Diagnosis and treatment of actinic prurigo

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ABSTRACT: Actinic prurigo (AP) is an idiopathic photodermatosis that affects mainly the mestizo population in Latin America. It has an early onset, a slight predominance in women, and affects the sun-exposed areas of the skin, causing erythematous papules and lichenified plaques secondary to intense and chronic pruritus. Lesions can be induced by both ultraviolet A (UVA) and ultraviolet B (UVB). An association with several human leukocyte antigen (HLA) alleles has been reported. AP is unique among all photodermatoses in its remarkable response to thalidomide. In the past the microscopic features of AP have been considered as nonspecific; however, the constant finding of dense lymphocytic inflammatory infiltrates and the immunogenetic features of AP support the existence of an immunologic mechanism in its pathogenesis.

KEYWORDS: actinic prurigo, photosensitivity, thalidomide

Clinical presentations

Various types of photodermatoses are frequently found throughout Latin America. Due to its geographical location, there is a high amount of solar radiation most part of the year. Furthermore, nutritional, economic, social, and particularly race factors affect the features of these diseases.

Mestizo refers to people of mixed Indian and European ancestry; it predominates in Mexico, Guatemala, Honduras, Colombia, Ecuador, Peru, and Bolivia, while it is rare or nonexistent in Costa Rica, Venezuela, Argentina, Uruguay, and Chile. In Nicaragua, Panama, and Brazil, the mixed race population is different, consisting of African and White ancestry (1).

One of the common photodermatoses is actinic prurigo (AP). Its polymorphic clinical features, well known to Latin American dermatologists, include erythematous papules, crusts, excoriations, and lichenified plaques due to chronic scratching (Fig. 1). Vesicles are absent as a primary lesion, but can be found as a result of secondary contact dermatitis, eczema, and impetigo. AP affects sun-exposed areas of the skin, such as the face (eyebrows, malar regions, nose, lips), neck, V-area of the chest, external regions of the arms and forearms, as well as the dorsum of the hands (Fig. 2).

The onset is usually at an early age, when the child is 4–5 years old and is constantly exposed to the sun. This disease runs a chronic course, with no remissions in patients seen in Latin American countries, where there is no significant variation in the sunlight throughout the year. In cases found in Canada (2–4), the United States (5), and England (6), the patient’s condition flares during the spring and summer and improves or remits during the winter. There is a predominance of women, with a ratio of 2:1. AP affects the inhabitants of regions located at altitudes greater than 1000 m above sea level, although cases have been found in coastal residents.

Involvement of the lips and the conjunctiva is common, and it causes cheilitis and pseudopterygium. Both the upper and lower lips can be affected, although it is found mainly on the lower lip; the lesions are characterized by edema, scales, fissures, and secondary ulceration.
The intensity of the cheilitis fluctuates from an acute phase with severe exudative lesions and yellowish adherent crusting (Fig. 3) to a chronic phase with dry and scaling lips (Fig. 4). The cheilitis is chronic and recurrent; it exacerbates with sun exposure. Conjunctival involvement includes hyperemia, photophobia, and increased lacrimation in its early stages. Later, there is brown pigmentation, hypertrophy of the papillae, and pseudopterigium formation associated with pruritus (7) (Figs. 5 and 6).

**Histology and Immunohistochemistry**

For a long time the histopathologic characteristics of AP were considered nonspecific. However, based on more recent data obtained from a large number of patients, these features are now considered to be distinctive, consisting of hyperkeratosis, ortho- or parakeratosis, regular acanthosis (this is a constant finding which correlates well with the clinical lesions), and thickening of the basal lamina. The superficial dermis shows a perivascular dense lymphocytic infiltrate, which rarely affects the middermis. There is no adnexal involvement or actinic elastosis (Fig. 7).

In lip biopsy specimens, there is hyperkeratosis with parakeratosis, regular acanthosis, spongiosis, and vacuolization of the basal cell layer. There may be epithelial ulceration. In the dermis one finds stromal edema, and dilated and congestive vessels. The dense lymphoplasmocytic infiltrate can have a band-like distribution, or form follicles or germinal centers (in up to 80% of the cases) (Fig. 8); abundant eosinophils are usually present.

Biopsy specimens of the affected conjunctiva show epithelial hyperplasia alternating with atrophy. Vacuolization of the basal cell layer is always present, as well as dilated capillaries in the dermis. The inflammatory infiltrate consists of lymphocytes that accumulate and form lymphoid follicles (88% of the cases). Eosinophils and melanophages are present in most cases (Fig. 9).

The presence of lymphoid follicles in skin biopsy specimens has been observed when there is a loss of epidermis (ulceration), which supports the protective role of the stratum corneum, and provides an explanation as to why these follicles are more frequently observed in the mucosae. With the use of immunohistochemical techniques, such as immunoperoxidase and immunophosphatase staining, the inflammatory cells forming follicles have been shown to be T and B lymphocytes. The T cells (CD45+, IL2+) (Fig. 10) are in the periphery.
and the B cells (CD20+) are in the center (Fig. 11). Furthermore, there are abundant eosinophils and extracellular deposits of IgM, IgG, and C3 in the papillary dermis. The keratinocytes show immunoreactivity with calprotectine and tumor necrosis factor (TNF)-α (8).

Photobiology

Our experience with phototests shows that the minimal erythema dose (MED) of ultraviolet B (UVB) was in the range of 50–60 mJ/cm², and experimental induction of lesions using a MED of UVB of 3–5 mJ/cm²/day for 15 days was successful in 100% of the cases (Fig. 12). With ultraviolet A (UVA) the lesions were produced with daily radiation of 2.5 J/cm² for 10 days in 90% of the patients. Consequently we were able to prove that these patients react to a broad spectrum of radiation (UVA and UVB) and their MEDs to UVB and UVA are usually normal.

Immunogenetics and pathophysiology

AP is associated with certain ethnic groups of North and South America, which suggests a genetic predisposition. There are reports of several human leukocyte antigen (HLA) alleles in association with AP. In Cree Indians from Saskatchewan, Canada (9), the most common antigens were HLA-A24 and HLA-Cw4. In the Chimila Indians from Colombia (10), a high frequency of HLA-Cw4 was found, and in Mexicans we reported an increased occurrence of HLA-A28 and HLA-B39(B16), as well as a very strong association with HLA-DR4 (DRB1*0407) (11).

Meanwhile, English investigators have also reported AP patients with HLA-DR4 (DRB*0407) (12). In the Inuit Indians of Canada, an association with HLA-DR4 (DRB1*14) was found (13).

The English patients with polymorphic light eruption (PMLE) (14) did not show an association with a particular HLA, which suggested that HLA-DR4 (DRB1*0407) can be utilized as a marker to distinguish these two diseases, AP and PMLE. One can speculate that HLA alleles may have a causal role in determining the response to a peptide antigen, probably induced by solar radiation, that would initiate the cutaneous reaction.

Differential diagnosis

Several conditions need to be considered.

Atopic dermatitis with photosensitivity

Most patients with atopic dermatitis have characteristic cutaneous manifestations, however, in some the dermatitis might be exacerbated by exposure to solar radiation. In these cases a personal and/or familial history of atopy, an early onset, the presence of xerosis, sparing of the tip of the nose, and a good response to topical or systemic corticosteroids and topical emollients can help differentiate it from AP.

Chronic actinic dermatitis

Patients with this condition present with erythematous papules, plaques, and lichenification on sun-exposed areas; they may have a positive reaction to multiple contact photoallergens. It has a marked predominance in older men.

The diagnostic criteria are based on phototest results which show an abnormally low response to
UVB, UVA, or visible light. Histopathologic changes range from dense lymphocytic inflammatory infiltrate to infiltrate with atypical mononuclear cells resembling lymphoma.

PMLE
Polymorphic light eruption has a worldwide distribution and affects all races. It is less frequent in Latin American countries, presumably due to the year-round presence of sunlight. Its clinical picture (e.g., presence of vesicles), as well as its intermittent course with complete remission, relapse, and exacerbation, recurring yearly, usually with sun exposure in the spring, is not observed in AP. The histopathology never shows lymphocytic infiltrate forming follicles, and it is not associated to any particular HLA antigens. Other entities such as discoid lupus erythematosus and lymphocytic infiltrate are clinically distinguishable, and as such are seldom mistaken for AP.

Treatment
As with all photodermatoses, the first and most obvious measure to control AP is avoiding sun exposure with adequate clothing, sunglasses, a hat, or an umbrella. In many cases we may need to treat other diseases related to AP, such as contact dermatitis and impetigo, before we can prescribe any type of sunscreen. A sun protection factor (SPF) greater than 15 with a proper vehicle is recommended. In our experience, creams are more effective, since lotions and gels may be poorly tolerated by damaged skin.

Topical and systemic corticosteroids and antibiotics are successful in treating the most frequent complications of AP. Oral antihistamines will help control the pruritus. Antimalarials are efficacious for PMLE and discoid or systemic lupus erythematosus; however, they are not effective for AP.

Thalidomide has proven to be the most effective drug in the treatment of AP (15,16). In fact, the response to thalidomide may be a marker in the diagnosis of AP (1,7). The initial dose is 100–200 mg/day, according to the severity of the clinical picture. It can be reduced when improvement is observed. We have been able to control many of our patients with a dose as low as 25 mg/week (Figs. 13 and 14). This drug must be used under strict safety measures; for women of childbearing age we administer intramuscular contraceptives and supply thalidomide only in quantity sufficient for 1 month.

Reported side effects, such as peripheral neuropathy, were not frequently observed in our patients. Somnolence and increased appetite are observed in some patients and morbilliform exanthema may be seen, albeit rarely.

Discussion
A viral photodermatosis that affects the Mestizo population of Latin America. Although there have been reports of cases in Indian communities in Canada and the United States, it is interesting to note that AP is not found in countries like Chile and Uruguay, where the Mestizo population is almost nonexistent. In Argentina there were some reports among a Mestizo group located in the northern region of the country. These last three countries have a predominantly Caucasian population because of European immigration.

According to Birt and Davis (2,3), Lane et al. (4) in Canada, and Fusaro and Johnson (5) in the United States, there is a hereditary factor present in AP. Yet Latin American authors found that familial cases reported are not more than 15%. It is probable that the difference reflects the different population of patients affected in each of these countries. In Canada and the United States, the patients affected by this disease are part of the closed Indian communities that represent a low percentage of the general population, consequently the American Indian genes are preserved among them. The contrary is found in Latin America, where the Mestizo group represents a very high percentage of the population. Therefore we can conclude that there is a difference in the “race dilution.”

It is not clear yet if immunologic mechanisms play a role in AP, but all available evidence points in that direction. Due to the clinical, histopathologic,
immunologic, and immunogenetic findings, as well as its response to thalidomide, AP has enough distinctive features to differentiate it from other forms of chronic photodermatoses.

Conclusion

AP has epidemiologic, clinical, histopathologic, immunogenetic, and immunopathologic features that give it a distinctive character. The diagnosis of this disease must be based on its clinical and histopathologic characteristics. Lesions on the lips and conjunctiva are specific, and the skin offers an adequate histopathologic correlation. The experimental induction of AP lesions is possible with UVB and UVA, but the radiation doses vary in every case.

In our experience, the best treatment is thalidomide, because of its rapid action, similar to its effects in leprosy. However, thalidomide has been indicated in other dermatoses, such as atopic dermatitis and other inflammatory diseases. In AP thalidomide induces remission of symptoms and improves the lesions in 30–60 days.

The immunogenetic and immunopathologic studies provide data involving possible pathogenesis of AP. The HLA-A28, B16, and DR4 antigens may represent a genetic susceptibility to AP among the Mexican population, and the presence of T and B lymphocytes in the lymphoid follicles or germinal centers indicate that there is a role for cellular and humoral factors in its pathogenesis.

References
