca2+, eliciting a sensory reponse of itch. Injection of the IL-33 cytokine intensified the itch induced behavior such as scratching and corresponding inflammation, demonstrating a strong relationship between the upregulation of IL-33 and the pruritic mechanism provoked by urushiol. In addition, the use of molecules that attenuated IL-33 showed decreased behavioral itch

responses, further indicating the association between the IL-33/ST2 cascade and pruritus, seen in Figure 1.

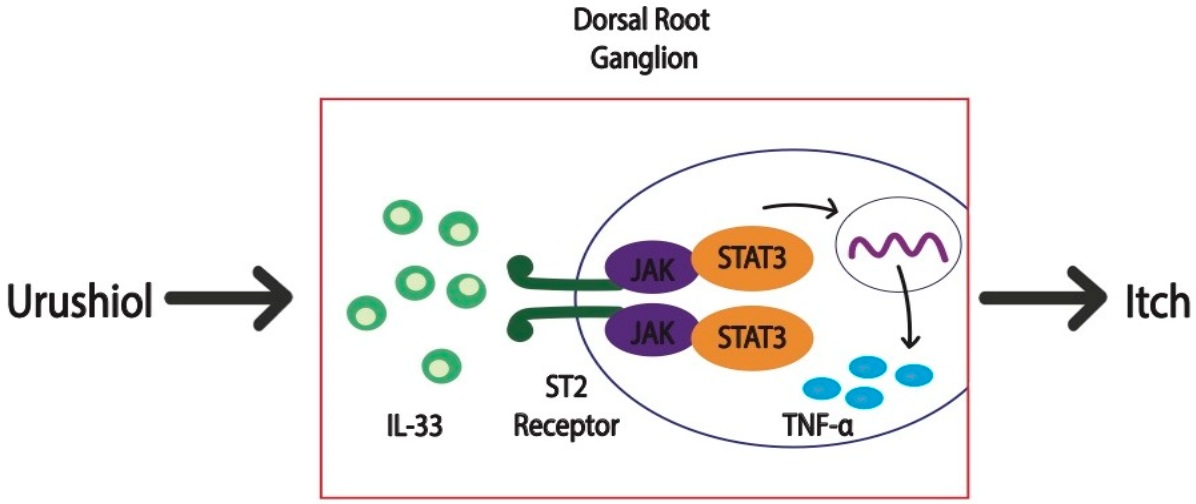

Figure 1. In response to urushiol, IL-33 is upregulated and binds to the ST2 receptor in dorsal root ganglia, mediating the transcription of TNF-α and subsequent inflammatory cascade that ultimately increases itch behavior.

Furthermore, the spinal IL-33/ST2 pathway was found to exacerbate chronic itch by increasing astrocytic Janus Kinase 2 (JAK2) binding to the signal transducer and activator of transcription 3 (STAT3) and upregulating the release of TNF-α [17]. TNF-α activated the release of gastrin releasing peptide (GRP), which binds to gastrin releasing peptide receptor (GRPR), mediating an increased itch response. Neutralization of IL-33, ST2, and JAK2 provided alleviation to chronic itch responses by diminishing the GRP/GRPR signaling cascade.

A similar model employed the use of whole transcriptomes and measured itch mediators and found that urushiol induced a TH2 immune response and upregulated the synthesis of cytokine thymic stromal lymphopoeitin (TSLP) [18]. TSLP is a cytokine that serves as a T-cell regulator and facilitates a pruritic response. In addition to TSLP, other molecules associated with itch-related behavior were serotonin (5-HT) and endothelin (ET-1). The use of anti-TSLP, 5-HT inhibitors, and ET-1 inhibitors reduced behaviors associated with itch, such as scratching, in the mouse model when exposed to urushiol, signifying a correlation between TSLP, 5-HT, and ET-1 and pruritus that may be translational to human exposure to Toxicodendron plant species.

Given that these reponses are largely histamine independent, blockage of IL-33/ST2 signaling pathways and TH2 dependent immunomodulators, such as TSLP, can provide therueptic relief to the itch response that is frequently observed in individuals sensitive to Toxicodendron dermatitis.

4. Clinical Features

Individuals who are sensitized to poison ivy, poison oak, and poison sumac will develop an acute response in response to re-exposure. Classically, the dermatitis that develops is described as a pruritic eczematous eruption that is often in the form of delineated streaks where contact with the plant brushed the surface of the skin [19]. The sharp demarcated eruptions consist of erythematous papules and vesicles that typically present within 24–48 h following exposure, however this can range from 5 h to 15 days in some individuals [20]. The clinical presentation of linear markings and sharp borders is a key feature that aids in the identification of this plant dermatitis.

Initially, individuals may experience erythema, edema, and an eruption of papules followed by vesicles and bullae. In more mild cases, vesicles and bullae may not occur.

Fluid from vesicles and bullae have not been found to contain antigen load and therefore do not contribute to the dissemination of the disease. Variations can occur in an individual due to differing concentrations of antigen and time of exposure. Occupational workers can experience additional sequelae of generalized dermatitis and respiratory tract inflammation due to aerosolization of urushiol in wildfire smoke [3]. The heightened response of the reaction can occur anywhere from 1–14 days after initial exposure. Without treatment, Toxicodendron dermatitis can last for 3 weeks and up to 6 weeks in highly sensitized individuals, significantly affecting individuals and their quality of life.

A rare manifestation of allergic contact dermatitis from poison ivy, poison oak, and poison sumac is black spot dermatitis [21]. The sap from the plants deposits on the skin and forms black lesions preceding an eruption of erythematous papules and vesicles. Additionally, there have been reports of erythema multiforme following severe reactions to allergic contact dermatitis [22]. In these cases, individuals did not have prior history of herpes simplex virus suggesting that erythema multiforme may be an underreported reaction in severe cases. These patients presented with generalized itchy papules and widespread target lesions on the torso and extremities.

Long-term complications are not common; the most prevalent are hyperpigmentation and secondary infection superimposed to the areas affected. Transient hyperpigmentation may occur following the localized inflammation and it is more common in individuals with darker skin tones [4]. Typically, hyperpigmentation can persist for a few months. One study analyzed the occurrence of secondary infection following allergic contact dermatitis to poison ivy and found that half of a total of 33 subjects developed infection. Isolates that were found from the areas of infection included Staphylococcus aureus, Group A β-hemolytic strep, Prevotella, Porphyromonas, and Fusobacterium [23]. A very rare complication of allergic contact dermatitis to the Toxicodendron species is the development of nephrotic syndrome [24].

5. Treatment and Prevention

The treatment and prevention of Toxicodendron dermatitis has not changed for many years. The main goal of treatment is therapeutic relief aimed at alleviating many of the symptoms that individuals experience, predominately pruritus. Baths with baking soda and colloidal oatmeal and the use of cold compresses can help improve the itch. Additionally, over the counter topical treatment includes the use of cooling agents, such as calamine lotion, which aids in relieving dryness and reducing itch with menthol and phenol [25,26].

The mainstay of treatment has been corticosteroids. Specifically, high potency topical steroid clobetasol has been found to be most effective during the early reaction. Alternatives to higher potency steroids are mid-potency topical steroids, such as triamcinolone and betamethasone, which may be a better alternative due to lower cost. In children, the use of low potency topical corticosteroids such as hydrocortisone can be used to prevent side effects such as atrophy of the skin [27]. Systemic corticosteroids may be used in severe and widespread cases. Cases that can benefit from the use of systemic steroids include individuals with greater than 20% body surface area affected, extensive vesicles, bullae, blistering, and itch, as well as involvement of sensitive areas such as the face or genitals [28]. Oral prednisone can be initiated at 1 mg/kg/day with a maximum dose of 60 mg/day for severe cases and should be continued for 2–3 weeks with tapering [29]. Alternatively, the use of intramuscular injection of triamcinolone for 3 weeks has been found to be therapeutic in severe cases and demonstrated increased compliance. One consideration when using triamcinolone intramuscular injections is the risk of rebound if the course of treatment is not sufficient [30]. Furthermore, the rebound dermatitis appears to be more steroid-resistant, so management of systemic steroid treatment must be closely followed [31]. The use of long-term systemic corticosteroids is limited by side effects such as risk of infection, hyperglycemia, and hypertension amongst other systemic effects.

The use of antihistamines has limited efficacy, considering the histamine-independent cascade that underlies the mechanism of itch [32,33]. While the effect is limited, antihis-

tamines are still considered one of the treatments for allergic contact dermatitis from the Toxicodendron species. Therefore, the newer studies on the IL-33/ST2 signaling cascade and TSLP show that it can be useful in treating the underlying mechanism of itch in unresponsive patients undergoing treatment with steroids and antihistamines or when contraindications are present.

Use of topical immunomodulators that reduce itch, such as tacrolimus and pimecrolimus, was reported in a few case reports. Tacrolimus and pimecrolimus are calcineurin inhibitors that diminish the immunological cascade by decreasing cytokine production as well as the activation of T cells and Langerhans cells in the dermal skin [34,35]. One study analyzed the use of topical tacrolimus ointment 0.1% in patients with orbital allergic contact dermatitis and found a significant improvement in symptoms and a positive trend in reduction of itch [36]. A randomized controlled trial compared the efficacy of tacrolimus ointment 0.1% to vehicle ointment and found it superior at minimizing dermatitis and that it significantly reduced pruritus [37].

We have also used a compounded Topical JAK/STAT inhibitor that reduced poison ivy itch. JAK/STAT pathway inhibition can decrease many cytokines that are involved in inflammatory processes [38]. As an emerging treatment, JAK/STAT inhibitors have been approved for use in rheumatoid and psoriatic arthritis, and are undergoing investigation for treatment of atopic dermatitis, dermatomyositis, and numerous other skin conditions. The use of topical JAK/STAT inhibitors requires further evaluation; however, there is evidence that shows promising efficacy in reducing itch in the treatment of allergic contact dermatitis.

Prevention can be achieved by various modalities, such as limiting exposure to Toxicodendron species, washing of affected areas, pretreatment with topical barriers, and desensitization. Upon exposure, washing the affected areas immediately can breakdown the oily sap containing urushiol and prevent a reaction. Significant water flushing can effectively remove urushiol from the skin; flushing within 10 min can remove 50%, flushing within 15 min can remove 25%, and flushing within 30 min can remove 10% of urushiol substance [3]. Following 30 min, breakdown of urushiol and penetration of skin is likely to occur. Additionally, there is some evidence that suggests the use of chemicals that inactivate urushiol and soap as effective methods to remove urushiol from the skin. The chemical inactivator Tecnu, the oil remover Goop, Dial Ultra dishwashing soap, and Zanfel soap have all been found to significantly remove urushiol from the skin [39,40]. Additionally, pretreatment with topical barriers such as quarternium-18 bentonite, linoleic acid, Hollister Moisture Barrier, and Hydropel have also demonstrated efficacy at preventing or limiting the extent of reaction to urushiol [41–43]. One longstanding practice implemented by Native Americans is desensitization to urushiol by ingesting poison ivy leaves; however, this mechanism is controversial [44]. Previous findings have shown that ingestion or parenteral intake of urushiol demonstrates hypo-sensitization rather than desensitization. However, further studies did not find hypo-sensitization to be statistically significant in human models [45,46]. Moreover, there have been reports of increased pruritus and urticaria with ingestion or injection of urushiol [3].

In addition to these treatments, there are currently clinical trials investigating the use of a vaccine injection to prevent poison ivy, oak, and sumac-derived contact dermatitis [47]. The name of the immunomodulating injection is 3-pentadecyl-1,2-phenylene *bis* (4-(4-aminophenyl)butanoate) (PDC–APB). A recent animal study, published in 2018, revealed that administration of intramuscular injection PDC–APB resulted in a very mild or nonexistent skin reaction following urushiol exposure in the experimental animal group when compared with the control animal group [48]. Currently, there is a phase I trial for the use of PDC–APB that will explore the efficacy and safety of its use against urushiol [49].

Overall, the landscape of treatment for allergic contact dermatitis from poison ivy, poison oak, and poison sumac is directed at eliminated or diminishing itch and has not substantially changed over the last few years. However, developments in understanding the primary mechanisms of itch can impact upcoming treatment mechanisms and decrease pruritis in affected individuals.

6. Conclusions

Toxicodendron dermatitis is one of the most common causes of allergic contact dermatitis and affects millions of individuals in the US yearly. Exposure to poison ivy, poison oak, and poison sumac in sensitized individuals evokes a weeping erythematous eruption of papules and vesicles that is highly pruritic. Many of the treatments for allergic contact dermatitis target the symptom of itch. There have been advancements in understanding the pathophysiology of itch in allergic contact dermatitis from urushiol that highlight the IL-33/ST2 pathway and cytokine TSLP. While management of urushiol-mediated allergic contact dermatitis has been unchanged, the effective targeting of underlying itch mechanisms can provide innovate treatments.

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