Neutrophilic dermatoses – Part II

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Abstract: This article addresses neutrophilic dermatoses, thus complementing the previous article (part I). The following dermatoses are introduced and discussed: subcorneal pustular dermatosis (Sneddon-Wilkinson disease), dermatitis cruris pustulosa et atrophicans, acute generalized exanthematous pustulosis, continuous Hallopeau acrodermatitis, palmoplantar pustulosis, infantile acropustulosis, Andrews’ pustular bacteride and eosinophilic pustular folliculitis. A brief review of neutrophilic dermatoses in pediatric patients is also conducted.

Keywords: Neutrophil infiltration; Pediatrics; Skin diseases

Resumo: Neste artigo são abordadas as dermatoses neutrofílicas, complementando o artigo anterior (parte I). São apresentadas e comentadas as seguintes dermatoses: pustulose subcórnea de Sneddon-Wilkinson, dermatite crural pustulosa e atrófica, pustulose exantemática generalizada aguda, acrodermatite contínua de Hallopeau, pustulose palmoplantar, acropustulose infantil, bacteride pustular de Andrews e foliculite pustulosa eosinofílica. Uma breve revisão das dermatoses neutrofílicas em pacientes pediátricos também é realizada.

Palavras-chave: Dermatopatias; Infiltração de neutrófilos; Pediatria

SNEDDON-WILKINSON’S SUBCORNEAL PUSSULOSIS

Sneddon-Wilkinson’s subcorneal pustulosis or subcorneal pustular dermatosis or Sneddon-Wilkinson disease (SWD) was first described in 1956. It is a rare, chronic disease, characterized by flaccid pustules, recurrent and coalescing, causing annular, circinate or serpiginous lesions. It is a benign condition, but it may be associated with neoplastic disease (having thus a worse prognosis). Its etiopathogenesis is still unknown. Neutrophil chemotactic factors such as tumor necrosis factor alpha, interleukin-8, complement fragment C5a, and immunoglobulin A were identified in vesiculopustular blood and fluid. However, the stimulus that occurs early in the process is still unknown.

Clinical manifestations, histopathological aspects and complementary evaluation

The disease is more common in women aged 40 to 50 years. Vesiculopustular lesions are small and characterized by the presence of “half-half” content (purulent portion located in the lower region and
clear portion in the upper region). The base of the lesion is composed of normal or slightly erythematous skin. The lesions coalesce, forming annular or serpiginous lesions. With the rupture of lesions, areas of superficial desquamation, crusting and hyperpigmentation are formed. 2

They are mostly located in the trunk, intertriginous areas and flexor region of the limbs. They may involve palms and soles, but they spare face and mucous membranes. 2

Patients may present with symptoms of mild pruritus and irritation. There are no other associated symptoms. 3

Several diseases have been described in association with SWD. Among them we highlight IgA and IgG monoclonal gammopathy, as well as myeloproliferative disorders, especially multiple myeloma. 7,8,9 The onset of these diseases may occur after years, which justifies the prolonged follow-up of these patients.

Pyoderma gangrenosum, rheumatoid arthritis, hyperthyroidism, Sjogren’s syndrome, Crohn’s disease, multiple sclerosis, SAPHO (synovitis, acne, pustulosis, hyperostosis and osteitis) syndrome, IgA myeloma, chronic lymphocytic leukemia, thymoma, apudoma and squamous cell carcinoma of the lung have also been described. 10-12

Histopathological examination reveals subcorneal pustule with neutrophils and rare eosinophils, non-pathognomonic. The epidermis shows minimal changes. There may be perivascular infiltrate in the dermis. 2,3

Direct and indirect immunofluorescence is generally negative. The finding of intercellular IgA deposition in the epidermis, granular layer or below the subcorneal zone still generates discussion about whether it is just a variant of SWD or a new entity called subcorneal IgA pemphigus. 2,3

Another test that should be performed in further investigation is proteinogram at diagnosis and periodically during follow-up. 2,3

Differential diagnosis must be done with pemphigus foliaceus, pustular psoriasis (localized and generalized), acute generalized exanthematous pustulosis, impetigo, dermatophytosis, dermatitis herpetiformis and necrolytic migratory erythema. 3

TREATMENT

Dapsone is the drug of first choice with doses ranging from 50 to 200mg, with gradual decrease after control of symptoms. 3 Systemic or topical corticosteroids, combined or not with dapsone, may also be used.

The use of retinoids is limited to acitretin and etretinate. Phototherapy with ultraviolet B and psoralen with ultraviolet A can also be used. 2

The use of immunobiological drugs such as infliximab and etanercept has been reported with good results. 21,22,23

DERMATITIS CRURIS PUSTULOSA ET ATROPHICANS

Dermatitis cruris pustulosa et atrophicans (DCPA) is a chronic disease characterized by folliculitis with symmetric topography and often limited to the lower limbs. 24

The pathogenesis of the disease is still not completely understood. Staphylococcus aureus has been isolated from the lesions, but some authors consider it only a contaminant. The use of occlusive agents in the lower limbs (with oily substances such as coconut oil), may be an etiological factor, although not always identified in the patients’ medical history. 24,25,26 Due to the chronicity of the manifestations, immunological alterations such as hypogammaglobulinemia, functional abnormalities of polymorphonuclear cells and reduction of C3 may play a role; however, the participation of immunological factors has not yet been defined. 27

Clinical manifestations, histopathological aspects and complementary evaluation

DCPA is a disease with higher incidence in tropical regions, especially Asia and Africa. It mainly affects young patients, male, in the second and third decades of life. Studies report prevalence ranging from 0.4 to 4.8% of ambulatory care patients in the most affected countries. 25,27

The clinical manifestations are characterized by the presence of pruriginous follicular pustules, edema, desquamation, shiny skin surface (fibrosis), alopecia and, ultimately, skin atrophy in both legs, mainly in the anterior portion. 21,27 The borders of the lesion are well demarcated. 21,25 The manifestations are usually symmetrical, involving the anterior legs between the knees and ankles; however, it may involve the face, forearms and scalp. 27 It tends not to leave residual hypo- or hyperpigmentation. 27 There are no systemic symptoms.

Anatomopathology of the lesions shows intraepidermal pustule and dermal inflammatory infiltrate composed of neutrophils and eosinophils. 24,28 Bens et al. suggest that DCPA may be a variant of eosinophilic panniculitis due to dermal flame figures, typical of this disease. 24

TREATMENT

There are reports of therapeutic success with the use of antiseptics, trimethoprimsulfamethoxazole, 29 PUVA in combination with antibiotics, 30 and topical mupirocin. 31
However, the disease can be refractory to various treatment options, including combinations thereof, with inevitable progression to atrophy. 27

**Acute generalized exanthematous pustulosis**

The term Acute Generalized Exanthematous Pustulosis (AGEP) was first proposed in 1980. Until then, this eruption had been described by several names, being considered as a variant of psoriasis. 32 However, due to its particular clinical characteristics such as sudden onset of numerous follicular pustules over an exanthem, accompanied by fever, history of frequent use of medication, histopathological differences and rapid spontaneous resolution, the authors considered it as a different entity from psoriasis. Some authors acknowledge that pustular psoriasis and AGEP may share a genetic background that would lead to the attraction of neutrophils 32-35

The most frequent causes of AGEP are reactions to acute infections (enterovirus), to drugs and mercury. 34

Although the infectious etiology of AGEP is still controversial, 32.36 there are reports of patients with skin lesions compatible with AGEP during an infectious process without use of any medication. 34,35,37

Approximately 90% of the cases are caused by medication. 34,38 Among the drugs commonly associated with the development of AGEP are antibiotics (macrolides and beta-lactams), antifungals, calcium channel blockers, carbamazepine, paracetamol, anti-malarial drugs, among others. 33,36 It is worth noting that the spectrum of agents associated with toxic epidermal necrolysis/Stevens-Johnson syndrome differs from the medication associated with AGEP. 35

The EuroScar multicentric study showed that some drugs are more likely (higher odds ratio) to lead to the development of AGEP (Table 1). 35

The sensitization phase is not well understood, but it is believed that antigen-presenting cells activate T cells by presenting the drug to the lymph node. Drug-specific CD4 and CD8 lymphocytes multiply and migrate to the dermis and epidermis. In the epidermis, tissue damage occurs by the death of keratinocytes, a process that involves a perforin/granzyme B and Fas/Fas-ligand. This destruction leads to vesicle formation, initially populated by T lymphocytes, which secrete cytokines (interleukin-8 (CXCL8), interferon gamma, tumor necrosis factor, granulocyte colony-stimulating factor, Interleukin -5 and others), attracting neutrophils and eosinophils, which will then form the pustules. 39-40 Thus, AGEP seems to be a disease model in which there is interaction between T cells and polymorphonuclear cells.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Odds Ratio (Confidence Interval)</th>
</tr>
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<tbody>
<tr>
<td>Macrolides</td>
<td>11 (2.7-48)</td>
</tr>
<tr>
<td>Aminopenicillins</td>
<td>23 (10-54)</td>
</tr>
<tr>
<td>(ampicillin and amoxycillin)</td>
<td></td>
</tr>
<tr>
<td>Quinolones</td>
<td>33 (8.5-127)</td>
</tr>
<tr>
<td>Anti-Malarial</td>
<td>39 (8-191)</td>
</tr>
<tr>
<td>Sulfonamide *</td>
<td>7.1</td>
</tr>
<tr>
<td>Terbinafine *</td>
<td>7.1</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>15 (5-48)</td>
</tr>
<tr>
<td>NSAIDs (oxicam)</td>
<td>8.4 (1.7-42)</td>
</tr>
<tr>
<td>Anti-epileptic drugs</td>
<td>7.6 (1.6-36)</td>
</tr>
<tr>
<td>(except valproic acid)</td>
<td></td>
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</tbody>
</table>

Positivity in the patch test, even after resolution of the skin manifestations, classifies the hypersensitive response involved in the pathogenesis of AGEP as a type IV delayed reaction, the Gell-Coombs classification. However, other endothelial changes may also be involved, leading to altered expression of cytokines and chemotaxis of eosinophils, neutrophils and lymphocytes. 36

Although rare, AGEP may be due to spider bites. The venom of the insect would lead to the release of interleukin-8 and granulocyte-macrophage colony-stimulating factor, which would explain the development of skin lesions. 41

**Clinical manifestations, histopathological aspects and complementary evaluation**

The incidence of AGEP is estimated to be between 1-5 cases per million patients per year and may occur at any age. 33 Studies have shown there is no predilection for sex 33, but the EuroScar has shown a slight female predominance (ratio male/female: 0.86). 35

The clinical manifestations are characterized by sudden onset of erythema and edema on intertriginous areas or face, with craniocaudal spread and emergence of hundreds of small, non-follicular pustules (Figure 1). It may be preceded or accompanied by fever and pruritus. The average duration of the pustules is 9 days (between 4-14 days), followed by spontaneous resolution with drug withdrawal and desquamation. 33,35 There may be polymorphism of lesions; erythema multiforme-like lesions, swelling of face and hands and purpuric lesions may be found. 33,35 Mucosal involvement may occur, but it is less pronounced than in toxic epidermal necrolysis and involves, in general, only one mucous membrane. 33,35,56

The time between drug administration and the appearance of lesions may be less than 24 hours in
some cases. Some authors suggest that this period is on average shorter after the use of antibacterial drugs. In cases with no previous sensitization or when the drug involved is not an antibiotic, the interval between onset of lesions and start of treatment is from one to three weeks.

The prognosis of AGEP is generally good, except in cases of high fever in elderly patients and secondary infection of the lesions. Histopathology shows subcorneal or intradermal pustules and spongiosis. There is edema of the papillary dermis, perivascular infiltrate of neutrophils and eosinophils, and sometimes leukocytoclastic vasculitis. Direct immunofluorescence shows deposits of C3 and occasionally IgM in the vascular wall.

Complementary examination may reveal leukocytosis on complete blood count, at the expense of neutrophils and eosinophils, transient loss of renal function and up to a two-fold increase in aminotransferases.

Bacteriological examination of the pustules is negative (unless there is superposed contamination).

Result of the patch test tends to be more frequently positive than in other drug eruptions, with the development of lesions similar to those of AGEP.

The lymphocyte transformation test (LTT) can be performed, measuring the proliferation of T lymphocytes stimulated by a drug and indicating sensitization, but it is a difficult test to perform, with different levels of specificity and sensitivity.

In Table 2, a scoring system for the diagnosis of AGEP is shown.

The following are among the skin diseases that should be considered in differential diagnosis:

- Pustular psoriasis (Table 3)
- Toxic epidermal necrolysis (greater involvement of the mucous membranes; necrosis and detachment of the entire epidermis with sparse inflammatory infiltrate are observed in anatomopathological examination). There are reports of clinical and histopathological overlap in some cases.
- Staphylococcal scalded skin syndrome (confluence of pustules and positive Nikolski sign)
- Septicemia caused by Staphylococcus aureus, Neisseria meningitidis and Neisseria gonorrhoeae.
- Sneddon-Wilkinson disease (less acute onset than AGEP, larger tense bullae).
- Follicular eruptions (bacterial folliculitis, furunculosis, acne)
  - Necrolytic migratory erythema (glucagonoma)
  - Kaposi varicelliform eruption
  - Drug hypersensitivity syndrome (DRESS - drug rash with eosinophilia and systemic symptoms - pustular component is less pronounced and there is systemic involvement such as pneumonitis, hepatitis, nephritis and myocarditis).

**Treatment**

The first measure is withdrawal of the suspected medication, which usually leads to resolution of symptoms. Symptomatic medication such as antipyretics, when not associated with the eruption, can be used. Antibiotics should only be used when the diagnosis of infection is clear and well documented. Corticosteroids may not be needed due to the self-limited character of the lesions. Other options have been reported for patients with more severe or resistant lesions. The use of cyclosporine, a drug with an inhibitory effect on T cells, and etarnecept, an inhibitor of TNF-alpha receptor, is justified and has been successfully reported in the literature.

**Acrodermatitis Continua of Hallopeau**

Acrodermatitis continua of Hallopeau (ACH) is a chronic, recurrent disease of unknown etiology. The disease is characterized by pustular lesions in the ungal and periungual regions. It is considered by some authors as a variant of psoriasis.

**Clinical manifestations, histopathological aspects and complementary evaluation**

ACH predominates in adult women. Most patients report onset of symptoms after minor trauma or infections.

The acute phase is characterized by recurrent episodes of erythematous lesions with coalescing pustules, often painful. It affects the periungual and...
### Table 2 – Scores for the diagnosis of AGEP (proposed by the EuroSCAR group)

<table>
<thead>
<tr>
<th>Morphology</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td><strong>Pústulas:</strong></td>
<td></td>
</tr>
<tr>
<td>Typical</td>
<td>+2</td>
</tr>
<tr>
<td>Compatible</td>
<td>+1</td>
</tr>
<tr>
<td>Insufficient</td>
<td>0</td>
</tr>
<tr>
<td><strong>Erythema:</strong></td>
<td></td>
</tr>
<tr>
<td>Typical</td>
<td>+2</td>
</tr>
<tr>
<td>Compatible</td>
<td>+1</td>
</tr>
<tr>
<td>Insufficient</td>
<td>0</td>
</tr>
<tr>
<td><strong>Distribution:</strong></td>
<td></td>
</tr>
<tr>
<td>Typical</td>
<td>+2</td>
</tr>
<tr>
<td>Compatible</td>
<td>+1</td>
</tr>
<tr>
<td>Insufficient</td>
<td>0</td>
</tr>
<tr>
<td><strong>Post-pustular desquamation:</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>+1</td>
</tr>
<tr>
<td>No/insufficient</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td><strong>Course</strong></td>
</tr>
<tr>
<td>Mucosal involvement:</td>
</tr>
<tr>
<td>Acute onset (&lt;10 days):</td>
</tr>
<tr>
<td>Resolution &lt;= 15 days:</td>
</tr>
<tr>
<td>Fever &gt;= 38 C:</td>
</tr>
<tr>
<td>PMN &gt; 7,000/mm³</td>
</tr>
</tbody>
</table>

| **Histopathology**        |
| Other diseases            | -10   |
| Not significant / no anatomopathological examination | 0 |
| Polymorphonuclear cell exocytosis | +1 |
| No subcorneal and/or intraepidermal spongiosis or unspecified, pustule(s) with papilledema or subcorneal and/or intraepidermal spongiosis or unspecified, pustule(s) without papilledema | +2 |
| Subcorneal and/or intraepidermal spongiform pustules with papilledema | +3 |

Interpretation (score):
0: not AGEP;
1-4: AGEP is possible;
5-7: AGEP is probable;
8-12: AGEP is established.

* Typical: typical morphology.
** Compatible: morphology is not typical, but strongly suggestive.
*** Insufficient: lesions cannot be evaluated (due to advanced stage of development).

Adapted source: Sideroff et al. 33
subungual regions and, occasionally, the dorsal region of the fingers. It begins in the distal phalanges, and proximal dissemination may occur. In most cases (80%), it involves only one of the ankles and, more frequently, the first finger of the hand.

Anatomopathological examination reveals, at this stage, superficial dermal lymphohistiocytic infiltrate with few neutrophils, surrounding moderately dilated vessels and some extravasated erythrocytes. There is mild epidermal hyperplasia and pustules with spongiform neutrophils below the nail plate.

The chronic phase is characterized by erythema and desquamation of the periungual region and hemorrhage of the nail bed (Figure 2). With recurrence of pustular lesions, onycholysis, onychodystrophy and anonychia may occur. In addition, sclerosis of adjacent soft tissue and osteolysis have also been described.

In the chronic phase, anatomopathological examination reveals edema of the papillary dermis with superficial infiltration of lymphocytes, histiocytes, and neutrophils surrounding tortuous and dilated vessels and erythrocyte extravasation. The epithelium of the nail bed shows psoriasiform hyperplasia, parakeratotic hyperkeratosis, spongiform-like pustules with neutrophils. Foci of hemorrhage with hemosiderin and erythrocytes are also seen in the nail bed.

There are no characteristic findings in laboratory tests. Mycological and bacteriological tests are negative. Radiographs may show osteolysis of the ankles.

**Differential Diagnosis**

Differential diagnosis should be done with paronychia (bacterial and fungal), pustular dyshidrotic eczema, contact dermatitis with secondary infection, psoriasis and atopic dermatitis.

The following are among the characteristics that distinguish ACH from psoriasis: pain in the lesions, local trauma as a triggering factor, nearly exclusive involvement of the distal extremity (no psoriatic lesions in other sites, central palmar-plantar region spared), early involvement of the nail apparatus, which may result in loss of the nail plate, bone involvement that may result in mutilation, absence of family history, lack of association with HLA-B13, B17 and BW37 and little response to commonly used drugs to treat psoriasis.

**Treatment**

ACH is a difficult disease to treat. In general, treatment is not satisfactory. In a case series, 20 patients were monitored for 5 years and none showed complete remission of symptoms.

There are several case reports or case series using different medication; however, due to the rarity of the disease, there are no randomized clinical trials to evaluate therapeutic options.

The therapeutic options reported in the literature are listed in Table 4.

**Palmoplantar Pustulosis**

Palmoplantar pustulosis (PPP) is a disease characterized by the presence of sterile pustules in the stratum corneum of palms and soles. In general, the disease is persistent and painful, causing the functional impairment of patients. Because PPP shares some common features with pustular psoriasis, some authors consider it a localized form of this disease.

Its conclusive pathogenesis is still unknown, but it is believed to be multifactorial.

A higher prevalence of HLA-B8 in Caucasian patients and HLA-DR9 in Japanese patients was found.

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**Table 3: Differences between AGEP and pustular psoriasis**

<table>
<thead>
<tr>
<th>AGEP</th>
<th>Pustular Psoriasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of psoriasis</td>
<td>Most patients</td>
</tr>
<tr>
<td>Distribution of lesions</td>
<td>Generalized</td>
</tr>
<tr>
<td>Duration of the pustules</td>
<td>Longer</td>
</tr>
<tr>
<td>Duration of fever</td>
<td>Longer</td>
</tr>
<tr>
<td>Recent use of medication</td>
<td>Rare</td>
</tr>
<tr>
<td>Histopathology</td>
<td>Subcorneal or intraepidermal pustules, acanthosis and papillomatosis</td>
</tr>
<tr>
<td></td>
<td>necrosis of keratinocytes</td>
</tr>
</tbody>
</table>

Fonte adaptada: Sideroff et al.
Presence of HLA-DR9 is associated with tumor necrosis factor beta gene polymorphism, with a higher frequency of type 2 allele in patients with PPP. No association with the TNFA gene was found. Variations in the genes that determine interleukin 19 (IL-19) subfamily of cytokines could influence susceptibility to palmoplantar pustulosis.

Smoking is considered a triggering and aggravating factor of PPP. The onset of symptoms is significantly associated with smoking and prevalence in PPP patients can reach 95%. Therefore, the onset of the disease is strongly related to this habit. The risk of developing the disease for women who smoke is 74 times higher than for those nonsmokers.

Similar data were found in a study conducted in Sao Paulo State. Sudoresis and the glandular apparatus appear to play an important role in the pathogenesis of PPP. Some studies have shown the presence of an abnormal portion of the acrosyringium in the epidermis of patients with PPP, suggesting its participation in the etiopathogenic process of pustule formation. Furthermore, nicotinic receptors expression is altered in the epidermis of patients with PPP, and nicotine would lead to an inflammatory response with altered expression of acetylcholinesterase (acetylcholine degrading enzyme), resulting in lesions of PPP. The triggering mechanism of inflammation is unknown.

Contactants may play a role in the etiopathogenesis of PPP, although the prevalence of positive patch tests varies. The allergens found include fragrances (mixed fragrance, cinnamic aldehyde and balsam of Peru) and various metals (nickel, copper, chromium, aluminum, gold, iron, silver and zinc).

Presence of focal infections is also considered as a triggering factor of PPP. Tonsillitis, periodontitis and infection by Helicobacter pylori are among the infections associated with PPP. Tonsillectomy and eradication of Helicobacter pylori lead to improvement of the dermatosis and osteo-articular symptoms, if present.

The mechanism involved in the stimulation of cutaneous lesions in chronic infections is unknown. Studies evaluate the participation of T lymphocytes (CD4 and CD28), antigens (cutaneous lymphocyte-associated antigen - CLA) and proteins (heat shock proteins) that would lead to the formation of cytokines (interleukin 6 and 8, C5a, platelet activating factor, interferon gamma and tumor necrosis factor alpha), which would be responsible for the chemotaxis of neutrophils, pustule formation and development of skin lesions.

Another triggering factor reported is the use of monoclonal antibody therapy against tumor necrosis factor alpha (infliximab), used to treat diseases such as rheumatoid arthritis, ankylosing spondylitis, Crohn’s disease, psoriatic arthritis, and even plaque psoriasis. The mechanism involved in this clinical deterioration remains unknown.

**Clinical manifestations, histopathological aspects and complementary evaluation**

PPP is a relatively rare disease; its prevalence is 0.01 to 0.05%. It is more common in women aged 30 to 50 years. It is more common in places with hot and humid climate. The prevalence of patients with PPP and classic psoriasis is about 10%.

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**TABLE 4:** Treatment Options for ACH

<table>
<thead>
<tr>
<th>Topical Treatment</th>
<th>Systemic Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcipotriol</td>
<td>Colchicine</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Dithranol</td>
<td>Cyclosporin A</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>Dapsone</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Infliximab</td>
</tr>
<tr>
<td>Tar</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>8-methoxypsoralen + narrow-band UVB</td>
<td>Nimesulide</td>
</tr>
<tr>
<td>PUVA</td>
<td>Retinoids</td>
</tr>
<tr>
<td></td>
<td>(Acitretin, etretinate)</td>
</tr>
<tr>
<td>Sulfones</td>
<td>Tetracyclines</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Efalizumab</td>
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<tr>
<td>Adalimumab</td>
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</tbody>
</table>

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**FIGURE 2:** Acrodermatitis continua of Hallopeau. Chronic phase with predominance of desquamation.
Lesions are characterized by the presence of sterile pustules in the palmoplantar region, over apparently normal skin or skin with erythema and desquamation (Figure 3). Sometimes there may be small erythematous scaling lesions on the legs, but dissemination to the dorsum of the hands and feet is rare. There may be 69 koebnerization in the palmoplantar region and in other locations. 70 Over time, pustules become brownish-yellow. 52 Pruritus is not always present. 60,65

The nails may be affected in one third of patients. 62 Subungual pustules, onycholysis, pitting and destruction of the nail plate may occur. Unlike lesions of psoriasis, those of PPP do not alter nail growth. 62

Symptoms may worsen in humid weather and in times of stress. 60,65 Patients with PPP experience more stress on a physiological (related to autonomic nervous system response) and cognitive level. 83 This finding may be associated with the course of the disease and these patients’ quality of life, suggesting the need to investigate these factors. 85

Osteoarticular symptoms were observed in 9.4% of the patients with PPP. This association is a clinical form of SAPHO (Synovitis, Acne, Pustulosis, Hyperostosis, and Osteitis), 84 a disease that includes other skin disorders such as acne conglobata, pustular psoriasis, Behçet disease, pyoderma gangrenosum and Sweet’s syndrome.

PPP usually affects the costosternoclavicular region (manubriosternal, clavicular and costosternal) and there may be pain, edema and radiological alterations such as abnormal ossification, hypertrophic-like osteomyelitis and erosive or sclerotic changes in the manubrioclavicular articulation. 85 The clinical course of the joint disease is usually chronic with periods of remission. 86 Skin manifestations can be found concurrently with joint disease, but they may be observed before or after the onset of joint disease symptoms. 60 The absence of cutaneous manifestations does not exclude the diagnosis of SAPHO. A higher frequency of HLA-DR9 in patients with osteoarthritis and PPP was identified. Some authors consider that SAPHO syndrome belongs to the group of seronegative spondyloarthropathies. 87

Histology shows intraepidermal pustule with polymorphonuclear cells at the periphery, and spongiform alterations. 41 There is evidence of the presence of mastocytosis with eosinophilia underneath the pustules; however, neutrophils and eosinophils are found inside the pustules. 60,71

Factors already established as potential triggers of palmoplantar pustulosis, such as infectious or allergic processes, should be appropriately investigated and treated. 72

Moreover, there is evidence that female patients with PPP have lower rates of bone mineral density, thus being at risk for the development of osteoporosis. This seems to be associated not only to the prolonged use of corticosteroids, but also to PPP-specific pathogenic factors. 80

PPP patients have autoimmune thyroid disease more frequently. Therefore, thyroid autoantibodies and T3 and T4 hormones should be monitored. 87

The association with PPP-celiac disease is still poorly defined, and so is antigliadin antibody dosage. 81,84

Some clinical and laboratory findings are different for PPP and psoriasis, which leads some authors to regard them as distinct entities. 87 These differences are as follows:

- None of the alleles at the PSORS1 locus, the main genetic factor associated with psoriasis vulgaris, was associated with the development of palmoplantar pustulosis. 92
- The incidence of HLA B 13, BW 17 or BW 35 is not increased in patients with palmoplantar pustulosis as compared with controls (unlike what happens in psoriasis). 85
- PPP has been associated with tumor necrosis factor B (TNFB) gene polymorphism and psoriasis, with TNFA gene polymorphism. 66
- Involvement of the sternoclavicular articulation is more common in PPP. 87
- Enthesitis are most frequently found in psoriasis 87.
- Erosive-like radiological alterations are more common in psoriasis, while ossification is more commonly found in PPP. 87

**Treatment and evolution**

Treatment is, in general, with short periods of remission. 42 Several treatments have been used for PPP, but none is accepted as truly effective. 93

Despite the small number of patients studied, there seems to be a significant clinical improvement with smoking cessation. 94

Topical corticosteroids, retinoids, phototherapy with psoralen UVA (topical or oral) and cyclosporine in small doses (1 to 2.5 mg / kg / day) are among the treatment options with better results. 95

In patients with concomitant lesions of psoriasis, methotrexate appears to provide some benefit. 95

Lately, biological drugs such as alefacept (blocks activation of T cells and leads to apoptosis of memory T cells) and etanercept (TNF inhibitor) have
been used with good results in the clinical improvement of lesions. 95,96

Infantile Acropustulosis

Infantile acropustulosis (IAP), first described in 1979 simultaneously by Kahn and Rywlin and by Jarret and Ramsdell, is a recurrent, pruriginous vesiculopustular eruption that affects the palms and soles of children in the first years of life. 97-99

The etiopathogenesis of the disease remains unknown. It is assumed that IAP represents a cyclic hypersensitivity skin reaction to antigenic components or antigens associated with prior infection with *Sarcoptes scabiei*. 100

**Clinical manifestations, histopathology, and complementary evaluation**

The disease often starts in the first year of life, but may be present at birth. 101 Early reports showed a prevalence of the disease in black male children. Larger case series have demonstrated an equal distribution among all races and both sexes. 97,102,103

Initial lesions are intensely pruritic papules that after 24-48 hours change into vesicles and pustules 1-4 mm in diameter (Figure 4). It mainly affects the palms and soles, occurring less frequently in the dorsum of hands and feet, trunk and face. Lesions persist for 7 to 14 days with recurrence every 2-4 weeks. 97,101,104

The first few episodes have a higher number of lesions, which decrease in subsequent outbreaks until complete resolution at the end of the second or third year of life. 97,105 Despite being an exclusively cutaneous and self-limited disease, it can cause sleep disturbances, irritability and poor appetite. 97, 98,101

Cytological examination of the pustule shows a large amount of neutrophils and some eosinophils. 98 Histopathology is characterized by intraepidermal vesicles containing neutrophils and occasional eosinophils, focal degeneration of keratinocytes, and in some cases, dermal edema. Direct immunofluorescence of the skin is negative. Occasionally, there is peripheral eosinophilia. 106

In the neonatal period, the differential diagnosis is done with erythema toxicum, transient pustular melanosis, congenital cutaneous candidiasis and staphylococcal pustulosis. Erythema toxicum and transient neonatal pustular melanosis have short duration and are asymptomatic. Negative potassium hydroxide smear and negative bacterial culture help to distinguish between congenital cutaneous candidiasis and staphylococcal pustulosis, respectively. 98,101,102

Dyshydrosis mainly affects adults and older children. Lesions predominate on the sides of fingers and subcorneal pustule is not seen on histopathology. 98 Pustular psoriasis has a later onset and prolonged course. 101 Impetigo has larger pustules and bacterial culture identifies the causative agent 98

Scabies is a disease in which differentiation with IAP is more difficult because it is located on the palms and soles, is intensely pruriginous and rapidly becomes pustular. 102 Lesion scraping is important to rule out active infection. 98

**Treatment**

The use of medium to high potency topical corticosteroids has shown beneficial results in disease control. 99,100

Oral antihistamines, when administered at high doses, can relieve the pruritus, suggesting that

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**FIGURE 3:** Palmoplantar pustulosis. Confluent pustules, erythema and palmar desquamation

**FIGURE 4:** Infantile Acropustulosis. Plantar pustules
sedation may be important for effectiveness. Macrolide antibiotics (erythromycin 40mg/kg/dia) can be used due to their antiinflammatory effects.

Dapsone (1 to 2 mg / kg / day) is used to treat severe and resistant cases because of its potential adverse effects.

Pustular Bacterid (Andrews’ disease)
It is a dermatosis described by Andrews in 1935. It is characterized by the onset of acute, symmetric vesicular or pustular lesions on the palms and soles, with small bleeding points in between the pustules. It usually begins in the medial regions and may spread to flexor regions of the hands and feet. Differently from tinea nigra plantaris, the interdigital spaces are spared. In general, skin manifestations are associated with a focus of infection (in the oropharynx). Skin symptoms resolve with treatment of the focus of infection. There are reports of the association of the this disease with serious episodes of arthritis.

In periods of acute exacerbation, there may be leukocytosis with polymorphonuclear cell predominance. Some authors contest the individuality of pustular bacterid. Thus, this skin disease is oftentimes viewed as palmoplantar pustulosis.

Eosinophilic pustular folliculitis
Eosinophilic pustular folliculitis (EPF), originally described by Ofuji in 1965, is a pruriginous skin eruption characterized by follicular papules or pustules, predominantly located on the face, neck and thorax. The three variants of EPF include classic EPF, immunosuppression-associated EPF and infancy-associated EPF.

Etiopathogenesis
The etiology and exact pathogenesis of EPF remain unknown. Even if the expression of adhesion molecules and production of cytokines and chemotactic factors are evidence of activation of the sebaceous follicular unit, the stimulus that triggers these changes is still unclear. Factors that appear to induce EPF include hypersensitivity reactions, mites, fungal infections, abnormal function of eosinophils or T lymphocytes, immune dysfunction caused by human immunodeficiency virus (HIV) and reconstitution of immune function in treated HIV patients. In this form of immunosuppression, abnormal TH2 immune response to a follicular antigen may be related to the pathogenesis of the disease.

Clinical manifestations, histopathology, and complementary evaluation

Classic variant:
Identified mainly in Japan, with a peak incidence between the third and fourth decades of life. The rate of onset men: women is about 5: 1.

It is clinically characterized by sterile papulopustular lesions, 1 to 2 mm in diameter, follicular, pruriginous, chronic and recurrent, with centrifugal extension and central clearing (Figure 5). They last 7-10 days, with recurrence every 3 to 4 weeks. They affect mainly the face and trunk. The disease may less frequently affect the extremities, palms and soles.

Immunosuppression-associated variant:
It is the most common variant, being associated in most cases to HIV infection. It occurs in individuals with late-stage infection and/or with CD4 count below 250-300 cells / m³.

Other forms of immunosuppression include immune dysfunction, lymphoma, leukemia, blood disorders and bone marrow transplantation.

It is clinically different from the classic variant, with papular, erythematous, and urticarial lesions, larger in diameter and intensely pruritic. They are mostly located in the trunk, the head and neck and proximal extremities.

Infancy-associated variant:
Onset occurs between 2 and 10 months of life. It presents with papulopustular lesions similar to those found in the classic variant. However, they are almost exclusively seen in the scalp without the characteristic annular pattern.

More than one disease has been described as infancy-associated EPF. It is questioned whether this form of folliculitis may be regarded as a distinct inflammatory skin disease.

In addition to the three clinical variants, there

![Figure 5: Eosinophilic Folliculitis. Erythematous papules on the forearm](image-url)
are cases of EPF associated with the following conditions: tissue filling with silicone, pregnancy, infection with hepatitis C virus and use of medication (carbamazepine, minocycline, allopurinol, timipidium bromide). Histopathology of EPF is characterized by an inflammatory infiltrate of lymphocytes and eosinophils in the follicular isthmus. Complete destruction of the follicle rarely occurs. In patients with EPF related to HIV infection, immunophenotypic studies show a predominance of CD8+ T lymphocytes. 113,125

Laboratory findings include mild to moderate leukocytosis in the classic form. In HIV seropositive individuals, lymphopenia occurs with CD4 cell count below 250-300 cells/mm³. Relative or absolute eosinophilia may occur in all individuals, as well as elevation of serum immunoglobulin E levels. 113,116,123

A summary of the main characteristics of the three variants of EPF is provided in (Table 5): 112,119

### Treatment

The unclear etiopathogenesis of EPF is confirmed by the different treatments suggested. Many options have been used with varying results. Furthermore, the effectiveness of certain therapies depends on the clinical variant. 113,116,120,124

The use of topical corticosteroids is usually the first choice treatment for all forms of EPF with a satisfactory response in adults and children. 113 Occasionally, oral corticosteroids may be used. When using this medication, adverse effects of prolonged use should be considered, especially in immunocompromised patients. 113,116

In the classic form, indomethacin tends to be the oral treatment of choice, although recurrences are frequent. Topical tacrolimus and pimecrolimus 111,116,125 have also been effective in treating this variant. 106,107 In resistant cases, cyclosporine and interferon gamma are therapeutic options. 116,125

Antihistamines, phototherapy and systemic isotretinoin are treatment options for the classic and HIV-associated variants. With regard to antihistamines, cyproheptadine and cetirizine appear to be more effective, the latter being preferred due to its anti-eosinophilic property. 111,113,121 The benefit of isotretinoin may be related to the inhibition of eosinophil chemotactic factors present in sebaceous gland lipids and the stratum corneum of patients with EPF. 111,125 Phototherapy with UVB and narrowband UVB has been effective in some case series and case reports. PUVA (psoralen + UVA) has been less used due to higher risk of adverse effects. 111,120 Other therapeutic options that have varying results include minocycline, doxycycline, trimethoprim/sulfamethoxazole, erythromycin, dapsone, colchicine and clofazimine. 111,113

In HIV-infected patients, other treatments described in case series and case reports include itraconazole, metronidazole and topical permethrin. 111,121 Regarding the effects of antiretroviral therapy on EPF, publications have suggested that this treatment may be beneficial due to restoration of TH1 immune response. 113,116,127 There are reports of development of EPF 2-6 months after initiation of antiretroviral therapy, due to immune reconstitution syndrome. 116,127

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<th>TABLE 5: General characteristics of EPF</th>
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EPF has a tendency to relapse or become chronic, although remission may occur in some cases.\textsuperscript{116}

**Neutrophilic dermatoses in children**

Neutrophilic dermatoses are very rare in children. They share clinical features and comorbidities associated with adult patients. Therefore, some particularities of dermatoses discussed in the previous article and neutrophilic dermatoses in childhood will be highlighted.

**Sweet’s syndrome (SS):**

The disease shows clinical and pathological findings similar to those found in adulthood.\textsuperscript{118}

In a review of literature cases from 2003, only 64 cases of children with SS were found. Of these, 21% had no associated diseases, 22% had transient illnesses such as infections (especially respiratory infections), 33% had inflammatory diseases (autoimmune diseases, immunodeficiencies) and 25% presented neoplastic diseases (leukemia, Fanconi anemia and myelodysplastic syndrome).\textsuperscript{129}

**Pyoderma Gangrenosum**

Pyoderma Gangrenosum (PG) in children shows clinical features similar to those observed in adults. It mainly affects the lower limbs; however, the frequency of PG in the head and neck is higher in pediatric patients.\textsuperscript{130} History of trauma preceding the onset of lesions is common.\textsuperscript{6} Patients younger than 2 years have a higher frequency of genital and perianal lesions.\textsuperscript{130,131} At this age the diseases most commonly associated with PG (ulcerative colitis, Crohn’s disease and myeloproliferative disorders) are not found.\textsuperscript{131}

**Behcet’s disease (BD)**

Behcet’s disease is a rare dermatosis in children. The clinical spectrum of BD in children is similar to that found in adult patients.\textsuperscript{132,133} However, children have a lower incidence of genital ulcers and vascular thrombosis and increased incidence of nonspecific gastrointestinal symptoms, neurological symptoms and arthralgia.\textsuperscript{134} The disease in children is less severe than in adults and the frequency of familial cases is higher.\textsuperscript{132,135}

**Palmoplantar eccrine hidradenitis**

It is also called neutrophilic eccrine hidradenitis. There are three variants of the disease: classic variant (associated with neoplasms and chemotherapy), a variant associated with pseudomonas infections and an idiopathic pediatric variant.\textsuperscript{128}

It is characterized by the presence of painful erythematous nodules and plaques, of abrupt onset, primarily in palmoplantar regions. Lesions develop after physical activity; hyperhidrosis appears to be a predisposing factor. Patients are usually healthy, there is no fever and no use of medication prior to the onset of symptoms. Normal physical examination, laboratory tests without alterations.\textsuperscript{128,134}

The main histological finding is the presence of neutrophilic infiltrate around and in the eccrine glands.

Clinical manifestations are self-limited, regressing in a few days. Bed rest and gradual return to activities are suggested by some authors.\textsuperscript{134}

**Chronic Recurrent Multifocal Osteomyelitis (CRMO)**

The description of the clinical manifestations of sterile osteomyelitis, also known as chronic recurrent multifocal osteomyelitis, associated with neutrophilic dermatosis in children, has become more frequent in the literature.\textsuperscript{135}

CRMO is a disease almost exclusive to pediatric patients. The presentation of the disease is insidious, with periods of remission and exacerbation of pain and edema in the affected bones. It most commonly involves the metaphyses of long bones. Among the abnormalities found in laboratory tests are slightly increased erythrocyte sedimentation rate and, sometimes, mild leukocytosis. X-ray shows lytic lesions with progressive sclerosis. Bone biopsy shows initial prevalence of neutrophils and cultures are negative.\textsuperscript{86,135}

Some authors consider that CRMO is the manifestation of pediatric SAPHO syndrome, but controversy whether these diseases are part of the same spectrum remains\textsuperscript{86,135}.\textsuperscript{\textcircled{}}
Neutrophilic dermatoses - Part II

REFERENCES


1. What is her diagnosis?
   a) pustular psoriasis
   b) dermatitis herpetiformis
   c) subcorneal pustular dermatosis
   d) generalized exanthematous pustulosis

2. We can state the following about this dermatosis:
   a) Its pathophysiology has been fully elucidated and involves neutrophil chemotactic factors such as tumor necrosis factor.
   b) The disease is more common in children.
   c) There is no report of illnesses associated with the development of this disease, so there is no need for patient follow-up.
   d) Dapsone is the drug of choice in early treatment.

3. It is correct to state the following about dermatitis cruris pustulosa et atrophicans:
   a) It is a common dermatosis in tropical countries in Asia and Africa.
   b) Its clinical manifestations are characterized by folliculitis-like lesions, especially in the lower limbs.
   c) Among the possible etiological factors are the presence of S. aureus, the use of occlusive agents and immunological factors such as hypergammaglobulinemia.
   d) All of the above.

4. It is assumed that medication is the main triggering factor of AGEP. We can state the following about the causative agents:
   a) The main drugs involved in the development of AGEP are anti-epileptic drugs.
   b) It appears that the time between administration of medication and the development of lesions is shorter for antibiotics.
   c) The agents involved in the development of toxic epidermal necrolysis are the same as those involved in the onset of AGEP.
   d) None of the above.

5. On complementary investigation of AGEP:
   a) Complete blood count always shows alterations, especially lymphopenia.
   b) Liver function may be slightly altered.
   c) The patch test may help confirm the measurement involved, even after resolution of lesions.
   d) Alternatives B and C are correct.

6. The following are not among the differential diagnosis of AGEP:
   a) psoriasis vulgaris
   b) drug hypersensitivity syndrome (DRESS)
   c) Sneddon-Wilkinson disease
   d) bacterial Folliculitis

7. We cannot state the following about the evolution and treatment of AGEP:
   a) Complete blood count always shows alterations, especially lymphopenia.
   b) Liver function may be slightly altered.
   c) The patch test may help confirm the measurement involved, even after resolution of lesions.
   d) Alternatives B and C are correct.

8. We can state the following about Acrodermatitis Continua of Hallopeau (ACH):
   a) Its main clinical feature is the development of pustular lesions in the sub and peri-ungual regions. In most cases the symptoms may appear after trauma or infection.
   b) Elderly patients may present a more severe course of the disease.
   c) Treatment is usually unsatisfactory
   d) All of the above.

9. Which of the following characteristics is true regarding the differences between acrodermatitis continua of Hallopeau and psoriasis?
   a) In both diseases lesions are not exclusive to the distal extremity.
   b) Acrodermatitis continua of Hallopeau responds quickly to treatments for psoriasis.
   c) Acrodermatitis continua of Hallopeau was not associated with HLA-B13,-B17 and BW37.
   d) There is no loss of the nail apparatus in psoriasis nor in ACH.

10. Several factors have been implicated or recognized in the pathogenesis of palmoplantar pustulosis (PPP). The following is included among these factors:
    a) Smoking
    b) Nickel
    c) Biological therapies
    d) All of the above
11. Which of the following diseases is not associated with PPP?
   a) Crohn's Disease
   b) Hashimoto's disease
   c) Osteoporosis
   d) Celiac Disease

12. Which of the following statements is incorrect about palmo-plantar pustulosis:
   a) PPP can show Koebner phenomenon.
   b) As in psoriasis, presence of tumor necrosis factor alpha gene polymorphism has been identified.
   c) There is no association between alleles at the PSORS1 locus and the development of palmoplantar pustulosis.
   d) Smoking cessation is one of the therapeutic measures in PPP.

13. We can state the following about osteoarticular involvement in PPP:
   a) The most common involvement is that of the sternocostoclavicular region.
   b) As in psoriasis, the involvement is usually polyarticular.
   c) The most common radiologic alteration in PPP is ossification.
   d) A and C are correct.

14. It is correct to state the following about neutrophilic dermatoses in children:
   a) The clinical presentation of lesions is usually different in children and adults.
   b) The site of lesions of pyoderma gangrenosum does not differ for children younger and older than 2 years.
   c) Children with Behcet's disease most often present with gastrointestinal and neurological symptoms and arthralgia, as compared with skin lesions.
   d) Sweet's syndrome in children is usually not associated with other systemic diseases.

15. The following are features of chronic recurrent multifocal osteomyelitis:
   a) Patients present with pain and edema in the bones affected, especially long bone metaphyses.
   b) Clinical manifestations correspond to non-sterile osteomyelitis associated with neutrophilic dermatoses.
   c) X-ray of the affected bones does not show significant changes.
   d) ESR is usually very high.

16. Choose the correct alternative in relation to infantile acropustulosis:
   a) The etiopathogenesis appears not to be related to prior infection with sarcoptes scabiei
   b) It often occurs in the first years of life, but may be present at birth
   c) It is more common in male children
   d) Cytological examination of the pustule shows a large amount of lymphocytes and some eosinophils

17. It is correct to state the following in relation to the treatment of infantile acropustulosis:
   a) Only low-potency topical corticosteroids are used
   b) Antihistamines, even at high doses, do not relieve the pruritus
   c) Macrolides can be used due to their anti-inflammatory effects
   d) Dapsone is considered a drug of first choice

18. Eosinophilic pustular folliculitis is characterized by:
   a) presence of non-pruriginous papular or pustular follicular lesions
   b) predominant involvement of limbs
   c) having a defined pathogenesis
   d) three clinical variants: classic, immunosuppression-associated, and infancy-associated.

19. Choose the correct alternative in relation to eosinophilic pustular folliculitis:
   a) the classic variant affects predominantly women
   b) The HIV-associated variant is less frequent
   c) the infancy-associated variant mainly affects the scalp
   d) Drugs are not involved in the onset of the disease

20. It is correct to state the following about eosinophilic pustular folliculitis:
   a) topical corticosteroids are usually the first choice treatment in all clinical forms
   b) isotretinoin is not used in any clinical variant
   c) loratadine is the most effective antihistamine
   d) phototherapy with narrowband UVB appears to be effective

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**Answers**

Neutrophilic dermatoses – Part II

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**Papers**

Information for all members: The EMC-D questionnaire is now available at the homepage of the Brazilian Annals of Dermatology: www.anaisdedermatologia.org.br. The deadline for completing the questionnaire is 60 days from the date of online publication.