Newer entities in dermatology: A short review on the newly defined dermatoses and acronyms

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Advancements in dermatologic diagnosis and the advent of genomics have given a boost to recognition and characterisation of many emerging clinical entities. Familiarity with these and recognising their differential diagnoses has important implications in clinical practice and better patient management [Table 1]. PubMed search was done using the terms "new", "emerging", "recently described", "entities", and "skin/dermatological" disease for the preceding decade, and the list of identified entities has been reviewed in the subsequent section. This shall assist clinicians in staying up to date on these recently defined clinical entities.

CARD-14 associated papulosquamous eruption (CAPE)

CAPE is an *autosomal dominant* skin disorder with incomplete penetrance, arising from the gain-of-function mutations in the *CARD-14* (Caspase Recruitment Domain Family Member 14) gene leading to activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB).[1] It is characterised by infantile onset skin lesions resembling psoriasis and pityriasis rubra pilaris (PRP), predominantly affecting the face—specifically the chin, cheeks, and upper lips with a characteristic sparing of the infralabial region. Histopathologically, alternating checkerboard parakeratosis and orthokeratosis and acanthosis is observed. Dilated dermal vessels and follicular plugging may be seen. Partial resistance to conventional antipsoriatic treatments is a significant finding. Management options include inhibitors targeting interleukins (IL)-12 (ustekinumab) and IL-23p19 (guselkumab).[2]

Midface toddler excoriation syndrome (MiTES)

MiTES manifests in the first year of life with deep, self-inflicted excoriations, primarily located on medial cheeks, nasal bridge, and central forehead associated with biallelic mutations in the Polyalanine tract (PR) domain-containing protein 12 (PRDM12) gene, which plays a role in the development of sensory neurons into nociceptors.[3,4] The presence of affected siblings, symmetrical excoriations localised to central face without the involvement of peripheries, absence of mental retardation and repetitive behaviour, and normal uric acid differentiates it from close differentials [Figure 1 and Table 1].

Reactive infectious mucocutaneous eruption (RIME)

It is a severe mucocutaneous eruption occurring predominantly in children and adolescents following bacterial or viral respiratory prodrome, commonly *Mycoplasma pneumoniae*.[5] Cutaneous manifestations range from vesiculobullous/targetoid lesions, morbilliform eruptions to transient macular or serpiginous annular eruptions with severe mucosal involvement [Figure 2].[5] The presence of acute onset of predominant mucosal eruption with prodromal respiratory illness without a relevant drug exposure in children favours RIME [Supplementary Table 1].

VEXAS syndrome (Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic)

VEXAS syndrome, a late-onset autoinflammatory disorder, is linked to acquired somatic mutations in the *UBA1* gene.[6] A typical patient is an elderly male presenting with bicytopenia,

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Table 1: A brief overview of the newer entities

Name	Age at Appearance of first symptoms	Differentials to be considered	Clinical features	Treatment
#CAPE	At or before 1 year of age	Psoriasis, Pityriasis rubra pilaris, PSEK (Progressive symmetric erythrokeratoderma)	Infantile onset skin lesions resembling psoriasis and pityriasis rubra pilaris (PRP), predominantly affecting the face, specifically the chin, cheeks, and upper lips with a characteristic sparing of the infralabial region.[1]	Management options include inhibitors targeting IL-12 and IL-23 such as ustekinumab and IL-23p19 inhibitors like guselkumab.[1]
MiTES	9 months to 1 year of age	Dermatitis artefacta, trigeminal trophic syndrome, Lesch-Nyhan syndrome, neurotic excoriations	Deep, self-inflicted excoriations, primarily located on the medial cheeks, nasal bridge, and central forehead.	Emollients and topical steroid–antibiotic combination, psychological support.
EPSR	20–40 years	Erythema annulare centrifugum (EAC)	Recurrent annular or semi-annular erythema with central regression, accompanied by tiny red peripheral maculopapules and itching.	Oral antihistamines, topical corticosteroid, and coal tar
PAMI	3.9years (before 6 years)	Pyoderma gangrenosum	Cutaneous manifestations include skin ulcers resembling pyoderma gangrenosum and painful, recurrent, aseptic monoarticular pyogenic arthritis.[9]	Non-steroidal anti-inflammatory drugs, calcineurin inhibitors, steroids, and tumour necrosis factor antagonists can be used for treatment.[9]
RIME	≥ 5 years	Erythema multiforme major, Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis, herpetic gingivostomatitis, paraneoplastic pemphigus, systemic lupus	Cutaneous lesions appear as vesiculobullous/ targetoid lesions, morbilliform eruptions, and transient macular or serpiginous annular eruptions. Mucosal involvement is severe and nearly universal, affecting oral, ocular, urogenital, nasal, and anal mucosa.[5]	Corticosteroids, IVIG, cyclosporine and tumour necrosis factor inhibitors.
CCV	>30 years	Generalised essential telangiectasia (GET)	Blanchable, non-urticating erythematous macules on the lower extremities, trunk, and upper extremities.	Pulsed dye laser (PDL).
VEXAS	>60 years	Neutrophilic disorders like Sweets syndrome	Cutaneous lesions resembling a variety of morphologies, including sweet syndrome, relapsing polychondritis, polyarteritis nodosa (PAN), urticarial lesions, erythema nodosum, and leukocytoclastic vasculitis.	Corticosteroids, biological and synthetic DMARDs, hypomethylating agents like azacitidine, and allogeneic hematopoietic stem cell transplant are treatment options.[7]
IgG4 related disease	> 40 years	Multicentric Castleman disease, Sjogren syndrome, Psoriasis vulgaris, B cell pseudolymphoma, anaphylactoid purpura, systemic sclerosis	Skin involvement in IgG4-RD includes erythematous papules, plaques, or nodules on the head and neck, sometimes preceding systemic symptoms.[8] The primary skin manifestations include cutaneous plasmacytosis, pseudolymphoma with angiolymphoid hyperplasia, and eosinophilia or Mikulicz disease. Secondary IgG4-related skin manifestations include psoriasis like eruption, maculopapular eruptions, purpura, urticarial vasculitis, and ischaemic digit.	Systemic and topical corticosteroids, intralesional corticosteroids, rituximab, azathioprine methotrexate.
BASCULE	4 months to 19 years	Chronic orthostatic intolerance	The lower limbs are typically affected by the clinical signs of BASCULE syndrome, which appear one to two minutes after standing. Erythrocyanosis first manifests as anaemic macules, which in a matter of minutes turn into itchy orange-red papules that protrude from their centres. Lying down causes all symptoms to spontaneously go away.	Skin lesions usually go away over many months to years. Assessment to rule out long-term orthostatic intolerance.
PLACK	Since infancy	Epidermolysis bullosa, pachyonychia congenita, and Bart-Pumphrey syndrome	Peeling skin, leukonychia, acral punctate keratoses, cheilitis, and knuckle pads.	Intravenous lipid infusion (Vitalipid®; an emulsion of fat-soluble vitamins and lipofundin-MCT/LCT 20%).[16]
Hereditary alpha tryptasemia	10–20 years	Anaphylaxis, Scombroid poisoning, mastocytosis	Flushing (47), itch (69), urticaria (37) and anaphylaxis (14–28).	Antihistamines, mast cell stabilisers, or IgE antibodies.

#CAPE can be differentiated from psoriasis and PRP by infantile onset, predominant facial involvement (especially upper lip area), lack of keratotic papules, non-responsiveness to conventional antipsoriatic treatments

MCT/LCT- medium chain triglycerides/long chain triglycerides, CAPE- CARD14 associated papulosquamous eruption, MiTES-Midface todller excoriation syndrome, EPSR-Erythema papulosa semicircularis recidivans, PAMI- PSTPIP1-associated myeloid-related-proteinemia inflammatory syndrome, RIME- Reactive infectious mucocutaneous eruption, CCV-Cutaneous collagenous vasculopathy, BASCULE- Bier anemic spots, cyanosis and urticaria like eruption, PLACK- peeling skin, leukonychia, acral punctate keratoses, cheilitis and knuckle. pads

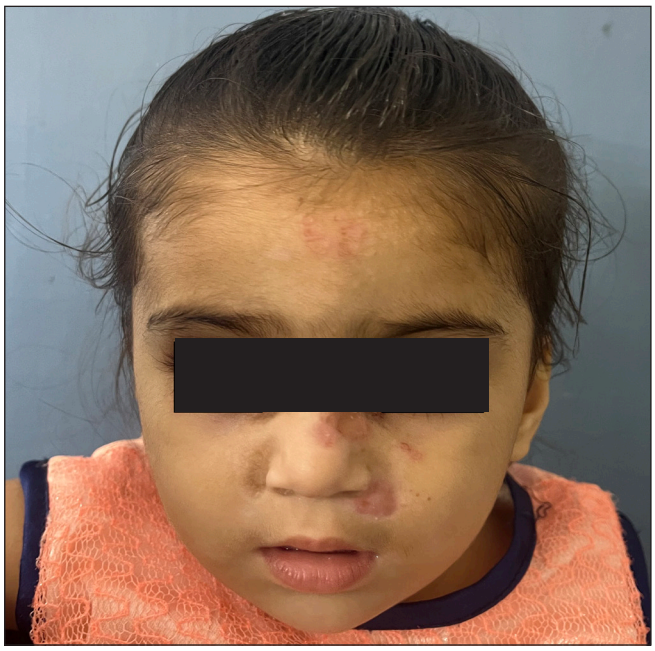

Figure 1: Symmetrical excoriations present over the central face in an X-shaped distribution in midface toddler excoriation syndrome (MiTES).

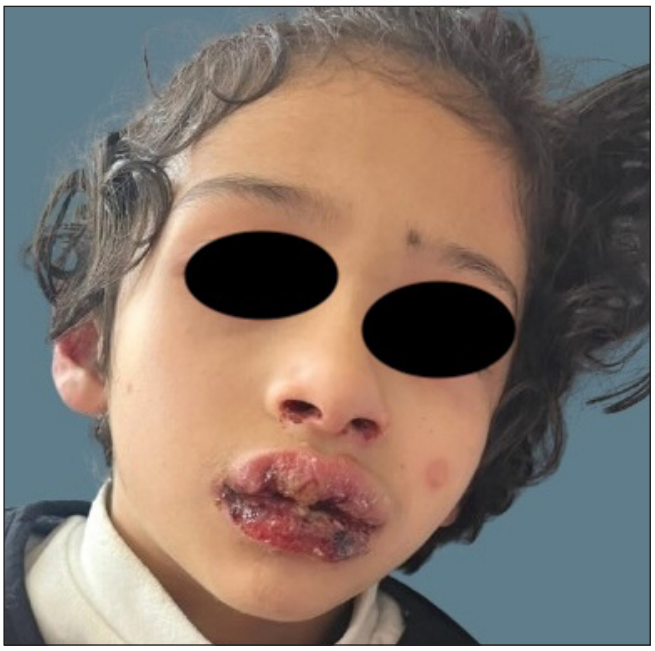

Figure 2: Extensive mucosal involvement in the form of haemorrhagic cheilitis and conjunctivitis in the child of RIME (reactive infectious mucocutaneous eruption).

mean corpuscular volume >100 fL with characteristic cytoplasmic vacuoles and systemic inflammatory features with prominent cutaneous lesions resembling a variety of morphologies, including sweet syndrome, relapsing polychondritis, polyarteritis nodosa (PAN), urticarial lesions, erythema nodosum and leukocytoclastic vasculitis [Figure 3].[7]

IgG4-related disease

Immunoglobulin G4 (IgG4)-related disease (IgG4-RD) is a recently defined fibroinflammatory disorder marked by elevated levels of circulating IgG4 and infiltration of IgG4+ plasma cells in multiple organs, including the pancreas, salivary glands, and lacrimal glands. It typically presents in middle-aged or elderly men with asthenia, weight loss, lymphadenopathy, pancreatitis, orbital pseudotumour, and allergic diseases like atopic dermatitis, allergic rhinitis, or asthma. Skin lesions are classified as primary or secondary, based on histological criteria [Figures 4 and 5] [Table 1].[8]

PSTPIP1-associated myeloid-related-proteinemia inflammatory syndrome (PAMI Syndrome)

It is a rare monogenic autoinflammatory disorder caused by pathogenic variants in *PSTPIP1* (proline-serine-threonine-phosphatase interacting protein) gene resulting in severe and chronic systemic inflammation, hepatosplenomegaly and pancytopenia.[9] Skin manifestations include pyoderma gangrenosum-like ulcers associated with painful, recurrent, aseptic pyogenic monoarthritis.[9]

Erythema papulosa semicircularis recidivans (EPSR)/Erythema papulatum centrifugum (EPC)

It is characterised by recurrent annular or semi-annular erythema with central regression, accompanied by tiny red peripheral maculopapules and itching. Exacerbations after sweating or consuming spicy food suggest a potential link to sweating-related dermatitis.[10] Erythema annulare centrifugum (EAC) is an important differential [Supplementary Table 2]. Histopathology involves spongiosis, parakeratosis, superficial perivascular mononuclear cell infiltrate, and inflammation around intraepidermal as well as dermal eccrine ducts.

Cutaneous collagenous vasculopathy (CCV)

It is a rare microangiopathy of dermal blood vessels characterised by blanchable, non-urticating macules, ecchymoses, and petechiae on the trunk, upper and lower extremities.[11] It predominantly affects Caucasians and is associated with diabetes mellitus, autoimmune and cardiovascular diseases. Histopathologically, CCV shows dilated cutaneous vessels with marked collagen deposition and luse bodies onelectronmicroscopy.It is often underdiagnosed due to its clinical similarity to generalised essential telangiectasia (GET); however, subtle features like mucosal involvement, predominant involvement of lower limbs, increased occurrence in women, and absence of collagen deposition in vessels favors the latter.[12]

BASCULE syndrome

BASCULE (Bier anemic spots, cyanosis and urticaria-like eruption) occurs as a benign vasomotor disorder due to exaggerated vasoconstrictive response of arterioles to tissue hypoxia.[13] It presents as red-orange urticarial lesions (paradoxical reaction to hypoxia) with a white anaemic halo on erythrocyanotic background over lower extremities precipitated on standing and relieved on lying down. There

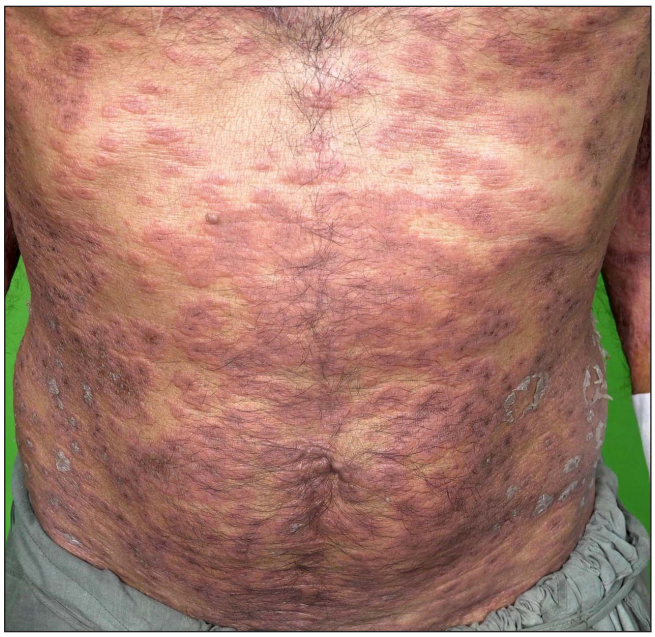

Figure 3: Edematous, erythematous plaques over the abdomen in a patient of VEXAS syndrome.

Figure 4: Edema and erythema over the left eyelid in a patient of IgG4 disease.

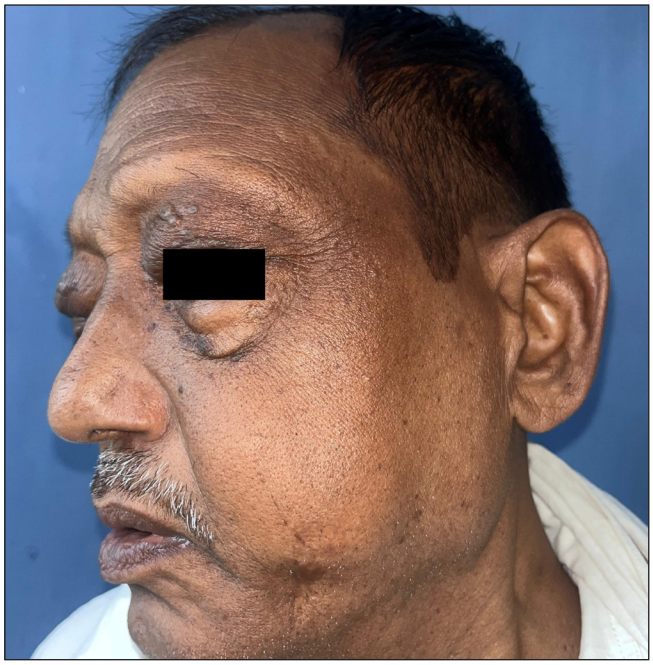

Figure 5: Swelling of eyelids and left cheek in a patient of IgG4 disease.

is associated pruritus and tenderness over affected areas in a variable number of cases. High-dose bilastine for pruritus and aspirin has been found to be effective with a spontaneous resolution by two years in some cases.[13]

PLACK syndrome

A recently reported variant of peeling skin syndrome (PSS) is known as peeling skin, leukonychia, acral punctate keratoses, cheilitis, and knuckle pads (PLACK syndrome). This autosomal recessive disorder occurs due to loss-of-function mutations in *CAST*, the gene-producing calpastatin – a particular inhibitor of calpains, which are calcium-dependent cysteine proteases leading to impaired intracellular adhesion and skin peeling.[14] It presents in infancy as superficial skin peeling, spontaneous/trauma-induced blisters, xerosis, perioral fissuring, white nails, and keratotic papules over knees and knuckles.[15] There is no effective treatment; however, low levels of vitamin A and essential fatty acids in some cases signify the role of intravenous lipid infusion.[16]

Hereditary alpha tryptasemia

About 5% of the general population is afflicted with hereditary alpha-tryptasemia (HαT), an autosomal dominant condition with excess copies of *TPSAB1*. Amongst afflicted families, elevated baseline tryptase levels are consistently seen. It is most frequently linked to neuropsychiatric symptoms like fatigue (85%), depression (59%), sleep difficulties (69%), memory impairment (59%), postural orthostatic tachycardia syndrome (POTS), and gastrointestinal symptoms like nausea (51%), reflux (49%) and irritable bowel syndrome (30–60%). Patients with systemic mastocytosis (SM; 12–21%) are more likely to have HαT. It is frequently linked to severe anaphylaxis brought on by unidentified triggers or insect poisons.[17]

Alpha-gal syndrome

It is an acquired mammalian meat allergy which occurs due to IgE sensitisation of humans to alpha-gal following tick bites. Alpha-gal is a sugar moiety (galactose-alpha-1,3-galactose) present in red meat and other mammalian products.[18] It clinically manifests as delayed urticarial rash, angioedema, abdominal pain and nausea two to six hours after consumption of red meat. Other features can include anaphylaxis, fixed pruritic rashes, subcutaneous nodules, arthritis, chronic

pruritus and recall urticaria.[18] Diagnosis is established by positive alpha-gal IgE blood testing and improvement on mammalian restricted diet. Management includes avoidance of red meat and occult alpha-gal exposures like live vaccines, catgut sutures, and more.

Acral histiocytic nodules

Representing an undescribed variant of non-Langerhans histiocytosis, acral histiocytic nodules pursue a benign course devoid of malignancy or extracutaneous involvement. Clinically, multiple, well-defined, skin-coloured to erythematous, firm nodules emerge on the palmar aspect of fingers.[19] Histopathology shows thinned-out stretched epidermis and effacement of rete ridges, along with multiple sclerotic, non-necrotising, nodular granulomas palisaded by spindle-shaped macrophages and occasional giant cells in the dermis and subcutis with strong positivity for CD68 and negativity for S100.[20]

Saurian papulosis

It is an epidermal keratinisation disorder which manifests as widespread, well-circumscribed, flesh-coloured, flat-topped polygonal papules covering most of the skin surface, excluding the face, palms, and soles; resembling the skin of reptiles, therefore called 'saurian papulosis'. It is possibly inherited as an autosomal recessive trait.[21] Histopathology exhibits compact eosinophilic orthokeratotic hyperkeratosis lacking parakeratosis, slightly acanthotic epidermis, no hypergranulosis, and a superficial perivascular lymphohistiocytic dermal infiltrate with diminished expression of connexin 43. Differential diagnoses include acrokeratosis verruciformis, epidermodysplasia verruciformis, flat warts, hyperkeratosis lenticularis perstans (Flegel's disease), keratosis lichenoides chronica (Nekam's disease) and porokeratosis.

Circumferential skin creases Kunze type

It is characterised by circumferential skin creases, cleft palate, intellectual disability, growth retardation, and typical facies with short upslanting palpebral fissures, epicanthal folds, broad nasal bridge, nicostomia, and micrognathia. It can occur either as an isolated anomaly or associated with other syndromes like the HITCH syndrome (hearing impairment, undescended testis, circumferential skin creases, and mental handicap).

Conclusion

To conclude, postgraduates and dermatologists should be aware of these emerging entities in dermatology due to different treatment outcomes and prognosis.

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