

Actinic Reticuloid – Photosensitivity or Pseudolymphoma? – A Review

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ABSTRACT

Actinic reticuloid (AR) or chronic actinic dermatitis is considered a sunlight-induced pseudolymphoma (PSL) on light exposed areas of the skin, which primarily affects elderly males. The disease is a severe, chronic photosensitive dermatosis, first described by Ive et al. in 1969. PSL is a group of non-cancerous lymphocytic skin disorders that simulate malignant lymphomas, but the changes usually spontaneously regress. The clinical appearance of Actinic reticuloid is variable, usually characterized by an eczematous, pruritic eruption, predominantly present on the head and neck, or other sun exposed areas, but can involve any area of the body. Thereby, crucial characteristic is photosensitivity, whereat action spectrum involves UVB, UVA and visible light beyond 400 nm. The disease is considered as PSL which histologically resembles lymphoma with immunohistochemical analysis of the cutaneous infiltrate revealing presence of activated T cells, numerous histiocytes, macrophages and B cells. Moreover, the development of malignant (non-cutaneous) T cell lymphoma in the course of AR has been reported. As the disease has chronic character, it requires significant changes in the patient's lifestyle and avoidance of provoking factors such as contact allergens or sources of intense light. Thus AR should be considered in every patient who presents with persistent, unclear, erythematous skin changes on the face and neck that are related to sun exposure.

Key words: actinic reticuloid, chronic actinic dermatitis, photosensitivity, pseudolymphoma

Introduction

Skin diseases that affect sun exposed skin and that are worsening by exposure to light are getting more common and they present difficult diagnostic and therapeutic problems. It was confirmed that exposure to sun and ultraviolet (UV) radiation (mostly UVA and UVB) may have an effect on numerous molecular processes that damage the skin, causing different skin changes and diseases^{1,2}. Thereby, we present Actinic reticuloid (AR) as a rare skin disease, but with increasing prevalence.

Pseudolymphoma

Pseudolymphomas (PSL) are reactive lymphocytic proliferations that appear in the skin and resemble a malignant lymphoma, but changes in PSL usually spontaneously regress (as the name says, the term »pseudo« means »not real«, and »lymphoma« means »a cancerous tumor of

lymphocytes«)^{3,4}. So the important characteristic of the PSL group is its reversible character. There are different causes and classifications of PSL, but the diseases are mostly classified based on their etiological and clinical features. Thus, there are various types: Idiopathic type (unknown cause); Lymphomatoid drug eruption (caused by systemic drugs); Lymphomatoid contact dermatitis (caused by topical allergens); Arthropod-induced PSL (caused by insects or scabies); Actinic reticuloid (caused by sunlight); Lymphocytoma cutis (caused by Lyme disease, shingles, tattoos, ear-piercing, acupuncture, etc.⁴

Causes of PSLs differ and include: drugs (topical or systemic); foreign agents (tattoo dyes, insect bites, scabies, vaccines, hyposensitization injections, trauma, acupuncture); infections (*Borrelia burgdorferi* infection, Lyme disease, Herpes zoster); photosensitivity (sensitivity to UV light); idiopathic (unknown causes). There are various

drugs reported to cause PSL of the skin: anticonvulsants; antipsychotics (chlorpromazine, thioridazine); antihypertensives (captopril, atenolol, verapamil, diltiazem, moduretic, hydrochlorothiazide); cytotoxics (cyclosporine, methotrexate); antirheumatics (gold, salicylates, phenacetin, D-penicillamine, allopurinol); antibiotics (penicillin, nitrofurantoin); antidepressants: fluoxetine, doxepin, desipramine, amitriptyline hydrochloride, lithium); anxiolytics (alprazolam, clonazepam, lorazepam); antihistamines (diphenhydramine, cimetidine, ranitidine); antiarrhythmics (mexiletine chloride), etc.⁴. However, the cause of PSL is not always known, as in the idiopathic type or in lymphomatoid papulosis.

All of these dermatoses usually affect young adults (25 to 40 years old) and are generally more common in females, except in the case of AR which mostly affects elderly males⁴. The group of PSLs also tends to be much more prevalent in Caucasians.

Clinical appearance of PSL is variable and is usually characterized by patches and plaques located on the head and neck, although any area of the body can be involved. They may be single or multiple, small or large, red to purple, doughy or firm. Patients with PSL may also present with a rash involving the entire body or with lesions located at the sites of trauma. The patients often complain of itch, which can sometimes be intense, especially in those who have lymphoid contact dermatitis, insect bites, scabies or AR.

Diagnosis of PSL requires a complete medical history and physical examination, followed by pathohistological analysis. In the diagnostics of PSL, skin biopsy is crucial, but laboratory parameters may also be examined. Sometimes a diagnostic dilemma appears, especially in the differentiation of PSL from malignant lymphoma, which is of great importance, as the clinical course and therapeutic options are quite different⁴.

Although the treatment depends on the type of PSL, mostly used are topical steroids (sometimes intralesional). It is important to remove possible causative agents and to avoid precipitating factors. Other therapy includes topical sunscreens, systemic antibiotics, local radiation, PUVA therapy, cytotoxic agents and other.

The course of PSL is variable as the disease lasts for a period of a few weeks to years. In general, PSLs eventually resolve either spontaneously or following the removal of the causative agent. It is important that patients with PSL have close follow-ups, especially in persistent and resistant cases, due to the possible association with malignant lymphoma⁴.

Characteristics of Actinic reticuloid

Actinic reticuloid is a chronic persistent photosensitive dermatosis, first described by Ive and co-workers in 1969^{5,6}. The disease is considered a sunlight-induced PSL which predominantly occurs in elderly men as pruritic infiltrated skin changes, papules and plaques on exposed parts with occasional extension to covered areas and rarely associated with episodes of erythroderma⁷. Al-

though AR particularly affects men over the age of 50, it also arises in women and is increasingly found in young, male and female patients, with atopic dermatitis.

Although the clinical pattern of AR is similar to that of persistent light reaction, histologically AR often includes cytologic atypia of lymphocytes, resembling Mycosis fungoides. The phrase »reticuloid« suggests that it is a pseudomalignancy (similar to lymphoma), yet in a few instances, patients develop genuine lymphomas.

It may be mentioned that for this dermatosis there are different synonyms: chronic actinic dermatitis (CAD), persistent light reaction, photosensitivity dermatitis/actinic reticuloid syndrome (PD/AR)⁴. Currently the most-ly used term for this dermatosis is chronic actinic dermatitis. We consider that the term AR is also suitable, since the disease doesn't include only actinic skin changes, but also has histological characteristics of PSL and sometimes even those of lymphoma. Namely, histologically and immunohistochemical analysis of the cutaneous infiltrate mostly reveals activated T cells, numerous histiocytes, macrophages and B cells. Most of the lymphocytes express a phenotype of suppressor T cells (CD8+)⁷.

In the etiopathogenesis, photosensitivity to both UVA and UVB, as well as to visible light beyond the wavelength of 400 nm is a crucial characteristic³.

History of Actinic reticuloid

In 1969 Ive et al. first described AR as a condition of elderly males characterized by erythematous thickening of light-exposed areas of the skin with formation of plaques, accentuation of skin creases, and often episodes of generalized erythroderma^{5,8}. On the other hand, the term chronic actinic dermatitis was first proposed by Hawk and Magnus in 1979 to unify the conditions known as Persistent light reactivity (Wilkinson, 1961), AR (Ive et al., 1969), Photosensitive eczema (Ramsay and Black, 1973), and Photosensitivity dermatitis (Frain-Bell et al., 1974)⁹.

Previously in 1973, Ramsay & Kobza Black proposed a new entity called Photosensitive eczema, which had clinical features of eczema limited predominantly to light exposed areas. Etiopathogenically, photosensitivity was emphasized as crucial and the irradiation monochromator findings showed abnormalities confined to the short wavelength UV (300–340 nm). It has been observed that photopatch tests may be negative, but patch tests often show positive results⁸.

In 1974 Frain-Bell et al. pointed out that cases with irradiation monochromator abnormalities (extending from the short into the long wavelength UV) may have a clinical and histological appearance of photosensitive eczema or that of AR and questioned whether there is a clear distinction between these two conditions⁸.

Generally, the three main criteria of AR (CAD) is reduction in the minimal erythema dose to UVA, UVB and/or visible light; persistent eczematous eruption predominantly on sun-exposed skin, sometimes extending to covered areas; and histopathologic changes consistent

with chronic eczema with or without cutaneous lymphoma-like changes⁹.

It is also necessary to mention that AR may occur after endogenous eczema, photoallergic or allergic contact dermatitis, oral drug photosensitivity, occasionally polymorphic light eruption and rarely following HIV infection⁹.

Clinical and histological picture of Actinic reticuloid

The clinical picture of AR is characterised by an eczematous, pruritic eruption, predominantly present on light exposed areas of the skin. The initial symptom is persistent erythema of the face, with subsequent development of an eczematous, patchy or diffuse, pruritic, often lichenified eruption on sun-exposed areas. The changes are particularly common on the face, the scalp, the V-area of the chest, on the back, the sides of the neck and on dorsal aspects of hands and forearms, often with sharp demarcation at the lines of clothing⁹. Patients may have palmar and plantar eczema, loss of eyebrows and scalp hair, occasionally erythroderma, as well as other changes. The erythrodermic variant of AR can resemble Sezary syndrome (a type of cutaneous T cell lymphoma – CTCL, with the presence of atypical lymphocytes in peripheral blood)⁶.

It is also important to mention that some affected patients with AR may not complain of abnormal reactions to sunlight because they may be so sensitive to UVA and visible wavelengths, which penetrate window glass, that no relationship to sunlight exposure is noticed⁹.

Histologically, AR is characterized by the presence of extensive dermal, predominantly perivascular, mononuclear-cell infiltrates, occasionally with large hyperchromatic convoluted nuclei and mitotic figures⁹. Those predominantly lymphocytic infiltrates show in some instances marked atypia, but progression to lymphoma is most uncommon¹⁰. The infiltrating cells show epidermotropism and sometimes even form Pautrier-like microabscesses⁶. Other histological changes include epidermal spongiosis, acanthosis, dermal fibrosis, sometimes with hyperplasia. Other cells include macrophages, eosinophils and plasma cells⁹. Generally, the histological features are similar to those characteristic of Mycosis fungoides (the most common variant of CTCL) and Sezary syndrome^{6,10}. However, it was confirmed that AR has a characteristic immunophenotype distinct from most cases of CTCL, with CD8+ cells in the epidermis and discordance between BF1 (β-chain constant region of T-cell receptor) cells and CD3 expression⁶. Because of the clinical and histological similarities between AR and CTCL and in particular, the presence of atypical T cells with cerebriform nuclei in the skin and peripheral blood, differentiating between these two diseases can be extremely difficult. Moreover, the development of malignant (non-cutaneous) TCL in the course of AR has been reported. Generally, the presence of a predominantly CD8+ T cell population in skin infiltrates or demonstration of an increased proportion of CD8+ T cells and a reversed CD4:CD8 ratio in peripheral blood have been considered as

useful additional criteria favouring a diagnosis of AR rather than CTCL⁶. However, some AR patients may demonstrate predominantly CD4+ T cell skin infiltrates, indicating that the immunophenotypic criteria cannot be relied on in all cases. Some studies demonstrated that morphometric analysis (nuclear contour indexing) of circulating atypical T cells may also contribute to the differentiation between AR and Sezary syndrome^{6,11}.

Pathogenesis of Actinic reticuloid

Although the cause of AR (CAD) is not known, it is suspected that the body's defence system overreacts to substances within the skin that are made 'allergic' by UV and visible light. This corresponds to the crucial characteristic of AR – photosensitivity, i.e. hypersensitivity to UVB, UVA and visible light beyond 400 nm. One theory has proposed that during an initial photoallergic reaction, a normal skin constituent is altered to become antigenic. Induction begins with UVA-dependent covalent binding of hapten to an endogenous protein and is followed by a delayed-type hypersensitivity response (type IV). As the disease progresses to AR, UVB and UVA alone may trigger the immune response without the hapten by continuing to form the antigenic photoproduct from the endogenous carrier protein⁹.

So diagnostic procedures, besides histopathological examination, include phototesting that uses specialised equipment which is accessible in some university dermatology centres. Phototesting consists of having areas of skin exposed to known amounts of light of specific wavelengths, observing thereafter skin reactions with comparison to the response of the average population. Phototests to UV and often visible irradiation (this reaction peaks in between 7 and 24 hours following exposure) may show erythematous or eczematous reactions, usually at doses much lower than the normal minimal erythema dose. The provoking wavelengths are UVB (280–320 nm), virtually in all patients, UVA (320–400 nm) in most patients, and visible light or UVA alone in only a few patients⁹.

Recent examination of AR has also confirmed delayed type hypersensitivity response (type IV)⁹. Histological and immunohistochemical analysis of lesions have confirmed increased ICAM-1 expression and a dermal infiltrate of predominantly CB8+ T cells, suggesting type IV response which is characteristic of contact allergy. It is also proven that allergic and/or photoallergic contact dermatitis commonly coexist with AR and often precedes the onset of photosensitivity. The analysis of testing AR (CAD) patients (89 patients) by patch or photopatch tests showed positive results in 74% patients. Thereby, patch test was positive to sesquiterpene lactone mix in 36%, to fragrance compounds in 21%, to colophony in 20% and to rubber chemicals in 14%. On the other hand, the analysis of photopatch test results showed 6% patients positive to musk ambrette, 7% to sunscreens, and one to both⁹. Thereby, the majority of AR patients have allergies to some substances which come into contact with their skin, particularly various flowers, types of wood, per-

fumes, sunscreens and rubber compounds. Patch testing to determine contact allergens is therefore useful in such patients and is conducted by most dermatologists.

Therapy for Actinic reticuloid

The mainstay of AR treatment is sunlight avoidance (protective clothing, non-irritating broad-spectrum sunscreens, filters for home and car windows) and, when applicable, allergen avoidance⁹. The most commonly used steroid creams/ointments are useful in the acute stage of the disease but are generally only partially effective (potent varieties should be used only in the short term). The use of topical tacrolimus ointment may also be of benefit. Treatment for resistant disease includes low-dose PUVA, narrow-band UVB, cyclosporine, azathioprine, systemic steroids (short time) and mycophenolate mofetil alone or in combination⁹. Thus, there are also good results with UVB in combination with prednisolone, azathioprine, B-carotene, hydroxychloroquine and cyclosporine⁷.

Many patients with AR are spontaneously cured, which may take up to several years. According to results of a clinical study, resolution of photosensitivity within 10 years occurred in some 20% of patients⁹. It was also shown that a severely abnormal UVB photosensitivity and positive polyvalent patch tests are predictors of a poorer prognosis. In such cases, there is usually a persistence of contact allergy, despite an eventual clinical improvement of photosensitivity⁹.

It is necessary for the patients to have sufficient information about their disease and to learn to live with the condition, managing it by minimising exposure to UV and visible light, as well as to contact allergens. According to their photosensitivity which involves non-sunburn wavelengths of light (longwave UV and visible light wavelengths), patients may develop skin changes even on cloudy days. Such patients have to be aware of the fact that clothing and windows offer for them often no real protection (unless the clothing totally blocks the light out). There is good evidence that this condition will completely clear in a number of patients without the need for therapy, although this may take many years.

Conclusion

AR is a term describing a nonspecific and overlapping appearance that encompasses multiple features, including that of photosensitivity and PSL characteristics. As the disease is chronic in nature, it requires significant changes in the patient's lifestyle and avoidance of provoking factors, including contact allergens and sources of intense light. AR should therefore be considered in every patient who presents with persistent, unclear, erythematous skin changes on the face and neck that are related to sun exposure.

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AKTINIČKI RETIKULOID – FOTOLEZIVNOST ILI PSEUDOLIMFOM?

SAŽETAK

Aktinički retikuloid (AR) ili kronični aktinički dermatitis se smatra sunčevom svjetlošću induciranim pseudolimfomom (PSL) na područjima kože izloženima svjetlosti, koji primarno pogađa starije muškarce. Bolest je teška, kronična fotosenzitivna dermatoza, prvi puta opisana od Ive i sur. 1969. PSL je grupa nekanceroznih limfocitnih poremećaja kože koji oponašaju maligne limfome, ali se promjene obično spontano povlače. Klinička slika AR je varijabilna, obično obilje-

žena ekcematoznom, pruritičnom erupcijom poglavito prisutnom na glavi i vratu ili na drugim područjima izloženima suncu, ali može zahvatiti bilo koje područje tijela. Stoga je ključna osobina fotosenzitivnost, pri čemu raspon djelovanja obuhvaća UVB, UVA i vidljivu svjetlost iznad 400 nm. Bolest se smatra pseudolinfomom koji histološki nalikuje limfomu uz nalaze imunohistokemijske analize infiltrata u koži koji otkrivaju prisutnost aktiviranih T stanica, brojne histiocite, makrofage i B stanice. Štoviše, opisan je nastanak malignog (ne-kutanog) T staničnog limfoma u tijeku AR. Budući da bolest ima kronični karakter, zahtijeva značajne promjene u bolesnikov načinu života i izbjegavanje provocirajućih čimbenika poput kontaktnih alergena ili izvora intenzivne svjetlosti. Stoga AR treba uzeti u obzir kod svakog bolesnika koji pokazuje perzistentne, nejasne, eritematozne promjene kože na licu i vratu, a koje su povezane s izlaganjem suncu.