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URTICÁRIA PAPULAR BOLHOSA – CASO CLÍNICO E BREVE REVISÃO DA LITERATURA

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RESUMO – A urticária papular (UP), também conhecida como prurigo estrófulo, é uma dermatose infantil relativamente frequente devida a hipersensibilidade à picada de mosquitos, pulgas, percevejos e outros insetos. Caracteriza-se pelo aparecimento de pápulas e, eventualmente, vesículas e/ou bolhas, apresentando evolução crónica ou recorrente. É geralmente pruriginosa e desconfortável, e o acto de coçar resultante pode originar erosões e infeção secundária. Os doentes afetados são frequentemente mal diagnosticados e submetidos a exames auxiliares de diagnóstico desnecessários, onerosos e/ou invasivos. De forma a evitá-lo, o clínico deve saber reconhecer as lesões cutâneas de UP, possíveis exposições e a história natural da doença. Os principais desafios na abordagem da UP são: convencer os pais/doentes de que as lesões estão relacionadas com a picada de inseto, desmistificar a convicção frequente da relação com a ingestão de certos alimentos e identificar e erradicar o insecto envolvido. Neste artigo, descrevemos uma doente de 25 anos de idade com UP bolhosa e efectuamos uma breve revisão da literatura, incluindo os aspectos clínicos, a utilidade da mnemónica "SCRATCH" no diagnóstico correcto e atempado, os principais diagnósticos diferenciais e a abordagem terapêutica baseada na regra dos 3 "P's" (Prevenção, controlo do Prurido e Paciência).

PALAVRAS-CHAVE – Urticária papular; Insetos; Criança; Prurigo.

BULLOUS PAPULAR URTICARIA – CASE REPORT AND BRIEF REVIEW OF THE LITERATURE

ABSTRACT – *Papular urticaria (PU), also known as prurigo strophulus, is a relatively common skin disorder of childhood caused by hypersensitivity to a variety of bites, including those of mosquitoes, fleas, bedbugs and others insects. It is characterized by a chronic or recurrent, papular or vesicobullous eruption, that is often pruritic and uncomfortable. The resultant scratching may lead to erosions and secondary pyoderma. Patients affected by these eruptions are frequently misdiagnosed and often subject to unnecessary, expensive and/or invasive evaluations. In order to avoid that, clinicians should be aware of the characteristic skin lesions of PU, possible exposures, and natural history of the disease. The most challenging aspects of PU is convincing parents/patients that the lesions are related to a bite reaction, demystify the common belief of the relationship with the ingestion of certain foods, and identifying and eradicating the source of the offending insect. We herein describe a 25-year-old female patient with bullous PU, and present a brief review of the literature, including the clinical features, utility of mnemonic "SCRATCH" to aid clinicians in making an early and accurate diagnosis, differential diagnoses, and 3 "P's" of therapy (Prevention, Pruritus control, and Patience).*

KEY-WORDS – *Skin diseases, vesiculobullous; Urticaria; Prurigo; Criança; Insects.*

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INTRODUCTION

Papular urticaria (PU) is a common and often distressing disorder occurring most frequently in young children, particularly in those with a history of atopic dermatitis, during late spring and summer[1,2]. Although the exact prevalence of PU is unknown, Hernandez and Cohen[3] noted that 5% of office visits to Johns Hopkins Pediatric Dermatology Clinic over a 4-week period (December 12, 2003 to January 11, 2004) were attributed to PU or insect bite reactions. This disorder is generally considered an immediate (type I) hypersensitivity reaction followed by a delayed (type IV) hypersensitivity reaction, occurring in sensitized individuals in response to a hematogenously disseminated antigen deposited by the bite or sting of fleas (most commonly cat flea [*Ctenocephalides felis*], dog flea [C. *canis*] and human flea [*Pulex irritans*]), bedbug (*Cimex lectularius*), mosquitoes, midges, flies and even caterpillars[1-4]. Which particular insect is the cause varies with the geographic location[5]. A difference seems to exist concerning insect aggressiveness, i.e., eruptions provoked by wild insects usually are more extensive and severe than those caused by domestic ones. PU is characterized by chronic or recurrent eruption of small, 3 to 10mm in diameter, extremely pruritic, urticarial papules, often with a central dot at the site of penetration of the insect bite or sting that may be surmounted by a small vesicle[1-3]. Bullous lesions may also develop, especially in tourists exposed to new insects[6,7]. Excoriation leads to central crusting, erosions, and occasionally secondary infection and need for antibiotics. The lesions tend to be grouped in clusters and develop in crops at irregular intervals[1-3].

CASE REPORT

We present a 25-year-old female patient with history of allergic rhinitis, but with no regular medication other than oral contraceptive, who was observed at our department due to acute onset of itchy papules followed by development of vesicles and bullae with yellowish content, located at the lower legs, hands and lumbar area. She referred a history of walking in a place with high grass and bushes the day before the onset of the rash, and was the only family member experiencing the itchy eruption. Approximately 4 years previously she had a similar episode requiring 5-day hospitalization at another hospital and treatment with oral steroids and antibiotic therapy. She did not know the final diagnosis, but the possibility of autoimmune disease was considered at that time, and she was worried about that. At physical examination, we observed multiple tense blisters with citrine content on the right leg, erythematous urticarial papules and plaques on the left leg, some of them with pseudovesicular appearance, and similar lesions with overt vesicles on the lumbar area and hands (Fig. 1). Based in clinical findings, the diagnosis of bullous PU was likely. After biopsy of a papulovesicular lesion on the left hand, treatment with oral prednisolone (40mg/day tapered over 3 weeks), levocetirizine (5mg/day) and once daily application of betamethasone/fusidic acid association was initiated. The rash progressively faded out, and after 4 weeks only a mild post-inflammatory erythema was noticed. Histologic examination revealed intraepidermal spongiotic bullae containing neutrophils, eosinophils and fibrin. In the dermis, marked subepidermal edema and perivascular mixed inflammatory infiltrate

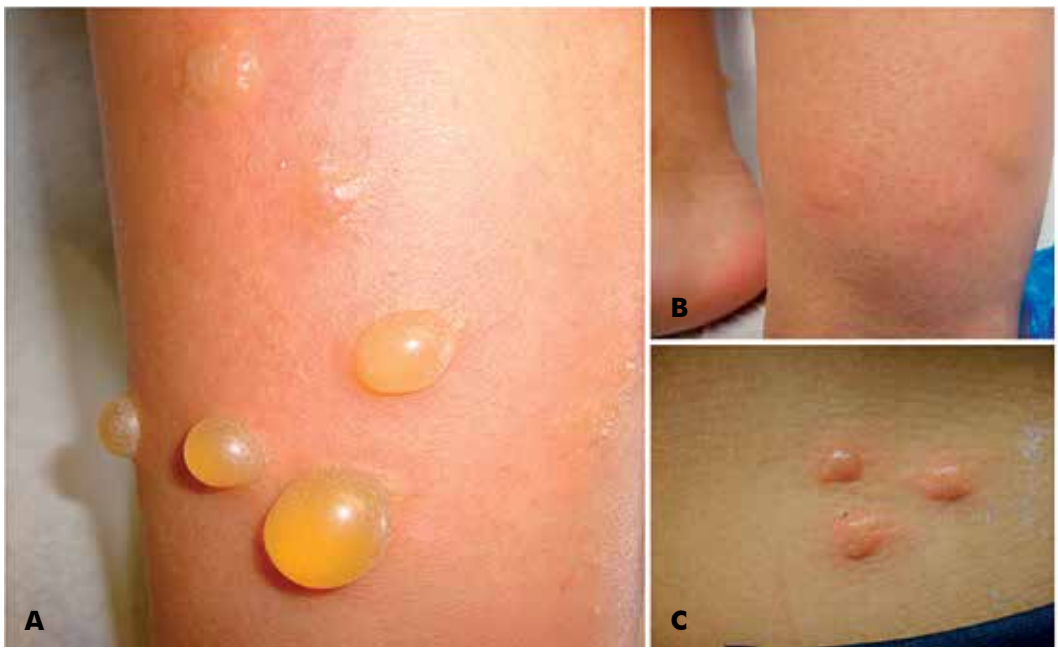

Fig 1 - Clinical appearance of our patient. Multiple tense blisters with citrine content in right leg (a), erythematous urticarial papules in left leg, some of them with small vesicles in the center (b), and similar lesions with overt vesicles on the lumbar area (c).

with eosinophils were present (Fig. 2). Direct immunofluorescence was negative. Blood tests revealed increased C-reactive protein (14.1 mg/L, normal: <3.0), total IgE (249 kU/L, normal: <114), C4 (39 mg/dL, normal: 12-36) and CH50 (333 UA, normal: 63-145), but the remaining exams, including complete blood count, liver and kidney function tests, anti-gliadin IgA antibody, anti-tissue transglutaminase IgA antibody, anti-basement membrane antibodies and circulating immune complexes were normal or negative. Based on the histological and analytical findings, the clinical diagnosis of bullous PU was confirmed.

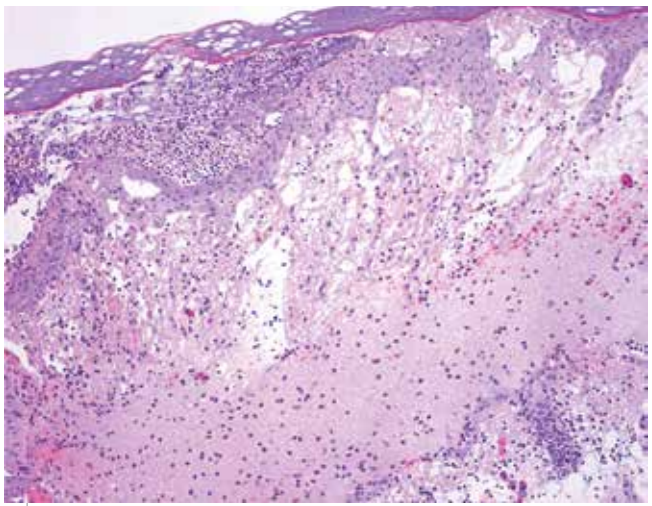

Fig 2 - Histology of a biopsy specimen obtained from the left hand: intraepidermal spongiotic bullae containing neutrophils, eosinophils and fibrin, subepidermal edema and perivascular polymorphic inflammatory infiltrate with eosinophils (hematoxylin-eosin stain).

DISCUSSION

PU was originally described in 1813 by Bateman[1]. Some misnomers and confusion are frequently associated with this condition, and its name often varies with physician specialty. For most pediatricians this entity is best known as *prurigo strophulus or strophulus*, while for dermatologists the disease is also recognized as *papular urticaria or acute prurigo of childhood*. Others synonyms that can be found on the literature include: *prurigo simplex acuta infantum (Brocq), strophulus infantum, urticaria papulosa infantum, lichen simplex acutus or lichen urticatus*[1,8]. A bullous, and sometimes extensive, type of PU exists, and the designation bullous prurigo or *bullous papular urticaria* can be used in such cases[6]. Our patient fits this subtype of PU. Theoretically, as stated before, more severe reactions could be related

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to wild insect bites, as it was the case of our patient, who referred a history of outdoor activity in the woods the day before the onset of the rash. As terminology used to describe insect bite reactions is confusing, some authors suggest the term *insect bite–induced hypersensitivity* to better describe the findings in this group of patients[3].

Although PU mostly affects children between 2 and 7 years of age, the disease occasionally occurs in adolescents, young adults and adults[1-5], as observed in our case. According to Raza *et al.*[9], children, adult males, non-locals and those belonging to urban/peri-urban areas are more vulnerable to PU in a particular region. Papules may occur on any part of the body but tend to be grouped in clusters on exposed areas, particularly the extensor surfaces of the extremities. They may appear to a lesser extent on the face and neck, trunk, thighs, and buttocks and generally spare the genital, perianal, and axillary regions[1-5]. However, location depends on the arthropod involved. Factors such as prolonged permanence outside, sweating, intense odors, increased body temperature and locomotion seem to increase susceptibility to bite[1]. It should be noted, however, that a single bite can produce several lesions over the body[1]. Most lesions persist for 2 to 10 days and, after resolution, may result in temporary post-inflammatory erythema or hyperpigmentation[1-3]. If exposure to the parasite continues, the attacks may persist for an average of 3 to 4 years, perennially or recurring seasonally; occasionally they may persist into adolescence or adulthood[1]. However, with repeated exposure to inciting antigen, immune tolerance to saliva proteins develops and spontaneous desensitization usually takes place, and the patient "outgrows" the condition[1,3,4].

For more experienced physicians the diagnosis of PU is not difficult, but it may represent a clinical challenge, particularly for those who are not familiarized with the condition or in severe cases simulating some of the more serious bullous skin diseases. Diagnosis is based on clinical appearance and, in some cases, on the identification of the putative insect[1-3]. The diagnosis of PU is sometimes questioned by physicians when there is no history of a pet in the patient's home. It should be noted, however, that a remote history of pet exposure, for example in a recent visit to a relative's house, is enough for a disease outbreak. Consequently, lack of pet at patient's home should not exclude the diagnosis of PU. Outdoor playing, camping, inhabiting a shelter or a history of recent hotel visit, should also be considered in the patient's history, due to the associated risk of exposure to mosquitoes or bedbugs[3]. Clinical diagnosis may be aided by using the mnemonic "SCRATCH," proposed by Hernandez and Cohen[3], which is described in Table 1. Ancillary studies are usually unnecessary, and these were only performed in our patient because she was stressed about an autoimmune disorder, suggested by internet search. However, skin biopsy may be useful both in confirming the diagnosis and in persuading the patients or parents regarding the nature of the condition[2]. Histologic features of typical PU can be classified into 4 variants: lymphocytic, eosinophilic, neutrophilic, and mixed cellular. Common findings encompass: localized perivascular infiltrate with lymphocytes, histiocytes, eosinophils and mast cells in the upper dermis; variable edema between collagen fibers; a light scattering of eosinophils and mast cells away from vessels in the upper and mid dermis; and spongiosis with exocytosis and vesicle formation in the epidermis, overlying the most marked and superficial perivascular infiltrate[10,11]. Increased serum IgE levels (as observed in our patient) and eosinophilia may be present, even in non-atopic patients.

Table 1 - The SCRATCH principles

S	Symmetric distribution (scalp, neck, face, torso, extremities)
C	Crops/clusters of different coloration (erythema, hypo-/hyperpigmentation)
R	Rover not required: pets are not necessary criteria for diagnosis
A	Age specific (usually occurring between 2 and 10 years of age)
T	Target lesions and time (may take weeks to years to resolve)
C	Confused pediatrician/parent: "We don't have fleas!"
H	Household with single family member affected

Since the histology of PU is not specific and the clinical features may be shared with other conditions, the differential diagnosis of this entity is broad and includes: varicella (chickenpox) in its early stages, scabies, "true" urticaria, papular forms of atopic dermatitis, allergic contact dermatitis, drug-induced reaction, id reaction, miliaria rubra, papulovesicular polymorphous light eruption, papular acrodermatitis of childhood (Gianotti Crosti syndrome), pityriasis lichenoides et varioliformis acuta (PLEVA), lymphomatoid

papulosis, urticaria pigmentosa, the pruritic papular eruption of human immunodeficiency virus disease, papulonecrotic tuberculid, delusions of parasitosis, and neurotic excoriations[1-4,10,12,13]. Although unlikely in our patient, autoimmune blistering diseases such as linear IgA bullous dermatosis, herpetiformis dermatitis and bullous pemphigoides could also be thought. Based on patient's age, absence of gastrointestinal symptoms, normal autoimmune blood tests and direct immunofluorescence of biopsy specimen, and histologic findings, these hypotheses were ruled out.

The most effective treatment for PU is identification and removal of its cause. In some cases, this may be difficult if not impossible, and patients should be treated symptomatically while the source of the rash is investigated[4]. Topical steroids and systemic antihistamines, as well as topical antipruritic preparations containing menthol, camphor or pramoxine are recommended for control of pruritus[1-4]. In case of secondary infection, topical or oral antibiotics are required. Preventive measures should be implemented, including wearing protective clothing for outdoor play with careful use of insect repellents, disinfecting all pets and fumigating the home, laundering bedding and mattress pads every 2 to 4 weeks and, in case of failure, consider professional application of pesticide treatments to assure removal of allergens[1-4]. Finally, patients and parents should be informed about the frustrating, persistent, recurrent nature of PU, emphasizing on patience and understanding of the natural history of the disease, in order to prevent multiple consultations, and expensive, unnecessary, invasive and/or painful investigative studies[2,3]. Additionally, the common belief of the relationship between PU and food allergies should be demystified[7]. The abovementioned statements may be summarized as the 3 "P's" of PU management: Prevention, Pruritus control and Patience[3].

In conclusion, the present case of PU is unusual for its severity (development of large tense bullae), extent (upper/lower limbs and lumbar area), and age of onset. Areas of future investigations might include flea-antigen patch testing to help in the diagnosis of PU[3], and induced specific desensitization to insect bites[14]. The last could be, theoretically, an effective means of prevention of this condition; however clinical trials have not yet proved its efficacy[14].

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