Chapter

Clinical Manifestations of Sarcoidosis and Granulomatous Disorders

Suchibrata Das

Abstract

Sarcoidosis is a multisystem granulomatous disease, mainly involving the lungs, mediastinal and peripheral lymph nodes, liver, eyes, and skin. Cutaneous manifestations of sarcoid are variable and behave as "great imitators" of other cutaneous disorders. Cutaneous lesions are classified as specific and nonspecific forms. A large number of systemic sarcoidosis patients have specific cutaneous lesions, and this may be the presenting feature; isolated skin lesions may also present in some patients. Specific lesions of sarcoid are red-brown or red-violaceous in color, asymptomatic, and usually multiple in number. Different types of lesions may present in the same patient. This clinical appearance is due to the presence of epithelioid cell granulomas in the dermis.

Keywords: sarcoidosis, cutaneous sarcoidosis

1. Introduction

The granuloma is the result of interplay of an invading organism or antigen, chemical, drug or other irritant, prolonged antigenemia, macrophage activity, a Th1 cell response, B cell overactivity, circulating immune complexes, and a vast array of biological mediators [1]. Cutaneous granulomatosis can be localized or more disseminated, depending on their etiology. The typical lesion is a painless infiltrated papule, rounded, well limited, and reddish-pink and takes a yellowish color on diascopy, called apple-jelly. Its surface is smooth or slightly squamous, as there is generally no epidermal participation [2]. From a clinical point of view, it is useful to divide cutaneous granulomatosis into localized and more disseminated forms, although this distinction may sometimes be artificial. From a pathogenic point of view, they are divided into noninfectious and infectious granulomas [3].

2. Comprehensive classification of granulomatous disorders

A comprehensive classification of granulomatous disorders of the skin (according to American Academy of Dermatology, 76th Annual Meeting San Diego, CA USA) (**Table 1**) [4].

Noninfectious granulomatous disorders	Infectious granulomatous disorders
Epithelioid granulomas	*Caseating granulomas*
Sarcoidosis	Tuberculosis
Granulomatous rosacea/POD	Leprosy
Cutaneous Crohn's	Atypical mycobacterium
Orofacial granulomas	Leishmaniasis
Palisading granulomas	*Suppurative granulomas*
Granuloma annulare	Deep fungal
Elastolytic giant cell granuloma	Pyodermas
Necrobiosis lipoidica	Granulomatous STDs
Rheumatic nodules	
Reactive granulomatous disorders	
Xanthomatous granulomas	
Adult onset XG	
Adult onset APXG	
NXG	
Multicentric reticulohistiocytosis	
Rosai-Dorfman	
Xanthoma disseminatum	
Others	
Granulomatous vasculitis	
Lymphomatoid granulomatosis	
Foreign body reactions	
Granulomatous drug reactions	

Table 1.
Classification of granulomatous disorders of skin (American Academy of Dermatology, 76th Annual Meeting San Diego, CA USA).

3. Noninfectious granulomatous disorders

3.1 Epithelioid granulomas

3.1.1 Sarcoidosis

Sarcoidosis is a multiorgan disease. The most commonly affected organs are skin, lungs, and lymph nodes. Different epidemiological factors such as age, sex and race, the duration of the disease, and the sites of involvement affect the presentation of sarcoid. Cutaneous manifestations are extremely variable. Lesions of sarcoidosis are classified as "specific" (noncaseating granulomas are present in biopsy specimens of tissue) or "nonspecific" (lesions develop as a result of a reactive process without the formation of granulomas) [5].

Specific lesions develop in 9–15% of all sarcoidosis patients [5]. These lesions are highly variable in presentations and may be confused with many other skin diseases. The most frequent specific lesions are papules, plaques, lupus pernio, scar sarcoidosis, and subcutaneous sarcoidosis [5]. Erythema nodosum is the most common nonspecific lesion which develops in up to 25% of sarcoidosis cases [6]. Women are more commonly affected than men (W/M, 2:1) and black people than other ethnic groups [7].

The clinical appearance is due to the presence of epithelioid cell granulomas in the dermis. The epidermis rarely appears to be clinically involved [8]. Specific lesions are red-brown or red-violaceous in color and generally multiple and do not cause any symptoms which on diascopy reveals the brown-yellow or apple-jelly color, characteristics of granulomatous diseases. But it is usually more opaque than in lupus vulgaris [9]. Different types of cutaneous lesions may coexist in one patient.

3.1.1.1 Specific lesions of sarcoid

3.1.1.1.1 Maculopapular sarcoidosis

Lesions of maculopapular sarcoidosis are usually red-brown to purple in color and less than 1 cm in diameter. Sometimes they may be skin-colored, yellow-brown, or hypopigmented. They are slightly infiltrated, with little epidermal change. They are located on the face, particularly on the eyelids, around the orbits and the nasolabial folds, and on the scalp, occipital area of the neck, trunk, buttocks, and extremities (**Figure 1**). Lesions are commonly disseminated, and mucous membranes may even be involved [7, 9–11]. Diascopy shows the typical apple-jelly color characteristic of granulomatous skin lesions. These lesions are sometimes transient and appear to herald the onset of the disease [11]. Patients with papular lesions had a mean age of 47 years (9–83 years), and the usual duration of disease to heal is less than 2 years [12]. Acute organ involvement, such as sudden lymphadenopathy, acute arthritis, and acute uveitis abnormal chest radiographs, has been associated with this type of

Figure 1.
Papular sarcoid.

eruption [9]. The intrathoracic involvement occurs in the early stage of the disease, bilateral hilar lymphadenopathy with or without parenchymal infiltration (up to stage II) (60%), and lymphadenopathy in 50% of the patients [13].

3.1.1.1.2 Nodular and plaque sarcoid

It more commonly develops on the back, buttocks, face, and extensor surfaces of the extremities [7]. It is as common as maculopapular sarcoid [10]. It is usually present as multiple round or oval, infiltrated reddish-brown plaques [7, 10], larger than 10 mm in diameter, more indurated, thicker, and persistent than papular sarcoid (**Figure 2**). Sometimes it is mammillated and can be associated with nodular dermal lesions [14]. More than 90% of cases are chronic with disease activity persisting after 2 years [12].

3.1.1.1.3 Lupus pernio

It is the characteristic cutaneous manifestation of sarcoidosis [15]. Lupus pernio refers primarily to diffuse, violaceous to telangiectatic plaque lesions of the nose, cheeks, ears, and fingers [16–19] (**Figure 3**). It tends to appear in older people, especially the black women affected more frequently [20, 21]. The lesions enlarge and become confluent to form progressively disfiguring nodular plaques on the nose and adjacent cheeks [21]. The lesions can involve the upper respiratory tract and cause nasal ulceration, obstruction, and perforation of the nasal septum [15, 22, 23]. Some cases have developed plaques on the arms, thighs, and buttocks [21, 24] and sausage-shaped expansion of the phalanges [16, 25]. This form of sarcoidosis can be recalcitrant to systemic corticosteroids and other immune-suppressants and may be an indicator of current or impending organ involvement [24]. Also it usually follows an extremely chronic course—2–25 years in published series [11, 13].

3.1.1.1.4 Scar sarcoid

Scar sarcoid presents as erythematous, cutaneous, or subcutaneous swelling in the area of an old scar or beside a scar and the development of papules and nodules within the original scars [26]. Scar sarcoidosis can occur on skin sites damaged by a range of factors, including mechanical injuries, venipuncture,

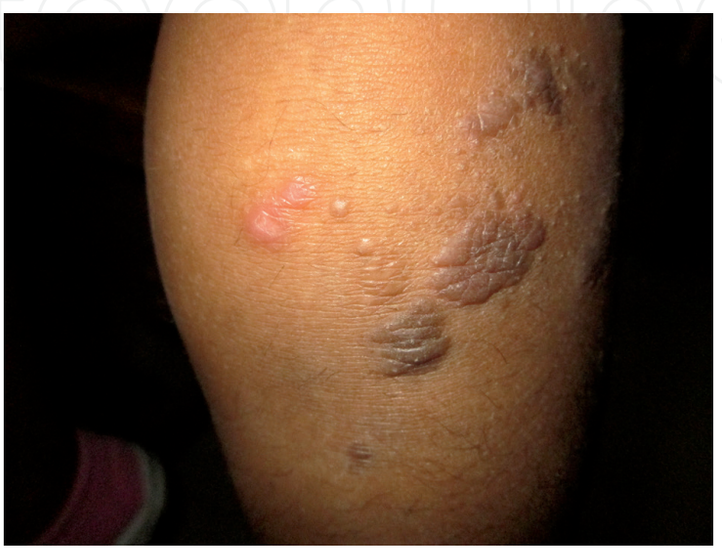

Figure 2.
Plaque sarcoid.

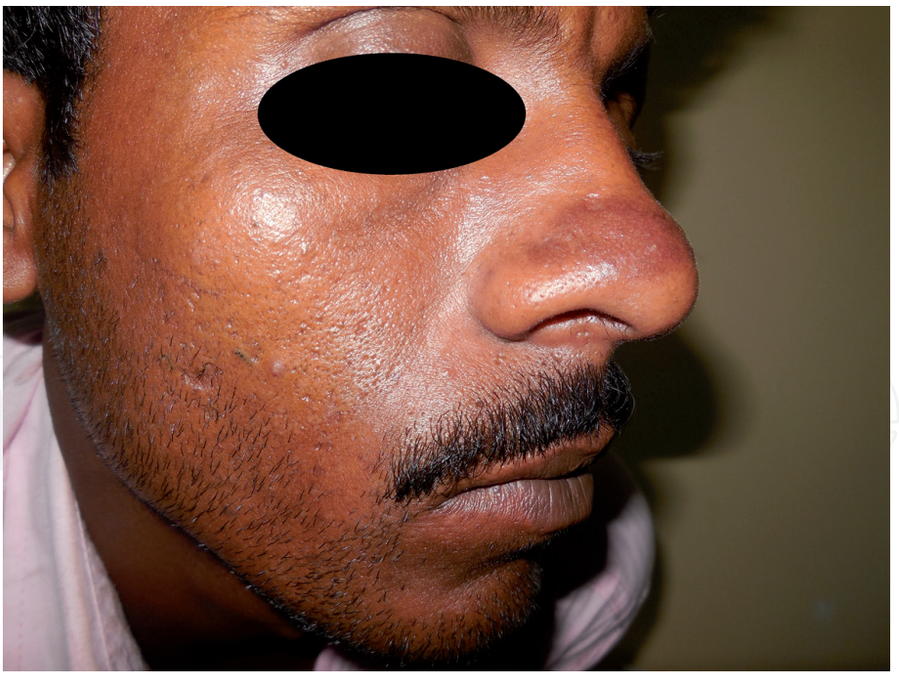

Figure 3.
Lupus pernio.

intramuscular injections, inoculations, tattoos, and infections such as herpes zoster [27] (**Figure 4**). Foreign material within the scar, deposited by external factors including those stated above, is a possible cause of epithelioid granuloma [28]. The specific skin lesions that occur and the resulting sarcoidosis may be associated with the severity and duration of the disease, with scar sarcoidosis often being accompanied by systemic involvement [29]. Alterations, such as further damage or stress to the existing scars, often prompt worsening of sarcoidosis [30]. Scar sarcoidosis can appear at the onset of disease and must be looked for whenever a diagnosis of sarcoid is considered [8]. However, more commonly it is associated with longstanding pulmonary and mediastinal involvement, uveitis, peripheral lymphadenopathy, bony cyst, and parotid infiltration [9, 11].

3.1.1.1.5 Subcutaneous sarcoid (Darier-Roussy sarcoid)

Peak incidence of subcutaneous sarcoid is the fourth decade of life; females are more affected than male; these are asymptomatic to slightly tender subcutaneous lesions typically involving the upper extremities. Majority lessons are erythematous (57%), followed by skin colored (30%), hypopigmented, or violaceous [7, 10] (**Figure 5**). Lesions are usually multiple, clustered, and bilaterally asymmetrical [32]. There are autoimmune disease associations in a subset of patients. There is strong association with a systemic disease component at the outset of disease, notably bilateral hilar adenopathy; noninfectious panicular sarcoidal or epithelioid granulomas with minimal lymphocytic inflammation; and a favorable response to oral corticosteroid therapy [31].

3.1.1.1.6 Less common form of cutaneous sarcoidosis

A wide variety of different cutaneous manifestations have been reported, and the clinical pictures are highly heterogeneous.

Annular sarcoid. Annular lesions are well-recognized forms of cutaneous sarcoidosis, amounting to around 8% of all skin lesions according to a recent study

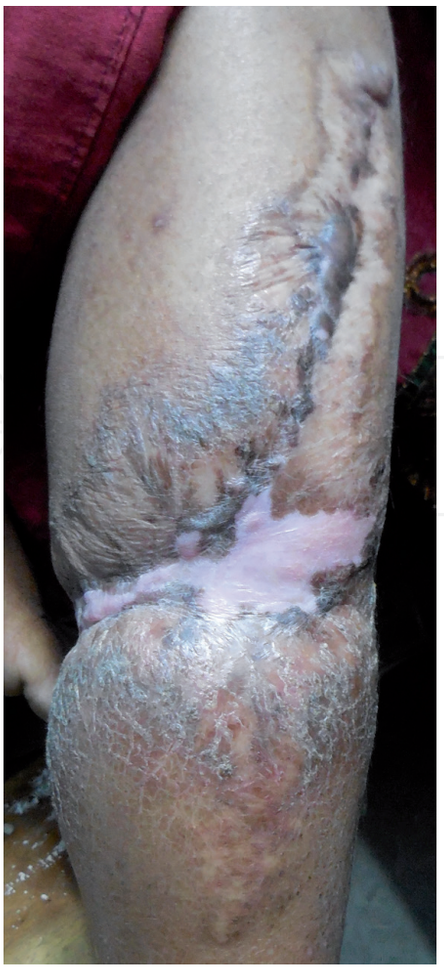

Figure 4.
Scar sarcoid.

from India [32]. Papular lesions may coalesce or be arranged in annular patterns, usually with a red-brown hue. Lesions are indurated, have central clearing with hypopigmentation, and atrophy and scarring may occur (**Figure 6**). Usually, the photo-exposed areas that are affected have a predilection for the face, forehead, and neck. Alopecia may occur in the center of the lesions [32, 33].

Angiolupoid sarcoidosis. Angiolupoid sarcoidosis is an infrequent variant of the disease, affecting 8% of patients with cutaneous sarcoidosis [32]. It manifests clinically as single plaques with central hypopigmentation, which eventually acquire annular shape with prominent telangiectasias, preferentially located on the face, ears, or scalp [32] (**Figure 7**). It is usually present in women [34]. The cutaneous manifestation may be the first sign of a systemic sarcoidosis with the lung (stage 2) and gland involvement that are refractory to several conventional drug therapies [34].

Hypopigmented sarcoid. Dermal nodules with surrounding hypopigmentation and macular hypopigmented areas occur predominantly on the limbs. They may be tender but have no associated anesthesia [35].

In the nodules, the pigment is retained in the center where the color is dark red-brown. The lesions are ill-defined, and perifollicular pigment is usually retained at the periphery. Nodules are unattached to underlying structures and tender when pressed or squeezed [35]. Sarcoid granuloma present in all nodules but in half of macules [36].

Morphea-like lesions. Clinical features are indistinguishable from those of true morphea, and the cutaneous lesions may precede or arise years after the extracutaneous sarcoidosis [37]. Lesions are coalescing hyperpigmented atrophic plaques, may be indurated, usually in limbs, mainly lower limbs [38] (**Figure 8**).

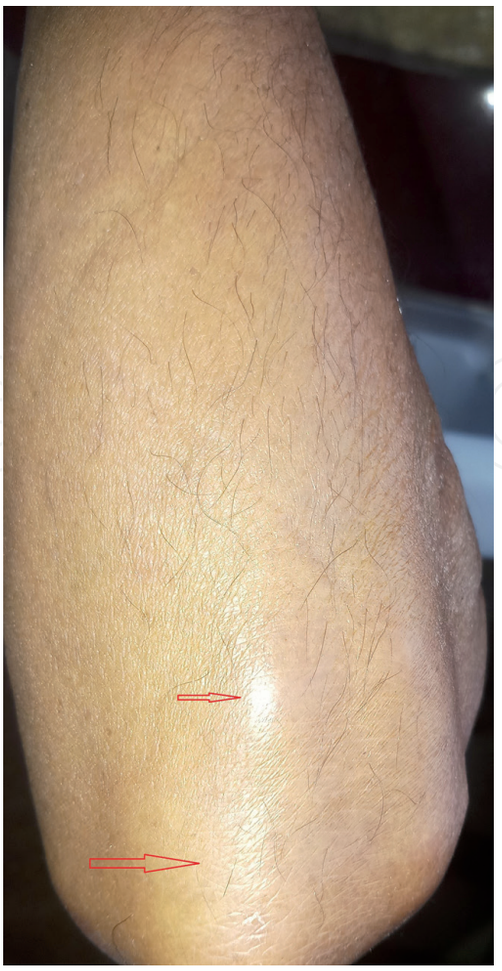

Figure 5.
Subcutaneous sarcoidosis.

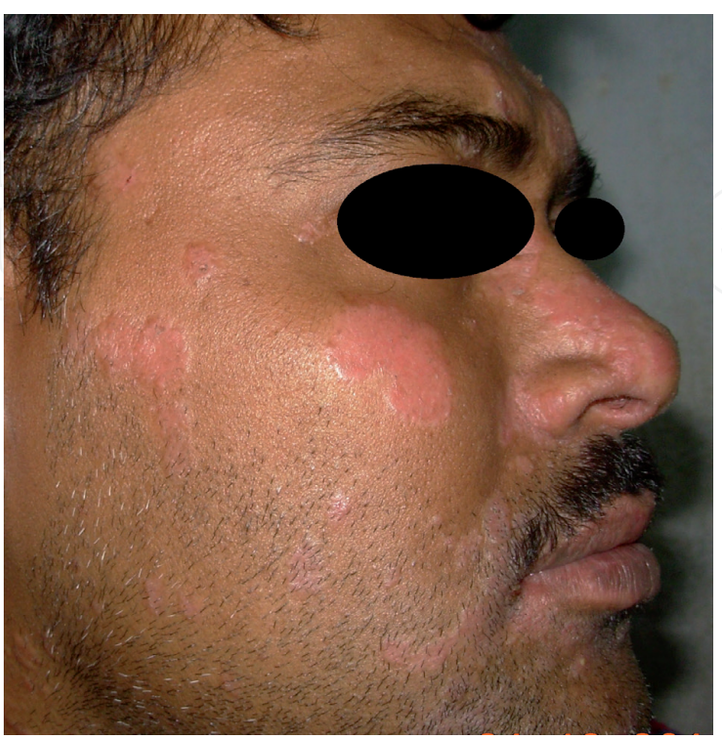

Figure 6.
Annular sarcoid.

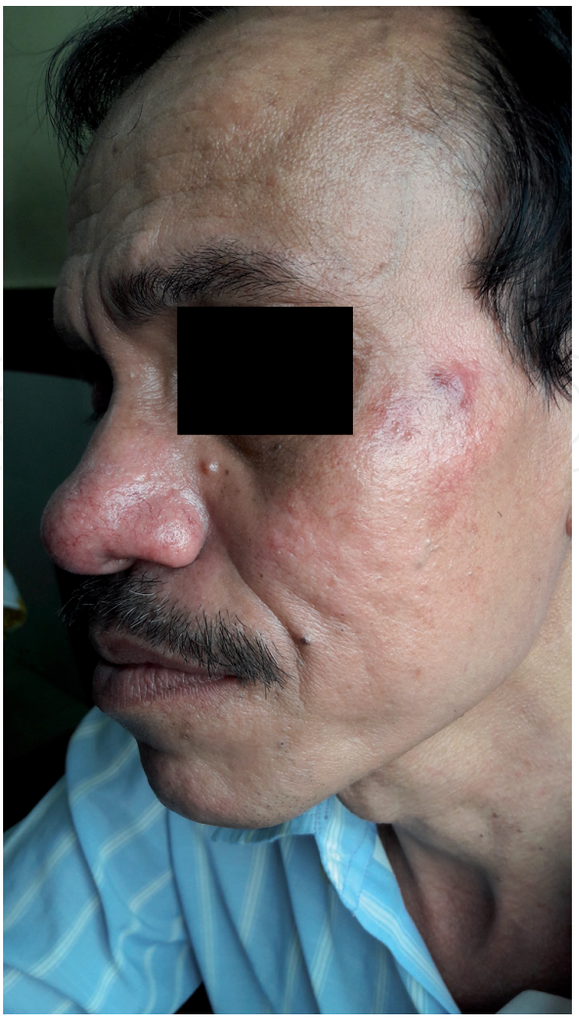

Figure 7.
Angiolupoid sarcoid.

Psoriasiform sarcoidosis. It is a rare morphologic manifestation of sarcoidosis. The appearance of its lesion are psoriasiform and infiltrated (**Figure 9**); some were annular, and others followed the natural lines of cleavage of the skin [39]. This type of sarcoidosis is usually peculiar to the dark skin [40].

Lichenoid sarcoidosis. About 1–2% of all cases of skin sarcoidosis are in this variety. It is characterized by abundant pinhead-sized yellowish lesions closely grouped in round or oval clusters, slightly scaling, mimicking lichen planus [41]. Lesions can occasionally show superficial scaling (**Figure 10a, b**). Sites commonly involved include trunk, limbs, and face [42]. It appears symmetrically and in crops and is associated with the eye and joint complications [41, 43]. The dermoscopy findings usually reveal circular or oval yellowish brown lesions with the absence of Wickham's striae. This feature is not specific for sarcoidosis, but such homogeneous appearance of lesions indicates a granulomatous skin disease [44].

Ulcerative sarcoidosis. Ulcerative sarcoidosis usually develops from the papulonodular sarcoid lesions by ulceration, but some arose de novo. Ulcers also developed in psoriasiform, atrophie, lymphedematous, erythrodermic, verrucous, suppurative, and elephantine lesions [45]. Lesions usually occur in the lower limb, and the upper limb may also be affected; sometimes lesions are generalized [45, 46]. Ulcers tended to heal with scarring [46] (**Figure 11**). Women are affected three times more than men, and blacks are affected slightly more than whites. Ulcer is a presenting feature in nearly 30% of patients, half of them having an initial lesion of other types [45], and cutaneous lesions are usually the presenting sign of sarcoidosis [45].

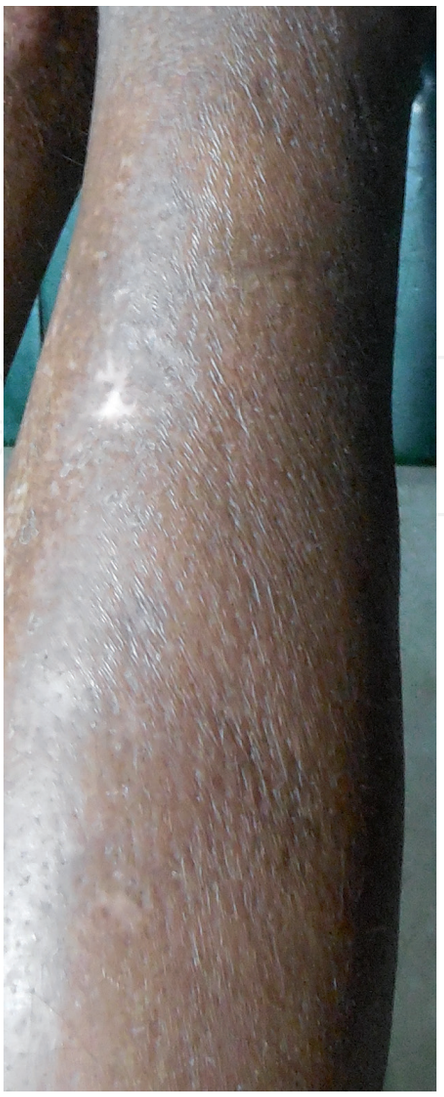

Figure 8.
Morpheaform sarcoidosis.

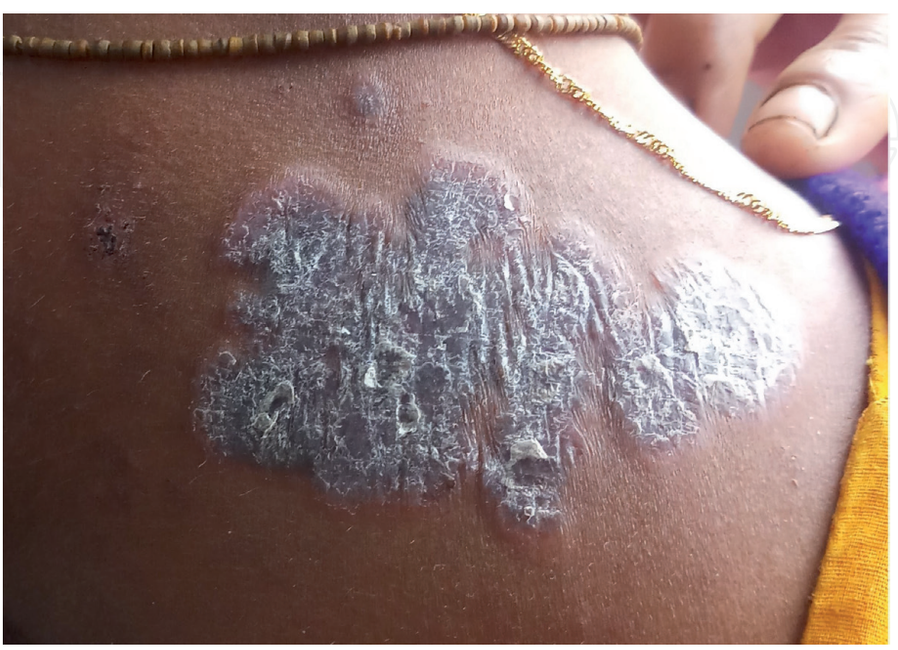

Figure 9.
Psoriasisform sarcoidosis.

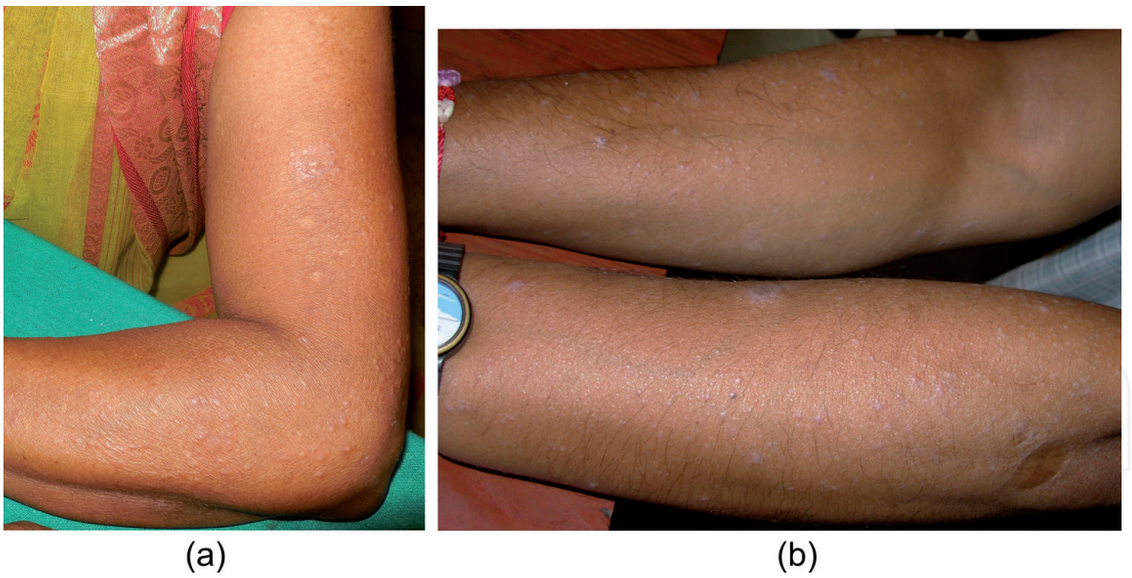

Figure 10.
(a and b) Lichenoid sarcoidosis.

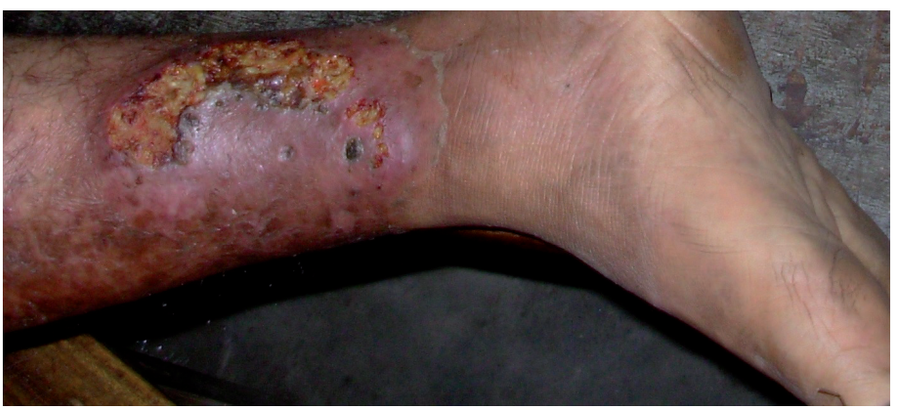

Figure 11.
Ulcerative sarcoidosis.

Verrucous sarcoidosis. All reported patients of verrucous sarcoidosis have been of African descent with a longstanding systemic disease. Usually, systemic sarcoidosis of other internal organs is present [47]. Lesions may be multiple exophytic, extensively verrucous yellowish-to-whitish lesions with a reddish-brown circinate border, size ranging from 1.0 to 2.0 cm in diameter [48].

3.1.1.2 Nonspecific lesions of sarcoid

Erythema nodosum, the most common nonspecific lesion, develops in 20–25% of sarcoidosis cases [6, 49]. Frequently, it is the initial manifestation of disease. It is the marker of acute and benign sarcoidosis and tends to affect younger people than infiltrative cutaneous lesions [12]. Sarcoidosis is the second most common cause of erythema nodosum [50]. If sarcoid is associated with EN, it usually runs a benign and self-limited course [51]. Women are affected three to six times more frequently than men [52]. EN can occur in all age groups, but it is typically seen between the second and fourth decades of life. The higher prevalence of erythema nodosum among young people is considered to be due to the higher incidence of sarcoidosis in this age group [11]. EN is characterized by sudden onset of symmetric, tender, erythematous, warm nodules and raised plaques, usually located on the shins, ankles, and knees (**Figure 12**). Nodules are from 1 to 5 cm or more in diameter and

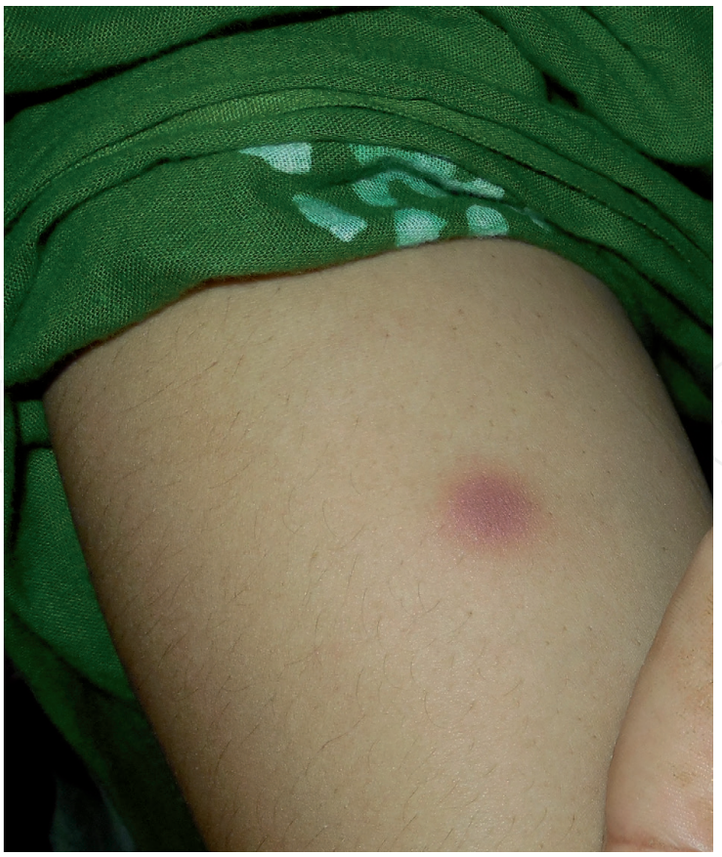

Figure 12.
Erythema nodosum.

distributed bilaterally. Nodules may become confluent, resulting in erythematous plaques. In rare instances, more extensive lesions may appear, involving the thighs, extensor aspects of the arms, the neck, and even the face. Initially the nodules are bright red in color; within a few days, they become flat, with a livid red or purplish color and finally a yellow or greenish appearance, often taking on the look of a deep bruise (erythema contusiformis). This contusiformis color evolution is quite characteristic of erythema nodosum and allows a specific diagnosis in late-stage lesions [53]. Ulceration is never seen in erythema nodosum, and the nodules heal without atrophy or scarring [54]. Usually, acute bouts of erythema nodosum are associated with a fever of 38–39°C, fatigue, malaise, arthralgia, headache, abdominal pain, vomiting, cough, or diarrhea. Episcleral lesions and phlyctenular conjunctivitis may also accompany the cutaneous lesions. Less frequent clinical manifestations associated with erythema nodosum are lymphadenopathy, hepatomegaly, splenomegaly, and pleuritis [55]. Eruption generally lasts from 3 to 6 weeks, but persistence beyond this time is not unusual. Recurrences are not uncommon. Erythema nodosum in children has a much shorter duration than in adults, arthralgias are seen in a minority of the patients, and fever is an accompanying manifestation in fewer than half of the cases [56].

Another nonspecific lesion of sarcoid is Lofgren's syndrome, an acute form of sarcoidosis characterized by erythema nodosum, bilateral hilar lymphadenopathy (BHL), and symmetric polyarthritis [57]. Arthritis in sarcoidosis is usually symmetrical; the ankles are involved in more than 90% of the cases; the knees, small joints of the hands or feet, wrists, and elbows are involved in 15–40% [58–60]. Local pain, soft-tissue swelling, periarticular tenderness, edema, and joint effusion may be present [61]. In 1953, Lofgren characterized 212 adult patients of bilateral hilar lymphadenopathy who were practically regarded as having sarcoidosis based on the absence of tuberculosis. Lofgren demonstrated that EN was present at the onset of

the disease in 113 cases in which articular symptoms were common (101 cases, 89%). There was either pain only in the joints (20%) or pain accompanied by swelling (69%) [62]. Lofgren's syndrome was regarded as a self-limiting disease that is generally resolved within the first year, with the mean duration ranging from 3 weeks to 3.7 months [57, 60]. However, 8% of patients had active symptoms 2 years after the onset; 6% had episodes of recurrent sarcoidosis 2.20 years after the diagnosis [62].

3.1.2 Granulomatous rosacea

Granulomatous rosacea is a distinct variant of rosacea. Lewandowsky described the "rosacea-like tuberculid" as having a clinical appearance similar to that of a papular form of rosacea; however, it appeared as yellow-brown "apple-jelly" nodules on diascopy and as tuberculoid granulomas on histologic examination [63]. Later it was noted that granulomas can be seen in typical rosacea [64]. Thus rosacea may be manifested by a clinical and a histologic spectrum that includes granuloma formation in some patients [65]. Lesions are persistent, firm, and non-tender; red to brown papule or nodule arises primarily on otherwise normal appearing skin around the mouth and eyes and on the cheeks [66] (**Figure 13**). Granulomatous rosacea often does not present facial erythema, is not limited to facial convexities, often has periocular lesions, and shows an asymmetrical distribution [67]. Some studies have demonstrated that patients with this variant present clinically with monomorphic yellow-brown and red papules or nodules situated predominantly over the cheeks and periorificial areas [68, 69]. Although clinical correlation is important, the diagnosis of GR is dependent upon the histopathologic finding of a granulomatous infiltrate [70, 71].

3.1.3 Cutaneous Crohn's disease

Skin manifestations of Crohn's disease (CD) have been classified into three principal classes: granulomatous or CD specific, reactive, and secondary to nutritional deficiency [72]. CD-specific lesions account for the majority of lesions

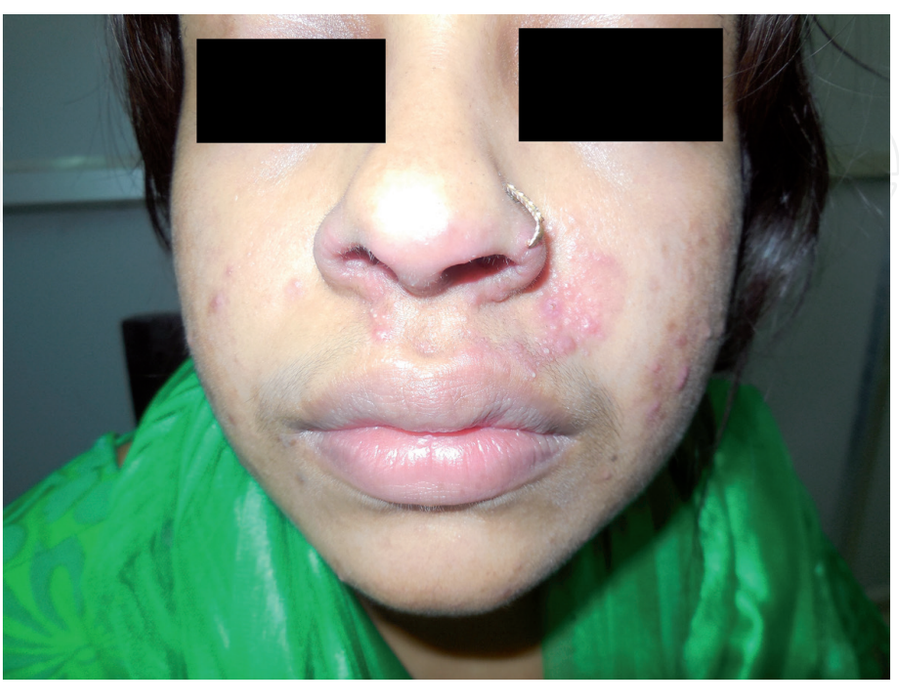

Figure 13.
Granulomatous rosacea.

observed. The best recognized are perianal and peristomal fissures and fistulae and oral disease [73]. Skin lesions commonly complicate CD with reported prevalence rates as high as 44% [74–76]. The characteristic lesions of metastatic Crohn's diseases are erythematous plaques and nodules and cutaneous ulceration. Secondary features like scale or crust may present [73] (**Figure 14**). Lesions involving intertriginous and genital skin usually ulcerate, owing to friction [77]. Lesions may be solitary or multiple, usually asymptomatic, but may be tender on palpation [77]. The oral manifestation of CD in the buccal mucosa is cobblestoning, while the gingival and alveolar mucosae often have tiny nodules. Linear ulcers are more common in sulci. The lips may become swollen, hardened, or ulcerated, especially at the angles of the mouth [78]. Genital lesions are the most common presentation of MCD in children; 85% of the cases present with swelling and/or induration of the genitals with or without erythema. In adults, the most frequent lesions are nodules and plaques, with or without ulceration on the arms and legs, followed by ulcers on the genitals [77].

3.1.4 Orofacial granulomatosis

The term orofacial granulomatosis (OFG) includes a group of disorders showing chronic, noncaseating granulomatous lesions involving the perioral tissue of the face and oral mucosa [79]. Possible systemic diseases, such as tuberculosis, sarcoidosis, and other diseases with the same clinical findings are to be excluded before to diagnose orofacial granuloma [80]. Clinically, OFG generally presents as swelling of upper and/lower lip, even the whole orofacial region including the chin, cheeks, periorbital and zygomatic tissues, eyelids, and forehead, unilaterally or bilaterally, either alone or in combination, though classic presentation is that of a non-tender recurrent labial swelling that may eventually become persistent [79] (**Figure 15**). Furthermore, manifestations include angular cheilitis, mucosal ulcerations, vertical fissures of the lips, mucosal tags, and lingua plicata [81]. However, the clinical

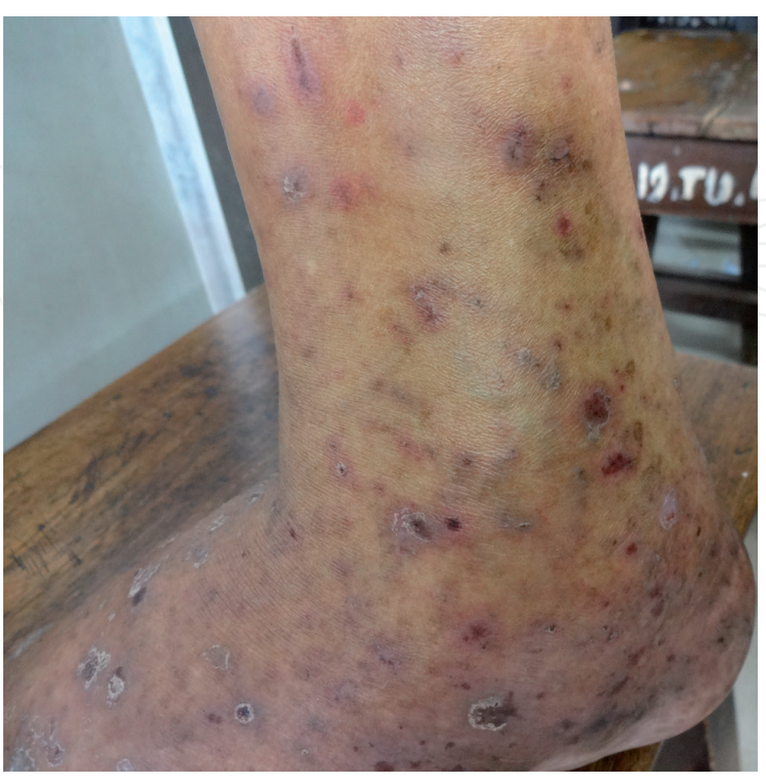

Figure 14.
Metastatic Crohn's disease.

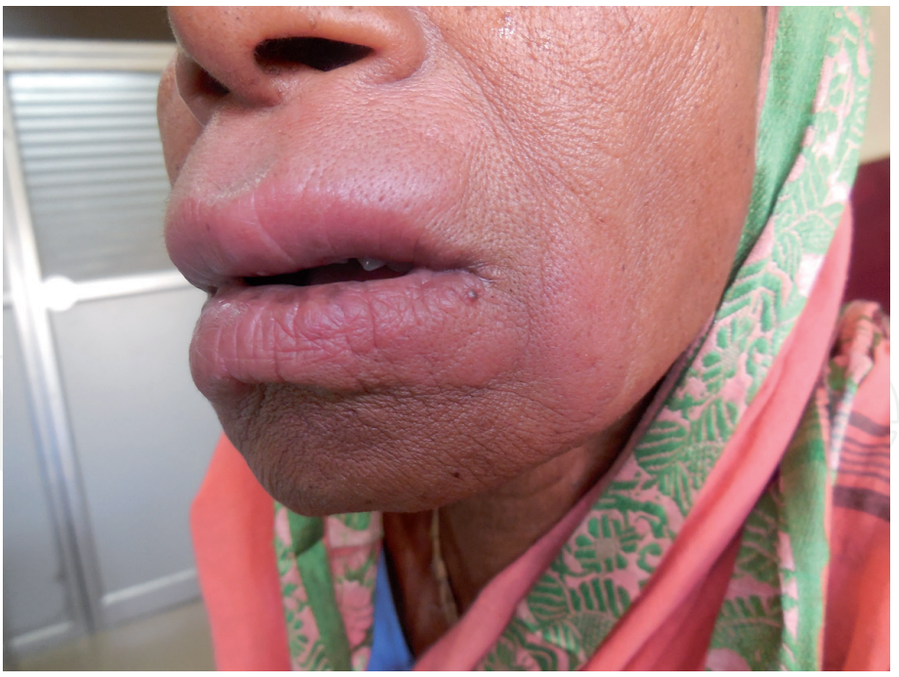

Figure 15.
Orofacial Granulomatosis.

presentation can be highly variable, making the diagnosis difficult to establish, i.e., intraoral involvement may take the form of hypertrophy, erythema, or nonspecific erosions involving the gingiva, oral mucosa, or tongue [80–82]. Clinicopathological correlation is required for final diagnosis.

3.2 Palisading granulomas

3.2.1 Granuloma annulare

It is characterized by ringed erythematous plaques with granulomatous inflammation seen histologically. There are four clinical variants of GA-localized, generalized, or disseminated, subcutaneous, and perforating [83].

The localized, commonest variety, nearly three-fourths of all GA cases, is in this group. Lesions are usually present as skin-colored or erythematous papules, without epidermal change, that are often arranged in arciform or annular patterns, usually less than 5 cm in diameter, and enlarge centrifugally [84–86] (**Figure 16**). Subcutaneous and superficial papular lesions may coexist in some patients, particularly in children [84]. The number of lesions may be single or multiple, in equal distribution. The commonest site of involvement is the hands and arms (63%), lower extremity in 20%, trunk alone in 5%, and all extremities affected in 7% of patients. Both sexes are equally affected [84]. Lesions are temporary in 70% of cases. In 51%, clearing happens within 2 years. The age of the patients did not affect the prognosis to any great extent, and usually three-fourths of patients recover [84].

In generalized (disseminated) granuloma annulare, innumerable number of lesions, arranged in symmetrical distribution, presents in any part of the body, but the face and also the palm and sole are usually spared. There may be macules, papules, or nodules [84], arranged in an annular fashion [86]; colors range from skin-tone to red, yellow, or tan. There is controversy about generalized and disseminated GA. In original description, granuloma annulare was defined as

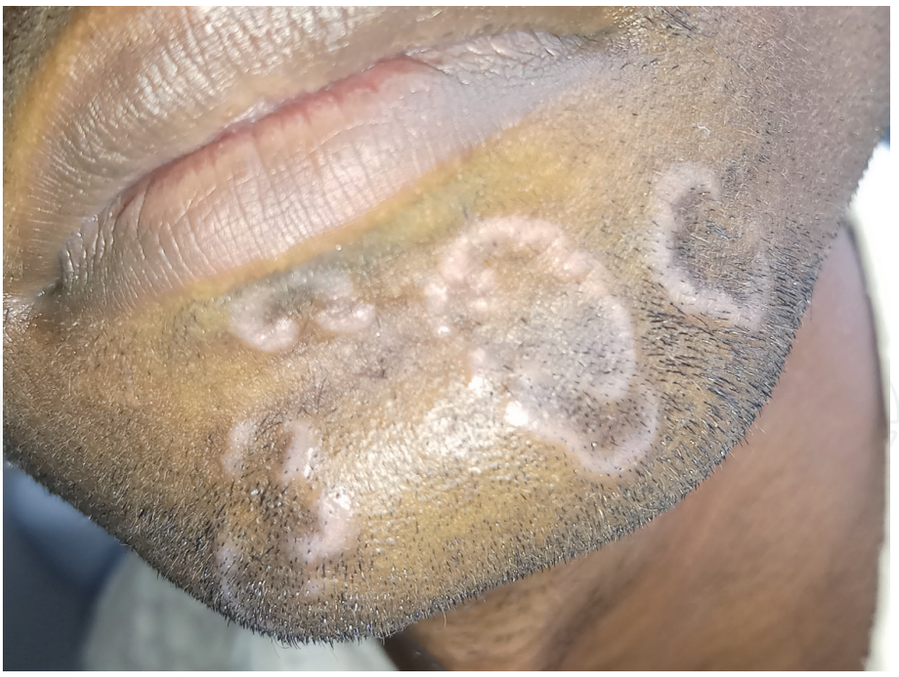

Figure 16.
Granuloma annulare.

generalized involvement of at least the trunk and the upper or lower extremities [86] (**Figure 17a, b**). It is asymptotic and usually persists for 3–4 years but may persist up to 10 years and recur [84]. The age of onset is bimodal in distribution, with 80% of patients presenting in the fourth to seventh decades and the remainder presenting before the age of 10 [84]. Female to male ratio is slightly higher [86].

Subcutaneous granuloma annulare, also known as pseudorheumatoid nodule, is a self-limiting disorder usually found between the ages of 3 and 6 years, and the sex ratio is 1:1 [84, 87, 88]. They are small, pinkish, asymptomatic, hard-elastic, nodular, isolated lesions, or associated with local annular granuloma. The overlying skin is healthy. Sites include the pretibial region, elbow, forearm, forehead, scalp, and dorsal surfaces of the hands and feet [84] (**Figure 18**). Lesions situated on the head adhere to the periosteum and are fixed with respect to the underlying layers, whereas those on the extremities adhere to the fascia and are therefore mobile [84, 89].

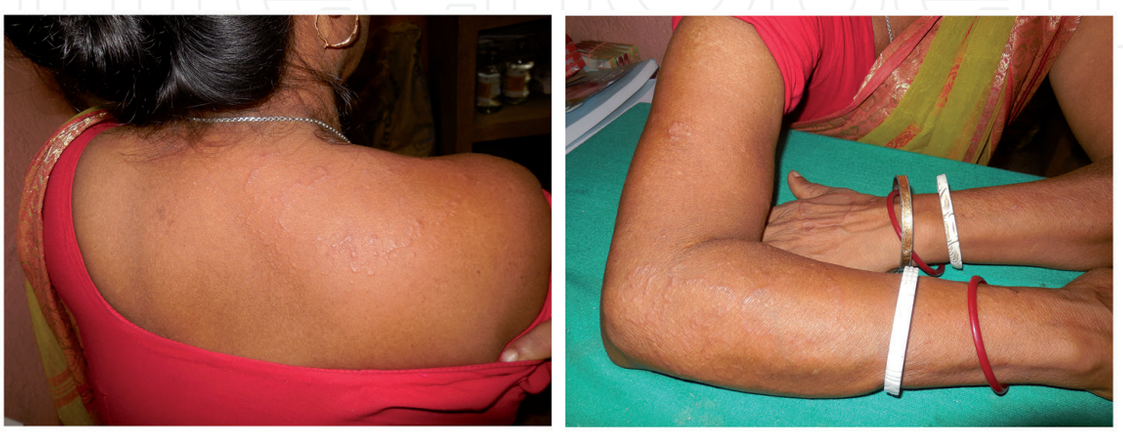

Figure 17.
(a and b) Generalized granuloma annulare.

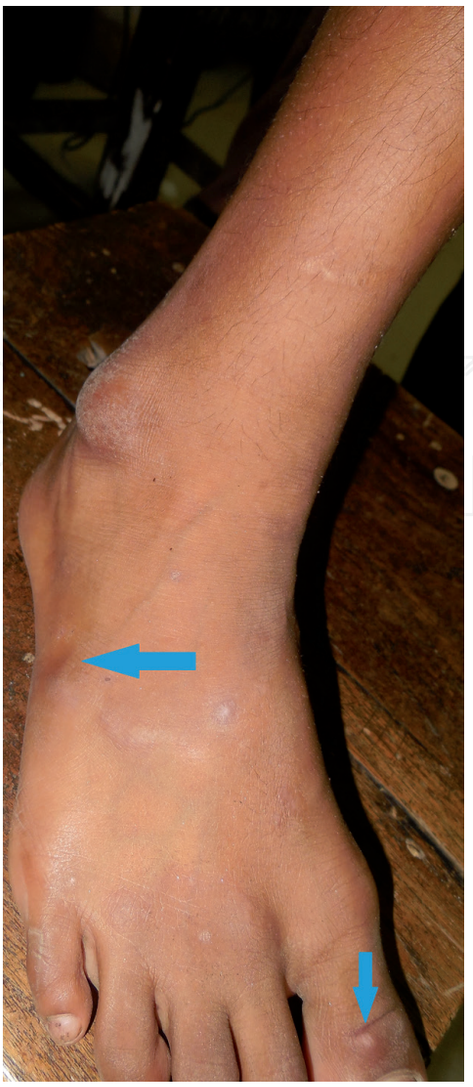

Figure 18.
Subcutaneous granuloma annulare.

3.2.2 Annular elastolytic giant cell granuloma

It is usually a disease of middle-aged, Caucasian women [90]. Onset is sudden but progressive, and varying in duration from 1 month to 10 years [91]. Clinically, AEGCG presents as multiple, large, annular plaques with a raised, erythematous border and central atrophy. The lesions are mostly located on sun-exposed areas such as the face and neck, but they are also seen on nonexposed skin although rare reports of a papular variant of AEGCG exist [92, 93]. It is currently unclear whether they simply represent a variant of granuloma annulare occurring on sun-damaged skin or distinct disease. There are two patterns. One is a single, asymptomatic, atrophic-appearing, yellow thin plaque on forehead, and the other is multiple, upper extremity, and trunk lesions occurring mainly on sun-exposed areas predominantly in women (**Figure 19**). A papular and arciform variant is also described [90, 91]. The histopathologic features are best demonstrated by a biopsy of the elevated edge of the plaque [94]. The lesions may persist for months to years resolving with either mottled pigmentation or normal-appearing skin [95]. Association with temporal arteritis is reported [96]. There have been reported cases of AEGCG associated with diabetes, sarcoidosis, and hematological malignancies [97, 98]. Patient of AEGCG may associate with Barrett's esophagus. The patient had hepatic nodules that showed nonspecific granulomas with elastolysis, similar to the skin lesions [99].

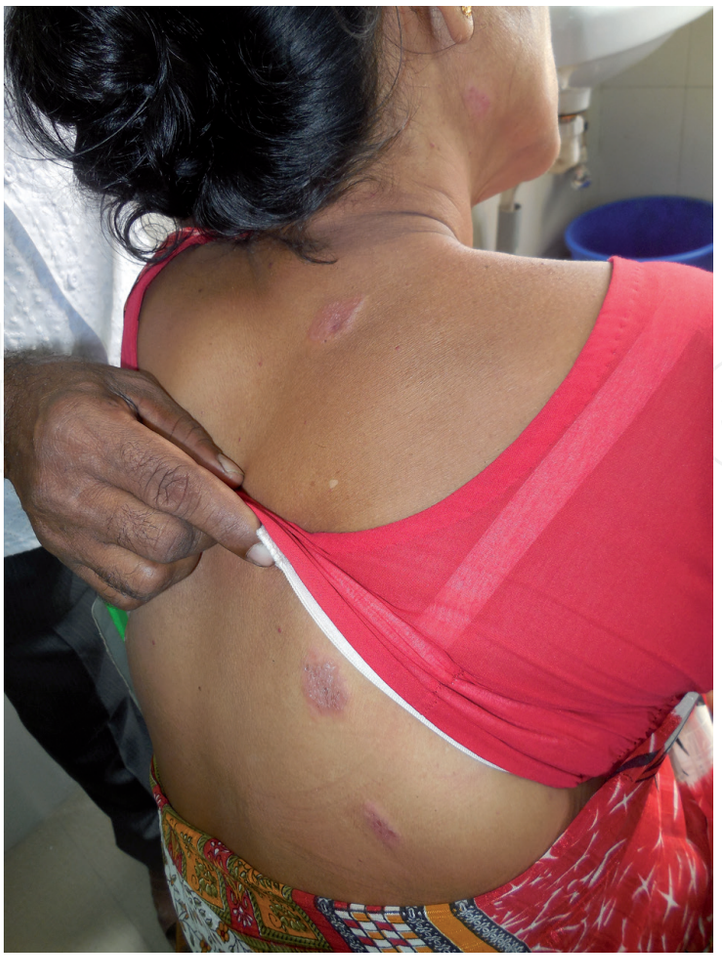

Figure 19.
Annular elastolytic giant cell granuloma.

3.2.3 Necrobiosis lipoidica

Necrobiosis lipoidica developed in the fourth decade of life and, in type 1 diabetes mellitus, in the third decade [100, 101]. Females are more affected than male (3:1). It is rare in childhood. NL is usually present on bilateral lower extremities, typically pretibial skin, but face, scalp, trunk, groin, and upper extremities can also be affected.

It forms as well-circumscribed papules and nodules with active erythematous borders that slowly coalesce into plaques. The plaques appear violaceous and contain a central area that initially appears red-brown but later progresses to a yellow-brown discoloration with atrophic, waxy appearance with prominent telangiectatic vessels [102]. But this classical presentation may not present in Indian patients where common presentation is erythematous plaque [103] (**Figure 20**). Lesions are 1–3 in number [102]. They are usually asymptomatic but may be painful or hypoesthetic or anesthetic [104]. NL lesions can also exhibit the Koebner phenomenon. Up to one-thirds of the patients with NL may develop ulcerations secondary to minor trauma [100]. Occasional reports of squamous cell carcinoma arising in areas of long-term lesions have also been reported [105].

3.2.4 Rheumatoid nodule

Rheumatoid nodules are commonly found in patients with rheumatoid arthritis as later manifestation of active arthritic disease [106]. It occurs as subcutaneous nodules;

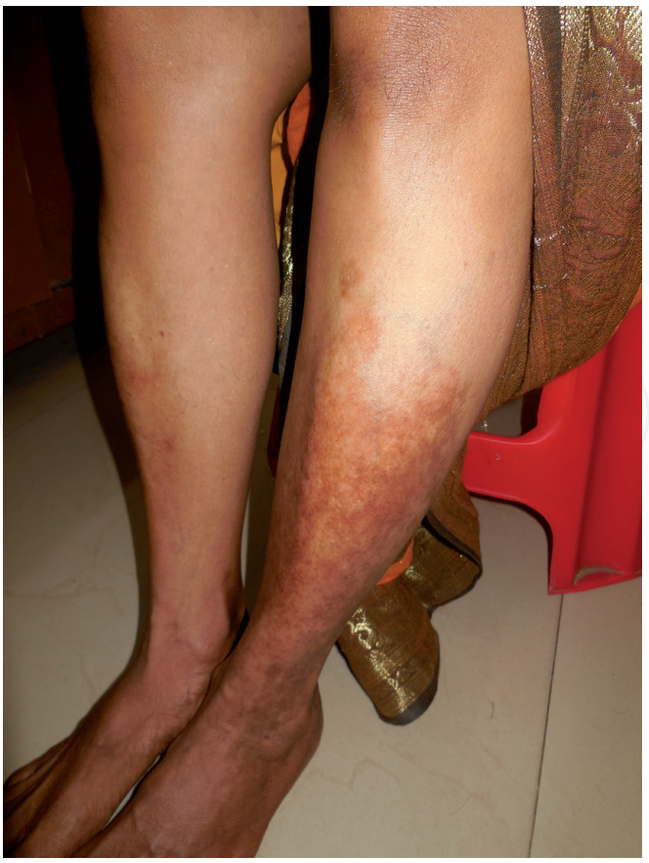

Figure 20.
Necrobiosis lipoidica.

the most common extra-articular feature of RA [107, 108] is present in about 25–42% [107, 108] of RA patients, although similar nodules have been observed in nonrheumatoid conditions, such as granuloma annulare and necrobiosis lipoidica [109]. Nodules are skin colored, can be solitary or multiple, and range from <5 mm to many centimeters in diameter [106] (**Figure 21**). They lie deeply subcutaneously and can adhere to underlying periosteum, tendons, or bursae, although others may be epidermal and freely movable [110]. Most are firm and painless and often go unnoticed by the average patient, but those found on the plantar surfaces of the feet or palms may feel uncomfortable [110].

3.2.5 Reactive granulomatous disorders

Reactive granulomatous disorders are reactive granulomatous processes, which present with a cutaneous granulomatous eruptions in response to medications, autoimmune disease, arthritides, and internal malignancies. There is a wide spectrum of clinical morphologic patterns and a broad array of histologic subtypes that may occur. The common RGDs are palisaded neutrophilic and granulomatous dermatitis (PNGD), interstitial granulomatous dermatitis (IGD), and interstitial granulomatous drug reaction (IGDR) [111].

The classic clinical presentation of PNGD is that of flesh-colored to erythematous papules, which may be umbilicated or crusted, appearing symmetrically on the extremities particularly around the elbows [112–114] (**Figure 22**). Palisaded neutrophilic and granulomatous dermatitis is seen in association with a number of systemic diseases. The diseases most commonly reported with PNGD include connective tissue diseases—particularly systemic lupus erythematosus—as well as inflammatory arthritis, hematologic disorders, and rarely infections or medications [111]. Patients

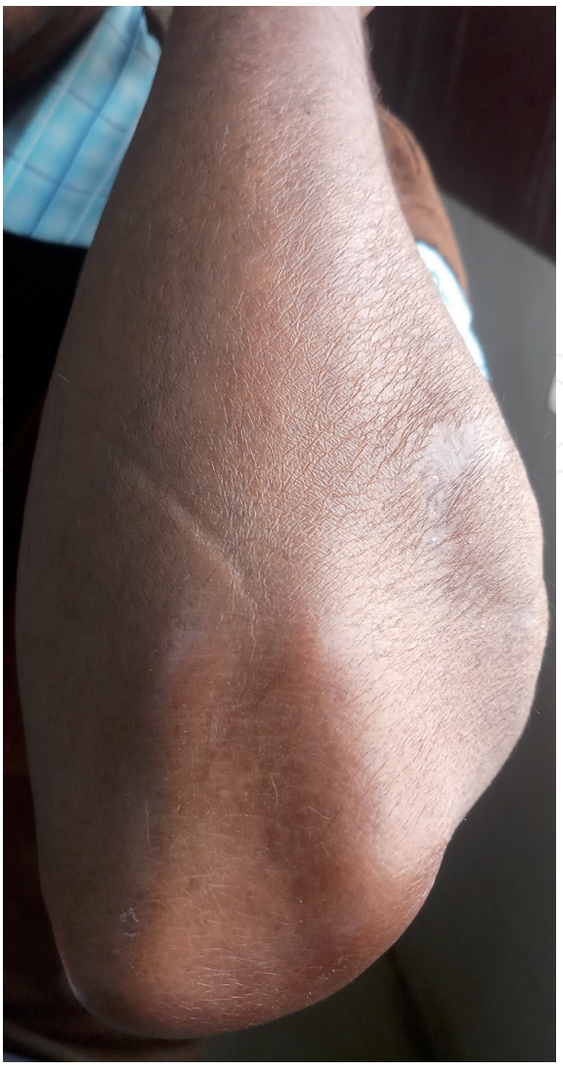

Figure 21.
Rheumatoid nodule.

of all ages may develop PNGD, although reports in childhood are rare [114]. Women are affected more frequently (approximately 3:1 ratio), likely owing to the systemic diseases associated with PNGD [114].

In interstitial granulomatous dermatitis (IGD), the initial description was linear subcutaneous cords or bands on the proximal trunk [115], and also erythematous to violaceous patches or plaques symmetrically on the upper trunk and proximal limbs are a frequent manifestation [116]. IGD is generally seen in the setting of an underlying systemic disease, similar to PNGD [111].

There is contradiction whether interstitial granulomatous drug reaction (IGDR) is another entity or subtype of interstitial granulomatous dermatitis [111]. The classic description of IGDR is erythematous to violaceous plaques, often annular, concentrated on the inner arms, proximal medial thighs, proximal trunk, and intertriginous sites, with distinctive histologic features [117].

3.3 Xanthomatous granulomas

3.3.1 Adult-onset xanthogranuloma

Xanthogranuloma (XG) is the most common non-Langerhans cell histiocytosis, which usually occurs in the early part of life [118]. It is rare in adults, usually occurring in the third and fourth decades of life [119].

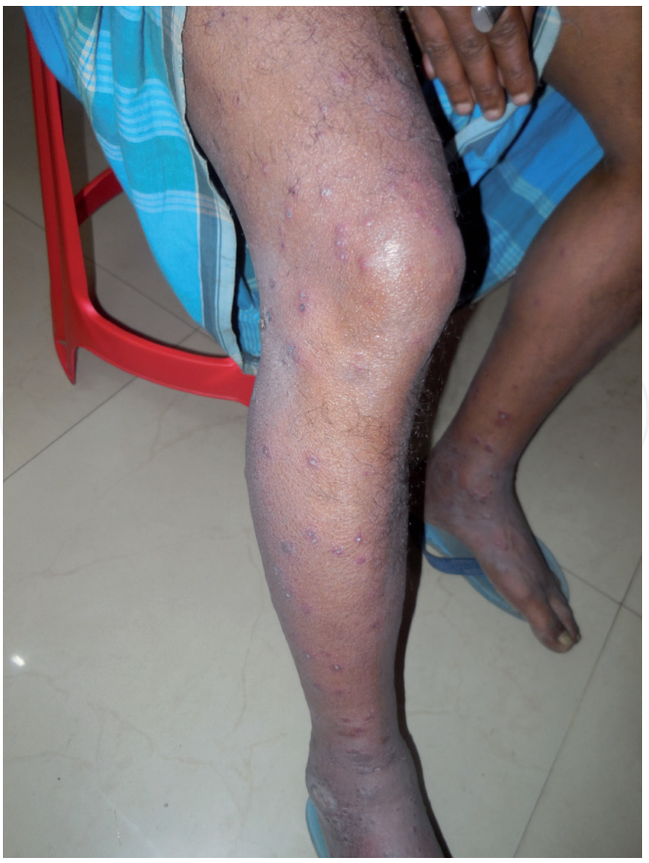

Figure 22.
Palisaded neutrophilic and granulomatous dermatitis.

Lesions of XG are usually orange or erythematous-brown papule nodule [120], varying the tonality with the age of the lesions [118]. XGA usually occurs as a single lesion in 2/3 of cases located on the face but may be seen in the trunk or limbs [119, 121].

There are three recognized main clinical forms of adult onset xanthogranuloma: a small nodular/papular (2–5 mm); large nodular (5–20 mm); and giant xanthogranuloma (more than 20 mm [122]). Multiple adult onset xanthogranuloma is defined when there are more than five XG lesions. It appears to be more common among men [121].

3.3.2 Adult onset asthma with periorbital xanthogranuloma (adult onset APXG)

Adult onset asthma with periorbital granuloma (AAPOX) syndrome was first described in 1993 by Jakobiec et al. and is considered to be a periorbital disease with a specific granulomatous inflammation [123, 124].

Skin surrounding the orbit is yellow-orange in color, with swelling of mainly upper and also lower eyelid with compromised eyelid movement. There is associated allergic sinusitis and adult onset asthma [125].

3.3.3 Necrobiotic xanthogranuloma

It is a chronic, progressive granulomatous disorder with cutaneous and extracutaneous involvement. The mean age is 61.6 years [126]. The mean (SD) age at presentation was 61.6 (14.2) years; females are more commonly affected (62.6%) than male. Most patients are white (87%) [126]. More than one site is usually involved [127].

It usually manifests as yellowish or yellow-orange, red or brown papules, plaques, and nodules [126]. The commonest site of involvement is the periorbital area [128]. Trunk [127] and also the extremities [126] are the second most common site.

Dermatologic symptoms may present up to 60% of patients such as itching, burning, tenderness, and pain. Nearly half of patients may ulcerate, the most common secondary feature [126, 127].

3.3.4 Multicentric reticulohistiocytosis

It is a rare histiocytic proliferative disease in which joints, skin, mucous membranes, and internal organs are affected [129]. Onset is usually insidious; cutaneous manifestations usually follow the articular signs and symptoms [130].

The peak occurrence is seen in middle age with the average age of 40–50 years at presentation, but MRH can present at any age [131–133].

The classic skin lesions are firm brown or yellow papule and plaque. Extensor surfaces are predominantly affected, particularly on the hands and forearm, and also the face, scalp, hands, and ears are often affected, but involvement of lower trunk and legs is rare. Coral bead-like lesions may occur around the nail folds which may lead to nail dystrophy. The size varies from a few millimeters to centimeters [134]. Lesions in proximity to joints may be largely nodular. Lesions may ulcerate. The vermicular erythematous lesions around the nostrils are thought to be a characteristic of MRH [135]. Mucosal lesions present from 30 to 50% patients [131, 133], oral and nasal mucosa are the frequently involved sites, but lesions may be distributed along the lips, buccal mucosa, tongue, and gingival and nasal septum. Usually lesions are asymptomatic; around 25% patients complain of pruritus.

3.3.5 Rosai-Dorfman syndrome

The hallmark of Rosai-Dorfman disease is massive cervical lymphadenopathy. Other lymph node groups like axillary, inguinal, and mediastinal nodes may also be affected. In about 10% of patients, the cutaneous manifestations present, which are asymptomatic xanthoma-like, yellowish, or reddish-brown papules, nodules, and plaques which may ulcerate [136]. Involvement of extra-nodal sites like the nasal cavity, paranasal sinuses, eyelids, orbit, skeletal system, salivary glands, and central nervous system has been reported [137, 138]. Fever, elevated ESR, neutrophilia, and polyclonal gammopathy are other common associations.

3.3.6 Xanthoma disseminatum

It occurs in children and adults and characterized by disseminated xanthomatous lesions. XD usually presents as erythematous, yellow brown papule and nodules, symmetrical in distribution. Lesions become confluent, sometimes form a xanthomatous plaque, and may become verrucous [139].

It usually starts before the age of 25 years in about 60% of patients. It is more common in males. It may occur anywhere on the body including the scalp, face, trunk, and extremities [140].

XD typically involves the skin, particularly the flexor folds, face, and trunk. It may also manifest in the central nervous system [141].

Mucous membrane involvement develops in 40–60% of patients, most commonly affecting the oropharynx, larynx, or cornea and conjunctiva [142].

There are three clinical patterns of xanthoma disseminatum: (i) a common persistent form in which lesions may never resolve; (ii) a rare, self-healing form

with spontaneous resolution; and (iii) a very rare, progressive form with organ dysfunction and central nervous system involvement [143].

3.4 Other granulomatous disorders

3.4.1 Granulomatous vasculitis

Granulomatous vasculitis is a spectrum of diseases. Lung involvement is very much common in GV. Small vessel vasculitis with granulomatosis is seen in granulomatosis with polyangiitis (Wegener granulomatosis) and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), and large-vessel vasculitis with granulomatosis is seen in temporal arteritis: Takayasu arteritis.

In Wegener granulomatosis, the incidence of skin disease is 45% [144]. The lesions can take several forms including papules, vesicles, palpable purpura, ulcers, and subcutaneous nodules [145]. Palpable purpura may be the most frequent (47%) skin finding [146]. The skin disease rarely dominates the clinical picture and is usually a minor part of the multisystem involvement, generally responds promptly to therapy, and parallels disease activity in other organ systems [147]. Other organs include the lungs, kidney, heart, joint, eye, and nervous system involvement [148]. Cutaneous findings are variable and nonspecific and usually affect the lower extremities [146].

Eosinophilic granulomatosis with polyangiitis was previously named as Churg-Strauss syndrome. In one-third to two-thirds of patients, skin involvement is a dominant feature and presents in the form of nodules. Urticaria and ulceration are less common. Neurologic involvement is seen in 60–70% patients and is commonly in the form of multiple mononeuropathies or symmetric polyneuropathy [149].

3.4.2 Lymphomatoid granulomatosis

Lymphomatoid granulomatosis (LYG) is a progressive lymphoproliferative disease by Epstein-Barr virus (EBV), in which the abnormal cells directly accumulate within affected tissues, usually in the form of infiltrative nodular lesions and with T-cell invasion and destruction of blood vessels [150]. Its incidence is low, clinical features are overlapping, pulmonary disorders are more common, and all contribute to frequent delays in diagnosis [150]. The lung is virtually always involved in bilateral fashion [151]. The skin is the extrapulmonary organ most commonly involved in LYG, occurring in 40–50% of patients [151]. Skin manifestations of LYG are quite heterogeneous. They typically appear as scattered subcutaneous or dermal nodules that vary in size, seen predominantly on the extremities. Erythematous or purplish maculopapular eruptions are the most common skin lesions observed, but some patients will have indurated plaques. Varying degrees of ulceration accompany the skin lesions and may become necrotic when the disease is not well controlled (**Figure 23**). In up to 10% of patients, the skin lesions will antedate the lung lesions, and, in these cases, dermal biopsy may lead to the diagnosis [150]. Skin lesion may develop after lung involvement, but majority of skin lesions develop at the time of lung involvement [151].

3.4.3 Foreign body reactions

The foreign body granuloma is a response of biological tissue to any foreign material in the tissue [152]. Foreign body granulomas may be due to reactions of endogenous products like keratin, hair, fat, urate crystals, mineral, and/or oil products; plant and animal products; and synthetic agents [153]. Depending on the individual host response and type of foreign materials, clinical findings can be variable. Sites depend on the area involved by endo- or exogenous material. The lesions may be

asymptomatic or tender, pink, red, red-brown or skin-colored, and firm papules, nodules, or plaques, which may or may not ulcerate or drain (**Figure 24**). Other presentations include sinus tracts and abscesses [153]. The foreign material may migrate, as in silicone, leading to granulomas at sites distant from the area of implantation [154].

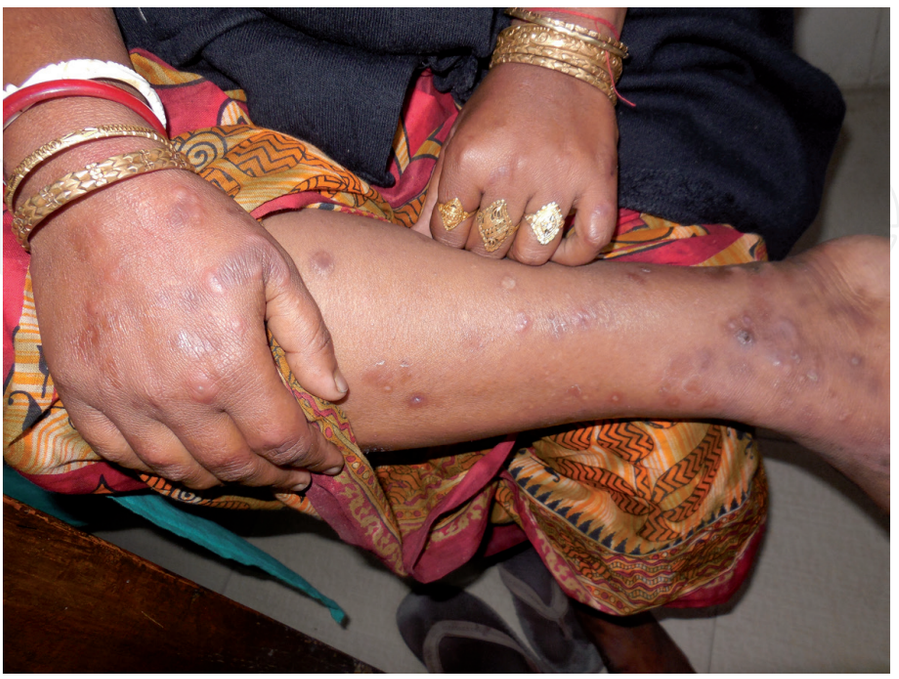

Figure 23.
Lymphomatoid granulomatosis.

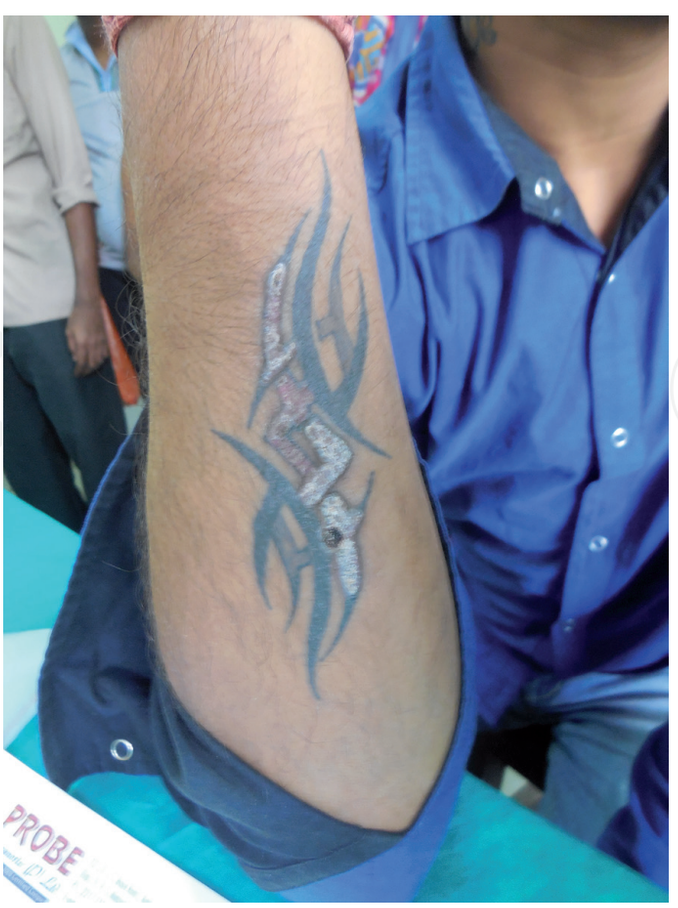

Figure 24.
Foreign body granuloma.

3.4.4 Granulomatous drug reactions

Granulomatous drug reactions include four major types: interstitial granulomatous drug reaction, drug-induced accelerated rheumatoid nodulosis, drug-induced granuloma annulare, and drug-induced sarcoidosis [155].

The most common cutaneous features of interstitial granulomatous drug reaction are symptomatic erythematous plaques and papules with a predilection for the flexures (intertriginous areas, medial thighs, and inner aspects of the arms) [117]. Trunks also may be involved [117]. Sharply demarcated symmetrical annular erythematous lesions [155] are also described. Lesions may be generalized [117]. Interstitial granulomatous drug reaction completely regresses with drug cessation [155]. Other drug-induced granulomatous disorders are drug-induced accelerated rheumatoid nodulosis, with development of tender subcutaneous lesions during treatment with methotrexate, and drug-induced granuloma annulare (GA), mainly generalized, developed with paroxetine and drug-induced sarcoidosis [156]. Drug-induced lesions are similar to the original lesions.

Author details

Suchibrata Das
Department of Dermatology, Venereology and Leprosy, Nilratan Sircar Medical College, West Bengal, India

*Address all correspondence to: suchibratadas@yahoo.com

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