Target and targetoid lesions in dermatology

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Target lesions are characterized by a distinct clinical morphology, presenting as three concentric zones. They classically occur in erythema multiforme, an acute, self-limiting, often recurrent mucocutaneous disease involving mainly the face and extremities and most frequently related to infections, particularly herpes simplex virus and *Mycoplasma pneumoniae*. Targetoid lesions are target-like in appearance, with usually two concentric zones and are seen in several dermatologic conditions other than erythema multiforme. In 1993, Bastuji-Garin *et al*. proposed a classification system and defined two disease spectra – (1) erythema multiforme (major and minor) and (2) Stevens-Johnson syndrome – toxic epidermal necrolysis, the latter are usually drug induced and associated with high mortality.[1] These diseases are classified based on the percentage of skin detachment and the pattern of individual target lesions.[1] The various types of target lesions are as follows:

i. Typical targets: Round regular lesions with well-defined borders, <3 cm in diameter and having classic three zones – the inner most purpuric or necrotic with or without blister, the middle pale edematous ring, and the outer erythematous ring
ii. Raised atypical targets: Round palpable edematous lesions that have two zones instead of three and/or an ill-defined border
iii. Flat atypical targets: Round non-palpable lesions with two zones and/or a poorly defined border. Blister may be present in the center
iv. Macules with or without blisters: Non-palpable erythematous macules of irregular size and shape with or without blisters.

Typical targets and raised atypical targets are seen in erythema multiforme, while flat atypical targets and macules with or without blisters are seen in Stevens-Johnson syndrome, Stevens-Johnson syndrome – toxic epidermal necrolysis overlap and toxic epidermal necrolysis.[1] A minor modification of this classification has categorized typical targets as raised typical targets and flat typical targets. Taking this into consideration, raised typical and raised atypical targets are characteristic of erythema multiforme, while flat typical, flat atypical targets and macules with or without blisters are a feature of Stevens-Johnson syndrome/toxic epidermal necrolysis.[2]

Erythema multiforme-like or targetoid lesions have been described in a wide range of other dermatoses [Table 1] which are briefly discussed below.

Connective Tissue Disorder

Lupus erythematosus

The occurrence of erythema multiforme-like lesions in lupus erythematosus, either systemic or cutaneous, is described as Rowell syndrome. It was first studied in 1963 in four women with discoid lupus erythematous, chilblain lupus, and lesions resembling erythema multiforme. Laboratory investigations revealed speckled pattern of antinuclear antibody, positive rheumatoid factor, positive anti-La, and pancytopenia.[3] Subsequently, in a review of 95 cases, erythema multiforme-like lesions associated with lupus erythematosus were grouped into two subtypes[4] – the first being subacute cutaneous/acute cutaneous lupus erythematosus with erythema multiforme-like lesions, in which there is no preferential location, mucous membranes

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are uncommonly involved, and triggering factor is identified occasionally but is never herpes simplex virus. On direct immunofluorescence, pattern of lupus erythematosus-specific lesions is observed in majority of the cases. Erythema multiforme-like lesions in this setting are regarded as morphologic variants of lupus erythematosus-specific skin lesions [Figure 1]. The second group comprises chronic cutaneous lupus erythematosus with erythema multiforme-like lesions, in which the clinical and immunological features resemble those originally described by Rowell *et al*. and hence some authors have reserved the term "Rowell syndrome" for this subset of patients.

Drug Reaction

Drug reaction with eosinophilia and systemic symptoms

Atypical purpuric target lesions not necessarily confined to acral sites are associated with severe systemic involvement in the form of serious liver dysfunction and increased mortality.[5]

Immunobullous Disorders

Bullous pemphigoid

Targetoid lesions along with widespread bullous lesions have been described in erythema multiforme-like bullous pemphigoid. Severe involvement of mucosae reminiscent of erythema multiforme major can be associated. Majority of these cases were classified as drug-induced erythema multiforme-like bullous pemphigoid and the drugs implicated were penicillins and furosemide.[6]

Linear IgA bullous dermatosis

Varied presentations can occur in adults, resembling bullous pemphigoid, dermatitis herpetiformis, erythema multiforme, and Stevens-Johnson syndrome/toxic epidermal necrolysis. Erythema multiforme and toxic epidermal necrolysis-like presentation with widespread bullae are seen in drug-induced cases, with vancomycin being the most common drug followed by phenytoin and lithium.[7] The lesions present as flat targetoid macules with a central bulla [Figure 2].

Pemphigoid gestationis

Clinical manifestations include tense bullae, herpetiform vesicles, and urticarial and targetoid plaques, usually involving the periumbilical area.[8] Although the lesions typically develop during late pregnancy, they can sometimes occur in early pregnancy and immediate postpartum period.

Paraneoplastic pemphigus

The earliest and the most consistent finding is severe mucositis. Although oral erosions can affect any site, they characteristically involve the vermilion of the lips and resemble erythema multiforme and Stevens-Johnson syndrome/toxic epidermal necrolysis. The cutaneous lesions are polymorphic and resemble those of pemphigus, bullous pemphigoid, lichen planus, erythema multiforme, toxic epidermal necrolysis, and graft versus host disease, depending on whether humoral or cytotoxic immunity is predominant. Erythema multiforme-like cutaneous lesions, extensive skin/mucosal involvement, and keratinocyte necrosis on histology are linked to more severe disease and shorter survival rate.[9]

Table 1: Diseases that present with targetoid lesions[2,7]

Connective tissue disorder
Lupus erythematosus
Drug reactions
Stevens-Johnson syndrome – toxic epidermal necrolysis
Drug reaction with eosinophilia and systemic symptoms
Immunobullous disorders
Bullous pemphigoid
Linear IgA bullous disease
Pemphigoid gestationis
Paraneoplastic pemphigus
Infections
COVID-19
Erythema chronicum migrans
Erythema nodosum leprosum
Mycoplasma-induced rash and mucositis
Syphilis
Inflammatory disorders
Erythema multiforme
Acute hemorrhagic edema of infancy
Erythema multiforme-like allergic contact dermatitis
Pityriasis rosea
Polymorphic eruption of pregnancy
Sweet's syndrome
Urticaria multiforme
Tumor
Targetoid hemosiderotic hemangioma

Infections

COVID-19

In a case series of four patients with erythema multiforme-like eruption, the sites involved were face, trunk, and limbs, with sparing of palms and soles. Two patients had typical target lesions. Oral mucosa showed palatal macules and petechiae.[10] All patients developed the lesions after the onset of coronavirus symptoms, with a mean interval of 19.5 days. The onset of erythema multiforme-like lesions was associated with worsening of one or more laboratory parameters (C-reactive protein, D-dimer, or lymphocyte count), but no recurrence of coronavirus symptoms.[10]

Erythema chronicum migrans

It develops 3–30 days after tick bite as an expanding round to oval, larger than 5 cm in size, erythematous lesion with a slightly dusky center indicating the site of bite.[11] After a few weeks, the center fades leaving behind an erythematous border. It has a predilection for lower limbs, axillary and inguinal areas in adults, and face in children.

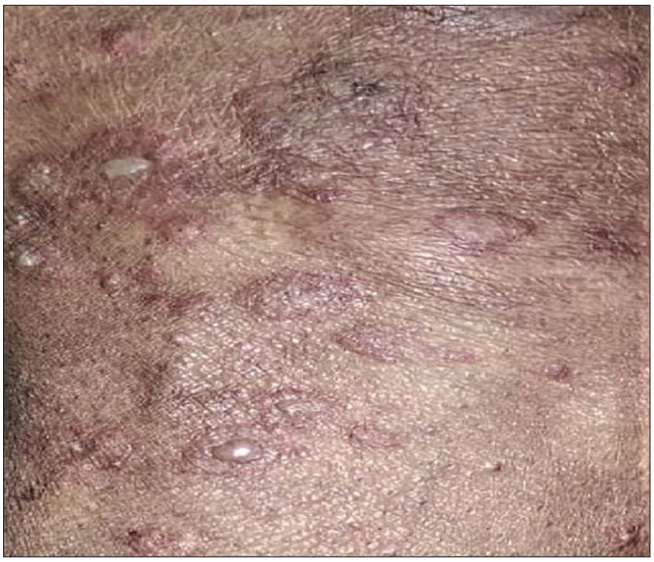

Figure 1: Raised typical and atypical target lesions in a patient of systemic lupus erythematosus

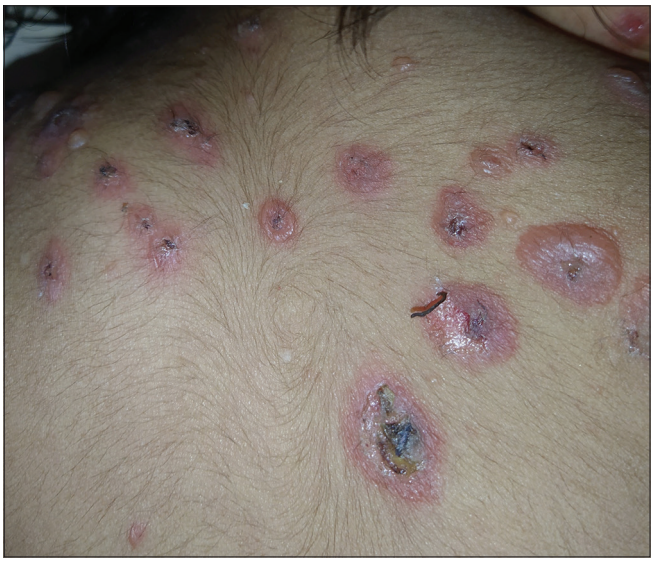

Figure 2: Erythematous plaques showing central vesiculation and crusting along with tense bullae on the back in linear IgA bullous dermatosis

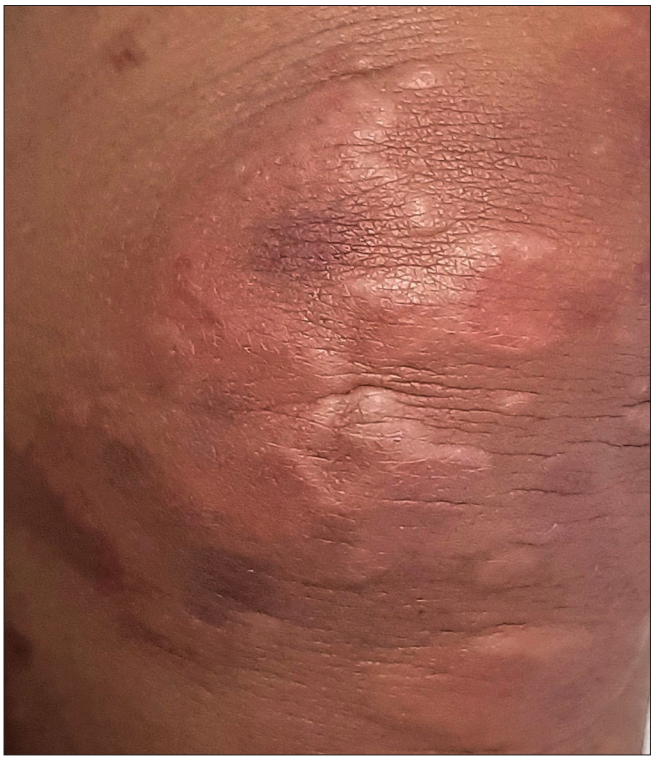

Figure 3a: Ill to well-defined targetoid plaques with central purpuric area surrounded by an edematous erythematous zone on the extensor aspect of the lower limb

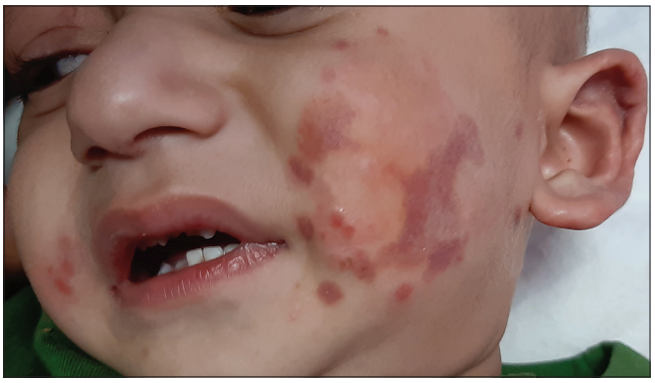

Figure 3b: Targetoid plaques on the cheeks with associated edema of the left auricle

Erythema nodosum leprosum

Erythema multiforme-like erythema nodosum leprosum has been described in around 4.5% of leprosy patients.[12] Concomitant lesions of classic erythema nodosum leprosum may be seen in some cases. Palmoplantar lesions and mucosal involvement are not observed. Histologically, subepidermal edema, occasionally bulla, and few apoptotic keratinocytes are described.[12,13]

Mycoplasma-induced rash and mucositis

M. pneumoniae associated mucocutaneous eruption consists of severe mucositis with sparse cutaneous involvement. The cutaneous lesions are polymorphic, with vesiculobullous being the most common (77%), followed by targetoid lesions (48%), macules, papules, morbilliform rash, and rarely toxic epidermal necrolysis-like presentation.[14] Targetoid lesions are often atypical flat purpuric macules, centrally distributed and associated with respiratory tract sequelae.[15] Serologic testing and polymerase chain reaction from throat swab confirm the diagnosis.

Syphilis

Erythema multiforme-like morphology has been reported in secondary and congenital syphilis.[7,16] The skin biopsy shows findings of erythema multiforme with or without plasma cells. *Treponema pallidum* has been demonstrated by immunoperoxidase staining and polymerase chain reaction in these lesions. It is hypothesized to occur due to direct spirochete invasion provoking specific immune response against *T. pallidum*.[7,16] In contrast, erythema multiforme

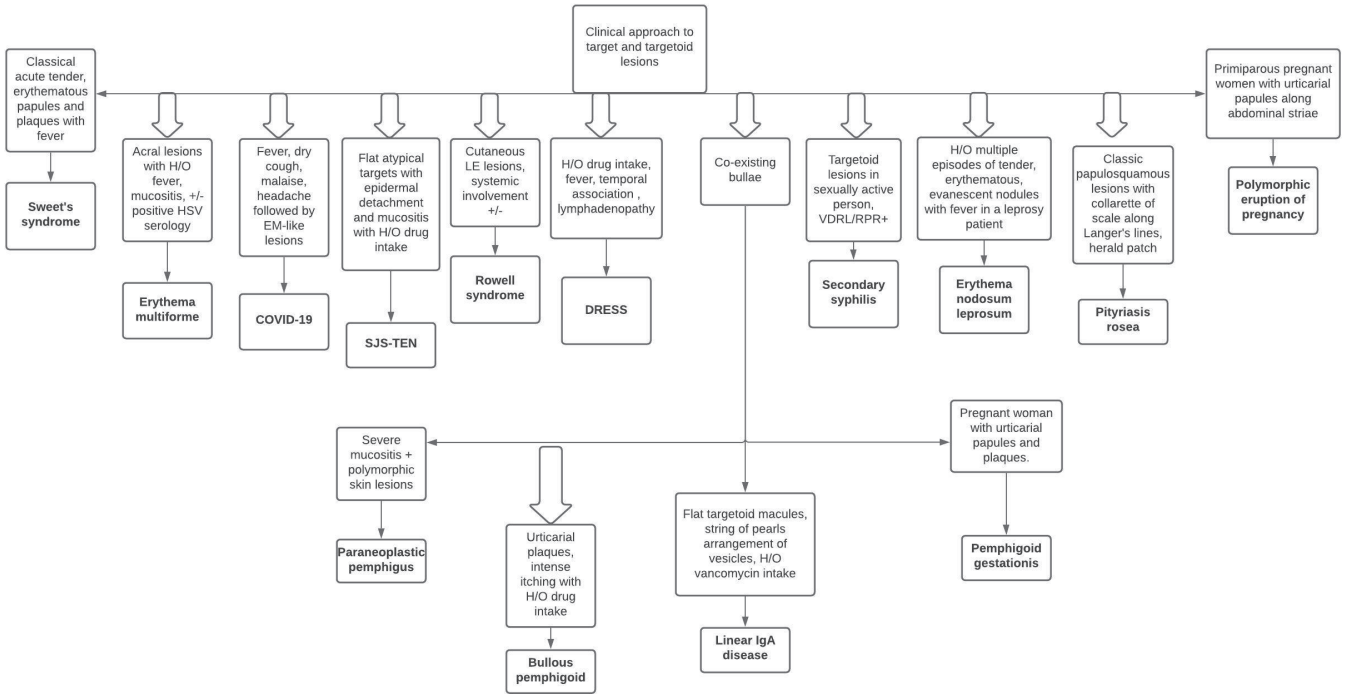

Figure 4: Flowchart showing clinical approach to targetoid lesions

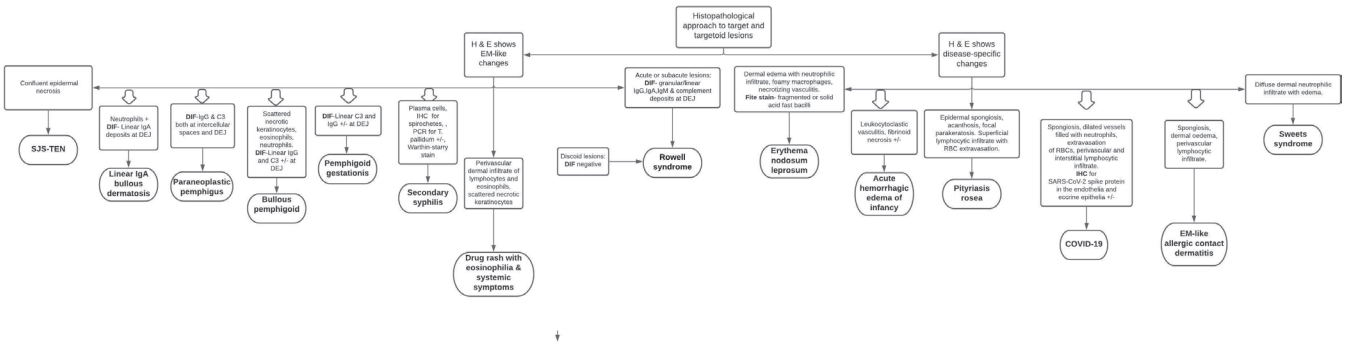

Figure 5: Flowchart depicting histopathological approach to targetoid lesions

triggered by syphilis shows mixed inflammatory infiltrate with the absence of treponemes.

Inflammatory Disorders

Acute hemorrhagic edema of infancy

It is a self-limiting form of leukocytoclastic vasculitis that affects children between four months and two years of age. It presents with mild fever, peripheral non-pitting edema, and skin lesions, which start as macules, papules, and urticarial plaques and later evolves into cockade or targetoid purpuric lesions on the face, auricles, and extremities [Figures 3a and b]. Systemic involvement is uncommon.[2,7]

Erythema multiforme-like allergic contact dermatitis

It is caused by plants such as *Primula*, *Toxicodendron* (poison ivy), Compositae, and quinones in exotic woods. Other allergens include medicaments such as triamcinolone acetonide, neomycin, bufexamac, and miscellaneous compounds such as paraphenylenediamine, clothing dyes, and rubber chemicals.[17] The lesions may be limited to the site of contact or become generalized in case of systemic exposure to a topically sensitized compound.

Pityriasis rosea

Erythema multiforme-like pityriasis rosea is an uncommon atypical morphological variant. The lesions may occur along with typical papulosquamous lesions in a Christmas tree pattern. It could also represent erythema multiforme in response to human herpes virus-6 and 7. Histopathology shows findings of pityriasis rosea with the absence of vacuolar degeneration and satellite cell necrosis. In a series of 40 cases of pityriasis rosea, four were reported to have erythema multiforme-like morphology.[18]

Polymorphic eruption of pregnancy

In a study of 181 patients, 51% developed features such as eczematous lesions (22%), vesicles (17%), non-urticarial erythema (6%), and targetoid lesions (6%), in addition to the classic pruritic urticarial papules and plaques.[19]

Sweet's syndrome

In a study of 90 patients, atypical targetoid lesions were reported along with the classic lesions in 11 cases. Significant correlation was observed between targetoid lesions and vasculitis on histological examination.[20]

Urticaria multiforme

It is an acute cutaneous hypersensitivity reaction, which presents in children as blanchable, annular, and polycyclic erythematous wheals with a dusky ecchymotic center [Figure 4]. However, true target lesions, skin necrosis, or blistering are not seen. It is associated with angioedema of face, hands, feet, and dermographism and resolves within 24 h.[7]

Tumor

Targetoid hemosiderotic hemangioma

It is a benign vascular tumor which exhibits a violaceous papule in the center surrounded by a pale area and an ecchymotic ring at the periphery.[2]

Approach to target and targetoid lesions

As the list of differential diagnoses for a patient presenting with targetoid lesions is quite extensive, a detailed history, clinical examination, and guided laboratory investigations including skin biopsy, direct immunofluorescence, serological, and other relevant tests are imperative in reaching a definitive diagnosis. A step-wise systematic approach to targetoid lesions, based on history, clinical presentation, and histopathological examination is depicted in Figures 4 and 5.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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