

COMMENTARY

Pustular diseases and keratinocyte–myeloid synergy

Abstract

Pustules are among the most common lesions produced in human skin. Infections by pathogens and drug-induced reactions are frequent causes of pustule formation. In recent years immune-mediated pustular diseases have drawn attention. It is proposed to classify pustular diseases according to the initiating events and sites: purely epidermal pustules, follicular pustules or pustules noted in autoinflammatory syndromes. The unifying pathology in all of the three categories is a microinvasion of activated neutrophils into epidermal or adnexal epithelia. Formation of pustules involves established IL-17 / IL-23, IL-36 / IL-36RN driven pathology, or IL-1 / caspase-activated autoinflammation. Pathophysiology demonstrates an intriguing synergy of keratinocytes with neutrophils. This is called keratinocyte–myeloid synergy (KMS). Non-infectious pustules are formed by IFN α controlling the production of chemoattractants (IL-8, LTB $_4$) or induced by IL-1-regulated inflammasomes and caspase/ IFN β -induced chemotaxins. The presence of physical barriers, for example, cornified cell layers (str. corneum), is instrumental in establishing chemotactic gradients and blocking migrating neutrophils. In follicular KMS-driven pustular disorders, in contrast to epidermal pustules, neutrophil-mediated toxicity propagates lasting and expanding ulcerating diseases with increased levels of circulating immunoglobulin A (IgA). Complexed IgA is suggested to propagate ongoing pustular diseases. These are prerequisites essential for developing pustules in burdensome human skin diseases.

Pustules are frequently seen lesions present in human skin. It is not uncommon to note one or the other pustule on normal-looking skin in otherwise healthy persons. Single or groups of pustules are 2 to 3 mm in diameter, with yellowish colour, and often are surrounded by slight erythema. Single pustules are filled with approximately 3 to 4 million leukocytes that have invaded the epidermis 4 to 5 h before clinical appearance. Accumulation of neutrophils in the form of pustules is a feature of human skin, rarely noted in other organs of the human body and near absent in the skin of other species.¹

Migration of activated peripheral neutrophils into the harmless-looking epidermis is noted at preferential sites, body folds, palms, soles, nail beds, the so-called ‘oily spots’ in psoriatic nail plates, face or entire body interfollicular skin. Neutrophilic microabscesses formed by invading PMN are known as Kogoj’s spongiform microabscesses and carried towards the keratinizing periphery by differentiating keratinocyte layers, and finally become visible as Munro abscesses.² They are hallmarks of plaque-type psoriasis and are considered the result of activated (‘squirting’) dermal papillas.³ Theoretically, microabscess-forming neutrophils, although not studied in detail, could also affect follicular structures such as hair follicles and sweat ducts of the apocrine type. These would appear as invisible signs of early pustule formation.

Healed skin is refractory for newly developing pustules, as best noted in annular forms of pustular psoriasis. During healing, a dry, scaly and slightly erythematous surface is left refractory without recurrence of new pustules in affected skin sites.

In the majority of patients, cutaneous mobilization of polymorphonuclear granulocytes (PMN) is caused by contacting pathogens or noted as unwanted side effects of drugs or by yet unknown mechanisms. Pustule formation in the absence of pathogens or drug-related molecules remains an impressive example of ‘frustrated’ antimicrobial defence.

In recent years, sterile, non-infectious pustules are described as symptoms in a growing number of disorders known as *Autoinflammatory Diseases*.⁴ These in many ways differ from classical autoimmune diseases.^{5,6} Systemic diseases including osteo-arthritic inflammation, intestinal inflammation, urticaria and recurrent fever were leading systemic features when this group of syndromes was first characterized.^{6,7} As presented in this issue of JEADV, an extensive survey on generalized pustular psoriasis is presented (Polat et al⁴³).

Pathophysiology of pustule formation

The formation of pustules represents one of the fundamental events of innate immunity, superbly visualized in human skin. Most studies concerned with neutrophil–epithelial interactions were carried out in intestinal epithelia in man and in common laboratory animals,⁸ elegantly summarized by Brazil and Parkos.⁹ In human skin, single steps of microabscess formation (formation of pustules) in the absence of pathogens (as, for instance, seen in pustular psoriasis) are time limited and come to an end when pustules have reached uniform sizes (approx. 3–5 mm in diameter). In addition, these (interfollicular) pustules

remain without overt signs of cell damage (toxicity) in neighbouring cells, keratinocytes, endothelial cells or connective tissue surroundings. When migration stops, neutrophils look ballooned with empty cytoplasm, while adjacent keratinocytes appear to flatten.¹⁰ Neutrophils and neighbouring keratinocytes are located next to each other forming spongiform nets.

Fundamental interest is concerned with the essential role of PMN in eradicating infectious pathogens. This is considered a two-step process where first bacteria-derived molecules or activated cytokines (TNF α , IFN γ , IL-8 and GM-CSF) prime quiescent and circulating PMNs. The cells subsequently transmigrate the endothelial and basal epithelial linings (in intestines, lungs, urinary system and gall bladder) towards the sites of infection or inflammation. During arrival, PMNs encounter further activating signals which initiate phagocytosis and pathogen killing.⁹

Most studies on neutrophil–epithelial interactions concentrate on pathogen/neutrophil pathology in the intestinal system, the respiratory tissue or urinary linings. In human skin, sterile pustules are exclusively filled with migrating neutrophils, rarely with eosinophils (folliculitis Ofuji) or abnormal lymphocytes (Pautrier abscesses). Mintz *et al.*¹¹ studied the scenario of neutrophils following bacterial infection of the gall bladder, mammary gland and urinary epithelial linings in mice. After transendothelial migration, neutrophils adhered to epithelial cells. They became invaginated into the host cells and, finally, while ending with apoptotic cell death, they were fragmenting their membranes and delivered their intracellular contents.

In patients with suspected reflux esophagitis, however, without visible signs of mucosal damage, oesophageal biopsies revealed a remarkably high prevalence of intraepithelial neutrophils and only minute epithelial changes.¹² These observations support the concept that invisibly altered environmental conditions including changes in cutaneous biotope initiate epithelial chemotactic responses in epithelia. In addition to microbial contacts, other environmental factors may play an important role in regulating the homeostasis of barrier tissues.

In human skin, pustular disorders of the soles and palms are frequently noted as part of underlying diseases, for example, psoriasis or autoinflammatory syndromes.¹³ They often present with diagnostic and more so with therapeutic problems. Recently, two conditions, pustulosis palmo-plantaris (PPP) and pompholyx (dyshidrotic eczema), were histologically re-examined by Masuda-Kuroki *et al.*¹⁴ Formation of empty vesicles with spongiosis in the surroundings was seen in pompholyx as first alterations, whereas microabscesses at the edges and in the vicinity of neutrophil-rich vesicles in PPP were re-emphasized as differentiating criteria between the two disorders. These findings confirm contrasting vesicular and pustular phenotypes as paradigms of opposing skin reactions, psoriasis (as in PPP) and eczema / atopic dermatitis. In a recent study of palmo-plantar pustulosis by Hagforsen *et al.*¹⁵ biopsies taken from lesional skin revealed the presence of Langerhans cells and

Table 1 Interfollicular and follicle-associated pustules in autoinflammatory

	Pustular Lesions	Diseases
Pustular psoriasis von Zumbusch	Hidradenitis suppurativa*	SAPHO
Psoriasis <i>cum</i> pustulatione	Pyoderma gangraenosum*	DIRA
Pustular psor. of the folds	Acne conglobata*	DITRA
Annular pust. Psoriasis	Erythema elevatum et diutinum*	PAPA
Impetigo herpetiformis	Sweet's Syndrome*	Behcet's disease
Acrodermatitis continua		CAMPS
Herpes gestationis		
Acropustulosis infantum		
Palmoplantar pustulosis *		
AGEP		
React arthritis Reiter		

Synovitis, acne, pustulosis, hyperostosis, osteomyelitis (SAPHO), IL-1 receptor antagonist (DIRA), deficiency of the IL-36 receptor antagonist (DITRA), pyogenic arthritis, pyoderma gangrenosum, acne (PAPA), CARD14-mediated pustular psoriasis (CAMPS) and reactive arthritis (RA).⁴ Syndromes reported with hyper-immunoglobulinaemia A are listed with *.

interleukin 17 expression close to inflamed sweat duct openings (acrosyringia), indicating activation of innate immune phenomena at these follicular sites.

In summarizing this discussion, we have attempted to classify pustular skin diseases according to phenotype appearance, presumed pathogenesis and their still enigmatic site specificities (Table 1). As shown, pustule formation is seen in three different categories: (i) pustular disorders affecting the interfollicular epidermis, mostly belonging to the psoriatic disease spectrum; (ii) microabscesses and pustules presumed to originate next to or within adnexal (follicular) epithelia and (iii) pustular eruptions as part of autoinflammatory and systemic diseases (Table 1).

Follicular pustules and microabscesses

In contrast to interfollicular pustules, microabscesses located within the adnexal epithelium demonstrate overt tissue damage caused by neutrophils unloading their bactericidal armamentarium (antibacterial enzymes, elastase, cathepsin G, defensins, proteinase 3, β -glucuronidase, lysozyme, metalloproteinases and oxygen radicals⁹). It would be of interest to observe such neutrophilic microabscesses as early pathology within follicular epithelia, for example, hair follicles, sweat ducts and sebaceous ducts. They could play an important role by representing the initial lesions in severe acne, acne conglobata, acne inversa (hidradenitis suppurativa) and pyoderma gangraenosum.

Unfortunately, the early formation of microabscesses in the adnexal epithelium remains overlooked or is poorly and insufficiently described. Instead, biopsies generally are taken in highly inflamed and expanding follicular disorders, acne inversa and others. Excised material demonstrates late-phase skin pathology

Table 2 KMS: Interfollicular and follicle (adnexa)-associated pustules show contrasting pathologies

Interfollicular	Follicle associated
Transient pustulosis, epidermal, relapsing	Necrotizing expanding lesions, dermal
Generalized or restricted areas (body folds, nail folds)	Early comedones at preferred sites (face, apocrine zones)
Overt infections lacking, rarely induced by drugs	Superinfected by pathogens
Autoinflammatory and/or psoriatic disorders	Elevated IgA immune globulins, CRP and amyloid
Pathogenesis-related comorbidities	Postinflammatory comorbidities (presumed)

without the focus on early lesional changes. The reason is that adnexal structures remain unlikely to be biopsied in the absence of early and initiating clinical symptoms.

Follicle-associated pustular diseases demonstrate the following characteristics: (i) expanding, non-healing skin lesions highly loaded with pathogens, (ii) necrotizing inflammatory activity with early abscess formation and (iii) heavy infiltration with neutrophils (Table 2). Affected areas demonstrate the formation of keratin plugs comedones within follicular infundibula, absence of spontaneous healing, restriction to special body sites and often they are associated with a set of comorbidities with symptoms of a metabolic syndrome known in psoriasis and recently discussed in patients with hidradenitis suppurativa¹⁶ (acne inversa).

Keratinocyte–myeloid synergy (KMS)

Pustules represent an intriguing and most common feature of human skin pathology. The phenomenon documents close association of neutrophils with epidermal keratinocytes and adnexal epithelia. In defining the unifying pathology, we have tentatively named this phenomenon *keratinocyte–myeloid synergy* (KMS) which stands for a unifying pathogenetic principle in human skin.¹⁷

- An intriguing affinity of migrating myeloid cells to keratinizing epithelia at both follicular and interfollicular sites,
- Chronic expanding adnexal (follicle-bound) skin lesions, loaded with neutrophils and pathogens and resistance to antibiotic therapy and the presence of leading chemotaxins within target sites (LTB4, C5a and Interleukin 8,^{8,9,18,19}),
- Presence of physical barriers (horny layer, corneocytes, nail plates, osseous and articular, connective tissue structures) for the build-up of chemotactic gradients,
- An emerging role of circulating IgA as an immune modulator (suppressor and activator),
- Comorbidities noted in severe and lasting diseases.

Questions concerning the early pathology of acne vulgaris, acne conglobata and acne inversa (hidradenitis suppurativa) still do not provide clear answers. An extensive discussion by

Dainichi and coworkers delineate acne and related disorders as due to hyperactive innate immunity of the folliculo-sebaceous units.²⁰ The authors suggest that inflammation is found to precede comedo formation and, as a second step, this is followed by infection, for example, *Cutibacterium* (previously *Propionibacterium*) *acnes* (*C. acnes*). In Plewig's monumental documentation, more than 100 patients with acne inversa were studied.²¹ As early changes, compact hyperkeratosis of terminal hair infundibula was described. Rupture of the follicular epithelium was supposed to be followed by granulocytic infiltrates.²¹ The prevailing concept as summarized in a series of articles hypothetically describes follicular hyperkeratosis and keratinous plugs together with rupture of glandular epithelium and subsequent granulocyte infiltration as primary events. 'Once the rupture has occurred, the disease spreads rapidly'.^{22,23} As reported by Giang and coworkers,²⁴ in uninvolved skin of acne patients, neutrophils migrating into intact follicular epithelium can be found together with the formation of 'micro-comedones'. These findings suggest that in the early stages of acne, neutrophils are activated possibly by *C. acnes*. In fact little is known as to which early events activate ductal epithelium to produce hyperkeratosis, plugs or comedones.^{25,26}

The Str. corneum cells as well as cornifying cell layers within follicular structures, hair shafts, sweat ducts, sebaceous ducts, nail plates and osseous structures provide physical barriers for neutrophil migration and enable chemotaxin gradients to become established. The presence of these physical barriers is of help in explaining the peculiar co-existence of epidermal, follicular and osteo-/arthro-articular inflammation in the disorders listed (Table 1). This may also help to conceptually understand the diverging scenario in pustular diseases as there is considerable overlap between the different disorders described as individual syndromes, as seen in DIRA, PAPA, SAPHO and others (Table 1).

As an example, Chamot and coworkers²⁷ first described SAPHO as a syndrome showing synovitis, acne, palmo-plantar pustulosis, hyperostosis and osteitis, with early onset in childhood. This syndrome is commonly listed as autoinflammatory and appears paradigmatic in showing the association of pustular dermatologic and osteo-articular disease as signs in compartmentalization in KMS-related disorders. Others include PASH and PAPASH.²¹

Role of immunoglobulin A in keratinocyte–myeloid synergy

During recent years, sporadically published and carefully written case reports mention hyperimmunoglobulinaemia A in patients with distinct forms of cutaneous inflammation, for example, pyoderma gangraenosum, acne conglobata, lasting and extensive psoriasis, Sweet's syndrome and subcorneal pustulosis Sneddon–Wilkinson^{28–34} (Table 1). Often this finding is noted as IgA hyperimmunoglobulinaemia and considered as accidental or suspected as IgA myeloma or simply called IgA gammopathy.

Work from our laboratory demonstrated increased IgA serum levels in a number of disorders (pyoderma gangraenosum, acne conglobata, Sweet's syndrome and severe psoriasis). IgA serum levels were measured three to four times higher as compared with normal levels or compared with patients suffering from chronic mucocutaneous candidiasis, eczema and atopic dermatitis, all showing normal values.³⁵

Immunoglobulin A shows a lasting evolutionary history. It was first noted in reptiles, birds and mammals as instruments of innate immunity before the adaptive immune system with the MHC, T-cell receptors and immunoglobulins started. Compared with other immunoglobulin classes in man (IgG, IgD, IgE and IgM), immunoglobulin A (IgA) is by far the most produced antibody isotype. Serum concentrations range around 1–3 mg/mL. Daily production of circulating monomeric IgA (66 mg/kg/day) exceeds the production of the other antibody classes.^{36, 37}

IgA is considered the principal immunoglobulin responsible for local immunity in mucous tissues, intestines and mucous epithelia. Immunoglobulin A appears as one of the earliest effector molecules in the evolution of innate immunity. Next to the antimicrobial strategies of dimeric IgA in mucosal barrier tissues, IgA demonstrates anti-inflammatory activity by suppressing local inflammation in keratinizing epithelia of skin. It is known that IgA contributes to the initiation of inflammation. This is by triggering the Fc alpha RI (FcαRI) on myeloid cells.³⁵ FcαRI is the predominant receptor for monomeric and complexed IgA to stimulate the production of pro-inflammatory cytokines by myeloid cells. As emphasized by Hansen and coworkers,³⁹ pathogen-linked opsonizing IgA-immune complexes and dimeric IgA are considered inducers of 'active' immunity, controlling the production of pro-inflammatory cytokines TNFα and IL-1β. The IgA Fc receptor 1I is seen as a molecular switch that mediates pro- as well as anti-inflammatory activities of IgA.³⁶

So far, increased circulating IgA concomitant with the above-mentioned skin diseases remains unexplained. These findings indicate that the chronic, severe and preferentially follicle-bound disorders, loaded with pathogenic bacteria eliciting a neutrophil-dominated inflammatory pathology, tend to become associated with elevated serum levels of IgA as part of the clinical phenotype. Better understood seems the role of IgA in inflammatory bowel diseases (IBD) including Crohn's disease and colitis ulcerosa. In chronically activated IBD patients, the impaired barrier function of the epithelial linings results in an invasion of IgA – opsonized bacteria and systemic IgA immune complexes.³⁴ These findings could suggest similarities in pathogenetic pathways noted in follicular KMS-driven disorders. TNFα inhibitory drugs successfully applied in IBD were recently found to be of benefit in hidradenitis suppurativa.³⁹

Finally, hypothetical ideas concerned with the formation of pustules are readily extended onto psoriasis. In a recent review by Griffith *et al.*⁴¹ the disease is pathogenetically linked with a

spectrum of clinical phenotypes including stable plaques and inflammatory papules of recent onset, and a variety of pustular entities including von Zumbusch-type generalized pustular psoriasis and, as a recent observation, paradoxical psoriasis.⁴² These are presented as three major inflammatory circuits controlled by IL-17 (in plaque-type psoriasis), IL-36 (in von Zumbusch-type pustular psoriasis) or IFNα (in paradoxical psoriasis). Two of these inflammatory circuits, pustular psoriasis and paradoxical, psoriasis are innate KMS-driven diseases, while the predominant phenotype (plaque-type psoriasis) would resemble autoimmunity.

Conclusions

Pustular disorders reflect innate immune defence patterns produced in human skin. The concept presented may help envision a new pathway called keratinocyte–myeloid synergy (KMS). This is defined as a background hypothesis for the distinct interaction of epidermal (interfollicular) keratinocytes and adnexal (follicular) epithelial cells with myeloid phagocytes (neutrophils). Interfollicular KMS-related disorders with microabscesses and pustules are part of the psoriatic disease spectrum. Follicular pustules located in deep skin adnexal epithelia are suspected to initiate long-lasting and devastating neutrophilic disorders. Examples are acne conglobata, acne inversa and pyoderma gangrenosum. Elevated inflammatory IgA levels reflect a scenario of attempted healing. Innate immunity of KMS-related disorders is of interest and related with the pathophysiology of IgA in human skin.

At present, precise mechanisms of pustule formation, for example, responsible TLRs, their ligands, danger signals and the time-limited secretion of chemoattractants and messenger peptides, are still insufficiently understood. This includes the extent to which KMSs can initiate subsequent adaptive immune responses (Th1 and Th23 / TH 17) as suggested in psoriasis.⁴³

Conflicts of interest

None.

Data availability statement

None.

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Linked article: A. Kara Polat *et al.* *J Eur Acad Dermatol Venereol* 2022; **36**: 1256–1265. <https://doi.org/10.1111/jdv.18103>.

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DOI: 10.1111/jdv.18279