Polymorphous Light Eruption

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Marcella Guarrera

Abstract

Polymorphous light eruption (PLE) is the commonest immuno-mediated photodermatosis. It occurs after solar or artificial UV-light exposure and affects only the sun-exposed areas with preference of the V-area of the chest, of arms and forearms, legs, upper part of the back, and rarely the face. The lesions are itching or burning, and vary morphologically from erythema to papules, vesico-papules and occasionally blisters, plaques, sometimes erythema multiforme-like, insect bite-like wheals and purpura. The clinical manifestations befall within a few hours to days from light exposure, last a few days, and subside in about a week without sequelae. Its diagnosis is based on history, morphology and phototests. PLE is considered as a delayed hypersensitivity response to newly UV induced, but still unidentified, antigen(s). Usually, MED is normal, but the provocative phototests with UVA or UVB reproduce the spontaneous lesions in about 50% of the patients. Broad spectrum sunscreens and antioxidants, photohardening with PUVA or narrow band UVB may be beneficial to prevent the disease. Therapy is based mainly on topical or systemic corticosteroids.

Keywords

Polymorphous light eruption • Idiopathic photodermatosis • Immunomediated photodermatosis • UV light • Phototests • Minimal erythema dose • Photoprovocation tests

6.1 Introduction

Polymorphous light eruption (PLE), once called idiopathic, is the commonest immuno-mediated photodermatosis. The first description dates back to the nineteenth century, when Bateman [1]

M. Guarrera (✉)
University of Genoa, Genoa, Italy
e-mail: guarrera@unige.it

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defined as *eczema solare* some recurrent non scarring eczematous lesions provoked by sun-exposure. PLE has been labeled also solar dermatitis, summer prurigo and sun allergy. The present title is due to Rasch in 1900 [2].

6.2 Epidemiology

PLE affects both genders, but women are most affected (f/m ratio 3:1–7:1) [3], and all ages, mostly adulthood [4]. Apparently, the prevalence depends on the latitude: about 21% in Scandinavia [5], 10–15% in northern United States [6] and United Kingdom [7], but only 5% in Australia [8], 1% in Singapore [5], and 0.6% in India [9]. In Italy, it occurs in 6% of the population [10], less than in some other European Countries (18%) [11]. It affects all skin types, preferring the fair ones, and all races with an apparently paradoxical prevalence (86%) in African-Americans [12, 13]. A positive family history can be found in one-sixth of patients [6] or even more [14].

6.3 Clinical Manifestations

PLE lesions occur always after solar or artificial UV-light exposure and affect only the sun-exposed areas with preference of the V-area of the chest, arms and forearms, legs, upper part of the back, and in the severest forms also the face. They are always itching or burning, but vary morphologically (explaining the adjective "polymorphous" or "polymorphic") from erythema to papules, vesico-papules and occasionally blisters, plaques, sometimes erythema multiforme-like, insect bite-like wheals and purpura [5, 15] (Figs. 6.1, 6.2, 6.3, 6.4 and 6.5). In the same patient, however, the lesions are monomorphic. Often, itching or burning shortly herald the appearance of the lesions.

The clinical manifestations befall within a few hours to days from light exposure, last a few days, and subside in about a week without sequelae but rare small hyper- or hypopigmentations. PLE may last for many years in several patients, often recurring annually in the same season, improves over the years in others, and sometimes remits spontaneously [16]. Usually, there are no systemic symptoms. Chills, headache, fever and nausea

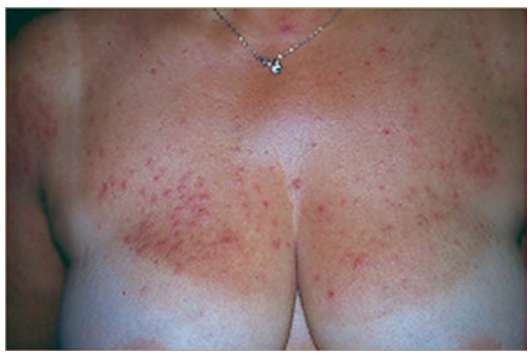

Fig. 6.1 Papular PLE of the chest

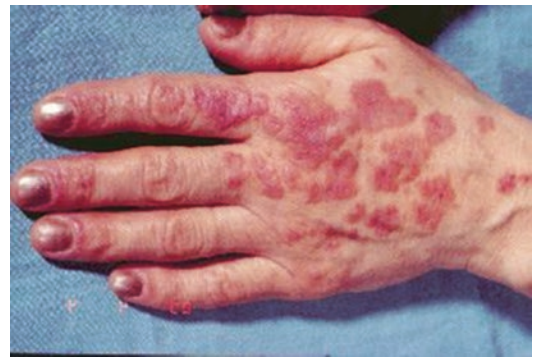

Fig. 6.2 PLE plaques on the hand

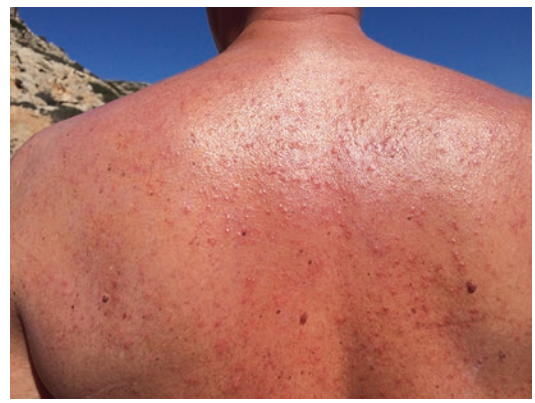

Fig. 6.3 Vesico-papular PLE of the dorsum

have been described, but they probably result from heatstroke or sunburn [5].

Particular forms have been reported, such as PLE sine eruption [17], pinpoint papular eruption [18, 19] especially in individuals with skin type IV-VI, characterized by 1–2 mm pinpoint papules, similar to the pinhead papular eruption form [20], persistent PLE after UVA1 therapy [21], PLE of the elbows [22, 23], solar brachioradial pruritus [24], that needs to be distinguished by the cervical spine disease form [25].

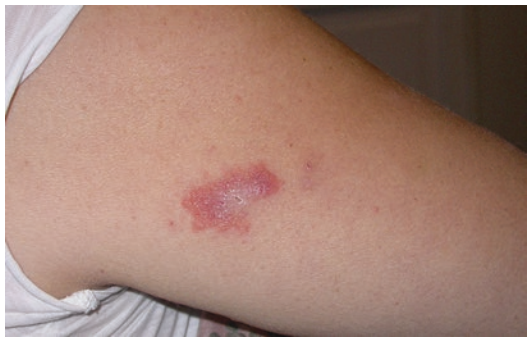

Fig. 6.4 Erythema multiforme-like PLE of the arm

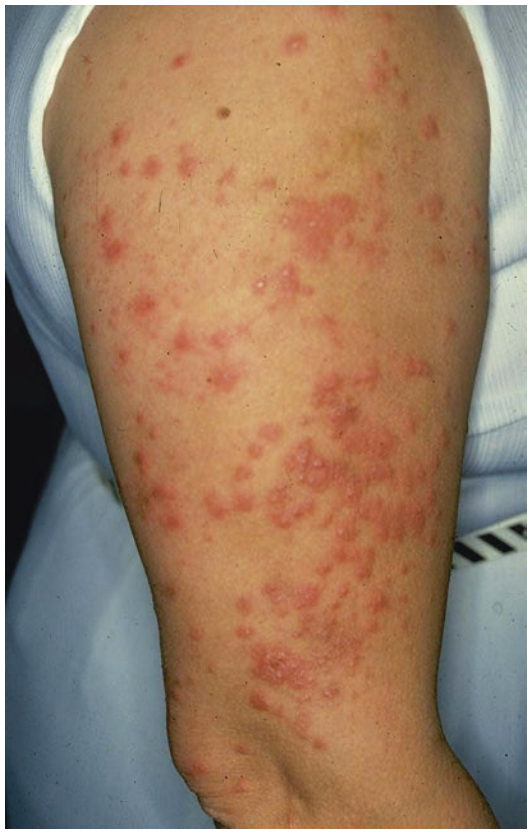

Fig. 6.5 Vesico-papular PLE of the arm

There are variants that should be distinguished, such as Juvenile spring eruption [26, 27] characterized by itching papules and vesicles of the ears in young boys occurring in spring, and Actinic prurigo, which is characterized by persistent, pruritic, excoriated, papular or nodular eruption of sun-exposed and unexposed areas in childhood often present also in winter. Actinic prurigo is a typical manifestation of native American people, in whom it is often hereditary with the presence of HLA DR4 in about 90% of cases and, in particular, the subtype DRB1*0407 present in 60% of cases [28–30]. Hydroa aestivale-vacciniforme is characterized by groups of vesicles with crusts that leave vacciniform scars on the face, chest and dorsum of the hands, more often in women in their first decade of life [31]. Another variant is the Benign summer light eruption (BSLE) [32], which affects mostly young women on the upper chest with small pruritic papules, shortly after an intense UV-light exposure and without annual relapse. In 2011, an Italian multicenter study [33] tried to distinguish BSLE and classical PLE enrolling 346 patients with typical clinical history and/or presentation of PLE, on the basis of some clinical and laboratory criteria. The studied criteria distinguished only a minority of BSLE patients. BSLE may be considered as a mild form of PLE [33], it is always positive to UVA-induced phototest, and is probably more frequent, but often goes unobserved by dermatologists because its mildness simply prevents their visit. This conclusion has been shared by others [34, 35].

6.4 Histology and Immunohistochemistry

The histology of PLE is not specific in accordance with the polymorphic clinical patterns, and depending also on the timing of the biopsy. Characteristic feature is a moderate to intense

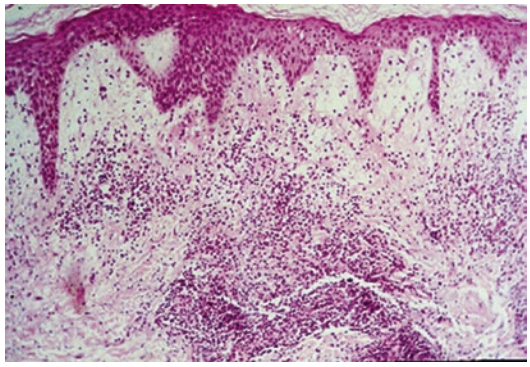

Fig. 6.6 Histopathology of PLE showing papillary edema and middermis lymphocytic infiltrate

perivascular T cell infiltrate [36] and the edema in the upper part of the dermis (Fig. 6.6), even though the latter may be observed in LE and dermatomyositis [37]. In the papular form, the edema of the papillary dermis is common, focal dyskeratotic cells and slight vacuolar alteration of the basal layer can be observed. The plaque-type PLE exhibits also a band like mononuclear cell infiltrate. The papulovesicular form shows spongiotic microvesicles, marked subepidermal edema, extravasation of erythrocytes and a mixed, mainly lymphocytic, dermal infiltrate. Lastly, the eczematous form shows parakeratosis, acanthosis, spongiosis and sporadic dyskeratosis. Immunohistochemistry shows an increase of Langerhans cells (OKT6) in the epidermis. The direct immunofluorescence is not contributory.

6.5 Diagnosis

Diagnosis is not difficult. Taking the history of sun or artificial light exposure (either professional or not), excluding the possible responsibility of photosensitizing cosmetics or drugs, and the clinical examination (morphology and the sun-exposed site of the pruritic lesion are highly suggestive). The age of the first manifestation, the interval from the light exposure (latency time), the duration and the seasonality are also helpful data, and a series of phototests may be confirmatory. MED (minimal erythema dose), the provocative UV phototests, patch and photopatch tests, the porphyrins blood levels and the antinuclear antibodies (ANA) assessment are mandatory. Biopsy may be helpful.

6.6 Differential Diagnosis

The commonest differential diagnoses are solar urticaria, which develops just a few minutes after sun-exposure, the rare photosensitive erythema multiforme, which occurs after intake of drugs like carbanilides, phenylbutazone and aflaqualone and affects the oral mucosa as well [38], and the photocontact allergic dermatitis, in which the photopatch tests are diagnostic. It should not be forgotten that PLE patients may also be suffering from photocontact allergic dermatitis.

The most important disease to be considered in the differential diagnosis, however, is systemic lupus erythematosus (SLE). Classically, SLE lesions last more than 2 weeks, and are accompanied by positive serology and direct immunofluorescence. Although ANA may be present in PLE as well, they do not exceed the 1:80 dilution. Ro (SSa) and LA (SSb) antibodies, which characterize the photosensitive LE subset (SCLE), are absent in PLE. Nonetheless, a relationship between the two diseases probably exists, though denied by some Authors [16, 39–42]. In fact, about 10% of PLE patients with positive ANA develop SLE over time [43], PLE symptoms have been reported in 50% of LE patients and LE diagnosis has been done in PLE patients up to 7 years after the PLE onset [44]. ANA may already be present many years before in 78% of PLE patients who are destined to develop LE, though there is no way to predict such an outcome [45]. Lastly, PLE symptoms have been described in 60% of DLE or SCLE patients and are more frequent in LE patients' relatives [46].

6.7 Pathogenesis

After the great intuition of Epstein [47], many details help consider PLE as a delayed hypersensitivity response to UV induced, but still uniden-

tified, antigen(s). The delayed occurrence of the lesions, the HLA-DR expression at least in 50% of patients, the pro-inflammatory cytokines and adhesion molecules expression are indicative findings. In addition, the presence in the dermis of T CD4+ cells within 72 h and, later, T CD8+, the presence of macrophages 1–5 h after irradiation, the increasing numbers of Langerhans cells in 5 h after UV exposure, the improvement after immunosuppression therapy, all justify such a conclusion.

The abnormal immune response has been attributed to the resistance of the PLE patients towards the immune suppressive effects of sunlight [48]. The exact UV-induced immunosuppression mechanism and the relative contribution of UVB and UVA in healthy subjects are as yet unclear, but the expression of TNF-alpha, IL-4 and IL-10 and the Langerhans cell depletion seem to be crucial phenomena [49]. In PLE, the resistance to immunosuppression is documented by a reduced expression of TNF-alpha, IL-4 and IL-10 and by an impaired Langerhans cell and neutrophil migration into the epidermis [50]. Incidentally, the UV-induced immunosuppression is lower in healthy women [51], possibly via 17β-estradiol [52] or estrogen receptors [53], explaining the disproportionate prevalence of PLE in women. Moreover, the disease can be favored by oral contraceptives and pregnancy [54], and, personally, I observed that, usually, PLE may occur during the first pregnancy (unpublished data).

Genetic factors also play a role, though with poor penetrance [55, 56]. There is no difference in the prevalence of the disease between monozygotic and dizygotic twins [7, 56], and a reverse link to glutathione-S-transferase1 allele, which is protective against the pathogenetic role of ROS, was advocated [57], but not confirmed [58]. However no gene has been identified till now. Heat-shock protein immunoreactivity has been suggested [59]. In fact, the heat-shock protein expression increases in keratinocytes and endothelial cells of dermal blood vessels in experimental PLE, 1 h to 6 days after UVR exposure [7].

Moreover, abnormalities in arachidonic acid metabolism, especially in the severest forms, and in prostaglandins have been reported [7]. The mentioned role of ROS would be confirmed by the decreased levels of epidermal (by 30%) [60] and blood catalase, superoxide dismutase and vitamin E levels [61] and of the global serum antioxidant capacity [62, 63].

Lastly, the 25-OH-vitamin-D3 serum level is lower than in controls, but may be increased after a prophylactic treatment with narrow band UVB [64]. PLE, like other severe photosensitive diseases, would be at high risk of low vitamin D status [65], which would contribute to the autoimmune process [66].

6.8 Photobiological Investigations

Most patients (almost 50% according to some Authors) [67] have a normal MED both to UVB or UVA, and do not react to Visible and Infrared lights [5, 33, 67]. Researchers do not agree as for the prevalence of the response to the provocative phototest and, furthermore, the action spectrum is still unclear. The positive reactions range from 47% up to 90% [15, 33, 42, 67–72]. The discrepancy may depend on numbers of variables, such as the different light sources, the number of the UV exposures or different UV light doses, the size of the irradiated skin area (exposed or not exposed, previously affected by the lesions or not) and the season in which the phototest is done. In brief, it depends on the lack of standardized phototest protocol. By irradiating an area divided into three parts, one receiving only UVA, one receiving only UVB and the middle one receiving both UVA and UVB (which is more similar to the natural sunlight irradiation) (Fig. 6.7), a positive reaction in the middle has been obtained in 10% of patients, a reaction that otherwise would be missed [33]. Generally, the provocative phototest, preferably on a previously involved skin area, yields positive response to UVA light in about 50% of patients. The best total doses may be 0.75–1.5 UVB MED, and 30–50 J/cm^2 for UVA for 3–5 consecutive days. The reading should be done the

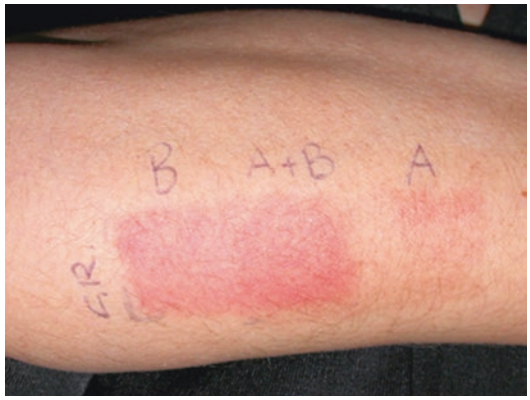

Fig. 6.7 Positive phototest to UVB and with less intensity to UVA. The figure shows the three areas irradiated with UVA, with UVB and in the middle one with both UVA and UVB

same day of irradiatons and repeated daily for up to 1 week. UVC as well may provoke PLE [73] as it has been described in welders [74]. Patch and photopatch tests are positive in about 7–10% of PLE patients [33, 75], although higher rates of positive results have also been reported [67]. Sunscreens are mostly responsible because of their large use.

6.9 Prognosis

PLE lasts for many years, often improving over time. In a study conducted for 7 years, 11% of the patients completely cleared [41], 24% in a 32-years follow up study [16] and 9% in a study in Mediterranean area [76]. The improvement is often obtained by educating the patients to avoid sunlight or to use topical and systemic photoprotection.

About 22% of PLE patients, mostly women, develop an autoimmune disease including thyroid dysfunction [16] especially autoimmune thyroiditis (8.7%) [76], and, as mentioned above, SLE in 2–10% [16, 33, 43]. On the contrary, PLE bears less risk of skin cancer [77].

Co-morbidities of PLE are respiratory allergy, such as asthma and allergic rhino-conjunctivitis [76], atopic eczema (19.8%) [33] or other photosensitive diseases like solar urticaria [78].

6.10 Quality of Life

In 40% of PLE patients, the psychosocial impact (greater in women) [79] leads to discomfort and loss of quality of life in spring and summer [80] and to high levels of anxiety and depression [81].

6.11 Prevention

The best prevention of PLE is avoiding UV light, but practically, especially in the southern Countries, such prescription is unrealistic. However, wearing clothing and hats and using broad spectrum sunscreens is useful. Broad spectrum sunscreens with a high UVA and UVB protection factor, may be beneficial in mild forms, even with only 1 mg/cm^2 (a minor thickness than guidelines suggest)[82]. Topical vitamin D3 analogs such as calcipotriol [4] may be useful. Sunscreens containing liposomal DNA repair enzymes, such as photolyase from *Anacystis nidulans* and T4 endonucleases from *Micrococcus luteus* lysate [4], proved to be effective. In addition, ectoin, a natural substance from halophilic bacteria, which protects Langerhans cells from UV-impairment, proved to reduce the *sunburn cells* and to counteract UVA-induced cell damage [83]. The low level of antioxidants [60–63] may suggest the use of topical and oral antioxidants such as beta-carotene (75–100 mg/day) [84] or oral nicotinamide (3 g/d for 2 weeks) to correct a possible error in the tryptophan pathway [85]. Results are however, controversial [86, 87]. The extract of *Polypodium leucotomas*, a fern from Central and South America, containing polyphenolic compounds, would be helpful both topically and orally [88–90]. More helpful is the desensitization treatment (photohardening). This procedure should be done in early spring or at least one month before the intense sun-exposure. Photohardening includes PUVA, the carcinogenic risk [91] notwithstanding, broad and narrow band UVB [92], the latter being more effective with less adverse effects [42, 93–97]. The starting dose should be 50% of the minimal phototoxic dose for PUVA or 75% of MED for UVB, followed by 20% increments three times a

week for 4–5 weeks [78]. Photohardening [4] increases the thickening of stratum corneum and the melanin production, depletes neoantigen(s) and the Langerhans cells, whose UV-induced less migration from and to epidermis is displayed in PLE [5, 98]. In any case the natural photohardening is preferable.

6.12 Therapy

Topical corticosteroids can be used in the milder forms, systemic corticosteroids in the severe one (prednisone 40–60 mg/d, tapered within 10–14 days) and even so in short-course therapy [99]. Antimalarial drugs (chloroquine or OH-chloroquine 125–500 mg/d) [100] as immunosuppressive agents are of benefit only in selected forms, always considering their adverse effects especially the ocular ones. Azathioprine (50–100 mg/d) has been used in severe forms [101]. Cyclosporin (3.3 mg/Kg/d) was reported to be effective in a single case of PLE associated to psoriasis [102] and (3–4 mg/Kg/d) in three cases of PLE without psoriasis who profited of it also as a preventing measure [103]. Thalidomide had good to excellent results in 88% of 25 patients. There are doubts however about the correct diagnosis of the treated patients [104]. Omega-3 polyunsaturated fatty acids may act modulating inflammatory and immune response [104], while antihistamine should be used only to reduce itching [4, 7]. In conclusion, PLE is the most common photodermatosis, affecting mostly young women. Although the relationship of PLE and SLE is unclear, the assessment of ANA is highly recommendable and positive patients should be monitored over time. Prevention with topical and oral photoprotection (sunscreens and antioxidants) associated with photohardening is advisable.

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