

Sunlight-induced Painful Skin (Sun Pain): A New Differential Diagnosis in Photodermatology

Piergiacomo CALZAVARA-PINTON¹, Marina VENTURINI¹, Chiara ROVATI¹, Mariachiara ARISI¹, Irene CALZAVARA-PINTON¹, Fabrizio RINALDI² and Maria Teresa ROSSI¹

¹Dermatology Department, ASST Spedali Civili di Brescia, University of Brescia, Brescia, and ²Department of Neurology, Franz Tappeiner Hospital, Merano, BZ, Italy

Photodermatoses are characterized by the development of skin eruptions following exposure to ultraviolet radiation or visible light. We report here the clinical findings and results of laboratory investigations and phototesting of 6 patients who experience debilitating and excruciating pain after sun exposure ("sun pain") in the absence of any skin eruption. Phototesting with sub-erythral doses of ultraviolet A radiation triggered localized pain in 4 patients. At follow-up, 3 female patients were found to have developed fibromyalgia, 2 male patients experienced a major depressive disorder, and another male patient had a conversion disorder. One patient also developed allodynia to tactile stimuli and one developed allodynia to thermal and tactile stimuli. Psychiatric conditions should be taken into consideration in patients presenting with excruciating and debilitating pain on exposure to ultraviolet radiation, but with absence of skin eruption. Further research is needed to evaluate whether it represents a type of allodynia triggered by exposure to ultraviolet radiation.

Key words: photodermatoses; photodermatology; phototherapy; sun pain.

Accepted May 26, 2021; Epub ahead of print May 27, 2021

Acta Derm Venereol 2021; 101: adv00485.

Corr: Piergiacomo Calzavara-Pinton, Dermatology Department, Università degli Studi di Brescia, Piazzale Spedali Civili 1, IT-25123 Brescia, Italy. E-mail: piergiacomo.calzavarapinton@unibs.it

Patients with photodermatoses have skin eruptions that develop or worsen with sun exposure: some patients develop skin eruptions that are qualitatively (a kind of rash) or quantitatively (a lower erythema threshold than that expected for a given phototype) different from sunburn eruptions in healthy people. These patients often have some type of autoimmune (previously reported as idiopathic) photo-dermatoses (1) or photo-toxic and photo-allergic reactions to systemic and topical drugs or other xenobiotics (2).

Genetic disorders with photosensitivity are much less frequent, but they represent a medical challenge because of their severity and poor prognosis.

All the above-mentioned disorders have a well-established diagnostic protocol with laboratory and instrumental examinations and photo-tests (3).

Other patients do not need further examinations, because their skin manifestations just representing a

SIGNIFICANCE

Patients with photodermatoses have skin eruptions that develop or worsen with sun exposure. We report here a case series of 6 patients who presented a type of skin discomfort that is not encapsulated by the description above: the development of excruciating and debilitating skin pain soon after the start of sun exposure and in the absence of skin eruptions. Intense pain without skin eruptions after sub-erythral sun exposure may represent the first clinical manifestation of fibromyalgia or other psychiatric disorders.

worsening or a flare of a pre-existing cutaneous and/or systemic disorder.

We report here a case series of 6 patients who presented a type of skin discomfort that is not described above: the development of excruciating and debilitating skin pain soon after the start of sun exposure and in the absence of skin eruptions.

MATERIALS AND METHODS

A retrospective monocentric study was conducted on patients with very intense skin pain in the absence of dermatological eruptions after very short periods of sun exposure. The study was performed at the Photobiology Unit of the Dermatology Department of the University of Brescia, Brescia, Italy, a tertiary referral centre for Photodermatology, from 2005 to 2020.

Five patients came from various Italian regions and one patient came from Israel. In all patients, pain was not improved by oral antihistamines, analgesics or corticosteroids, and could not be prevented by careful application of high sun-protection factor (SPF) sunscreen.

Routine blood chemistries, haematology, urinalysis, erythrocyte sedimentation rate, C3, C4, total complement activity, C-reactive protein, antinuclear antibodies (ANA), anti-double-stranded DNA anti-ds-DNA), antibodies against extractable nuclear antigens (ENA), anti-neutrophil cytoplasm antibodies (ANCA), total serum immunoglobulin E (IgE) and levels of urinary and erythrocytic porphyrins were assessed by routine methodology in all patients.

The minimal erythral dose (MED) of broadband (BB)-UVB and UVA were assessed at baseline by exposing 2 series of 6 2×2 cm² areas of untanned skin on the back to increasing doses of BB-UVB (dose range 0.015–0.08 J/cm²) and UVA (dose range 1.5–8 J/cm²) with each consecutive dose increased by the factor 1.414 (√2). If no threshold responses (pain without skin eruptions or MED) were elicited by these tests, a second series of BB-UVB (dose range 0.11–0.64 J/cm²) and UVA (dose range 11.3–64 J/cm²) was delivered 2–7 days later (4). The tested areas were observed

during and soon after irradiation, and then after 10 and 30 min and 1, 2, 4, 8, 24 and 48 h.

For phototesting, BB-UVB and UVA were delivered by a filtered metal halide lamp (Dermalight Vario, Dr Hönle AG, Martinsried, Germany) equipped with filter H1-UVB and filter H2-UVA. UV radiation was quantified with a SR9910 spectroradiometer (Macam Photometrics Ltd, Livingstone, UK). Response to visible light was investigated by exposing a single 5×5 cm² area for 20 min to visible light from a slide projector equipped with a 300-W bulb (Kodak AG, Stuttgart, Germany) at a distance of 20 cm. The irradiance and spectrum of the slide projector lamp were not measured.

In 2020, all patients were called for a follow-up examination. The course of the disease was rated as a partial improvement when patients reported an increase in the duration of tolerated sun exposure before the onset of pain and/or a reduction in pain intensity. Remission was considered to be complete when the painful sensations were fully eradicated. The disease was rated as “stable” if the patients did not report any improvement.

All patients provided signed written informed consent. The study followed the principles of the Declaration of Helsinki and was approved by the local ethics committee (Spedali Civili di Brescia, protocol number: 4277).

RESULTS

The main personal features, clinical findings and treatment dosages of the 6 patients are summarized in **Table I**. Four patients had skin type III, one had skin type II and one had skin type IV. Patients were in good health and did not report any history of traumatic brain injury. All patients denied smoking, excessive alcohol consumption and use of recreational drugs. As for comorbidities, one patient had hypertension treated with amlodipine. Two

patients reported a mild depression, for which one patient was treated with a low dose of sertraline (25 mg/day) and both patients occasionally took benzodiazepines. The other patients did not report any somatic, psychological or behavioural symptoms that could be indicative of systemic or psychiatric pathology.

The median (range) age at the onset of the disease and the age at first presentation at our centre were 28 (16–42) and 46 (26–60) years, respectively.

Patients described the onset of pain to be within 5 and 30 min from the beginning of sun exposure, regardless of environmental temperature and without seasonal variation. The intensity of the pain was not measured with a numerical rating scale; nonetheless, it was rated by all patients as the most intense pain they had ever experienced. Patients described the pain as a burning sensation, and they reported that it regressed spontaneously in 6–36 h. All body areas were affected if exposed and, in one patient, the pain was not solely confined to the exposed skin. All patients denied development of any kind of observable eruptions, in either the exposed or the unexposed skin.

The application of a highly protective UVA and UVB sunscreen could only partially prevent the pain, or did not prevent the pain at all; in addition, oral antihistamines and/or analgesics did not work in relieving the pain. Therefore, all patients adopted sun avoidance strategies as a “self-medication”, by preventing even short or unintentional exposures. In fact, all patients reported serious damage to their work and social life.

Table I. Main clinical features of patients at baseline and at last follow-up examination

Clinical features	1	2	3	4	5	6
Patient	1	2	3	4	5	6
Sex	M	F	F	F	M	M
Fitzpatrick's skin type	III	III	III	II	IV	III
First dermatological examination						
Age (years)	37	46	52	46	60	26
Age at onset of symptoms, years	24	40	30	16	42	26
Treatments at the time of onset of the disease	No	Benzodiazepine (alprazolam)	Benzodiazepine (clotiazepam)	No	Amlodipine	No
Pain/ Burning after sun exposure	Yes	Yes	Yes	Yes	Yes	Yes
Associated symptoms	No	Low fever / fatigue	No	No	Low fever/fatigue, faintness, loss of consciousness	No
Pain of exposed skin only	Yes	Yes	Yes	Yes	Yes	No
Delay from the beginning of the sun exposure, min	20–30	20–30	10	5	20–30	10–20
Duration of symptoms, h	24	24	24–36	6	6–12	12–24
Concomitant diseases	No	Mild depression	Mild depression	No	Hypertension	No
Concomitant treatments	No	Sertraline (25 mg qd)	No	No	No	No
Last dermatological follow-up visit						
Age, years	52	60	58	52	66	29
Concomitant neuro-psychiatric diseases	Major depressive disorder	Fibromyalgia	Fibromyalgia	Fibromyalgia	Conversion disorder, hypertension	Major depressive disorder
Age at diagnosis of concomitant neuro-psychiatric disease	40	41	54	50	66	30
Other symptoms		Tactile allodynia		Thermal and tactile allodynia		No
Oral treatment	Duloxetine (30 mg bid) Olanzapine (10 mg qd)	Duloxetine (30 mg bid), pregabalin (75 mg bid)	Duloxetine (30 mg bid), pregabalin (75 mg bid)	Amitriptyline (25 mg bid), fluoxetine (20 mg qd)	Venlafaxine (75 mg bid) Bromazepam (3 mg qd)	Venlafaxine (150 mg bid)
Course of sun pain over time	Improved	Improved	Stationary	Stationary	Improved	Improved

Bid: twice daily; qd: daily.

Two patients reported that the pain was associated with low fever and fatigue, and one of them also reported episodes of faintness and loss of consciousness. This patient underwent a neurological examination with an electroencephalogram (EEG) with intermittent photic stimulation (IPS) and a brain magnetic resonance imaging (MRI): neither examination showed any anomalies.

Laboratory biochemical and immunological blood and urine tests were always negative or within a normal range.

MED phototesting triggered pain at the site of UVA irradiation in 4 patients at doses ranging from 8 to 45 J/cm² and these “painful” doses were always lower than the erythematous threshold. UVB doses equal, higher or lower than the MED, never triggered the painful reaction. VIS phototesting was negative in all patients (Table II).

The biopsy of the skin phototesting area with the minimal “painful” dose was performed soon after the exposure and the onset of pain in 3 patients and the histopathology showed a completely normal skin.

In 2020 the patients were recalled for a follow-up visit. At clinical reassessment, the median (range) age of the patients was 55 (29–66) years, and the median (range) time interval from the first visit at our centre was 6 (1–15) years. Three female patients had developed painful neuromuscular symptoms leading to a diagnosis of fibromyalgia at the age of 60, 58 and 52 years, respectively. One of these patients reported that, at the time of the diagnosis of fibromyalgia, pain was no longer triggered only by sun exposure, but also by tactile stimuli and another patient described it to be stimulated by both tactile and thermal stimuli. However, these patients still also felt pain with sun exposure alone, in the absence of any tactile and/or thermal stimuli. Two of these patients were treated with pregabalin combined with duloxetine and the third was under treatment with amitriptyline and fluoxetine. Only one of the first 2 reported a good control of her fibromyalgia and an improvement of both painful reaction to sun exposure and tactile allodynia (individual drug dosages are reported in Table I). A patient was diagnosed a few months earlier with a conversion disorder (5) and, after the start of the treatment with venlafaxine and bromazepam, sun pain improved and only some residual discomfort remained, with full remission of the associated episodes of faintness and loss of consciousness.

Table II. Results of phototesting and photoprophylactic treatment cycle with narrow-band-ultraviolet B (UVB)

Patients	1	2	3	4	5	6
Threshold of symptoms						
UVA, J/cm ²	45	No	16	11	8	No
UVB, J/cm ²	No	No	No	No	No	No
VIS, min	No	No	No	No	No	No
MED, at 24 h						
UVA, J/cm ²	>64	45	>64	45	23	45
UVB, J/cm ²	0.32	0.18	0.18	0.08	0.08	0.35
Biopsy of painful phototesting area	Normal	ND	ND	Normal	Normal	ND

VIS: visible; MED: minimal erythematous dose; ND: not done; NB: narrow-band.

Furthermore, 2 male patients had received a diagnosis of major depressive disorder at the ages of 29 and 52 years, respectively. One of these patients was being treated with venlafaxine and the other with duloxetine combined with olanzapine, and both patients reported an improvement of both depression and sun pain (Table I).

DISCUSSION

This paper describes the characteristics of 6 patients with excruciating and debilitating pain shortly after sun exposure, in the absence of skin eruptions. This pain was combined with low fever and fatigue in one patient and with low fever, fatigue, faintness and episodes of loss of consciousness in another patient. At phototesting, 4 out of 6 patients reported the onset of pain with suberythematous UVA exposures, without the appearance of any eruption.

Findings of laboratory investigations and histology were negative or within normal limits.

However, in the following years, 3 female patients developed a panel of symptoms, which led to a diagnosis of fibromyalgia, a complex disorder in which neuropsychological factors play an important pathogenetic role (6). Two male patients were diagnosed with major depressive disorder and one patient was diagnosed with conversion syndrome. The neuropsychiatric treatment not only improved the neuropsychiatric symptoms, but it also improved the sensitivity to the sun in 1 out of 3 patients with fibromyalgia, in the 2 patients with major depressive disorder and in the patient with the conversion disorder (Table I).

Since we are dealing with 3 different neuropsychiatric conditions, we do not know if the neurological or psychological mechanisms of this abnormal reaction to the sun are the same, or different and specific for each disease or individual patient.

However, unlike healthy peoples, some patients with fibromyalgia (6) and major depression (7, 8) are known to experience an unexpectedly painful response to stimuli that normally would not cause discomfort or pain. This symptom is known as allodynia. Known stimuli are touch, pressure, pinprick, cold, and heat (9).

It is notable that one of the current patients developed allodynia in response to tactile stimuli, while another patient developed it in response to both thermal and tactile stimuli.

Recent evidence demonstrates that allodynia occurs when the patient's nervous system is persistently in a state of “central sensitization” (9) with increased responsiveness to peripheral stimulation by nociceptive neurones in the central nervous system, even if the painful stimuli are limited and sub-threshold (7–10). It is the result of a complex interaction of upregulation of the ascending pain pathways, downregulation of the descending inhibitory pain pathways and deficiency in central pain processing and inhibition systems (6, 11, 12).

In addition to maladaptive central changes, peripheral activation of channels that are usually insensitive to a given stimulus (13) may contribute to the generation and maintenance of various subtypes of allodynia, with separate mechanisms according to the triggering stimuli (13, 14).

The findings of the current study suggest that sub-erythral ultraviolet exposure could be an additional trigger, but we do not know which peripheral nervous receptors could be activated and which neurological pathways they could excite.

Much more is known about hyperalgesia and hyperesthesia, which are very common neurological symptoms of sunburned skin. These conditions consist of stable and prolonged (up to 72–96 h) reduced mechanical and thermal pain thresholds (15–17). They are underpinned by an alteration in the coding properties of peripheral nociceptors that is independent by an activation threshold and leading to a net shift towards a C-fibre mediated input to the spinal cord (16, 18). However, the extension of hyperalgesia in non-inflamed skin at some distance from the site of inflammation occurs frequently and suggests that central sensitization may also play a role (19).

Sun tolerance improved in the 2 patients with major depressive disorder (one treated with venlafaxine and the other with duloxetine and olanzapine), a patient with fibromyalgia (treated with duloxetine and pregabalin) and the patient with conversion disorder (treated with venlafaxine and bromazepam). This improvement could be a consequence of the improvement of the neuropsychiatric conditions, but a therapeutic effect on neurological mechanisms of allodynia can be taken into account, because selective serotonin reuptake inhibitors (SSRIs) and pregabalin are known to be effective in the treatment of allodynia with other causes, although the precise mechanism of action remains unclear (20).

Special consideration needs to be given to the patient later diagnosed with conversion disorder (21). This is a complex condition in which the patients display symptoms of altered motor or sensory functions that are not better explained by another medical or neurological health disorder (5). In this patient, sun pain was also associated with atypical symptoms, such as low fever, fatigue, faintness and episodes of loss of consciousness.

The clinical cases reported here have some similarities with the 9 cases of facial dysaesthesia triggered or aggravated by short exposure to sunlight that were described by Lai et al. in 2019 (22). These patients developed burning-tingling sensations or pain in the exposed skin in the absence of skin eruptions. Three patients also had flares when exposed to heat. Responses to phototesting were normal and laboratory immunological investigations were unremarkable. Three patients had pre-existing anxiety and/or depressive symptoms. One patient had benefited from oral gabapentin and another patient from an oral SSRI (duloxetine). Unlike the current patients, their

symptoms were localized only on the head or selected areas of it. However, the authors did not report whether “dysaesthesia” also developed to other body areas when they were exposed to the sun (22).

Another condition with similarities to those of the current patients is skin pain with psoralen plus ultraviolet A (PUVA). As in the current patients, the pain is very intense and distressing, it is refractory to analgesic treatments, is not associated with the appearance of skin eruptions, does not correlate with a history of burns, low minimal phototoxic dose or skin type, and the pathogenic mechanisms are unknown (23). However, unlike the current patients and the patients with facial dysesthesia (22), accessional episodes of pain occurred for days or weeks even in the absence of sun exposure, often following scratching or pressure to the skin, and usually resolving spontaneously and definitively only after several weeks (23, 24). It is notable that good results were reported with gabapentin (25) that was also used successfully for improving symptoms in patients with facial dysesthesia (22) and in one of the 2 current patients with fibromyalgia.

Finally, for the differential diagnosis, we can also consider a rare variant of polymorphic light eruption, termed polymorphic light eruption sine eruptione (PLESE) that was described in 7 patients in 1988 (26) and in another patient in 2020 (27). They experienced sun-induced pruritus and/or intense burning without evidence of cutaneous eruption (26, 27). Unlike the current patients, low-dose broadband UVB phototherapy or PUVA photochemotherapy were always successful in reducing symptoms during subsequent summers. However, information on any concomitant diseases and treatment was not reported.

In conclusion, we report here that intense pain without skin eruptions after sub-erythral sun exposures may represent the first clinical manifestation of fibromyalgia or other psychiatric disorders. Early diagnosis may prevent the need for unnecessary, expensive and time-consuming photobiological and laboratory investigations and treatments. In addition, early identification of fibromyalgia and psychiatric disorders can lead to earlier treatment and improvement in symptoms (5).

REFERENCES

1. Rhodes LE, Bock M, Janssens AS, Ling TC, Anastasopoulou L, Antoniou C, et al. Polymorphic light eruption occurs in 18% of Europeans and does not show higher prevalence with increasing latitude: multicenter survey of 6,895 individuals residing from the Mediterranean to Scandinavia. *J Invest Dermatol* 2010; 130: 626–628.
2. Hinton AN, Goldminz AM. Feeling the burn: phototoxicity and photoallergy. *Dermatol Clin* 2020; 38: 165–175.
3. Murphy GM. Diseases associated with photosensitivity. *J Photochem Photobiol B* 2001; 64: 93–98.
4. Calzavara-Pinton P, Zane C, Rossi M, Sala R, Venturini M. Narrowband ultraviolet B phototherapy is a suitable treatment option for solar urticaria. *J Am Acad Dermatol* 2012; 67: e5–e9.

5. Tsui P, Deptula A, Yuan DY. Conversion disorder, functional neurological symptom disorder, and chronic pain: comorbidity, assessment, and treatment. *Curr Pain Headache Rep* 2017; 21: 29.
6. Chinn S, Caldwell W, Gritsenko K. Fibromyalgia pathogenesis and treatment options update. *Curr Pain Headache Rep* 2016; 20: 25.
7. den Boer C, Dries L, Terluin B, van der Wouden JC, Blankenstein AH, van Wilgen CP, et al. Central sensitization in chronic pain and medically unexplained symptom research: A systematic review of definitions, operationalizations and measurement instruments. *J Psychosom Res* 2019; 117: 32–40.
8. Ushinsky A, Reinhardt LE, Simmons AN, Strigo IA. Further evidence of emotional allodynia in unmedicated young adults with major depressive disorder. *PLoS One* 2013; 8: e80507.
9. International Association for the Study of Pain (IASP). IASP terminology. 2021. [Accessed 21-06-2021] Available from: <https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698#Centralsensitization>.
10. Yunus MB. Central sensitivity syndromes: a new paradigm and group nosology for fibromyalgia and overlapping conditions, and the related issue of disease versus illness. *Semin Arthritis Rheum* 2008; 37: 339–352.
11. Clauw DJ. Fibromyalgia: an overview. *Am J Med* 2009; 122: S3–S13.
12. Cagnie B, Coppieters I, Denecker S, Six J, Danneels L, Meeus M. Central sensitization in fibromyalgia? A systematic review on structural and functional brain MRI. *Semin Arthritis Rheum* 2014; 44: 68–75.
13. Lolignier S, Eijkelkamp N, Wood JN. Mechanical allodynia. *Pflugers Arch* 2015; 467: 133–139.
14. Jensen TS, Finnerup NB. Allodynia and hyperalgesia in neuropathic pain: clinical manifestations and mechanisms. *Lancet Neurol* 2014; 13: 924–935.
15. Gustorff B, Sycha T, Lieba-Samal D, Rolke R, Treede RD, Magerl W. The pattern and time course of somatosensory changes in the human UVB sunburn model reveal the presence of peripheral and central sensitization. *Pain* 2013; 154: 586–597.
16. Bishop T, Marchand F, Young AR, Lewin GR, McMahon SB. Ultraviolet-B-induced mechanical hyperalgesia: a role for peripheral sensitization. *Pain* 2010; 150: 141–152.
17. Obata H. Analgesic mechanisms of antidepressants for neuropathic pain. *Int J Mol Sci* 2017; 18: 2483.
18. Bishop T, Ballard A, Holmes H, Young AR, McMahon SB. Ultraviolet-B induced inflammation of human skin: characterisation and comparison with traditional models of hyperalgesia. *Eur J Pain* 2009; 13: 524–532.
19. Rössler B, Paul A, Schuch M, Schulz M, Sycha T, Gustorff B. Central origin of pinprick hyperalgesia adjacent to an UV-B induced inflammatory skin pain model in healthy volunteers. *Scand J Pain* 2013; 4: 40–45.
20. Anderson G, Berk M, Maes M. Biological phenotypes underpin the physio-somatic symptoms of somatization, depression, and chronic fatigue syndrome. *Acta Psychiatr Scand* 2014; 129: 83–97.
21. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*. Washington, DC: APA, 2013.
22. Lai F, Fassihi H, Sarkany R. Photosensitive facial dysaesthesia: a case series. *Br J Dermatol* 2019; 181: 97–103.
23. Tegner E. Severe skin pain after PUVA treatment. *Acta Derm Venereol* 1979; 59: 467–470.
24. Roelandts R, Stevens A. PUVA-induced itching and skin pain. *Photodermatol Photoimmunol Photomed* 1990; 7: 141–142.
25. Zamiri M, Bilisland D. Treatment of bath PUVA-induced skin pain with gabapentin. *Br J Dermatol* 2004; 151: 516–517.
26. Dover JS, Hawk JL. Polymorphic light eruption sine eruption. *Br J Dermatol* 1988; 118: 73–76.
27. Vellaichamy G, Chadha AA, Hamzavi IH, Lim HW. Polymorphic light eruption sine eruption: A variant of polymorphous light eruption. *Photodermatol Photoimmunol Photomed* 2020; 36: 396–397.