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Clinical Manifestations of Sarcoidosis and Granulomatous Disorders

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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
<i>Epithelioid granulomas</i>	<i>Caseating granulomas</i>
Sarcoidosis	Tuberculosis
Granulomatous rosacea/POD	Leprosy
Cutaneous Crohn's	Atypical mycobacterium
Orofacial granulomas	Leishmaniasis
<i>Palisading granulomas</i>	<i>Suppurative granulomas</i>
Granuloma annulare	Deep fungal
Elastolytic giant cell granuloma	Pyodermas
Necrobiosis lipoidica	Granulomatous STDs
Rheumatic nodules	
Reactive granulomatous disorders	
<i>Xanthomatous granulomas</i>	
Adult onset XG	
Adult onset APXG	
NXG	
Multicentric reticulohistiocytosis	
Rosai-Dorfman	
Xanthoma disseminatum	
<i>Others</i>	
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 lesions 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, atrophic, 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 polyarthritides [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 hypoaesthetic 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 extra-cutaneous 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.

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References

- [1] Geraint James D. A clinicopathological classification of granulomatous disorders. *Postgraduate Medical Journal*. 2000;**76**:457-465
- [2] Lapointe A-K, Laffitte E. Disseminated cutaneous granulomatosis. *Revue Médicale Suisse*. 2009;**5**(900):902-906
- [3] Asai J. What is new in the histogenesis of granulomatous skin diseases? *The Journal of Dermatology*. 2017;**44**(3): 297-303. DOI: 10.1111/1346-8138.13662
- [4] English JC, Rosenbach M. F092—Granulomatous disorders of adult skin. In: 76th Annual Meeting San Diego, CA USA. American Academy of Dermatology. 2018. Available from: www.aad.org/faculty.handout
- [5] Sanchez M, Prystowsky S. Sarcoidosis of the skin. In: Basow D, editor. *UpToDate*. Waltham, MA: UpToDate; 2010
- [6] Sam WM, Lynch PJ, editors. *Principles and Practice of Dermatology*. 2nd ed. New York: Churchill Livingstone; 1996. pp. 629-639
- [7] Elgart ML. Cutaneous sarcoidosis: Definitions and types of lesions. *Clinics in Dermatology*. 1986;**4**:35-45
- [8] Gawkrödger DJ. Sarcoidosis. In: Burns T, Breathnach S, Cox N, Griffiths C, editors. *Rook's Textbook of Dermatology*. 8th ed. Oxford: Wiley-Blackwell; 2010. pp. 61.1-61.23
- [9] Scadding JG, Mitchell DN, editors. *Sarcoidosis of the Skin*. London: Chapman & Hall Medical; 1985. pp. 181-206
- [10] Mañá J, Marcoval J, Graells J, Salazar A, Peyrí J, Pujol R. Cutaneous involvement in sarcoidosis. Relationship to systemic disease. *Archives of Dermatology*. 1997;**133**:882-888
- [11] James DG. Dermatological aspects of sarcoidosis. *The Quarterly Journal of Medicine*. 1959;**28**:109-124
- [12] Veien NK, Stahl D, Brodthagen H. Cutaneous sarcoidosis in Caucasians. *Journal of the American Academy of Dermatology*. 1987;**16**:534-540
- [13] Sharma OP. Cutaneous sarcoidosis: Clinical features and management. *Chest*. 1972;**61**:320-325
- [14] Marcoval J, Mana J. Sarcoidosis. In: Griffiths C, Barker J, Bleiker T, Chalmers R, Creamer D, editors. *Rook's Textbook of Dermatology*. 9th ed. West Sussex, UK; 2016. pp. 98.1-98.17
- [15] Jorizzo JL, Koufman JA, Thompson JN, White WL, Shar GG, Schreiner DJ. Sarcoidosis of the upper respiratory tract in patients with nasal rim lesions: A pilot study. *Journal of the American Academy of Dermatology*. 1990;**22**:439-443
- [16] Kerdel FA, Moschella SL. Sarcoidosis: An updated review. *Journal of the American Academy of Dermatology*. 1984;**11**:1-19
- [17] Callen JP. Relationship of cutaneous sarcoidosis to systemic disease. *Clinics in Dermatology*. 1986:446-453
- [18] Moschella SL. Disease of the mononuclear phagocytic system. In: Moschella SL, Hurley HJ, editors. *Dermatology*. Philadelphia: WB Saunders; 1985. pp. 915-916
- [19] Scheig RL. Sarcoidosis. In: Demis DJ, editor. *Clinical Dermatology*. Philadelphia: JB Lippincott; 1988. pp. 1-5
- [20] English JC III, Patel PJ, Greer KE. Sarcoidosis. *Journal of the American Academy of Dermatology*. 2001;**44**:725-743

- [21] Spiteri MA, Matthey F, Gordon T, et al. Lupus pernio. A clinico-radiological study of thirty-five cases. *The British Journal of Dermatology*. 1985;**112**:315-322
- [22] Paller AS, Surek C, Silva-Walsh I, Krespi Y, Freinkel RK. Cutaneous sarcoidosis associated with sarcoidosis of the upper airway. *Archives of Dermatology*. 1983;**119**:592-596
- [23] Neville E, Mills RG, James DG. Sarcoidosis of the upper respiratory tract and its relation to lupus pernio. *Annals of the New York Academy of Sciences*. 1976;**278**:416-426
- [24] James DG. Lupus pernio. *Lupus*. 1992;**1**:129-131
- [25] Young RJ 3rd, Gilson RT, Yanase D, Elston DM. Cutaneous sarcoidosis. *International Journal of Dermatology*. 2001;**40**:249-253
- [26] Henrichs MP, Streithürger A, Gosheger G, Surke C, Dierkes C, Hardes J. Scar sarcoidosis on a finger mimicking a rapidly growing soft tissue tumour: A case report. *BMC Research Notes*. 2012;**5**:545-549. DOI: 10.1186/1756-0500-5-545
- [27] Choi SY, Hyun MY, No YA, Park KY, Li K, Kim BJ, et al. Scar sarcoidosis on a hypertrophic scar. *Clinical and Experimental Dermatology*. 2014;**39**:945-947. DOI: 10.1111/ced.12417
- [28] Cervigon I, Palomo A, Torres LM. Cutaneous lesions on scars. *Actas Dermo-Sifiliográficas*. 2007;**98**:433-434 (in Spanish)
- [29] Marchell RM, Judson MA. Chronic cutaneous lesions of sarcoidosis. *Clinics in Dermatology*. 2007;**25**:295-302. DOI: 10.1016/j.clindermatol.2007.03.007
- [30] Marcoval J, Mañá J, Rubio M. Specific cutaneous lesions in patients with systemic sarcoidosis: Relationship to severity and chronicity of disease. *Clinical and Experimental Dermatology*. 2011;**36**:739-744. DOI: 10.1111/j.1365-2230.2011.04128.x
- [31] Ahmed I, Harshad SR. Subcutaneous sarcoidosis: Is it a specific subset of cutaneous sarcoidosis frequently associated with systemic disease? *Journal of the American Academy of Dermatology*. 2006;**54**(1):p55-p60
- [32] Mahajan VK, Sharma NL, Sharma RC, Sharma VC. Cutaneous sarcoidosis: Clinical profile of 23 Indian patients. *Indian Journal of Dermatology, Venereology and Leprology*. 2007;**73**: 16-21
- [33] James WD, Berger TG, Elston DM, editors. Macrophage/monocyte disorders. In: *Andrews' Diseases of the Skin*. 12th ed. Philadelphia: Elsevier; 2016. pp. 699-725
- [34] Arias Santiago S, Fernández-Pugnaire MA, Aneiros-Fernández J, Falcón CS, Callejas-Rubio JL, Ortego-Centeno N, et al. Recurrent telangiectasias on the cheek: Angiolupoid sarcoidosis. *The American Journal of Medicine*. 2010;**123**(1):e7-e8. DOI: 10.1016/j.amjmed.2009.08.014
- [35] Meyrick RH, Thomas MA, McKee PH, Black MM. Hypopigmented sarcoidosis. *Journal of the Royal Society of Medicine*. 1981;**74**
- [36] Clayton R, Breathnach A, Martin B, Feiwel M. Hypopigmented sarcoidosis in the negro report of eight cases with ultrastructural observations. *British Journal of Dermatology*. 1977;**96**:119
- [37] Burov EA, Kantor GR, Isaac M. Morpheaform sarcoidosis: Report of three cases. *Journal of the American Academy of Dermatology*. 1998;**39**(2):345-348. DOI: 10.1016/s0190-9622(98)70386-x

- [38] Choi S-C, Kim H-J, Kim C-R, Byun J-Y, Lee D-Y, Lee J-H, et al. A case of morpheaform sarcoidosis. *Annals of Dermatology*. 2010;**22**(3):316-318
- [39] Klauder JV. Multiple sarcoid-like granulomas of the skin. *Archiv für Dermatologie und Syphilis*. 1925;**12**:171-173
- [40] Elgart ML. Skin manifestations of sarcoidosis. *Cutis*. 1968;**1**:283-291
- [41] Fujii K, Okamoto H, Onuki M, et al. Recurrent follicular and lichenoid papules of sarcoidosis. *European Journal of Dermatology*. 2000;**10**:303-305
- [42] Seo SK, Yeum JS, Suh JC, Na GY. Lichenoid sarcoidosis in a 3-year-old girl. *Pediatric Dermatology*. 2001;**18**:384-387
- [43] Sinha P, Bhattacharjee S, Raman DK, Sood A. A rare case of lichenoid sarcoidosis mimicking papular amyloidosis. *Indian Journal of Dermatology*. 2020;**65**:50-52
- [44] Vazquez-Lopez F, Palacios-Garcia L, Gomez-Diez S, Argenziano G. Dermoscopy for discriminating between lichenoid sarcoidosis and lichen planus. *Archives of Dermatology*. 2011;**147**:1130
- [45] Albertini JG. Ulcerative sarcoidosis. *Archives of Dermatology*. 1997;**133**(2):215. DOI: 10.1001/archderm.1997.03890380087013
- [46] Verdegem TD, Sharma OP. Cutaneous ulcers in sarcoidosis. *Archives of Dermatology*. 1987;**123**:1531-1534
- [47] Shmunes E. Verrucose sarcoidosis. *Archives of Dermatology*. 1970;**102**(6):665. DOI: 10.1001/archderm.1970.04000120083016
- [48] Stockman DL, Rosenberg J, Bengana C, Suster S, Plaza JA. Verrucous cutaneous sarcoidosis. *The American Journal of Dermatopathology*. 2013;**35**(2):273-276. DOI: 10.1097/dad.0b013e318262ed4c
- [49] James DG, Neville E, Siltzbach LE. A worldwide review of sarcoidosis. *Annals of the New York Academy of Sciences*. 1976;**278**:321-334
- [50] Chowaniec M, Starba A, Wiland P. Erythema nodosum—Review of the literature. *Reumatologia*. 2016;**54**(2):79-82
- [51] Milman N, Selroos O. Pulmonary sarcoidosis in the Nordic countries 1950-1982. Epidemiology and clinical picture. *Sarcoidosis*. 1990;**7**:50-57
- [52] Sö derstrom RM, Krull EA. Erythema nodosum: A review. *Cutis*. 1978;**21**:806-810
- [53] Requena L, Yus ES. Erythema nodosum. *Dermatologic Clinics*. 2008;**26**(4):425-438. DOI: 10.1016/j.det.2008.05.014
- [54] Blake T, Manahan M, Rodins K. Erythema nodosum—A review of an uncommon panniculitis. *Dermatology Online Journal*. 2014;**20**(4):22376
- [55] Psychos DN, Voulgari PV, Skopouli FN, et al. Erythema nodosum: The underlying conditions. *Clinical Rheumatology*. 2000;**19**:212-216
- [56] Kakourou T, Drosatou P, Psychou F, et al. Erythema nodosum in children. *Journal of the American Academy of Dermatology*. 2001;**44**:17-21
- [57] Gran JT, Bohmer E. Acute sarcoid arthritis: A favourable outcome? A retrospective survey of 49 patients with review of the literature. *Scandinavian Journal of Rheumatology*. 1996;**25**:70-73
- [58] Kang EH. Sarcoidosis in Korea: Revisited. *Journal of the Korean Medical Association*. 2008;**51**:925-932

- [59] Zisman DA, Shorr AF, Lynch JP 3rd. Sarcoidosis involving the musculoskeletal system. *Seminars in Respiratory and Critical Care Medicine*. 2002;**23**:555-570
- [60] Mana J, Gormez-Vaquero C, Montero A, Salazar A, Marcoval J, Valverde J, et al. Lofgren's syndrome revisited: A study of 186 patients. *The American Journal of Medicine*. 1999;**107**:240-245
- [61] James DG, Neville E, Carstairs LS. Bone and joint sarcoidosis. *Seminars in Arthritis and Rheumatism*. 1976;**6**:53-81
- [62] Lofgren S, Lundback H. The bilateral hilar lymphoma syndrome; a study of the relation to tuberculosis and sarcoidosis in 212 cases. *Acta Medica Scandinavica*. 1952;**142**:265-273
- [63] Lewandowsky F. Uber Rosacea-ahnliche Tuberkulide des Gesichts. *Corr BI Schweiz Arzte*. 1917;**47**:1280-1282
- [64] van Ketel WG. Rosacea-like tuberculid of Lewandowsky. *Dermatologica*. 1958;**116**:201-210
- [65] Mullanax MG, Kierland RR. Granulomatous rosacea. *Archives of Dermatology*. 1970;**101**:206-211
- [66] Wilkin J, Dahl M, Detmar M, et al. Standard classification of rosacea: Report of the National Rosacea Society Expert Committee on the classification and staging of rosacea. *Journal of the American Academy of Dermatology*. 2002;**46**:584-587
- [67] Crawford GH, Pelle MT, James WD. Rosacea: I. Etiology, pathogenesis, and subtype classification. *Journal of the American Academy of Dermatology*. 2004;**51**:327-341
- [68] Wilkin J, Dahl M, Detmar M, et al. Standard grading system for rosacea: Report of the National Rosacea Society Expert Committee on the classification and staging of rosacea. *Journal of the American Academy of Dermatology*. 2004;**50**:907-912
- [69] Khokhar O, Khachemoune A. A case of granulomatous rosacea: Sorting granulomatous rosacea from other granulomatous diseases that affect the face. *Dermatology Online Journal*. 2004;**10**:6
- [70] Helm KF, Menz J, Gibson LE, et al. A clinical and histopathologic study of granulomatous rosacea. *Journal of the American Academy of Dermatology*. 1991;**25**(6 pt 1):1038-1043
- [71] Sánchez JL, Berlingeri-Ramos AC, Dianette Vázquez D. Granulomatous rosacea. *The American Journal of Dermatopathology*. 2008;**30**:6-9
- [72] Danese S, Semeraro S, Papa A, et al. Extraintestinal manifestations in inflammatory bowel disease. *World Journal of Gastroenterology*. 2005;**11**:7227-7236
- [73] Kurtzman DJ, Jones T, Lian F, Peng LS. Metastatic Crohn's disease: A review and approach to therapy. *Journal of the American Academy of Dermatology*. DOI: 10.1016/j.jaad.2014.04.002
- [74] Crowson AN, Nuovo GJ, Mihm MC Jr, Magro C. Cutaneous manifestations of Crohn's disease, its spectrum and its pathogenesis: Intracellular consensus bacterial 16S rRNA is associated with the gastrointestinal but not the cutaneous manifestations of Crohn's disease. *Human Pathology*. 2003;**34**:1185-1192
- [75] Albuquerque A, Magro F, Rodrigues S, Lopes J, Lopes S, Dias JM, et al. Metastatic cutaneous Crohn's disease of the face: A case report and review of the literature. *European Journal of Gastroenterology & Hepatology*. 2011;**23**:954-956

- [76] Chen W, Blume-Peytavi U, Goerdts S, Orfanos CE. Metastatic Crohn's disease of the face. *Journal of the American Academy of Dermatology*. 1996;**35**:986-988
- [77] Palamaras I, El-Jabbour J, Pietropaolo N, Thomson P, Mann S, Robles W, et al. Metastatic Crohn's disease: A review. *Journal of the European Academy of Dermatology and Venereology*. 2008;**22**:1033-1043
- [78] Issa MA. Crohn's disease of the mouth. *British Dental Journal*. 1971;**130**:247-248
- [79] Wiesenfeld D, Ferguson MM, Mitchell DN, et al. Orofacial granulomatosis—A clinical and pathological analysis. *The Quarterly Journal of Medicine*. 1985;**54**:101-113
- [80] Mignogna MD, Fedele S, Lo Russo L, Lo Muzio L. The multiform and variable patterns of onset of orofacial granulomatosis. *Journal of Oral Pathology & Medicine*. 2003;**32**:200-205
- [81] Grave B, McCullough M, Wiesenfeld D. Orofacial granulomatosis—A 20-year review. *Oral Diseases*. 2009;**15**(1):46-51. DOI: 10.1111/j.1601-0825.2008.01500.x
- [82] Singhal P, Chandan GD, Das UM, Singhal A. A rare case report of orofacial granulomatosis in a pediatric patient. *Journal of the Indian Society of Pedodontics and Preventive Dentistry*. 2012;**30**:262-266
- [83] Piette EW, Rosenbach M. Granuloma annulare. Clinical and histologic variants, epidemiology, and genetics. *Journal of the American Academy of Dermatology*. 2016;**75**:457-465
- [84] Muhlbauer JE. Granuloma annulare. *Journal of the American Academy of Dermatology*. 1980;**3**:217-230
- [85] Cyr PR. Diagnosis and management of granuloma annulare. *American Family Physician*. 2006;**74**:1729-1734
- [86] Dabski K, Winkelmann RK. Generalized granuloma annulare: Histopathology and immunopathology. Systematic review of 100 cases and comparison with localized granuloma annulare. *Journal of the American Academy of Dermatology*. 1989;**20**:28-39
- [87] McDermott MB, Lind AC, Marley EF, et al. Deep granuloma annulare (pseudorheumatoid nodule) in children: Clinicopathologic study of 35 cases. *Pediatric and Developmental Pathology*. 1998;**1**:300-308
- [88] Felner EI, Steinberg JB, Weinberg AG. Subcutaneous granuloma annulare: A review of 47 cases. *Pediatrics*. 1997;**100**:965-967
- [89] De Aloe G, Risulo M, Sbano P, Pianigiani E, Fimiani M. Congenital subcutaneous granuloma annulare. *Pediatric Dermatology*. 2005;**22**(3):234-236. DOI: 10.1111/j.1525-1470.2005.22311.x
- [90] Goncalves RR et al. Annular elastolytic giant cell granuloma—Case report. *Anais Brasileiros de Dermatologia*. 2011;**86**:S69-S71
- [91] Arora S, Malik A, Patil C, Balki A. Annular elastolytic giant cell granuloma: A report of 10 cases. *Indian Dermatology Online Journal*. 2015;**6**(Suppl S1):17-20
- [92] Ishibashi A, Yokoyama A, Hirano K. Annular elastolytic giant cell granuloma occurring in covered areas. *Dermatologica*. 1987;**174**:293
- [93] Kato H et al. Annular elastolytic giant cell granuloma: An unusual case with papular lesions. *The Journal of Dermatology*. 1991;**18**:667

- [94] Meadows KP, O'Reilly MA, Harris RM, Petersen MJ. Erythematous annular plaques in a necklace distribution. *Archives of Dermatology*. 2001;**137**:1647-1652
- [95] Gutierrez-Gonzalez E, Gomez-Bernal S, Alvarez-Perez A, Sanchez-Aguilar D, Toribio J. Elastolytic giant cell granuloma: Clinic-pathologic review of twenty cases. *Dermatology Online Journal*. 2013;**19**:20019
- [96] Shoimer I, Wismer J. Annular elastolytic giant cell granuloma associated with temporal arteritis leading to blindness. *Journal of Cutaneous Medicine and Surgery*. 2011;**15**(5):293-297
- [97] Djilali-Bouzina F, Grange F, Krzisch S, Schnebelen MP, Grosshans E, Guillaume JC. Annular elastolytic giant cell granuloma. *Annales de Dermatologie et de Vénéréologie*. 2010;**137**(8-9):536-540
- [98] Rongioletti F, Baldari M, Burlando M, Parodi A. Papular elastolytic giant cell granuloma: Report of a case associated with monoclonal gammopathy and responsive to topical tacrolimus. *Clinical and Experimental Dermatology*. 2010;**35**(2):145-148
- [99] Das S, Chowdhury J, Patra S, Achar A. Annular elastolytic giant cell granuloma—A rare case with systemic involvement. *Bangladesh Journal of Medical Science*. 2016;**15**:488-491
- [100] Muller SA, Winkelmann RK. Necrobiosis lipoidica diabetico-rum: A clinical and pathological investigation of 171 cases. *Archives of Dermatology*. 1966;**93**:272-281
- [101] Peyri J, Moreno A, Marcoval J. Necrobiosis lipoidica. *Seminars in Cutaneous Medicine and Surgery*. 2007;**26**:87-89
- [102] Reid SD, Ladizinski B, Lee K, Baibergenova A, Alavi A. Update on necrobiosis lipoidica: A review of etiology, diagnosis, and treatment options. *Journal of the American Academy of Dermatology*. 2013;**69**:783-791
- [103] Thomas M, Khopkar US. Necrobiosis lipoidica: A clinicopathological study in the Indian scenario. *Indian Dermatology Online Journal*. 2013;**4**:288-291
- [104] Mann RJ, Harman RRM. Cutaneous anaesthesia in necrobiosis lipoidica. *British Journal of Dermatology*. 1984;**110**(3):323-325. DOI: 10.1111/j.1365-2133.1984
- [105] Santos-Juanes J, Galache C, Curto JR, Carrasco MP, Ribas A, Sanchez del Rio J. Squamous cell carcinoma arising in long-standing necrobiosis lipoidica. *Journal of the European Academy of Dermatology and Venereology*. 2004;**18**:199-200
- [106] Sayah A, English JC 3rd. Rheumatoid arthritis: A review of the cutaneous manifestations. *Journal of the American Academy of Dermatology*. 2005;**53**(2):191-209 quiz 210-2
- [107] Ziff M. The rheumatoid nodule. *Arthritis and Rheumatism*. 1990;**33**(6):761-767. DOI: 10.1002/art.1780330601
- [108] Gordon DA, Stein JL, Broder I. The extra-articular features of rheumatoid arthritis. A systematic analysis of 127 cases. *The American Journal of Medicine*. 1973;**54**:445-452
- [109] Wood MG, Beerman H. Necrobiosis lipoidica granuloma annulare and rheumatoid nodule. *Journal of Investigative Dermatology*. 1960;**34**:139-147
- [110] Kaye BR, Kaye RL, Bobrove A. Rheumatoid nodules. Review of the spectrum of associated conditions and proposal of a new classification, with

a report of four seronegative cases.
 The American Journal of Medicine.
 1984;**76**:279-292

[111] Rosenbach M, English JC 3rd.
 Reactive granulomatous dermatitis:
 A review of palisaded neutrophilic and
 granulomatous dermatitis, interstitial
 granulomatous dermatitis, interstitial
 granulomatous drug reaction, and a
 proposed reclassification. *Dermatologic
 Clinics*. 2015;**33**(3):373-387

[112] Chu P, Connolly MK, LeBoit PE.
 The histopathologic spectrum
 of palisaded neutrophilic and
 granulomatous dermatitis in patients
 with collagen vascular disease. *Archives
 of Dermatology*. 1994;**130**:1278-1283

[113] Finan MC, Winkelmann RK. The
 cutaneous extravascular necrotizing
 granuloma (Churg-Strauss granuloma)
 and systemic disease: A review of
 27 cases. *Medicine (Baltimore)*.
 1983;**62**:142-158

[114] Hantash BM, Chiang D, Kohler S,
 et al. Palisaded neutrophilic and
 granulomatous dermatitis associated
 with limited systemic sclerosis.
*Journal of the American Academy of
 Dermatology*. 2008;**58**:661-664

[115] Dykman CJ, Galens GJ, Good AE.
 Linear subcutaneous bands in
 rheumatoid arthritis. *Annals of Internal
 Medicine*. 1965;**63**:134-140

[116] Peroni A, Colato C, Schena D, et al.
 Interstitial granulomatous dermatitis:
 A distinct entity with characteristic
 histological and clinical pattern.
The British Journal of Dermatology.
 2011;**166**:775-783

[117] Magro CM, Crowson AN,
 Schapiro BL. The interstitial
 granulomatous drug reaction: A
 distinctive clinical and pathological
 entity. *Journal of Cutaneous Pathology*.
 1998;**25**:72-78

[118] Luz FB, Gaspar AP, Kalil-Gaspar N,
 Ramos-e-Silva M. Histiocytes and
 non-Langerhans cell histiocytoses
 in dermatology. *Anais Brasileiros de
 Dermatologia*. 2003;**78**:99-118

[119] Achar A, Naskar B, Mondal PC,
 Pal M. Multiple generalized
 xanthogranuloma in adult: Case report
 and treatment. *Indian Journal of
 Dermatology*. 2011;**56**:197-199

[120] Chisolm SS, Schulman JM,
 Fox LP. Adult xanthogranuloma,
 reticulohistiocytosis, and Rosai-
 Dorfman disease. *Dermatologic Clinics*.
 2015;**33**:465-472

[121] Saad N, Skowron F, Dalle S,
 Forestier JY, Balme B, Thomas L.
 Multiple adult xanthogranuloma:
 Case report and literature review.
Dermatology. 2006;**212**:73-76

[122] Caputo R, Grimalt R, Gelmetti C,
 Cottoni F. Unusual aspects of juvenile
 xanthogranuloma. *Journal of the
 American Academy of Dermatology*.
 1993;**29**:868-870

[123] Jakobiec FA, Mills MD,
 Hidayat AA, et al. Periocular
 xanthogranulomas associated with
 severe adult-onset asthma. *Transactions
 of the American Ophthalmological
 Society*. 1993;**91**:99-125

[124] Sivak-Callcott JA, Rootman J,
 Rasmussen SL, et al. Adult
 xanthogranulomatous disease of
 the orbit and ocular adnexa: New
 immunohistochemical findings and
 clinical review. *The British Journal of
 Ophthalmology*. 2006;**90**:602-608

[125] London J, Martin A, Soussan M,
 Badelon I, Gille T, Uzunhan Y, et al.
 Adult onset asthma and periocular
 xanthogranuloma (AAPOX), a rare
 entity with a strong link to IgG4-
 related disease. *Medicine (Baltimore)*.
 2015;**94**(43):e1916

- [126] Nelson CA, Zhong CS, Hashemi DA, Ashchyan HJ, Brown-Joel Z, Noe MH, et al. A multicenter cross-sectional study and systematic review of necrobiotic xanthogranuloma with proposed diagnostic criteria. *JAMA Dermatology*. 2020. DOI: 10.1001/jamadermatol.2019.4221
- [127] Mehregan DA, Winkelmann RK. Necrobiotic xanthogranuloma. *Archives of Dermatology*. 1992;**128**:94-100
- [128] Girisha BS, Holla AP, Fernandes M, Noronha TM. Necrobiotic xanthogranuloma. *Journal of Cutaneous and Aesthetic Surgery*. 2012;**5**(1):43-45
- [129] Rao AG, Lakshmi TS, Vani V. Multicentric reticulohistiocytosis. *Indian Journal of Dermatology, Venereology and Leprology*. 2003;**69**:35-36
- [130] Trotta F, Castellino G, Monaco AL. Multicentric reticulohistiocytosis. *Best Practice & Research. Clinical Rheumatology*. 2004;**5**:759-772
- [131] Barrow MV, Holubar K. Multicentric reticulohistiocytosis. A review of 33 patients. *Medicine (Baltimore)*. 1969;**48**:287-305
- [132] Rapini RP. Multicentric reticulohistiocytosis. *Clinics in Dermatology*. 1993;**11**:107-111
- [133] Luz FB, Gaspar NK, Gaspar AP, Carneiro S, Ramos-e-Silva M. Multicentric reticulohistiocytosis: A proliferation of macrophages with tropism for skin and joints, part I. *Skinmed*. 2007;**6**:172-178
- [134] Sinha A, Dhungana S, Dipankar D, Prakash M, Sharma SK, Das A. Multicentric reticulohistiocytosis: A clinikoradiological review. *Indian Journal of Rheumatology*. 2018;**13**:195-201
- [135] Farraj S. Familial histiocytic dermatoarthritis. A new syndrome. *American Journal of Medicine*. 1973;**54**:793-800
- [136] Pennys NS, Ahn YS, McKinney EC, McCleod T, Byrne G Jr, Byrnes J, et al. Sinus histiocytosis with massive lymphadenopathy. A case with unusual skin involvement and a therapeutic response to vinblastine loaded platelets. *Cancer*. 1982;**49**:1994-1998
- [137] Innocenzi D, Silipo V, Giombini S, Ruco L, Bosman C, Calviero S. Sinus histiocytes with massive lymphadenopathy-Rosai-Dorfman syndrome: Case report with nodal and diffuse mucocutaneous involvement. *Journal of Cutaneous Pathology*. 1998;**25**:563-567
- [138] Sanchez R, Rosai J, Dorfman RF. Sinus histiocytosis with massive lymphadenopathy. An analysis of 113 cases with special emphasis on its extranodal manifestations. *Laboratory Investigation*. 1977;**36**:21-22
- [139] Tran TH, Pope E, Weitzman S. Cutaneous histiocytosis. In: Griffiths C, Barker J, Bleiker J, Chelmers R, Creamer D, editors. *Rooks Textbook of Dermatology*. 9th ed
- [140] Kang TW, Kim SC. A case of xanthoma disseminatum presenting as pedunculating nodules and plaques. *Korean Journal of Dermatology*. 2007;**45**:290-293
- [141] Alexander AS, Turner R, Uniate L, Pearcy RG. Xanthoma disseminatum: A case report and literature review. *The British Journal of Radiology*. 2005;**78**:153-157
- [142] Rupec RA, Schaller M. Xanthoma disseminatum. *International Journal of Dermatology*. 2002;**41**:911-913
- [143] Seaton ED, Pillai GJ, Chu AC. Treatment of xanthoma disseminatum with cyclophosphamide. *The British Journal of Dermatology*. 2004;**150**:346-349

- [144] Wolff SM. Wegener's granulomatosis. *Annals of Internal Medicine*. 1974;**81**(4):513. DOI: 10.7326/0003-4819-81-4-513
- [145] Fauci AS, Wolff SM. Wegener's granulomatosis: Studies in eighteen patients and a review of the literature. *Medicine (Baltimore)*. 1973;**52**:535-561
- [146] Daoud MS, Gibson LE, DeRemee RA, Specks U, El-Azhary RA, Daniel Su WP. Cutaneous Wegener's granulomatosis: Clinical, histopathologic, and immunopathologic features of thirty patients. *Journal of the American Academy of Dermatology*. 1994;**31**(4):605-612. DOI: 10.1016/s0190-9622(94)70224-1
- [147] Fauci AS, Haynes BF, Katz P. The spectrum of vasculitis: Clinical, pathologic, immunologic, and therapeutic considerations. *Annals of Internal Medicine*. 1978;**89**:660-676
- [148] Fauci AS. Wegener's granulomatosis: Prospective clinical and therapeutic experience with 85 patients for 21 years. *Annals of Internal Medicine*. 1983;**98**(1):76. DOI: 10.7326/0003-4819-98-1-76.
- [149] Sharma A, Dogra S, Sharma K. Granulomatous vasculitis. *Dermatologic Clinics*. 2015;**33**:475-487
- [150] Roschewski M, Wilson WH. Lymphomatoid granulomatosis. *The Cancer Journal*. 2012;**18**(5):469-474. DOI: 10.1097/ppo.0b013e31826c5e19
- [151] Katzenstein AL, Carrington CB, Liebow AA. Lymphomatoid granulomatosis: A clinicopathologic study of 152 cases. *Cancer*. 1979;**43**:360-373
- [152] Rapini RP, Bologna JL, Jorizzo JL. *Dermatology: 2-Volume Set*. St. Louis: Mosby; 2007. p. 1443. ISBN: 978-1-4160-2999-1
- [153] Hirsch BC, Johnson WC. Pathology of granulomatous diseases: Foreign body granulomas. *International Journal of Dermatology*. 1984;**23**:531-538
- [154] Delage C, Shane JJ, Johnson FB. Mammary silicone granuloma: Migration of silicone fluid to abdominal wall and inguinal region. *Archives of Dermatology*. 1973;**108**:104-107
- [155] Dodiuk-Gad RP, Shear NH. Granulomatous drug eruptions. *Dermatologic Clinics*. 2015;**33**:525-539
- [156] Laura A, Luca P, Luisa PA. Interstitial granulomatous drug reaction due to febuxostat. *Indian Journal of Dermatology, Venereology and Leprology*. 2014;**80**(2):182-184