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AUTOINFLAMMATORY PUSTULAR NEUTROPHILIC DISEASES

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SYNOPSIS

The inflammatory pustular dermatoses constitute a spectrum of non-infectious conditions ranging from localized involvement to generalized disease with associated acute systemic inflammation and multi-organ involvement. Despite the variability in extent and severity of cutaneous presentation, each of these diseases is characterized by non-infectious neutrophilic intra-epidermal microabscesses. Many share systemic findings including fever, elevated inflammatory markers, inflammatory bowel disease and/or osteoarticular involvement, suggesting potential common pathogenic links (Figure 1). The recent discoveries of several genes responsible for heritable pustular diseases have revealed a distinct link between pustular skin disease and regulation of innate immunity. These genetic advances have led to a deeper exploration of common pathways in pustular skin disease and offer the potential for a new era of biologic therapy which targets these shared pathways.

This chapter provides a new categorization of inflammatory pustular dermatoses in the context of recent genetic and biologic insights. We will discuss recently-described monogenic diseases with pustular phenotypes, including deficiency of IL-1 receptor antagonist (DIRA), deficiency of the IL-36 receptor antagonist (DITRA), CARD14-associated pustular psoriasis (CAMPS), and pyogenic arthritis, pyoderma gangrenosum, acne (PAPA). We will then discuss how these new genetic advancements may inform how we view previously described pustular diseases, including pustular psoriasis and its clinical variants, with a focus on historical classification by clinical phenotype.

Keywords

Pustular psoriasis; Palmoplantar pustulosis; Subcorneal pustular dermatosis; Deficiency of IL-1 receptor antagonist (DIRA); PAPA syndrome; SAPHO syndrome

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DIRA

In 2009, Goldbach-Mansky and colleagues described an autosomal recessive autoinflammatory disorder known as *deficiency of the interleukin-1 (IL-1) receptor antagonist (DIRA)*[1–6]. DIRA is caused by homozygous loss of function mutations in *IL1RN*, the gene encoding the IL-1 receptor antagonist. Mutations lead to unopposed IL-1 signaling and resultant uncontrolled life-threatening systemic inflammation. Heterozygous carriers of loss of function mutations in *IL1RN* appear to be asymptomatic[1–6]. To date, fewer than 20 cases from the United States, Canada, the Netherlands, Brazil and Puerto Rico have been described. First generation mutations in these distinct geographic populations are believed to be founder mutations. The allele frequencies of the founder mutations in Newfoundland and Puerto Rico are estimated at 0.2% and 1.3%, respectively.

DIRA is characterized by perinatal onset pustular dermatitis resembling pustular psoriasis, multifocal aseptic osteomyelitis, periostitis, leukocytosis and elevated acute phase reactants. Affected individuals present between birth and 2.5 weeks of age with fetal distress, pustular rash, joint swelling, oral lesions and pain with movement. Premature birth is sometimes noted. Fever is typically absent. Cutaneous eruptions range from discrete crops of pustules to generalized pustulosis (Figure 2). Ichthyosiform changes can be seen. Nail changes include pitting and onychomadesis. Respiratory insufficiency and thrombotic events have also been reported. Bony changes include epiphyseal ballooning of long bones, anterior rib-end widening, periosteal elevation of long bones, and multifocal osteolytic lesions. Less commonly, widening of the clavicles, metaphyseal erosions and osteolytic skull lesions can be seen[2]. Mortality secondary to multi-organ failure in the setting of severe inflammatory response and pulmonary hemosiderosis with progressive interstitial fibrosis has been reported. Laboratory abnormalities include leukocytosis and marked elevation of serum erythrocyte sedimentation rate and C-reactive protein levels. Cutaneous histopathology is characterized by epidermal acanthosis and hyperkeratosis, extensive neutrophilic infiltration of epidermis and dermis by neutrophils and pustule formation[1].

The differential diagnosis of DIRA includes bacterial osteomyelitis, infantile cortical hyperostosis, infantile pustular psoriasis and chronic recurrent multifocal osteomyelitis (CRMO). Genetic sequencing is required for definitive diagnosis. DIRA can be effectively treated with the IL-1 receptor antagonist anakinra[1, 5, 7], suggesting a potentially important role for IL-1 antagonism in the management of diseases with pustular phenotype. Individuals with less deleterious mutations have also been managed with corticosteroids and acitretin[2]. Given the severity of disease and availability of effective therapy, the key to successful management and reduced morbidity and mortality is early recognition of this condition and early implementation of anti-IL-1 therapy prior to the development of irreversible bony lesions, respiratory disease or other life-threatening events.

DITRA, a monogenic form of pustular psoriasis

Although the majority of pustular psoriasis patients lack a family history of similar disease, a number of familial cases have been reported, leading to a potential insight into common pathways of pustular skin disease[8–15]. In 2011, Marrakchi and colleagues identified inactivating mutations in the IL-36 receptor antagonist (*IL-36RN*) gene in 9 Tunisian families with an autosomal recessive form of generalized pustular psoriasis (GPP)[13]. This disease, known as *deficiency of the IL-36 receptor antagonist (DITRA)*, was also reported in a second group of 5 individuals from the United Kingdom who did not have a family history of GPP[14], as well as in one Japanese adult male[16]. IL-36 is an IL-1 family cytokine that binds to the IL-36 receptor, enabling the recruitment of the IL-1 receptor accessory protein and subsequent signal transduction involving nuclear factor kappa B (NFkB) and mitogen

activated protein (MAP) kinases. The IL-36 receptor antagonist (IL-36RA) is encoded on chromosome 2 and competitively binds the IL-36 receptor, thereby providing negative feedback to IL-36 signaling[13, 14]. Deficiency of IL-36RA leads to an exaggerated inflammatory response, analogous to that resulting from IL-1RA deficiency in patients with DIRA, and further implicates the relevance of these pathways in pustular disease pathogenesis.

DITRA is characterized by sudden-onset, recurrent and severe GPP, high-grade fever, asthenia, neutrophilia and elevated inflammatory markers. While disease onset occurs during childhood in the majority of cases, adult-onset has also been described. Death due to septicemia has been reported in 5 cases[13]. Of note, concomitant psoriasis vulgaris, palmoplantar pustulosis, or psoriatic arthritis have not been reported, supporting the assertion that *IL36RN* mutations are responsible for a specific subtype of GPP. Histopathological studies have shown spongiform pustules, acanthosis with elongation of rete ridges and parakeratosis in the stratum corneum, consistent with histopathology of pustular psoriasis[13]. The differential diagnosis of DITRA includes generalized pustular psoriasis and acute generalized exanthematous pustulosis (AGEP). Acitretin, topical and oral steroids, adalimumab and phototherapy have been used with varying degrees of success in patients with DITRA[13].

CAMPS

De novo mutations in *caspase recruitment domain family member 14* (*CARD14*) have also been described in a monogenic form of childhood GPP called *CARD14-mediated pustular psoriasis (CAMPS)*[9, 10]. *CARD14* mutations have also been previously implicated in plaque-type psoriasis and pityriasis rubra pilaris (PRP)[9, 10, 17]. CARD14 activates NFkB. Activating missense mutations in *CARD14* upregulate NFkB, subsequently increasing the transcription of psoriasis-associated chemokines and cytokines, including IL-8, CCL20 and IL-36[10].

CAMPS is characterized by childhood-onset generalized pustulosis, fevers, palmoplantar keratoderma and nail pitting. Psoriatic arthritis has not been described in CAMPS, although it has been reported in CARD14-associated plaque psoriasis and PRP[9, 10]. Poor response to methotrexate, cyclosporine, infliximab and anakinra have been reported, however, one case of CAMPS has been successfully managed with IL-12/23 antagonist ustekinumab[18].

PAPA SYNDROME

The syndrome of *pyogenic arthritis, pyoderma gangrenosum and acne (PAPA)* was coined by Lindor and colleagues in 1997[19], although it was first described in 1975 in a patient with "streaking leukocyte factor"[20]. This rare autosomal dominant autoinflammatory syndrome is caused by mutations in the gene encoding CD2-binding protein 1, also known as *p*roline-*s*erine-*t*hreonine-*p*hophatase-*i*nteracting *p*rotein1 (*PSTPIP1*). Mutations in *PSTPIP1* lead to hyperphosphorylation of the protein and subsequent increased binding affinity to pyrin, thereby causing dysregulation of IL-1β production[21–24]. Genotype analyses of families have demonstrated variable penetrance, including genetic carriers without symptoms and others with typical PAPA syndrome features within the same family[25].

Clinically, PAPA syndrome is characterized by aseptic inflammation of the skin and joints. Painful, recurrent, sterile monoarticular arthritis with prominent neutrophilic infiltrate usually occurs in the first decade of life and may be the presenting sign of disease. Elbows, knees and ankles are most often involved, and the natural history of persistent disease leads to significant joint destruction. Skin involvement is variable. Pathergy is a commonly observed phenomenon and pustule formation followed by ulceration may be induced early

in life upon vaccination or minimal trauma. (Figure 3) Severe nodulocystic acne and pyoderma gangrenosum tend to develop around puberty and may persist into adulthood[19,20,26–32]. Cystic acne persisting until the 7th decade of life has been reported[19]. Hidradenitis suppurativa has also been reported in a few cases, but is not a consistent clinical feature[19]. Other dermatologic manifestations described in the setting of PAPA include rosacea and psoriasis[30]. Sulfonamide-induced pancytopenia has also been reported in 23–40% of PAPA patients, although the significance of these observations is not well understood[19,32].

Laboratory findings in PAPA syndrome reflect a systemic inflammatory state with leukocytosis and elevated acute phase reactants, but are otherwise non-diagnostic. Elevations in IL-1β and TNFα production in peripheral blood leukocytes have been observed. Infectious processes, vasculopathy, coagulopathy and autoimmune disease should be ruled out in the evaluation of patients. Histopathology of cystic acne lesions reveals distended follicles with cystic spaces and follicular openings filled with keratinaceous debris and numerous bacteria. Ruptured cystic contents induce a brisk neutrophilic inflammatory infiltrate surrounding expanded follicles. Histopathology of pyoderma gangrenosum is similar to that seen with pyoderma gangrenosum in other settings. Early lesions demonstrate a neutrophilic vascular infiltrate. Actively expanding lesions demonstrate neutrophilic infiltrates with leukocytoclasia. Marked tissue necrosis with surrounding mononuclear cell infiltrates are seen in ulcers. Synovial fluid aspirations demonstrate sterile neutrophil-predominant infiltrate[30].

The differential diagnosis for articular manifestations of PAPA syndrome includes monoarticular septic arthritis and, in children, chronic multifocal osteomyelitis (CRMO). The presence of both severe acne and PG, or the presence of PAPA findings in family members, should prompt consideration of PAPA syndrome, SAPHO syndrome and pyoderma gangrenosum secondary to underlying inflammatory bowel disease. *Pyoderma, acne and suppurative hidradenitis (PASH)* syndrome is a recently described autoinflammatory disorder that may also be considered in the differential diagnosis of PAPA syndrome[33]. Although mutations in *PSTPIP1* were not found in the 2 reported patients with PASH, heterozygous repetition of the CCTG microsatellite motif in the *PSTPIP1* promoter were detected. The significance of these findings is unknown. In contrast to PAPA syndrome, joint involvement was not reported in the 2 reported patients with PASH.

Medications targeting IL-1 and TNFα have been most successful in managing the manifestations of PAPA syndrome. The most consistent responses have been observed with the anti-TNFα antagonists etanercept, adalimumab and infliximab[27,34–36]. Response to anti-IL-1 agent, anakinra, has been more variable[26, 28, 34], but appears to be more effective in the management of joint manifestations rather than cutaneous disease[28]. Joint disease is also responsive to corticosteroids, however acne may be exacerbated with systemic therapy. Joint effusions may also be surgically managed with drainage and/or intra-articular steroid injection. Combination therapy with anakinra and anti-TNF agents is associated with increased risk of infection, and should be undertaken with caution. Topical and systemic retinoids have been effective in combination with biologic agents for the management of cystic acne. Patients should be counseled regarding the pathergic component of disease, and advised to avoid trauma to the integument.

SAPHO SYNDROME

Since the 1960s, associations between pustular dermatologic manifestations and osteoarticular manifestations have been reported under various designations including *pustulotic arthro-osteitis*, *sternocostoclavicular hyperostosis*, *acne-associated*

spondyloarthropathy, *acquired hyperostosis syndrome*, and *chronic recurrent multifocal osteomyelitis*. In 1987, Chamot and colleagues proposed a unifying syndrome known as *synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO)* syndrome[37]. The prevalence of this rare syndrome is estimated to be less than 4 in 10,000, with a female predilection. SAPHO can present at any age, however onset is most common in children and young adults. A similar condition first described in 1972, known as *chronic recurrent multifocal osteomyelitis* (*CRMO*), is now largely thought to represent a subset of SAPHO which predominates in the pediatric population[38]. CRMO, congenital dyserythropoietic anemia, and Sweets syndrome are features of Majeed syndrome, a very rare autosomal recessive disorder reported in 3 Middle Eastern families[39–41]. Other associated findings include fevers and growth failure. Mutations in the *LPIN2* gene, which encodes lipin-2, are implicated in Majeed syndrome[42]. Lipin-2 is a protein which plays a role in lipid metabolism, however lipid abnormalities have not been reported in patients with Majeed syndrome. The genetic basis of SAPHO/CRMO is still unknown.

Osteoarticular manifestations are the hallmark of SAPHO syndrome, and occur regardless of the presence of dermatologic manifestations[37]. The most commonly involved areas include the anterior chest wall (65–90%) followed by the spine (30%), particular the thoracic spine. Sacroileitis may also occur, and mandibular lesions can be seen in up to 10% of adults[43, 44]. Long bone involvement is rare in adults, but involvement of the tibia and femur is common in children[45, 46]. Synovitis distant from sites of bony involvement is seen in up to 30% of adults, but rarely noted in children[46]. Surrounding soft tissue swelling and erythema can also develop, and morning stiffness is common. The essential features of SAPHO syndrome, including osteitis, hyperostosis and palmoplantar pustulosis (PPP), can also be seen in CRMO; however, bony involvement in CRMO frequently affects the metaphyses of tubular bones, a feature not typically seen in SAPHO[47].

Dermatologic manifestations of SAPHO may occur concurrently, before or after osteoarticular disease, and are more frequent in adults than in children[48–50]. Seventy percent of children and 15% of adults never exhibit cutaneous disease. Cutaneous lesions consist of neutrophilic pustular dermatoses. Palmoplantar pustulosis is most common, affecting up to 60% of patients who develop dermatologic manifestations[48]. Acne conglobata and acne fulminans occur in approximately 25% of patients, with a notable male predominance[48]. Similarly, hidradenitis suppurativa may also be seen and predominates in men[51, 52]. Rarely, pyoderma gangrenosum and Sweet syndrome may occur[53–55]. Although systemic manifestations are uncommon in SAPHO syndrome, fever and moderate elevations in acute phase reactants may occur, and up to 10% of patients with SAPHO syndrome develop inflammatory bowel disease, most commonly after the onset of SAPHO symptoms[46, 48, 53, 56]. Histopathology of SAPHO-associated PPP is identical to that of PPP.

The differential diagnosis for the osteoarticular manifestations of SAPHO syndrome includes bacterial osteomyelitis, primary bone tumors, metastatic disease and eosinophilic granuloma. SAPHO syndrome should be considered in patients with palmoplantar pustulosis and/or nodulocystic acne in conjunction with a history of bony pain, particularly anterior chest wall pain. Dermatologic and osteoarticular findings should also be evaluated in patients with inflammatory bowel disease. Many individual signs and symptoms of SAPHO syndrome are nonspecific, and therefore it is a diagnosis of exclusion. Although validated diagnostic criteria do not exist, inclusion criteria for diagnosis have been proposed[57]. (Table 1) The presence of 1 of the 4 listed inclusion criteria is sufficient for diagnosis of SAPHO syndrome. Diagnostic criteria have also been established for CRMO and nonbacterial osteitis. (Table 2) The diagnosis of Majeed syndrome can be established by genetic evaluation performed in the setting of CRMO, anemia and inflammatory neutrophilic dermatosis.

Although the disease course is highly variable between individuals, the prognoses for SAPHO syndrome and CRMO is relatively good, and disabling complications are rare [48, 53]. Peripheral arthritis may lead to erosive joint disease in adults. Adults may also suffer from bony deformities and limb length discrepancies. CRMO is generally considered to be a self-limiting condition with healing of sclerotic bone lesions and normalization of bone within 5 years of disease remission[58].

The pathogenesis of SAPHO is poorly understood and, as such, a variety of therapies have been employed with variable benefit. Nonsteroidal anti-inflammatory agents and intra-articular corticosteroids have been useful in the management of joint inflammation[37, 48]. Bisphosphonates may achieve pain relief and sustained remission of bony disease, presumably due to inhibition of bone resorption and anti-inflammatory properties, however responses are variable [59–63]. Systemic corticosteroids in combination with disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate and azathioprine have been used with some benefit for the management of bony and cutaneous disease[48, 56]. Anti-TNFα agents including etanercept, adalimumab and infliximab have shown promise in the management of bone disease in SAPHO syndrome, with generally rapid improvement in bone pain as early as after the first treatment[64–67]. TNFα blockade has also been beneficial for the management of pustular dermatoses associated with SAPHO syndrome. Notably, however, the development of SAPHO syndrome was reported in a patient with inflammatory bowel disease treated with infliximab[68]. The paradoxical induction of skin diseases treated with anti-TNFα agents is a well-known phenomenon[69]. In 6 of 7 patients with SAPHO, improvement in cutaneous and bony manifestations have been reported with the IL-1 antagonist anakinra, suggesting a potential targeted therapy for this syndrome[70, 71].

PUSTULAR PSORIASIS AND CLINICAL VARIANTS

Overview

Genetic advances in monogenic pustular diseases such as DIRA and DITRA have implicated IL-1 family proteins in the development of pustular disease, and have led to the successful use of targeted IL-1 blocking agents for these conditions. These insights may provide clues to the pathogenesis of other pustular dermatoses which are thought to have a polygenic etiology, such as pustular psoriasis and its variants, and to the potential application of similar targeted therapy for these recalcitrant skin conditions.

Pustular psoriasis is characterized by non-infective macroscopic pustules. In 85% of patients, typical plaque psoriasis precedes the appearance of generalized pustular psoriasis (GPP)[72]. Twenty-five percent of children with pustular psoriasis have a family history of psoriasis, suggesting a strong genetic component. In adults, pustular psoriasis is much less common than plaque-type psoriasis, with an estimated prevalence of 0.1% in the general population and a female predominance (F:M 3:2)[73, 74]. In children, however, a male predominance is seen (M:F 3:2). Male children have an earlier age of disease onset (3.5 months of age), as compared with females (8 years of age)[75]. Although pustular psoriasis has long been thought to be a variant of psoriasis, pustular psoriasis and its variants have distinct HLA susceptibility loci that suggest that these two categories of disease may be genetically distinct[76, 77]. Whereas skin manifestations of psoriasis vulgaris are strongly associated with HLA-Cw6, as well as HLA-DRB1*0701/2, HLA-B13, HLA-B17 and HLA-B37[78], these alleles are not associated with GPP, acrodermatitis continua of Hallopeau (ACH) or palmoplantar pustulosis (PPP)[77, 79]. Peripheral psoriatic arthritis alone has been associated with HLA-B27, however this allele is most strongly associated with radiographic sacroileitis[80]. HLA-B27 is also associated with GPP and ACH in the setting of axial arthritis[77, 81], as well as PPP in the context of SAPHO syndrome[54, 82] and reactive arthritis, which is characterized by uveitis, urethritis and spondyloarthritis[83].

In 1968, Baker and Ryan described two distinct clinical presentations of pustular psoriasis[73, 84]. The first group was characterized by onset of plaque psoriasis before age 40. Individuals developed pustular psoriasis following exposure to a precipitating factor (List 1), and lesions tended to resolve with a return to more classic plaque-type psoriasis following treatment. In contrast, the second group was characterized by disease onset later in life, with a peak incidence between ages 41 and 60 years[73]. Initial psoriatic lesions in this group tended to occur in atypical distributions such as the flexural areas, palmoplantar surfaces and/or the fingertips. These lesions were followed shortly thereafter by pustular lesions that progressed rapidly, often with accompanying systemic manifestations including fever and leukocytosis. Of note, a significant subset of this group presented with pustular psoriasis without antecedent plaque disease. External precipitating factors were less common in this group, and individuals typically had significant morbidity and mortality attributable to both the aggressiveness of the disease and advanced age of some patients. Baker and Ryan also noted that localized and generalized forms of pustular psoriasis could overlap with one another over time[73].

Pustular psoriasis can also be divided into two phenotypic categories, localized and generalized disease. Other more specific classification systems have been proposed, however one system has not been uniformly utilized[73, 84, 85].

Generalized pustular psoriasis

Generalized pustular psoriasis (GPP) consists of von Zumbusch type generalized pustular psoriasis and annular pustular psoriasis. In pregnant women, von Zumbusch type GPP is termed *impetigo herpetiformis*. Subcorneal pustular dermatosis (SCPD) is a controversial variant of pustular psoriasis characterized by superficial pustules forming annular and gyrate patterns.

von Zumbusch-type generalized pustular psoriasis—In 1910, Leo Ritter von Zumbusch described a fulminant variant of GPP characterized by sudden-onset, inflamed plaques studded with sterile pustules[86]. Clinical diagnostic criteria for GPP have been proposed[87]. (Table 3)

The first manifestations of von Zumbusch type GPP are typically fever and leukocytosis for 1–2 days, followed by skin edema and erythema[88]. Pustules appear shortly thereafter within erythematous plaques in crops which coalesce into ‘lakes of pus.’ Generalized erythroderma may occur. Skin pain, burning, diaphoresis and pruritus are common symptoms. Systemic findings, including malaise, fatigue, anorexia and arthritis parallel skin disease in adults. Arthritis develops in approximately one-third of patients, often involving the distal interphalangeal joints but may also involve the sacroiliac and other joints[73]. Joint disease is uncommon in children with pustular psoriasis[89, 90]. Nail findings typical of psoriasis, including hypertrophy, thickening, subungual pustulation, nail pitting and onycholysis, are commonly seen in von Zumbusch type GPP [11, 89–91]. Although cutaneous infections are uncommon, pulmonary infections, pyogenic abcesses and cystitis may occur[88].

Oral findings in von Zumbusch type GPP include migratory arcuate and circinate plaques on the dorsal tongue consistent with geographic tongue. Similar findings may occur on the buccal mucosa[92, 93]. Some speculate that these oral manifestations may represent a *forme fruste* of pustular psoriasis[92], while others believe oral mucosal manifestations are a harbinger of GPP[91, 94]. The most commonly reported ocular manifestation is purulent sterile conjunctivitis[11, 12, 95, 96], however iridocyclitis[12], corneal ulceration[12] and corneal exfoliation[97] may develop.

Leukocytosis is the most common laboratory abnormality in von Zumbusch type GPP. Decreased serum calcium concentration is a result of hypoalbuminemia[73, 98]. Ionized calcium is typically normal and patients are therefore not symptomatic. Elevated alkaline phosphatase, transaminases and bilirubin may also be seen[73, 95]. Absolute hypovolemia secondary to fluid losses may lead to pre-renal azotemia[91, 98]. Gram positive septicemia and herpes simplex virus conjunctivitis have been reported in juvenile cases[75]. Mortality in patients with von Zumbusch type GPP is most commonly due to cardiac failure, sepsis or acute respiratory distress syndrome[84,99–102].

The course of von Zumbusch type GPP is episodic, and symptoms may recur several times a year or only upon exposure to precipitants. Cutaneous and systemic symptoms may spontaneously remit or may require prolonged therapy to induce remission. Despite the significant morbidity associated with acute episodes of von Zumbusch type GPP in children, the prognosis of affected patients is generally quite good. Conservative topical management with corticosteroids and topical calcipotriol, or narrowband UVB in combination with topical therapy, is the preferred first-line therapies for management of von Zumbusch type GPP in children, and resolution with supportive conservative topical management can usually be achieved in this patient population[103]. Second-line agents include cyclosporine, methotrexate and systemic retinoids[104]. Methotrexate 0.2mg/kg/week has been shown to be effective in the management of von Zumbusch type GPP in children[105–107]. Etanercept has also been used safely for von Zumbusch type GPP in children, and may be considered for recalcitrant disease[108].

In adults, systemic retinoids are considered by some to be first-line therapy for von Zumbusch type GPP[87, 109–111]. Isotretinoin may be preferred to acitretin in women with von Zumbusch type GPP of child-bearing age given its short half-life, however it may be less efficacious than acitretin[112]. Response is typically seen within several days to weeks. Methotrexate, cyclosporine and infliximab are alternative options[113, 114]. Given the rapid response following cyclosporine and infliximab treatment, many clinicians now consider these first-line agents for the management of von Zumbusch type GPP. Care should be exercised with methotrexate use in the elderly and individuals with hepatic disease, and methotrexate and cyclosporine must be used with caution in patients with renal dysfunction. Psoralen plus ultraviolet A (PUVA) has also been combined with acitretin for management of von Zumbusch type GPP[110].

Although systemic corticosteroid taper may induce a flare of pustular disease, judicious use of corticosteroids in the setting of disease flare may be helpful for acute management. Corticosteroids are best used in combination with steroid-sparing agents such as biologics or DMARDs and require slow tapering[87]. Adalimumab, etanercept and alefacept have been used with some success in the management of GPP, but are considered second line agents for von Zumbusch type GPP[115, 116]. The IL-1 antagonist anakinra and IL-12/23 antagonist ustekinumab have been used in isolated cases, but have not been systematically studied in this population[117, 118].

Impetigo herpetiformis—Impetigo herpetiformis refers to the development of von Zumbusch type GPP during pregnancy. A personal or family history of psoriasis may be present in these patients[91, 119, 120]. Disease onset is typically in the third trimester, although it may occur earlier in pregnancy, and both cutaneous and systemic symptoms resolve gradually following delivery or termination of pregnancy[15, 91, 120–122]. Recurrence may occur with subsequent pregnancy, ovulation or oral contraceptive use, suggesting a role for progesterone in disease precipitation [15, 91, 120, 121, 123, 124]. In addition, von Zumbusch type GPP has been reported in the setting of progesterone challenge[95] .

Like von Zumbusch type GPP, cutaneous and systemic findings of impetigo herpetiformis are abrupt in onset. Unlike von Zumbusch type GPP, however, early involvement of the flexural surfaces and healing with hyperpigmentation is common in impetigo herpetiformis[91, 120, 122, 125]. Erosive and circinate plaques involving the tongue, buccal mucosa and esophagus may occur. Subungual pustules may result in onycholysis[126]. Symptomatic hypocalcemia is common and necessitates close monitoring of mother and fetus. Fetal mortality rates as high as 89% have been reported[15]. Placental insufficiency is the most frequently cited cause for fetal mortality[15, 122].

First-line therapy for impetigo herpetiformis includes topical calcipotriol, topical and oral corticosteroids, and cyclosporine. Cyclosporine is FDA pregnancy category C, however, it has been utilized in the setting of acute disease flares with significant systemic manifestations[111, 127, 128]. Narrowband UVB in combination with topical steroids and cyclosporine has also been used during pregnancy[129]. Biologics including etanercept, adalimumab and infliximab are FDA pregnancy category B, and data for their use in this clinical scenario is limited. Infliximab has been used successfully for impetigo herpetiformis in the post-partum period[130]. Topical and systemic retinoids and methotrexate are FDA pregnancy category X and thus contraindicated in pregnancy. Patients treated in the postpartum period with these agents should be advised not to breastfeed while receiving therapy[131–134]. PUVA has been used with success in one case but is not advisable given fetal exposure to psoralens[135].

Annular pustular psoriasis—Annular pustular psoriasis (APP), also known as *erythema circine recidivants*, is a rare variant of GPP with a recurrent course but good overall prognosis[136]. Although APP does not have a predilection for childhood, it is the most frequent presentation of pustular psoriasis in childhood, with mean age of onset of 11 years in children[136, 137]. Adult-onset APP typically presents during the sixth or seventh decades of life and appears to have a greater predilection for females than males[73, 93].

APP onset is not typically preceded or followed by plaque psoriasis. Unlike von Zumbusch type GPP and impetigo herpetiformis, APP has a less severe course characterized by diffuse, slowly migrating, annular and gyrate erythematous plaques with sterile pustules along the advancing edges involving the trunk, neck and extremities[73, 138]. (Figure 4) Polyarthritis can develop. Pruritus may be present, however other systemic symptoms and laboratory abnormalities, including leukocytosis, hypocalcemia and elevated acute phase reactants are typically absent in both children and adults[84]. Recurrent courses may occur over decades, but episodes are typically much less severe than seen in von Zumbusch type GPP. Of note, features of von Zumbusch type GPP and APP may overlap within the same patient.

Given the subacute nature of APP, some patients with mild disease respond well to topical corticosteroids and warm water compresses, while others may require systemic therapy. Acitretin[139], dapsone[138, 140, 141], and methotrexate have been successful in patients requiring systemic therapy. Low-dose methotrexate has been used with success in the pediatric setting[105]. Success with systemic retinoids has also been reported, but must be used with care in the pediatric population[142, 143].

Subcorneal pustular dermatosis—Subcorneal pustular dermatosis (SCPD), or *Sneddon-Wilkinson disease*, was first described by Sneddon and Wilkinson in 1956[144]. Since SCPD was first described, controversy has ensued regarding its classification[145–148]. Some experts contend that SCPD is not a distinct entity but rather part of the spectrum of psoriasis and pustular psoriasis, resembling the annular pattern of pustular psoriasis[145]. In a review of 103 patients, Baker and Ryan reported 10 patients with annular pustular psoriasis, some of whom exhibited subcorneal pustules resembling SCPD[73]. One longitudinal study

reported that 10 of 23 patients with SCPD progressed to clinical and histopathologic evidence of pustular psoriasis or plaque psoriasis 3–40 years after initial diagnosis of SCPD[149]. Four of these 10 patients had a family history of psoriasis or pustular psoriasis. These data suggest that SPCD and pustular psoriasis may be closely related conditions.

This rare disorder is more common in females than males (F:M 4:1). Onset typically occurs between the 5th and 7th decades of life, although cases in children as young as 3 months of age have been reported[150–153]. SCPD is clinically characterized by abrupt onset of superficial flaccid pustules distributed in the flexural surfaces including the axillae, groin and inframammary folds, which progress over 24 to 48 hours to form annular and gyrate patterns in a generalized distribution. Pustules are typically seen in the setting of normal-appearing skin, but may be found in the setting of erythematous skin. The disease course is chronic, characterized by exacerbations and remissions sometimes for many years. (Figure 5) Acral skin, face, nails and mucosal surfaces are rarely involved. Associated symptoms include irritation and skin pain, but patients rarely complain of pruritus[144, 154]. Lesions heal with hyperpigmentation without scarring. SCPD has been associated with pyoderma gangrenosum[155, 156], inflammatory bowel disease[148, 149, 157] and IgA monoclonal gammopathy, including IgA myeloma [155, 158, 159],. Infectious precipitants including urinary tract infections and upper respiratory infections have also been described[160]. Systemic manifestations including fever, malaise, fatigue and arthralgias are rare in SCPD[149]. In the first reported cases in children, fever and leukocytosis were noted, but subsequent case reports have indicated that there is no difference in clinicopathologic features and prognosis of SPCD between adults and children[152, 153].

Histopathologically, SCPD is characterized by accumulation of subcorneal neutrophils atop fairly normal appearing epidermis in which spongiosis and acantholysis are absent[144]. In contrast to pustular psoriasis, neutrophils may migrate through the epidermis, but do not form spongiform pustules. Spongiosis, microabscesses, acanthosis and regular elongation of rete ridges are not observed. SCPD can be differentiated from pemphigus and benign familial pemphigus by the lack of acantholysis, although acantholysis can be seen in older lesions[161]. Bacteria and fungal elements are absent. Direct and indirect immunofluorescence studies are negative. Flexural distribution, subcorneal (rather than subepidermal) pustules and lack of pruritus distinguish SPCD from dermatitis herpetiformis.

Cases clinically resembling SCPD but showing IgA deposition in the skin and circulating IgA antibodies have been reported and termed *IgA pemphigus*, *intraepidermal IgA pustulosis*, *intraepidermal neutrophilic IgA dermatosis* and *intercellular IgA dermatosis*. Controversy exists over whether these cases represent a subgroup of SCPD or are a distinct entity[162]. Clinically, IgA pemphigus frequently involves the scalp and face which may aid in distinguishing this condition from SCPD. Further confusing matters, some reports have noted that IgA deposits may not be seen by immunofluorescence early in disease onset, and multiple skin biopsies may be required to make a diagnosis of IgA pemphigus[163]. Serum and urine protein electrophoresis are prudent components of the evaluation of SCPD patients.

Most but not all patients with SCPD respond to sulfones, presumably due to their ability to inhibit neutrophil chemotaxis. Dapsone should be used with caution and close monitoring in pediatric patients given hematologic adverse effects. In addition to dapsone, other anti-neutrophilic drugs including colchicine, sulfapyridine and sulfamethoxypyrazine have also been employed with variable success[149, 152, 164]. Topical steroids have also been used successfully as monotherapy or in combination with dapsone[165]. Variable results have been reported with oral retinoids[166, 167]. Broad and narrow band UVB, PUVA and re-PUVA have been reported to be successful in the management of SCPD, although PUVA was found

ineffective in one case[124, 159, 168–170]. Recalcitrant disease has been managed successfully with infliximab[171, 172].

Localized pustular psoriasis

Localized pustular psoriasis can be quite debilitating because of the sites affected, but unlike GPP, it is not commonly associated with systemic symptoms. This group of diseases includes acrodermatitis continua of Hallopeau, palmoplantar pustulosis and palmoplantar pustular psoriasis.

Acrodermatitis continua of Hallopeau—In 1890, Francois Henri Hallopeau described a painful acral pustular condition characterized by sterile pustules involving the distal fingers and, less often, the toes[173]. This rare and often disabling condition, termed *acrodermatitis continua of Hallopeau* (ACH) or *dermatitis repens*, is most common in middle-aged women[174]. Disease onset often occurs after localized trauma or infection involving a single digit[174]. Pustules develop with hyperemia involving the distal aspect of one or two digits, and progress proximally. Pustulation may involve the nail bed and nail matrix, leading to onychodystrophy, destruction of the nail plate and anonychia. Inflammatory paronychia is common. ACH may progress to involve the hands, forearms and feet. Skin atrophy, dermal sclerosis, osteolysis of the distal phalanges and arthropathy of the interphalangeal joints are seen in prolonged, refractory or untreated cases[175]. ACH has a chronic relapsing course with intermittent episodes of acute pustulation that is frequently refractory to therapy. Spontaneous remission is uncommon. In rare instances, syndactyly and involvement of the nasal tip may occur[176]. In the setting of long-standing disease, most often in the elderly, subsequent episodes of generalized pustular eruption have been reported[84, 177].

ACH is often refractory to therapy. Attempts to treat with numerous different topical, systemic and biologic agents have met with mixed results. (List 2)

Palmoplantar pustulosis and palmoplantar pustular psoriasis—Palmoplantar pustulosis (PPP) is a painful, debilitating inflammatory skin condition characterized by crops of sterile pustules localized to the palms and soles. Disease onset tends to occur between ages 30 and 50, with a female predilection (F:M 3:2). A higher prevalence of smoking is noted in patients with PPP than in patients with other dermatoses, and a higher prevalence of PPP is noted in smokers as compared with nonsmokers[178–181]. Other precipitating factors include trauma, stress, warm weather and upper respiratory infection[182].

The majority of cases of PPP are chronic, however acute cases of PPP following febrile illness with sudden onset (24–48 hours) and rapid resolution (2–3 weeks) have been reported and seem to portend a favorable prognosis[183]. Whereas acute PPP may last several days to weeks, chronic PPP may last several decades, with periods of resolution lasting less than 1 year in the majority of patients[182].

PPP is characterized by pustules in a background of normal-appearing or inflamed skin on the palmar or plantar surfaces[182]. (Figure 6) PPP can be disabling secondary to painful fissures, pruritus and burning sensation of the skin. Nail dystrophy from subungual pustulation can progress to nail destruction, and onycholysis may occur in 1/3 of patients[184, 185]. Both arthritis and arthralgias have also been reported in the setting of PPP[186, 187]. Aseptic osteitis of the sternoclavicular joint has been reported in association with PPP in the context of SAPHO syndrome[37]. An increased prevalence of antithyroid antibodies and thyroid disease are noted in patients with PPP[188,189].

Approximately 10–20% of PPP patients have plaque psoriasis on other parts of the body, a distinction termed *palmoplantar pustular psoriasis*. The dorsal surfaces of the hands and feet may also be involved in these cases. The relationship between PPP and palmoplantar pustular psoriasis is controversial—whereas some clinicians speculate that both conditions lie on a spectrum of pustular psoriasis, others assert they are distinct entities. Similarities in histopathology, neutrophil dysfunction and chemokines profiles have been reported in PPP and psoriasis, suggesting a common pathogenic mechanism[190], however, as mentioned earlier, genetic predisposing factors differ between PPP and psoriasis[191].

Disease clearance can be achieved with medium-potency topical corticosteroids under hydrocolloid dressing occlusion, however recurrence is common upon cessation of therapy[192]. UVA can induce clearance in approximately 40% of people with PPP[193]. Acitretin has been shown to improve disease in about two-thirds of people with PPP, but may require continued treatment after achieving remission to avoid recurrent symptoms[194, 195]. Low-dose cyclosporine (1–2.5mg/kg/day) led to moderate objective improvement in about two-thirds of PPP patients within one month[196, 197]. Tetracycline antibiotics also produced objective improvement in about one-half of patients with PPP, however, complete clearance is rarely seen [198, 199]. There are no randomized controlled trials supporting the use of methotrexate, although one uncontrolled prospective study showed benefit in one-third of treated patients, who primarily represented individuals with evidence of psoriasis at other sites [200].

Studies of biologic agents in PPP have resulted in conflicting data. A placebo-controlled trial of etanercept in 15 patients did not demonstrate a statistical benefit[201]. Adalimumab was associated with improvement in cutaneous and articular disease in a single patient[202]. Sequential therapy with adalimumab and infliximab was effective in the management of refractory PPP in 1 case[203]. Caution must be exercised with the administration of TNF inhibitors as paradoxical induction of psoriasis, pustulosis and PPP have been reported with these agents[204, 205]. More recently, ustekinumab resulted in disease clearance in 6 of 9 PPP patients[111].

Acropustulosis of infancy—Acropustulosis of infancy (AI) is one of the most common forms of pustular psoriasis presenting in childhood[75, 136, 206]. This condition predominates in male children of African descent, however may occur in both sexes and in all races[207, 208]. One series reported acropustulosis in 4.7% of juvenile psoriasis patients, with approximately two-thirds of cases occurring in children less than 5 years of age[206].

AI is characterized by intermittent crops of intensely pruritic vesiculopustules occurring on the acral surfaces. Vesiculopustules do not coalesce. Disease onset typically occurs prior to 10 months of age, and lesions tend to persist for about two years, resolving by age 3 [207, 208]. Although AI will spontaneously remit, potent topical steroids are useful for disease management. Pustular lesions show a striking response to sulfones, particularly dapsone,[208] however the risks of methemoglobinemia and other hematologic adverse events may outweigh its benefit for a self-limited condition.

Histopathology of pustular psoriasis and variants

Neutrophils are the predominant feature upon histopathologic examination of pustular psoriasis and its variants in both children and adults. The epidermis is notable for variable hyperplasia, absent granular layer, parakeratosis, suprapapillary thinning, intracorneal aggregates of neutrophils (Munro microabscesses) and epidermal spongiosis with neutrophils (spongiform pustules of Kogoj). Prominent and dilated vessels are noted in the superficial dermis, with sparse mononuclear cell infiltrate and scattered neutrophils in the dermis[161]. Special stains for bacteria or fungal elements are negative. In annular pustular

psoriasis, subcorneal pustules may be observed[136]. In SCPD, subcorneal neutrophils accumulate atop fairly normal appearing epidermis in which spongiosis, spongiform pustules, microabscesses, acanthosis and acantholysis are absent[144]. In palmoplantar pustulosis, eosinophils and mast cells may be seen surrounding pustules in the upper dermis, and the normal spiral columnar architecture of eccrine ducts is absent [182]. In acropustulosis of infancy, both neutrophils and eosinophils may be seen within intraepidermal vesicles both on histopathology and smear[208].

Differential diagnosis of pustular psoriasis and variants

The differential diagnosis for generalized pustular psoriasis includes acute generalized exanthematous pustulosis (AGEP), subcorneal pustular dermatosis (SCPD), reactive arthritis and cutaneous infections including impetigo, folliculitis, miliary tuberculosis and generalized candidiasis. In addition, tinea corporis and gyrate erythemas should be considered in the differential diagnosis of annular pustular psoriasis. In children, childhood bullous dermatosis, miliaria pustulosa, staphylococcal scalded skin syndrome and generalized seborrheic dermatitis should also be considered. IgA pemphigus, pemphigus foliaceus and dermatitis herpetiformis should be considered on the differential for SCPD. (Table 4)

The differential diagnosis of acral pustulosis includes cutaneous fungal infection, bacterid eruption and dishidrotic eczema. If pustulosis is limited to the digits, herpetic whitlow, secondarily-infected malignancy and chronic bacterial, fungal or viral paronychia should also be considered. In children, acral pustular eruptions should prompt skin examination for scabies.

CONCLUSION

Pustular psoriasis and its variants share a number of overlapping cutaneous, systemic and osteo-articular features. The classification of these diseases will continue to evolve over the coming years as underlying biologic pathways are elucidated, allowing differentiation based on shared mechanisms of disease rather than clinical similarities alone. Recent genetic insights into several rare monogenic forms of pustular disease have already revealed new autoinflammatory pathways and highlight the potential for new targeted interventions for these challenging conditions.

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KEY POINTS

- Deficiency of the IL-1 receptor antagonist (DIRA) is an autosomal recessive autoinflammatory disease characterized by perinatal onset pustular dermatosis resembling pustular psoriasis, multifocal aseptic osteomyelitis and periostitis. It can be effectively treated with IL-1 receptor antagonists.
- Pyogenic arthritis, pyoderma gangrenosum and acne comprise PAPA syndrome, an autosomal dominant autoinflammatory syndrome caused by mutations in the *PSTPIP1* gene.
- Synovitis, acne, pustulosis, hyperostosis and osteitis comprise the autoinflammatory syndrome known as SAPHO. Chronic recurrent multifocal osteomyelitis (CRMO) is likely a subtype of SAPHO that predominantly affects children.
- Pustular psoriasis constitutes a spectrum of inflammatory pustular dermatoses ranging from localized acrodermatitis continua of Hallopeau and palmoplantar pustulosis to generalized disorders including von Zumbusch pustular psoriasis and impetigo herpetiformis.
- The clinical similarities between defined autoinflammatory diseases with neutrophilic pustules and pustular psoriasis provides potential new mechanisms of treatment with biologic agents targeting autoinflammatory pathways.

List 1

Precipitants of pustular psoriasis

Infection (most notably Streptococcal infection, vaccines*)

Drugs

- Corticosteroids
- NSAIDs (aspirin, phenylbutazone, oxyphenbutazone)
- Salicylates (aspirin*)
- penicillin
- sulfonamides
- lithium
- morphine
- topical coal tar
- pyrogallol
- topical chrysarobin
- potassium iodide
- progestins
- arsenicals
- hydrochloroquine
- anti-TNF agents

Pregnancy

Menstruation

Stress

Surgery

Alcohol

Sunlight, sunburn

Exertion

Seasonal variation

Birch pollen*

Milk

Pork

* denotes precipitant associated with juvenile GPP

List 2

Potential therapies for acrodermatitis continua of Hallopeau

Systemic antimicrobials[176, 177]

- Tetracyclines
- Azithromycin
- Dapsone

Topical medications[176, 177, 209]

- Topical steroids
- Calcipotriol
- Tazarotene
- Betamethasone
- Topical 5-fluorouracil
- Topical tacrolimus

Phototherapy[176, 209–211]

- Narrow band UVB
- Psoralen ultraviolet A
- Grenz rays

Immunomodulators [176, 209, 211]

- Prednisone
- Acitretin
- Hydroxycarbamide
- Colchicine
- Methotrexate
- Cyclosporine

Biologic agents

- Adalimumab- ^6 cases[211–215]
- Infliximab- 2 cases[211, 216, 217]
- Etanercept- #5 cases[211, 218–222]
- Ustekinumab-1 case [211]
- Anakinra-1 case [211]

^ Some patients treated in combination with topical steroids and cyclosporine

Some patients treated in combination with topical steroids or acitretin

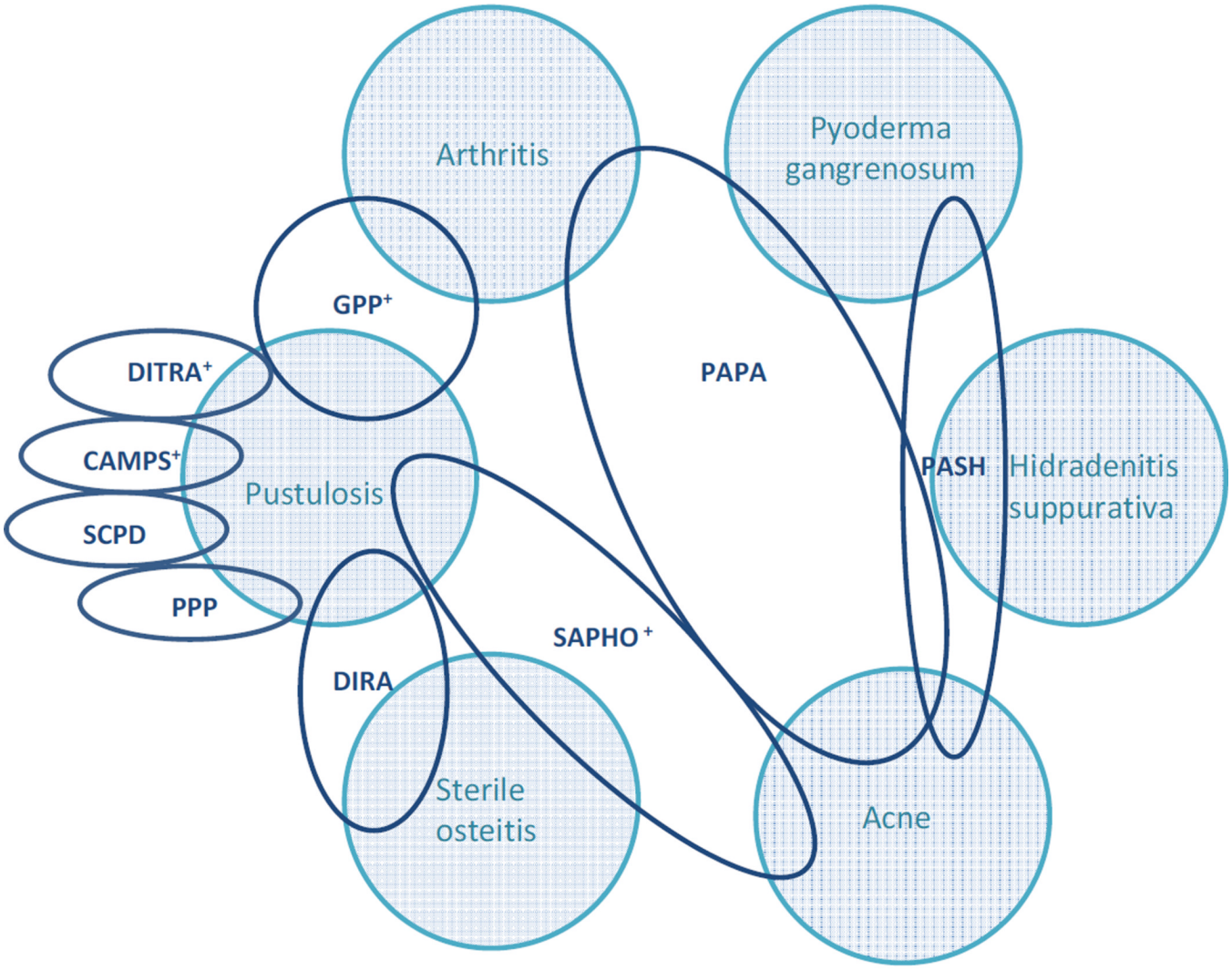

Figure 1. Overlapping clinical features of pustular dermatoses

CARD 14-mediated pustular psoriasis (CAMPS); deficiency of IL-1 receptor antagonist (DIRA); deficiency of the IL-36 receptor antagonist (DITRA); generalized pustular psoriasis (GPP); pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA); pyoderma, acne and suppurative hidradenitis (PASH); palmoplantar pustulosis (PPP); synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO); subcorneal pustular dermatosis (SCPD).

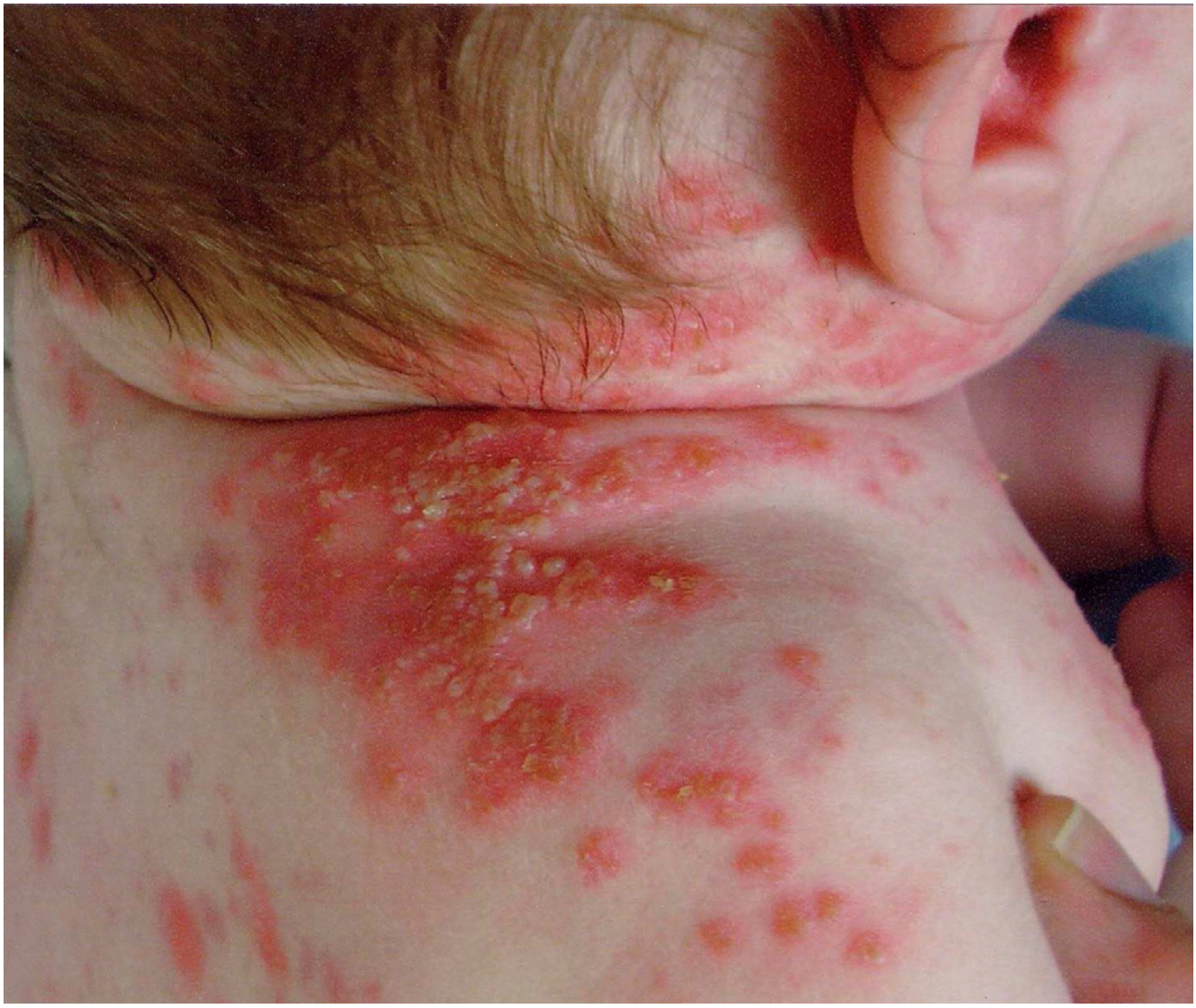

Figure 2. Deficiency of IL-2 receptor antagonist (DIRA)
Bright red plaques studded with crops of pustules in an infant. *Photo courtesy of Raphaela Goldbach-Mansky*.

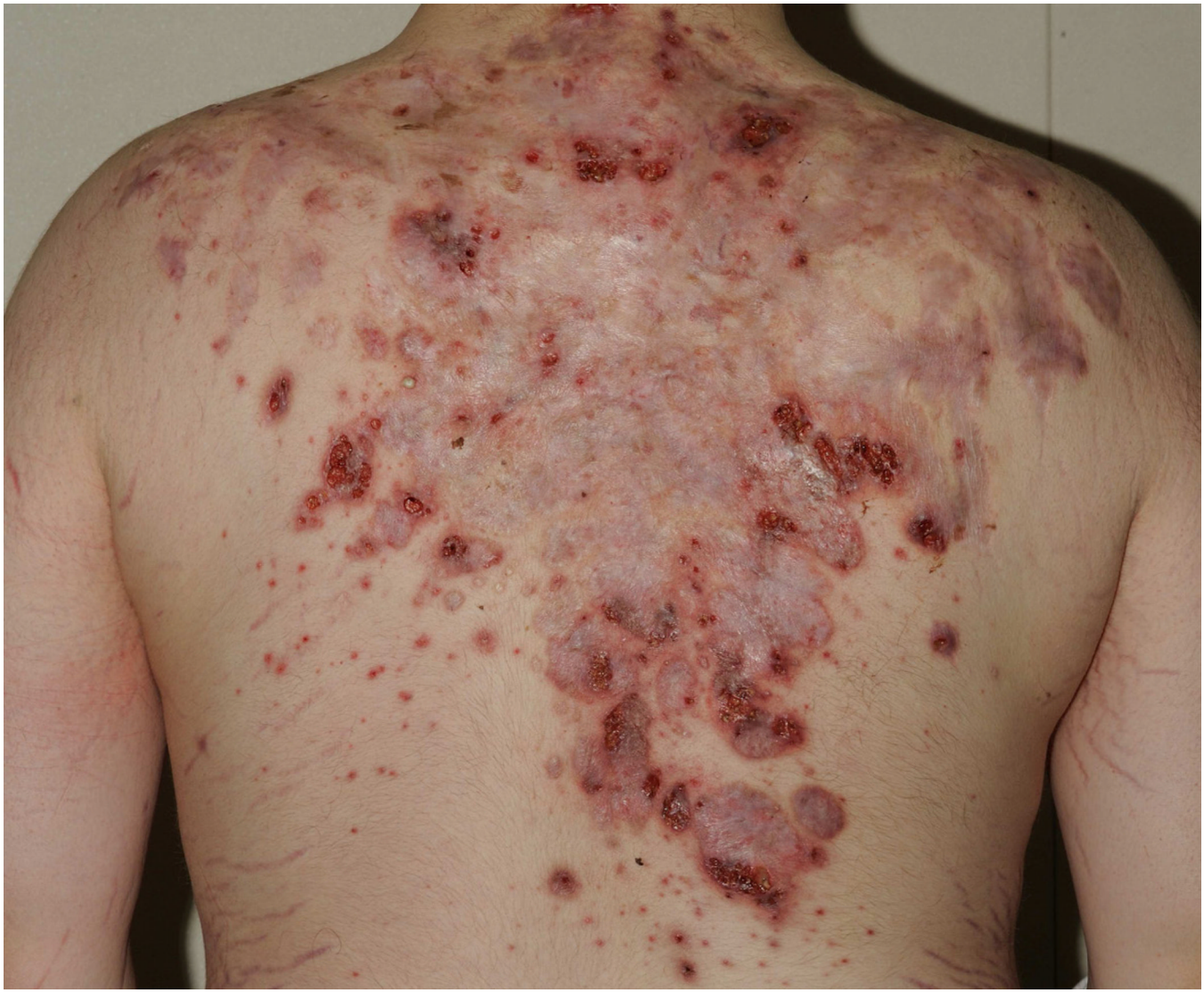

Figure 3. PAPA syndrome
Cribiform pyoderma gangrenosum ulcers in the setting of severe scarring from acne conglobata.

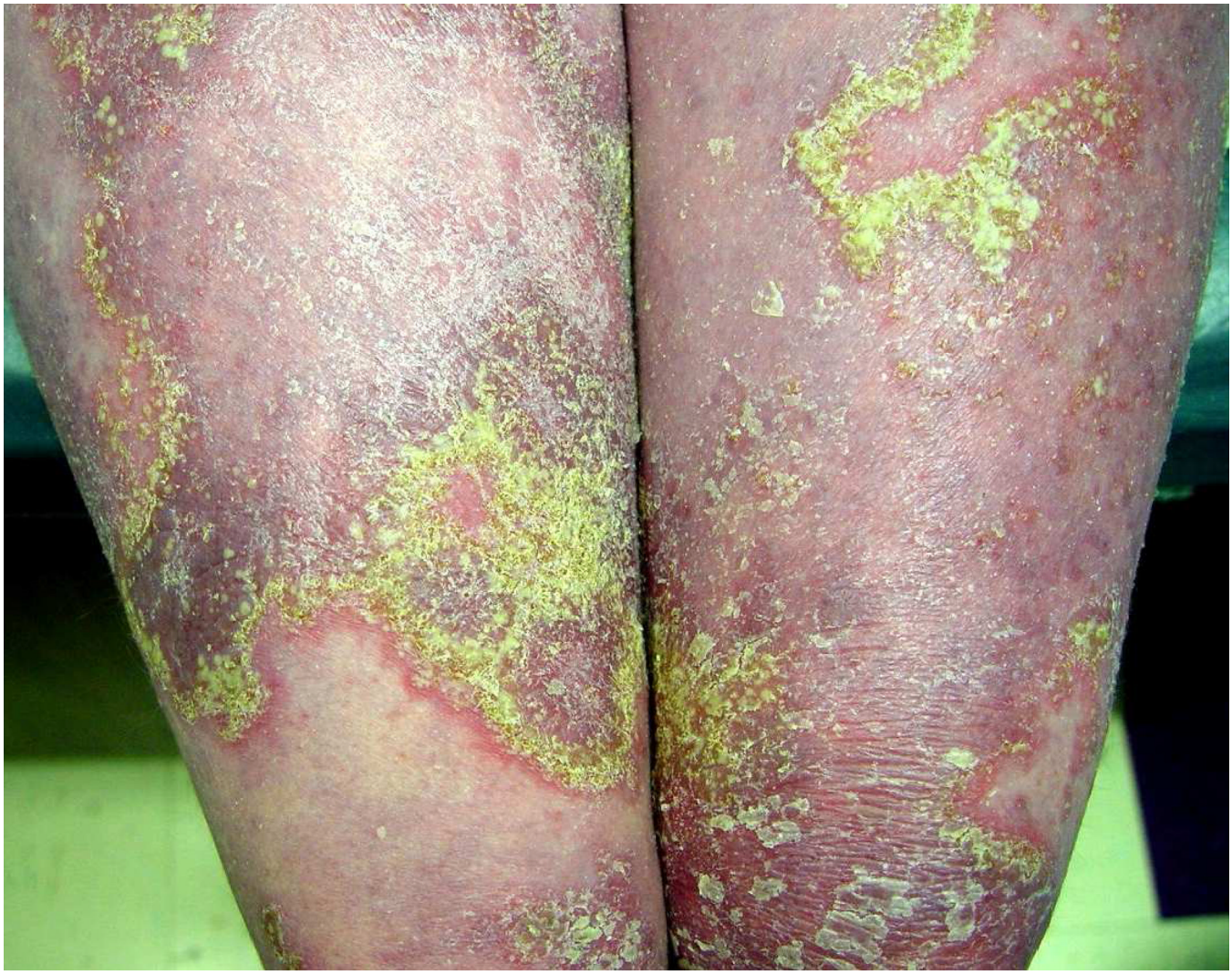

Figure 4. Annular pustular psoriasis

Gyrate plaques of annular pustular psoriasis notable for central sparing and erythematous border studded with pustules and yellow crusting. *Photo courtesy of Jeffrey Callen.*

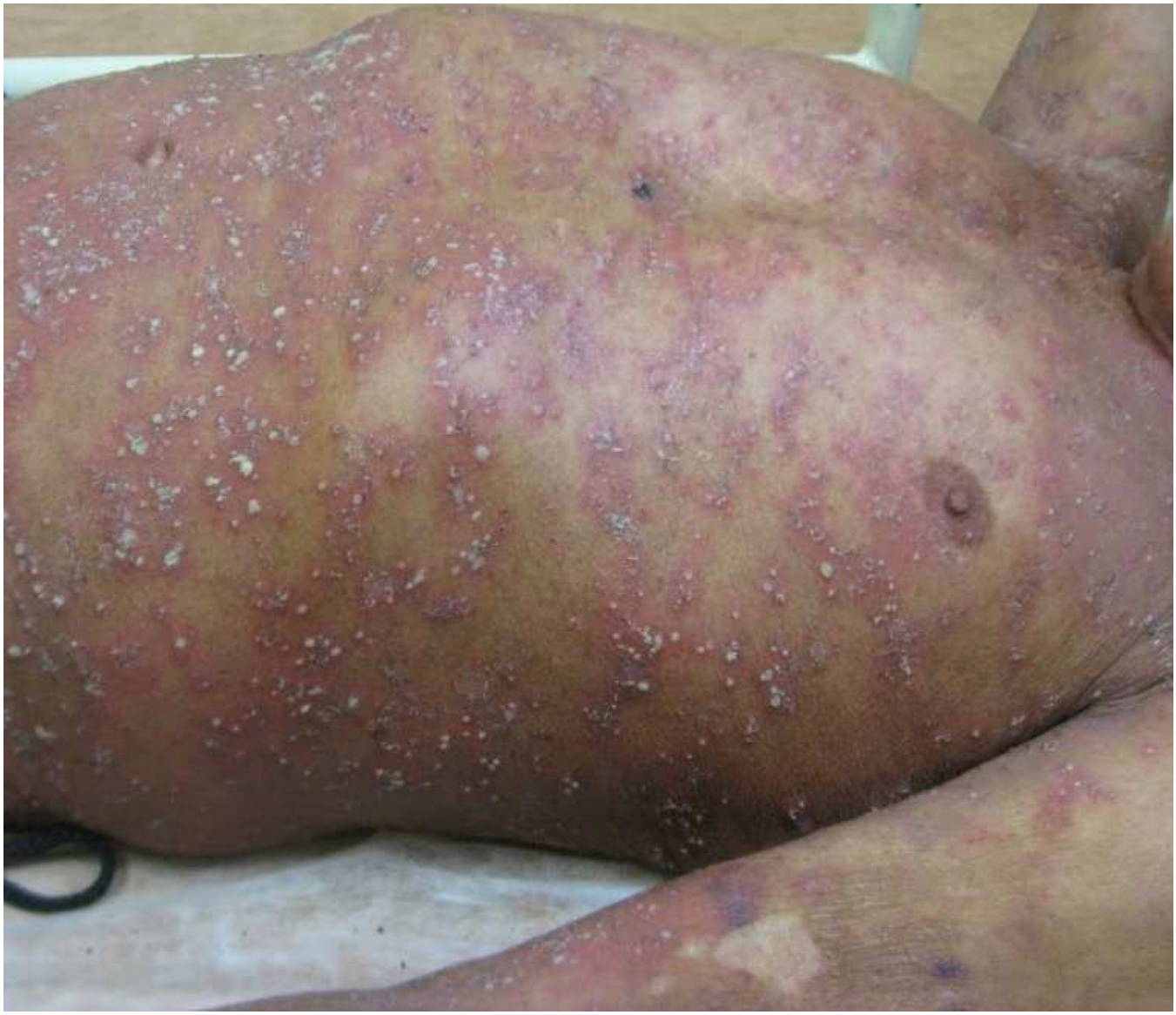

Figure 5. Subcorneal pustular dermatosis

Superficial pustules and scale collarettes in annular and gyrate patterns overlying a relatively non-inflammatory background.

Figure 6. Palmoplantar pustular psoriasis

Pustules, scaling and painful erosions with overlying hemorrhagic crust on the palmar surfaces. *Photo courtesy of Kristina Callis-Duffin.*

Table 1

Inclusion and exclusion criteria for SAPHO syndrome[57]

Inclusion criteria	Osteo-articular manifestations of acne conglobata, acne fulminans, or hidradenitis suppurativa (i.e., inflammatory synovitis, anterior chest wall hyperostosis or osteitis, hyperostosis or osteitis at another site,or spondylitis or spondylodiscitis)
	Osteo-articular manifestations of palmoplantar pustulosis (i.e., inflammatory synovitis, hyperostosis +/− osteitis, or spondylitis or spondylodiscitis)
	Hyperostosis (of the anterior chest wall, limbs or spine) with or without dermatosis
	CRMO involving the axial or peripheral skeleton with or without dermatosis
Exclusion criteria	Septic osteomyelitis
	Infectious chest wall arthritis
	Infectious palmoplantar pustulosis
	Palmoplantar keratoderma
	Diffuse idiopathic skeletal hyperostosis (DISH), except for fortuitous association
	Osteoarticular manifestations of retinoid therapy
Other reported features	Possible association with psoriasis vulgaris
	Possible association with an inflammatory enterocolopathy
	Features of ankylosing spondylitis
	Presence of low-virulence bacterial infections

The presence of 1 of the 4 inclusion criteria is sufficient for diagnosis of SAPHO syndrome.

Table 2

Proposed criteria for CRMO and non bacterial osteitis[56]

Major diagnostic criteria		Minor diagnostic criteria	
1	Radiologically proven osteolytic/-sclerotic bone lesion	**1**	Normal blood count and good general state of health
2	Multifocal bone lesions	**2**	CRP and ESR mildly to moderately elevated
3	PPP or psoriasis	**3**	Observation time longer than 6 mo
4	Sterile bone biopsy with signs of inflammation and/or fibrosis, sclerosis	**4**	Hyperostosis
		5	Associated with other autoimmune diseases apart from PPP or psoriasis
		6	Grade I or II relatives with autoimmune or autoinflammatory disease, or with non-bacterial osteitis

Two major criteria or one major and three minor criteria is sufficient for diagnosis of CRMO.

Table 3

Diagnostic criteria for generalized pustular psoriasis[87]

All 5 criteria must be met for diagnosis.

1. Systemic symptoms such as fever and general malaise are present
2. Multiple, isolated non-infectious pustules are present in the flushed skin all over the body or over a wide area
3. Kogoj's spongiform pustules are histopathologically confirmed
4. Some of the following laboratory test results are obtained during the clinical course
   - Leukocytosis and shift to the left
   - Precipitated ESR, positive C-reactive protein and high anti-streptolysin O antibody levels
   - Increases in IgG or IgA
   - Hypoproteinemia, hypocalcemia, etc
5. Recurrence of the above-listed clinical and histological findings

Table 4

Differential diagnosis of pustular psoriasis and its variants

Condition	Differential Diagnosis
von Zumbusch type generalized pustular psoriasis	Acute generalized exanthematous pustulosis
	Subcorneal pustular dermatosis
	Diffuse impetigo
Impetigo herpetiformis	Folliculitis
	Miliary tuberculosis
	Tinea corporis
	Cutaneous candidiasis
	Subcorneal pustular dermatosis
	Generalized seborrheic dermatitis
	Reactive arthritis
	Childhood bullous dermatosis*
	Miliaria pustulosa*
	Staphylococcal scalded skin syndrome*
Annular pustular psoriasis	Erythema annular centrifugum
	Erythema gyratum repens
	Tinea corporis
	Granuloma annulare
	Urticaria
	Erythema multiforme
	Erythema chronicum migrans,
	Subcutaneous lupus erythematosus
	Annular erythema of infancy*
Subcorneal pustular dermatosis	IgA pemphigus
	Annular pustular psoriasis
	Dermatitis herpetiformis
	Tinea corporis
Acrodermatitis of Hallopeau	Herpetic whitlow
	Tinea manuum or pedis
	Dishidrotic eczema
	Bacterial or fungal paronychia
	Secondarily-infected malignancy
	Secondarily-infected contact dermatitis
Palmoplantar pustulosis	Tinea mannum/pedis/unguium
Palmoplantar pustular psoriasis	Dishidrotic eczema
	Contact dermatitis
	Bacterial or fungal infection

* consider especially in children