Paediatric Dermatology Column: Review Article

Neutrophilic dermatoses and the concept of autoinflammation from a paediatric perspective

從兒科角度解讀嗜中性白血球增多性皮膚病及其自身炎症的概念

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Neutrophilic dermatoses have primarily been classified based on their histological appearance and many have overlapping associations with systemic diseases. This article provides a brief overview of the two most common neutrophilic dermatoses, Sweet's syndrome and pyoderma gangrenosum. The clinical presentation, systemic associations, histology, treatment and the occurrence in the paediatric population of these entities are discussed. A clear understanding of the pathogenesis of these conditions remains elusive. The concept of autoinflammation is introduced, and how further investigation and knowledge of the pathways of the innate immune system may lead to the potential reclassification of neutrophilic dermatoses and more targeted treatment is discussed.

Keywords: Inflammasome, paediatric, pyoderma gangrenosum, Sweet's syndrome

關鍵詞: 炎性體、兒科、壞疽性膿皮病、史維特症候群

Introduction

Neutrophilic dermatoses (NDs), conditions whereby there is an inflammatory infiltrate of mature polymorphonuclear neutrophils in the skin and mucosa, have primarily been classified based on their histological appearance. Many have overlapping associations with systemic diseases. However, a clear understanding of the pathogenesis and the development of targeted treatments for these conditions remain elusive. This article provides a brief
overview of the two most common NDs, Sweet's syndrome and pyoderma gangrenosum, focusing on the paediatric population. It also discusses the concept of autoinflammation for the potential reclassification of NDs.

Sweet's syndrome

**Clinical presentation**
Sweet's syndrome (SS), also known as acute febrile neutrophilic dermatosis, was first described in 1964 as episodic, painful, erythematous plaques with associated fever and leucocytosis. Clinical presentation may also include arthralgia, headache, nausea and vomiting. The typical lesions are well defined erythematous plaques with a mammillated surface due to extensive dermal oedema. They may express pathergy and there is typically no ulceration, although pseudo-vesiculation or pustules may be present. The natural course for untreated lesions is resolution within 6-8 weeks, without scarring. However, new lesions may continue to occur. The limbs, neck and face are frequently affected in an asymmetrical pattern. It tends to present from the ages of 30-60 and is four times more common in women. Presentation is often preceded by symptoms consistent with a viral upper respiratory tract infection. Blood tests tend to show a leucocytosis with elevated neutrophils and raised inflammatory markers.

**Systemic associations**
Sweet's syndrome is frequently associated with underlying systemic disorders and diseases, such as connective tissue disorders, malignancies (especially myeloproliferative disorders such as acute myeloid leukaemia), medications, infections (predominantly upper respiratory and gastrointestinal), inflammatory bowel disease, thyroiditis and pregnancy. Case reports have also linked SS to HIV, chronic granulomatous disease and Takayasu's arteritis. The increasingly reported association with vasculitis is particularly notable, questioning the separation drawn in the past between Sweet's syndrome and vasculitis. Medications documented to have caused SS include granulocyte colony-stimulating factor, minocycline, nitrofurantoin, trimethoprim-sulphamethoxazole, carbamazepine, hydralazine and retinoids.

**Histology**
Lesions of SS are characterised by massive neutrophilic invasion of the dermis. There is typically no vessel wall destruction. However, some vasculitis may be seen, which has historically been considered as secondary to the release of inflammatory mediators from surrounding neutrophils, rather than as a primary disease process. The inflammatory cells tend to be found in the papillary and upper reticular dermis.

**In the paediatric population**
Approximately 5-8% of patients with SS are children, and unlike in the adult population, no gender bias is seen. In contrast to adult SS, paediatric SS is more likely to be associated with an infection, and less likely to be associated with malignancy. Associated vasculitis has been reported in several recent reports. It has been suggested that the malignancy workup in children need not be as comprehensive, and should include a full blood count and peripheral smear, with consideration for a bone marrow biopsy if there is persistent anaemia, leucocytosis or thrombocytopenia. Paediatric SS has been reported to be less likely to respond to first-line treatment.

**Treatment**
Treatment for SS usually consists of 1) treating the underlying cause and 2) treatment of the cutaneous manifestations with oral corticosteroids 0.5-1.5 mg/kg/day for 10 days, followed by gradual taper over 4-6 weeks. SS typically responds rapidly to corticosteroid therapy, but approximately one in three patients with classical SS experience a
Second-line treatments have included dapsone, colchicine, potassium iodide, indomethacin, methotrexate, clofazimine, isotretinoin, doxycycline, metronidazole, anti-TNF agents and chlorambucil. Recurrence. Second-line treatments have included dapsone, colchicine, potassium iodide, indomethacin, methotrexate, clofazimine, isotretinoin, doxycycline, metronidazole, anti-TNF agents and chlorambucil. Recurrence. Second-line treatments have included dapsone, colchicine, potassium iodide, indomethacin, methotrexate, clofazimine, isotretinoin, doxycycline, metronidazole, anti-TNF agents and chlorambucil.

**Pyoderma gangrenosum**

**Clinical presentation**
The features of pyoderma gangrenosum (PG) were first described in 1908, and this condition named in 1930. The classical form is an inflammatory and neutrophilic disease in which initial maculopapular or pustular lesions rapidly evolve into ulcerative skin lesions with violaceous, well demarcated, undermined borders and a centralised area of necrosis. Scarring occurs upon healing of the lesion and is often defined as cribiform. Skin lesions are associated with pathergy in 30% of patients. There are often multiple lesions and pain is the predominant symptom. Lesions can occur anywhere, in order of prevalence, the lower extremities are the most common followed by the abdomen, arms, chest, buttocks, genitals and face. Extracutaneous manifestations may occur, with the most common areas of involvement being the lungs, joints and digestive tract. There is a slight preponderance for women and the most common age of presentation is 30-60 years. Systemic symptoms may include fever, malaise, arthralgia and myalgia. Four other clinical variants of PG have been described: pustular, which presents as multiple pustules surrounded by an erythematous halo commonly on the trunk and extensor aspects of the limbs; peristomal, which occurs after the formation of a surgical stoma; pyostomatitis vegetans, which is a pustular eruption of the oral mucosa; and atypical or bullous, which involves bullous lesions mostly of the lower limb.

**Systemic associations**
PG is associated with an underlying systemic disease in approximately 50% of cases. More common associations include inflammatory bowel disease, both ulcerative colitis and Crohn’s disease; arthritic disorders such as rheumatoid arthritis and sero-negative arthropathies; and haematological disorders such as myeloproliferative disease, myelodysplasia and leukaemia. Other reported associations include thyroid disease, sarcoidosis, hepatitis C, diabetes mellitus, hydradenitis suppurativa, Behçet’s disease, acne conglobata, systemic lupus erythematosus, HIV infection, solid-organ malignancy and Takayasu’s arteritis. Like SS, ANCA associated vasculitides (granulomatosis with polyangiitis and microscopic polyangiitis) have also been reported in association with PG.

Pustular PG, peristomal PG and pyostomatitis vegetans are most commonly seen in inflammatory bowel disease. Atypical/bullous disease is associated with haematological and malignant diseases. PG is also a component of the autoinflammatory PAPA syndrome (pyogenic arthritis, pyoderma gangrenosum and acne) and the recently described PASH syndrome (pyoderma gangrenosum, acne and suppurative hidradenitis).

**Histology**
Histology for PG is not diagnostic. Initially, there is a diffuse dermal infiltration of neutrophils with follicular involvement. There can be varying degrees of vasculitis, but like Sweet’s syndrome, this has been historically considered as a secondary phenomenon rather than a primary disease process. In more developed lesions, neutrophilic infiltration is more concentrated in the deeper levels of the dermis which may extend to the subcutis and there is often a mixed picture of inflammation and necrosis.

**In the paediatric population**
Pyoderma gangrenosum occurs in children 4-5% of the time. In children, lesions are most commonly found on the head, neck and perineum. Consistent with the process of
pathergy, children may describe a history of a spider bite or trauma. Lesions often begin as pustules in children, whereas in adults they tend to be maculopapular. In children, the most frequently associated condition is ulcerative colitis, quoted as high as 26% in one case series, rather than rheumatoid arthritis which is the most common association in adults. In infants, PG typically responds well to therapy.

**Treatment**

There is no universally accepted treatment for PG. Corticosteroids have been used with greatest effect. Alternative therapies include other systemic immunosuppressants, colchicine, minocycline, clofazamine, thalidomide, nitrogen mustard, pimecrolimus, tacrolimus and intravenous immunoglobulin. Surgical debridement of PG ulcers is contraindicated, due to the common occurrence of pathergy, and for this reason intralesional corticosteroids have also been advised against by some authors.

Schadt and Callan propose local wound care preventing trauma and maintaining a moist environment and topical high potency corticosteroids +/- topical tacrolimus for mild localised disease. If widespread or refractory to this treatment, systemic corticosteroids 0.5-2 mg/kg/day, tapered over 4-6 weeks are recommended. If this fails, other treatments to consider include cyclosporine, mycophenolate mofetil, dapsone, anti-TNF agents, IVIG, chlorambucil and cyclophosphamide. Anti-TNF alpha agents should be particularly considered in those with associated inflammatory bowel disease.

**Histological classification of NDs**

The current classification of neutrophilic dermatoses by histopathologic appearance is based solely on a shared visible endpoint of disease progression that relates, however, to a plethora of seemingly disparate medical conditions. It does not at all explain the pathogenesis (Figure 1). Butler and Shinkai have hypothesised that for these diverse medical conditions to lead to the same phenotype, there are common inflammatory pathways lead to alterations in the recruitment of neutrophils or changes in neutrophil homeostasis.

Considering NDs within the autoinflammatory spectrum is a recent development seeking to explain the pathogenesis. It involves the correlation of NDs with better understood, albeit rare, autoinflammatory syndromes. Critical in-vivo inflammatory pathways are being better identified and clarified in these latter conditions that may shed light on the pathogenesis of the more common neutrophilic dermatoses and aid in the development of more targeted treatments for NDs.

**The concept of autoinflammation**

The term 'autoinflammatory' was first coined in 1999. Classically, autoinflammatory diseases (AIDs), also known as periodic fever syndromes, are a group of rare hereditary inflammatory disorders which are unprovoked and occur in the absence of infection. Tissue inflammation and damage results from the chronic activation of the innate immune system. Unlike autoimmune conditions, the adaptive immune system is not involved and patients with an AID do not have auto-antibodies or auto-reactive antigen-specific T cells. Initially, conditions regarded as autoinflammatory were clearly familial, monogenetic and characterised by recurrent fever. However the spectrum of autoinflammation is now considered to encompass other diseases considered polygenic or acquired that share similar clinical features. There may be triggers for these conditions such as physical trauma in PAPA syndrome, and also cross-talk between the innate and adaptive immune system. To address these developments, Kastner et al have put forward a new definition for AIDs: 'clinical disorders marked by abnormally increased inflammation, mediated predominantly by the cells and molecules of the innate immune system, with a significant host predisposition.'
The innate immune system is the host’s primary defence mechanism. It detects pathogens and foreign molecules and then responds with an inflammatory process to restrict their dispersion and assist in the activation of the adaptive immune system. Cells involved in innate immunity are phagocytes including macrophages, dendritic cells and other antigen presenting cells. These cells recognise pathogen associated molecular patterns (PAMPs) or damaged cell associated molecular patterns (DAMPs) via pattern recognition receptors (PRR), which include Toll-like receptors (TLR), nucleotide-binding oligomerisation domain (NOD)-like receptors (NLR) and retinoic-acid-inducible gene-1 (RIG-1)-like receptors (RLR). The activation of these receptors leads to intracellular pathways which result in the expression of inflammatory mediators including interferon alpha, interferon beta, tumour necrosis factor and interleukin 1.

NLR proteins have been implicated in the formation of large protein complexes known as inflammasomes, including NLRP1 and NLRP3 (cryopyrin) inflammasomes. These contribute to the activation of pro-caspase-1, which then cleaves and activates pro-forms of interleukin-1 beta (IL-1β) and interleukin 18 (Figure 2).

AIDs may be monogenic or polygenic disorders, and the genes involved commonly encode for proteins of the inflammasome. Excessive IL-1β has been strongly implicated in a number of inflammasomopathies, including familial Mediterranean fever, Muckle-Wells syndrome (MWS), PAPA syndrome, hyperimmunoglobulinaemia D syndrome (HIDS) and deficiency of the interleukin receptor antagonist (DIRA) syndrome. The molecular categories for AIDs include inflammasomopathies, NF-κB activation disorders, protein misfolding...
disorders, complement disorders, cytokine signalling diseases and macrophage activation syndromes. Monogenic disorders often present clinically in the neonatal period or during early infancy, but may persist into adolescence and early adulthood. Polygenic AIDs tend to present during adolescence. AIDs commonly have cutaneous manifestations (Table 1).

**Conclusion**

Progress in the understanding of AIDs is occurring at a rapid rate and has come a long way in the last decade. The detection of genetic abnormalities and analysis of the molecular mechanisms of these disorders has contributed to our understanding of inflammatory processes, particularly related

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**Figure 2.** NLRP-3 inflammasome mediated activation of IL-1β. (Modified figure based on Kambe N, Satoh T, Nakamura Y, Iwasawa M, Matsue H. Autoinflammatory diseases and the inflammasome: mechanisms of IL-1β activation leading to neutrophil rich skin disorders. Inflamm Regen 2011;31:72-80)
Table 1. Autoinflammatory diseases and their cutaneous manifestations

<table>
<thead>
<tr>
<th>Autoinflammatory disease</th>
<th>Classification based on molecular mechanism(^{36})</th>
<th>Genetic defect(^{36})</th>
<th>Cutaneous manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial Mediterranean fever (FMF)</td>
<td>IL-1β activation disorder (inflammasomopathy)</td>
<td>Monogenic</td>
<td>Patients may display an erysipelas-like erythema on the dorsum of the foot and fingers during febrile episodes. The rash usually lasts less than 72 hours and resolves spontaneously. Histology shows dermal infiltration of neutrophils.(^{33})</td>
</tr>
<tr>
<td>Cryopyrin-associated periodic syndromes (CAPS) (Familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), Neonatal onset multi-system inflammatory disease (NOMID))</td>
<td>IL-1β activation disorder (inflammasomopathy)</td>
<td>Monogenic</td>
<td>Urticarial-like rash with pale red non-pruritic macules of the trunk, lower and upper limbs. Histologically lesions can resemble neutrophilic urticaria, with a perivascular and interstitial neutrophilic infiltrate without vasculitis and dermal oedema.(^{33})</td>
</tr>
<tr>
<td>Pyogenic arthritis</td>
<td>IL-1β activation disorder (inflammasomopathy)</td>
<td>Monogenic</td>
<td>Pyoderma gangrenosum and severe cystic acne, especially in adolescence, are the characteristic cutaneous manifestations.(^{31})</td>
</tr>
<tr>
<td>Pyoderma gangrenosum Acne (PAPA) syndrome</td>
<td>IL-1β activation disorder (inflammasomopathy)</td>
<td>Monogenic</td>
<td>Severe cystic acne and palmoplantar pustulosis are the characteristic cutaneous manifestations.(^{39})</td>
</tr>
<tr>
<td>SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis and osteitis)</td>
<td>IL-1β activation disorder (inflammasomopathy)</td>
<td>Polygenic</td>
<td>Most commonly, patients have a maculopapular rash, small erythematous macules, papules and nodules, vasculitic purpura and petechiae. Histology shows mild vasculitis and cellulitis-like findings.(^{33})</td>
</tr>
<tr>
<td>Hyper-immunoglobulinaemia D syndrome (HIDS)</td>
<td>IL-1β activation disorder (inflammasomopathy)</td>
<td>Monogenic</td>
<td>Patients may have a diffuse pustular rash.(^{35}) Neonatal lupus like lesions have also been described.(^{33})</td>
</tr>
<tr>
<td>Deficiency of the interleukin-1 receptor antagonist (DIRA) syndrome</td>
<td>IL-1β activation disorder (inflammasomopathy)</td>
<td>Monogenic</td>
<td>Patients may have a maculopapular rash, small erythematous macules, papules and nodules, vasculitic purpura and petechiae. Histology shows mild vasculitis and cellulitis-like findings.(^{33})</td>
</tr>
<tr>
<td>TNF receptor-associated periodic syndrome (TRAPS)</td>
<td>Protein folding disorder</td>
<td>Monogenic</td>
<td>Most commonly, patients have a centrifugal migratory, erythematous rash with patches overlying the areas of myalgia. Urticaria-like lesions, serpiginous patches or plaques, purpuric vasculitic-like lesions are less common manifestations. Histology may show a perivascular and interstitial infiltrate of mononuclear cells, small vessel vasculitis and recurrent panniculitis.(^{33})</td>
</tr>
</tbody>
</table>
to the NLRP3-inflammasome-IL-1β cascade, which is now considered the main axis of autoinflammation. Clinical evidence of anti-IL1 therapy, for example anakinra, in the treatment of AIDs is emerging. NDs share many features of these AIDs. For example PG has a chronic remitting course and involves the dysregulation of the innate immune system, including neutrophil migration and excessive cytokine production. A primary pathogenic pathway based on disordered innate immunity could also explain the overlap between NDs and their diverse related systemic diseases, as well as the more recent recognition of their overlap with vasculitis, with which they have been historically separated based on limited and arbitrary histological grounds. The ongoing study of NDs in the context of AIDs, holds promise to potentially critical developments in understanding the molecular and cellular pathways that lead to NDs, which in turn may result in more effective and targeted treatments.

References