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Cutaneous Granulomatosis: a Comprehensive Review

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Abstract

Cutaneous granulomatosis is a heterogeneous group of diseases, characterized by a skin inflammatory reaction triggered by a wide variety of stimuli, including infections, foreign bodies, malignancy, metabolites, and chemicals. From a pathogenic point of view, they are divided into non-infectious and infectious granulomas. Pathophysiological mechanisms are still poorly understood. Non-infectious granulomatous skin diseases include granuloma annulare, necrobiosis lipoidica, rheumatic nodules, foreign body granulomas, cutaneous sarcoidosis, and interstitial granulomatous dermatitis. Necrobiosis lipoidica is more frequent in diabetic patients. Infectious granulomas of the skin are caused by mycobacteria, in particular *Mycobacterium tuberculosis* or atypical mycobacteria; parasites, such as Leishmania; or fungi. Pathogenic mechanisms of *M. tuberculosis*-related granuloma are discussed. From a clinical point of view, it is useful to divide cutaneous granulomatosis into localized and more disseminated forms, although this distinction can be sometimes artificial. Three types of localized granulomatous lesions can be distinguished: palisaded granulomas (granuloma annulare, necrobiosis lipoidica, and rheumatoid nodules), foreign body granulomas, and infectious granulomas, which are generally associated with localized infections. Disseminated cutaneous granulomas can be divided into infectious, in particular tuberculosis, and non-infectious forms, among which sarcoidosis and interstitial granulomatous dermatitis. From a histological point of view, the common denominator is the presence of a granulomatous inflammatory infiltrate in the dermis and/or hypodermis; this infiltrate is mainly composed of macrophages grouped into nodules having a nodular, palisaded or interstitial architecture. Finally, we propose which diagnostic procedure should be performed when facing a patient with a suspected cutaneous granulomatosis.

Keywords Granulomatous disease · Granuloma annulare · Necrobiosis lipoidica · Foreign body granulomas · Infectious granulomas · Sarcoidosis · Interstitial granulomatous dermatitis

Abbreviations

DCs	Dendritic cells
T cells	T lymphocytes
MΦs	Macrophages
TLR	Toll-like receptors
NOD	Nucleotid-binding oligomerization domain
DAMPs	Damage-associated molecular patterns
PAMPs	Pathogen-associated molecular pattern
IFN	Interferon
M1	Macrophages 1
M2	Macrophages 2
IL	Interleukin
APCs	Antigen presenting cells
Th	T helper cells
GA	Granuloma annulare
HLA	Human leukocyte antigen
TNF	Tumor necrosis factor
NL	Necrobiosis lipoidica
P.	Propionibacterium
IGD	Interstitial granulomatous dermatitis
PNGD	Palisaded neutrophilic and granulomatous dermatitis
RGD	Reactive granulomatous dermatitis
Mtb	Mycobacterium tuberculosis
DG-SIGN	DC-specific intercellular adhesion molecule-3-grabbing non-integrin
PDT	Photodynamic therapy
MAL-PDT	Methyl aminolevulinate-photodynamic therapy
PUVA	Psoralen and UVA
M.	Mycobacterium
PCR	Polymerase chain reaction

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Introduction

Cutaneous granulomatosis is a heterogeneous group of skin diseases whose pathophysiological mechanism is still poorly understood. It is a granulomatous inflammatory reaction to a wide variety of stimuli, including infections, systemic inflammations, neoplasia, metabolic disorders, and chemicals [1, 2]. This explains the wide variety of clinical and histological presentations.

Depending on their etiology, cutaneous granulomatosis can be localized or more disseminated. The elementary lesion corresponds to an infiltrated papule, which is painless, rounded, well limited, 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 [3].

From a histological point of view, the common denominator is the presence of a granulomatous inflammatory infiltrate in the dermis and/or hypodermis; this infiltrate is mainly composed of macrophages (MΦs) grouped into nodules having a nodular, palisaded, or interstitial architecture (Fig. 1) [2, 4].

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 non-infectious and infectious granulomas [2].

Pathogenesis

The pathogenesis of skin and systemic granulomatous diseases is unknown. Granuloma is a specific form of inflammation involving mostly dendritic cells (DCs), T lymphocytes (T cells), and MΦs, which are the dominant cell type. The main functions of tissue MΦs, referred to as histiocytes, are phagocytosis and elimination of microorganisms, as well as antigen presentation. They also play a role in induction and production of cytokines, chemokines, and chemotactic lipids [5–8].

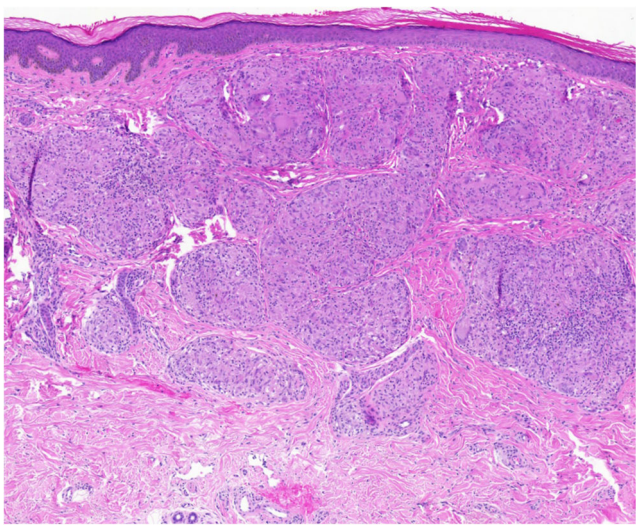

Fig. 1 Sarcoidosic granulomatous inflammatory infiltrate in the dermis mainly composed of lymphocytes and macrophages having a nodular architecture (HE)

It has been proposed that granuloma formation is driven by either a non-specific inflammation induced by foreign bodies or a specific delayed hypersensitivity reaction to an antigen [9, 10]. Both innate and adaptive immunity are involved in this inflammatory process [7]. Cell membrane receptors such as Toll-like receptors (TLR) and cytoplasm receptors such as NOD (nucleotid-binding oligomerization domain)-like receptors are major players of innate immunity acting as microbial-sensing proteins. By a process called pattern recognition, a small number of these receptors can detect a broad range of human pathogens, as well as a variety of other molecules that indicate tissue damage: when endogenous (damage-associated molecular patterns, DAMPs) or environmental antigens (pathogen-associated molecular patterns, PAMPs) bind to these receptors, an inflammatory cascade is triggered with release of proinflammatory cytokines leading to activation of neutrophils, MΦs, and DCs [7]. The MΦ within the granuloma belongs to one of the two differently activated types of macrophages: namely the classically activated (M1) and alternatively activated (M2) macrophages. M1 macrophages, stimulated by TLR ligands and IFN-γ, are characterized by the expression of high levels of pro-inflammatory cytokines, and high production of reactive nitrogen and oxygen intermediates. They promote a T helper cell (Th)1 response, and have strong microbicidal activity. M2 macrophages, stimulated by IL-4, IL-10, and IL-13, are characterized by the expression of anti-inflammatory cytokines, and promotion of tissue remodeling and immunoregulatory functions. They prevail in parasitic infections. Though one type of MΦ tends to prevail in specific forms of granuloma, both MΦ phenotypes can coexist, possibly to maintain a balance between pro- (M1) and anti-(M2) inflammatory response [7, 11].

The cytokine-rich milieu produced during the activation of the innate immunity promotes maturation of antigen presenting cells (APCs), particularly DCs. By presenting an antigenic peptide to T lymphocytes, these APCs activate the adaptive immune response, triggering T cell differentiation [7]. Different combinations of soluble factors—cytokines and chemokines—released by M1 and M2 macrophages determine different patterns of activation, migration, and type of T cell response in granulomatous disorders. M1 macrophages are associated to a Th1 (IL-2, IFN-γ) and Th17 (IL-17) response [12, 13]. M2 macrophages are associated to Th2 response, which can be triggered by parasites, and contributes to the maintenance of the chronic fibrotic tissue of granulomas [14].

Non-infectious Granulomatous Skin Diseases

Non-infectious granulomatous skin diseases include granuloma annulare (GA), necrobiosis lipoidica, rheumatic nodules,

foreign body granulomas, cutaneous sarcoidosis, and interstitial granulomatous dermatitis.

The etiopathogenesis of GA is unknown. A genetic predisposition has been suggested by some reports. Friedman and Winkelmann [15] reported on two sisters with GA and identical histocompatibility antigens (human leukocyte antigen (HLA)-Bw35). Knoell [15] described two monozygotic twin sisters with difficult-to-treat generalized GA who showed a striking response to anti-tumor necrosis factor (TNF)-α. They were showed to carry the human ancestral haplotype 8.1, linked with increased production of TNF-α by peripheral blood mononuclear cells [16, 17]. An infectious origin has been supposed in the past; however, molecular or culture-based evidence for bacterial, mycobacterial, or fungal microorganisms was not confirmed by a recent study [18]. Many trigger factors for GA have been reported: lightning strike, tattoo, saphenectomy, vaccinations, bee and octopus bite, varicella zoster virus, collagen injections, mesotherapy, and drugs such as allopurinol, topiramate, gold, anti-TNF-α, and IFN-α [19]. GA can occur at the site of previous varicella zoster or herpes simplex virus infection, a condition referred to as Wolf isotopic response [20]. There are conflicting data regarding a potential link between GA and diabetes; a definitive evidence remains to be proven by controlled studies [19]. An association with autoimmune thyroiditis, autoimmune hepatitis, primary biliary cholangitis, sarcoidosis, Sweet's syndrome, and dyslipidemia has also been evoked [19, 21–23]. Finally, GA triggered by infectious agents including *Borrelia* species, hepatitis B and C virus, and HIV has been reported, leading to the recommendation to screen for HIV patients with newly diagnosed GA, particularly in case of perforating GA [19]. GA is self-resolving in most cases [19].

Necrobiosis lipoidica (NL), similarly to GA, is characterized histologically by palisaded and interstitial granulomas. NL, also called NL diabeticorum, is a rare chronic granulomatous dermatitis that affects 0.3% of diabetic patients [4, 24]. The strength of the association with diabetes is debated, since the early study by Muller and Winkelmann [25], reporting over 60% of NL cases being associated with diabetes, has not been confirmed by O'Toole et al. [26], who found only 22% of NL cases being diagnosed in diabetic or pre-diabetic subjects. However, it has been shown that NL is more frequent in diabetic patients than in non-diabetic ones [2]. The etiology and pathogenesis of NL are still unclear. A pathogenic role of microangiopathy is suggested by the frequent association with diabetes, whereby chronic hypoxia leads to small vessel wall thickening due to glycoprotein deposition [27, 28]. Boateng et al. [29] demonstrated a local alteration of microcirculation also in non-diabetic patients with NL. However, a few years later, Ngo and colleagues demonstrated that the blood flow was higher in NL lesions as compared with normal skin, in contrast with the previous results [30]. In addition, some data suggest a potential pathogenic role of the human erythrocyte glucose transporter Glut-1, which has been found to be overexpressed in NL skin lesions both in diabetic and non-diabetic patients [31]. Other pathogenic mechanisms have been discussed, including deposition of immunoglobulins; abnormal collagen fibrils; and traumatic, inflammatory, and metabolic changes, but neither of these hypotheses has been confirmed [27, 32].

The pathogenesis of rheumatic nodules has recently been reviewed in detail in this journal [33].

The introduction of foreign material into the skin can induce a tissue reaction and lead to a foreign body granuloma [4]. Most frequently, foreign body granulomas are characterized histologically by mononuclear MΦs and giant cells with multiple nuclei. Rarely, the foreign body reaction occurs in patients with sarcoidosis, and, in this case, it is characterized histologically by an epithelioid cell pattern [4]. The precise immunopathogenic mechanisms leading to foreign body granulomas are not clear. It is supposed that immunocompromised cutaneous districts have an increased susceptibility to formation of granulomas caused by infections or injuries [1].

The pathogenesis of cutaneous sarcoidosis also remains poorly understood [34]. A genetic predisposition has been observed [2]. In Japan, several HLA alleles have been found to be associated with sarcoidosis [35, 36]. Environmental factors are also involved in triggering sarcoidosis [2]: a case-control study aiming at identifying environmental risk factors showed an increased frequency of sarcoidosis in workers having industrial organic dust exposure [37]. Mycobacteria and *Propionibacterium* (*P.*) spp. are the most frequently reported infectious agents potentially triggering sarcoidosis [2, 38]. Genomic or protein material of mycobacterial origin has been identified by molecular techniques in sarcoidosis tissues [39]. *P. acnes* is currently the only microorganism that has been isolated from sarcoid lesions by bacterial culture [40]. In particular for Japanese patients, *P. acnes* is considered the most plausible causal agent for sarcoidosis [40]. The chronicity of the disease is caused by a persistence of upregulation of Th1 cytokines, such as TNF-α and IL-8, after the initial event of activation of naïve T cells by antigen presentation [41]. Judson et al. [41] analyzed the Th1 and Th17 pathways in cutaneous sarcoidosis. They confirmed that IL-12 and the IFN pathway are upregulated and demonstrated also an upregulation of IL-23 and IL-21. Concomitant sarcoidosis and psoriasis may suggest a common pathogenic mechanism involving both Th1 and Th17 pathways [42], but this overlap is rare. Skin sarcoidosis resolves spontaneously within 2–5 years in up to 60% of cases: Th2 cytokines, such as IL-10, may contribute to the downregulation of immune response and the resolution of granulomatous skin lesions [2].

Interstitial granulomatous dermatitis is further divided into two clinical and histological entities: interstitial granulomatous dermatitis (IGD), and palisaded neutrophilic and granulomatous dermatitis (PNGD) [2, 33]. Rosenbach and English

[43] proposed the unifying umbrella term of reactive granulomatous dermatitis (RGD), to clarify that IGD and PNGD have clinical and histopathological overlapping features, and share associations with systemic diseases. The pathogenesis is not entirely clear, but may be related to immune complexes induced by associated diseases [33].

Infectious Granulomatous Diseases

Infectious granulomas of the skin are mostly caused by mycobacteria (*Mycobacterium tuberculosis* (*Mtb*) or atypical mycobacteria), parasites, or fungi. Usually, in disseminated forms, the germ is not detected in skin lesions, which are considered as delayed hypersensitivity reactions to infectious antigens. Pathogenic mechanisms of *Mtb*-related granuloma are discussed here.

In tuberculosis, the defensive role of granulomas is based on limiting growth of *Mtb* [44]. Bone marrow-derived MΦs differentiate according to the tissue environment in which they are located [45]. MΦs and DCs recognize, bind, and internalize foreign particles, including bacteria, and this process contributes to control the intercellular growth of *Mtb*, involving the production of cytokines and chemokines. These latter stimulate the activation of anti-microbial phagocytosis and recruit neutrophil leukocytes. The early stage of infection is marked by M1 MΦ polarization. At this stage, a Th17 immune response is also present. In lung granulomas, IL-17 promotes neutrophilic leukocytes recruitment and organization around the foci of infection [45]. MΦs and neutrophils kill phagocytosed *Mtb*. Granuloma keep the growth of intracellular *Mtb* under control and limit bacillary dissemination. A latent infection is established when M1 polarization predominates. Its persistence depends upon production of Th1 type cytokines, IFN-γ and IL-12, by *Mtb*-specific T cells. However, *Mbt* continue to replicate inside the granuloma; therefore, the granulomatous response is not fully protective [45]. Indeed, *Mtb* has developed strategies to interfere with M1 polarization [46]. *Mtb* inhibits IFN-γ activation of MΦs, leading to a shift towards M2 polarization. As a consequence, IL-4 and IL-13 levels increase and inhibit microbicidal activity in M1 MΦs [47]. The balance shifts in favor of M2 MΦs, which are poorly microbicidal and have been implicated in the inhibition of fibrosis development. A key mechanism in this shift is the *Mtb*-induced expression of the immunosuppressive IL-10. Consequently, M2 MΦs polarization is promoted and the anti-mycobacterial effector mechanisms diminish, leading to disease progression [46].

Localized Cutaneous Granulomatosis

Three types of localized granulomatous lesions can be distinguished: palisaded granulomas (granuloma annulare, necrobiosis lipoidica, and rheumatoid nodules), foreign body granulomas, and infectious granulomas, which are generally associated with localized infections [4].

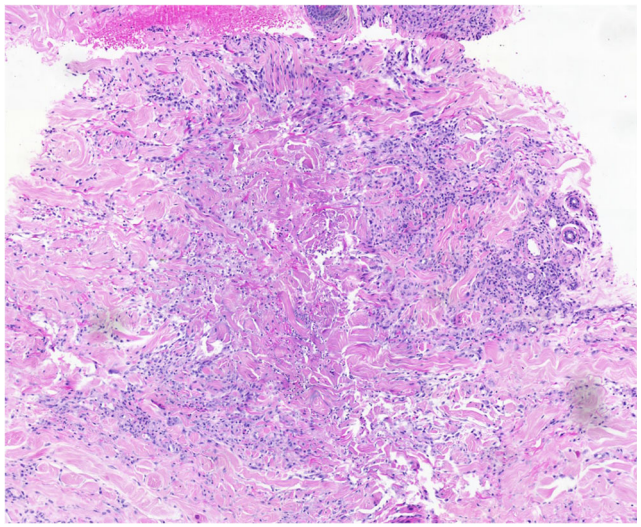

Fig. 2 Nodular inflammatory granulomatous lesion characterized by a central zone of altered connective tissue, surrounded by histiocytes disposed in palisade (HE)

Palissadic Granulomas

This term corresponds to a histological description: it is a nodular inflammatory granulomatous lesion characterized by a central zone of altered connective tissue, surrounded by histiocytes disposed in palisade (Fig. 2). The anomalies observed at the center of the granulomas generally make it possible to distinguish the different forms: mucin deposits in granuloma annulare, necrosis in necrobiosis lipoidica, and massive necrosis with fibrin deposits in rheumatoid nodule. In most cases, the differential diagnosis of these entities can be made on standard histopathological examination [48].

Granuloma Annulare

This is the most commonly occurring form of cutaneous granulomas; two thirds of patients are under 30 years of age, with a male to female ratio of 2:1. Skin involvement predominates at the extremities and rarely involves the face. Among the many variant forms of the disease, the localized form is the most common (75% of the cases). It appears clinically as erythematous flesh-colored plaques, grouped in rings with centrifugal progression. These plaques are themselves made up of small, firm, and well-defined papules (Fig. 3). These lesions are asymptomatic and generally located on the back of the hands and feet, wrists, ankles, and dorso-lateral faces of the fingers. Rarely the lesions can be more disseminated, arranged symmetrically, mainly on the trunk and the extremities [49].

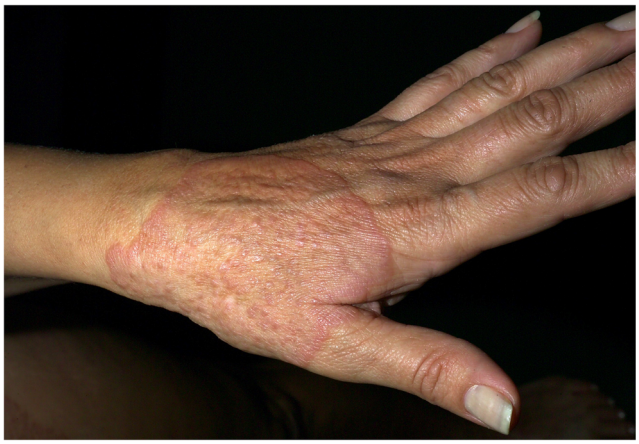

Fig. 3 Typical granuloma annulare of the hand with plaques made up of small, firm, and well-defined papules

One of the rarer lesions is the subcutaneous (deep dermal) form, which is more common in children and consists in firm, painless nodules located at the extremity of the lower limbs (Fig. 4). These lesions can be mistaken for rheumatoid nodules and are known as "pseudo-rheumatoid" nodules [16, 17].

The diagnosis is a clinical one. A skin biopsy is helpful in doubtful cases and can also lead to a regression of the lesion. This classic phenomenon has never received a satisfactory explanation.

Disseminated or generalized GA has also been described, sometimes isolated, and sometimes in association with several conditions. In particular, paraneoplastic forms associated with solid organ tumors or lymphoma have been reported [50]. In these patients, the clinical picture is often atypical (Fig. 5). Thus, in case of disseminated or atypical GA, an underlying malignancy should be ruled out [50].

The evolution of these skin lesions is unpredictable but generally benign. Typically, the skin lesions disappear spontaneously within a few months to 2–3 years [19]. Treatment is often considered for esthetic reasons [19]. For localized GA,

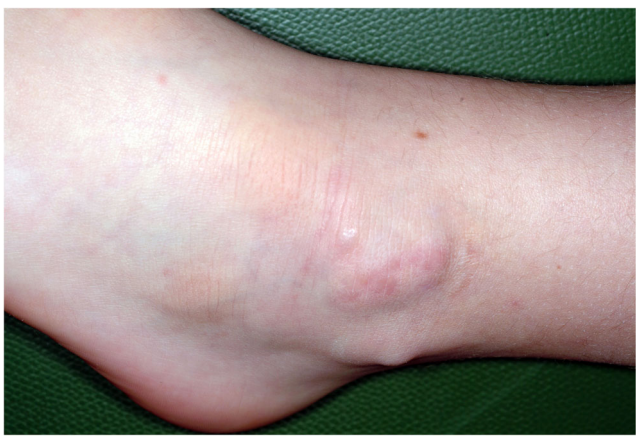

Fig. 4 The subcutaneous (deep dermal) form of granuloma annulare, which is more common in children and consists of firm, painless nodules located at the extremity of the lower limbs

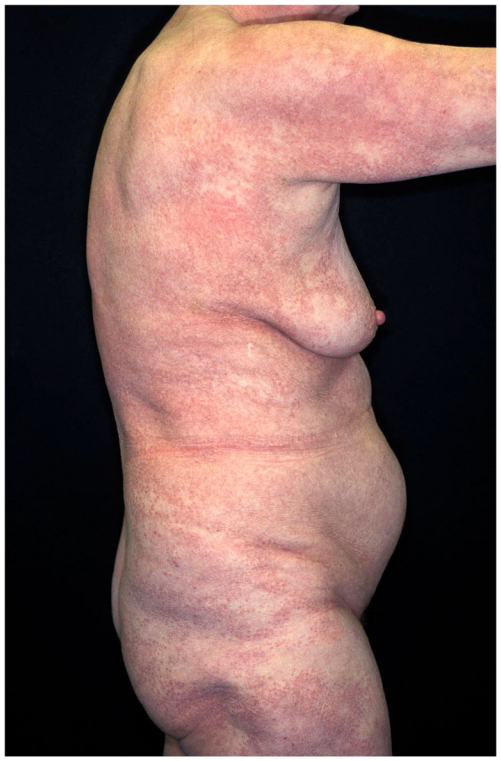

Fig. 5 Disseminated granuloma annulare in a patient with myelodysplastic syndrome; the patient died a few years later of a blastic transformation

first-line therapies are local cryotherapy, and topical or intralesional corticosteroids [19]. Evidence is lacking for second-line options: laser, photodynamic therapy (PDT), imiquimod, UVA1 phototherapy, intralesional IFN-γ injections, scarification, surgery, and combination of oral antibiotics (rifampicin, ofloxacin, and minocycline) have been tried [19]. For generalized or atypical forms, treatment is a real challenge because of the recalcitrant nature of the lesions and the absence of evidence-based therapies. First-line treatments usually are topical steroids, UVA1 phototherapy or Psoralen and UVA (PUVA), hydroxychloroquine, doxycycline, dapsone, oral isotretinoin, or acitretin; other second-line treatments have been proposed but benefit is unclear, given the lack of clinical trials [19].

Necrobiosis Lipoidica

This idiopathic granulomatosis usually occurs in young or middle-aged adults, with a female to male ratio of 3:1. The name describes its features: "necrobiosis" refers to the histological inflammation triggered by cell death, and "lipoidica" to the clinically yellowish appearance of the lesions due to lipid deposits secondary to collagen degeneration [51].

The typical lesions are bilateral papules or nodules, which progressively widen and converge into well-defined oval plaques with a raised erythematous border

surrounding the central area, which is initially reddish-brown, and later becomes yellowish, smooth, and atrophic with telangiectatic scarring (Fig. 6) [24]. Dermatoscopy of early-onset NL may be useful for the diagnosis: it shows branching telangiectasia, hairpin-like vessels, and a yellow background [52]. Over time, the plaque becomes indurated and adherent to the underlying osteo-periosteal planes, with a remaining active border. The lesions are usually painless, except in cases of ulceration often due to minor trauma. Rare cases of squamous cell carcinomas have been reported arising in long-standing lesions [53]. The course of the disease is chronic. Today, there is insufficient evidence to support or reject the hypothesis that glycemic control does improve the skin lesions [54].

Evidence for NL treatment is also lacking. Stop smoking and optimizing the diabetes therapy are recommended. The most commonly used pharmacological treatments are intralesional or topical corticosteroids under occlusion [55]. Second-line treatments are systemic corticosteroids under tight glycemic control and acetylsalicylic acid alone or in association with dipyridamole, ticlopidine, nicotinamide, topical PUVA, clofazimine, or topical tacrolimus [55]. Third-line options based on anecdotally reported cases are fumaric acid esters, cyclosporine A, mycophenolate mofetil, antimalarial drugs, TNF-α inhibitors, intravenous immunoglobulins, pentoxiphylline, UVA1 therapy and granulocyte-macrophage colony stimulating factor, or skin graft surgery in case of ulceration [55–58].

Rheumatoid Nodules

This is the most frequent extra-articular manifestation of rheumatoid arthritis. About 15–20% of adult patients with rheumatoid arthritis have rheumatoid nodules [33]. Patients with rheumatoid nodules are more often rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) positive [54]. Their presence in newly diagnosed patients can be considered as a clinical predictor of severe seropositive and erosive arthritis associated with extra-articular involvement, including rheumatoid vasculitis [59]. They consist of deep dermo-hypodermic nodules of variable size (2 mm to more than 5 cm) adherent to the periosteum. They are located at the extension faces of large joints or at pressure points (mostly at the elbow), but are also found on tendons [33, 60]. Visceral localizations are possible. Generally painless, they can cause discomfort or pain when ulcerating.

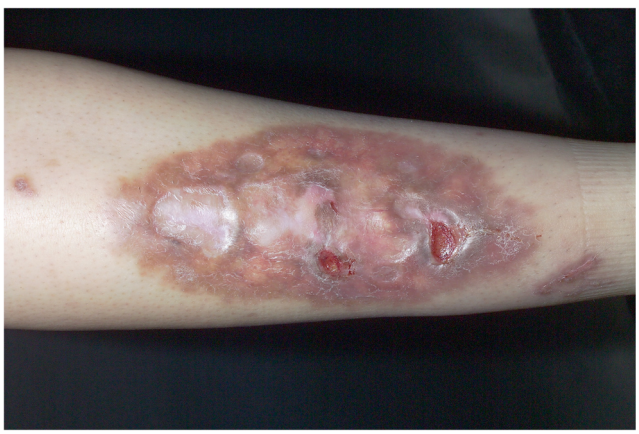

Fig. 6 Necrobiosis lipoidica: well-defined oval plaques with a raised erythematous border surrounding the central area, which is initially reddish-brown, and later becomes yellowish, smooth, and atrophic with telangiectatic scarring

Rheumatoid nodules appearing without clinical or biological rheumatic symptoms are most often deep granuloma annulare or "pseudorheumatoid nodules," particularly in children and in the cephalic region.

The evolution of rheumatoid nodules is variable (growth, regression, recurrence, or persistence). For mild cases, symptomatic lesions can be treated by injection of intralesional corticosteroids or surgical excision. For severe cases, the treatment is based on systemic corticosteroids, dapsone, antimalarial drugs, or colchicine [33].

Foreign Body Granulomas

Foreign body granulomas consist of a cutaneous inflammatory response to any material in the dermis or subcutis (endogenous or exogenous, Table 1) [61]. The clinical presentation depends on several factors: tissue response to the foreign body, anatomical site, penetration, composition, and amount of material involved. They may appear as papules, nodules, or erythematous plaques which harden over time due to fibrosis. The time between introduction of the foreign body into the skin and appearance of granuloma is very variable, sometimes being as long as several years [4].

As the use of different cosmetic fillers has increased in recent years, we currently observe granulomatous reactions

Table 1 Foreign bodies which may cause the formation of granulomas

Endogenous foreign bodies	Exogenous foreign bodies
• Hair	• Vegetal fragments
• Keratin	• Sea urchins
• Calcifications	• Insects
• Cholesterol crystals	• Silica (talc)
• Elastic fibers	• Zirconium
• Content of a cyst	• Chromium
• Sebum	• Beryllium
• Uric acid	• Aluminum
	• Paraffin, vegetable oils
	• Tattoo inks
	• Injections of cosmetic products and implants
	• Implantable medical devices or suturing equipment

to filler products (resorbable or not) (Fig. 7). This can lead to dramatic esthetic and psychological consequences in affected patients [62, 63].

Infectious Granulomas

Infectious granulomas are usually chronic and localized skin infections, the agent being mycobacteria (*Mtb*, atypical mycobacteria), parasites (e.g., leishmaniasis), or fungi (e.g., cryptococcosis, rare in the immunocompetent host) [64].

Cutaneous tuberculosis represents 1–1.5% of all extrapulmonary tuberculosis manifestations, and occurs in 8.4–13.7% of all tuberculosis cases [65]. Skin manifestations of tuberculosis represent a clinical polymorphism that can be explained by various factors such as the pathogenicity of the bacterial strain, the immune status of the host, any previous treatment, or local factors (proximity to lymph nodes) [40, 41, 43]. Localized forms include, among others, lupus vulgaris, a violaceus yellowish cutaneous plaque with serpiginous centrifugal extension, desquamation, and central atrophy (Fig. 8); scrofuloderma, an erythemato-violaceous painless nodule, with suppuration as sign of per contiguitatem extension of ganglionic, osteoarticular, or epididymal tuberculosis; or verrucous cutaneous tuberculosis, a keratotic plaque with irregular edges and dystrophic scarring on skin hands [65, 66].

With the exception of cutaneous leishmaniasis, the abovementioned granulomatous infections have to be considered as skin manifestations of systemic infections. They therefore need a systemic treatment directed against the responsible germ.

Cutaneous leishmaniasis, a flagellate protozoan disease, involves exposed body parts, causing nodules, ulcers, and scarring. This disease is endemic in the tropics, subtropics, and Mediterranean area, but leishmaniasis has also been reported at Northern latitudes among travelers returning from endemic areas. Different ways of transmission such as migrant flow, transportation of dogs from endemic regions, and climate change are suggested for spread of the disease northwards [67]. Today, polymerase chain reaction (PCR) is the best method for the confirmation of the diagnosis [68]. First-line treatments for cutaneous leishmaniasis are intralesional

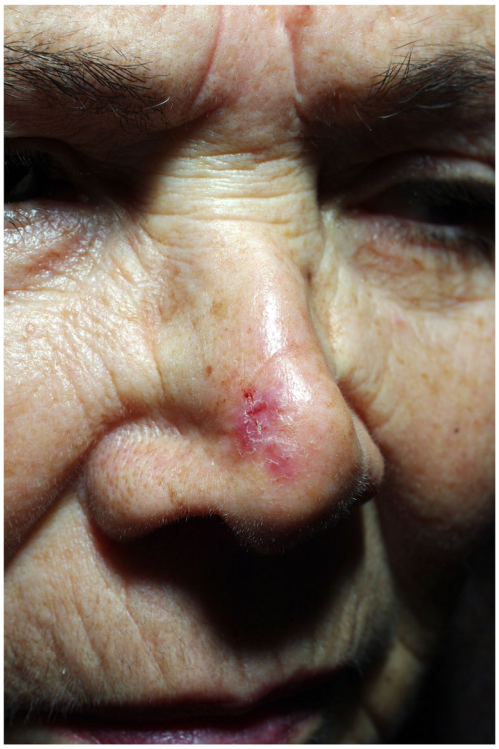

Fig. 8 Tuberculosis of the nose in an immunosuppressed patient for Wegener's disease; the granulomatous lesion had initially been mistakenly considered as a dermal localization of Wegener's disease

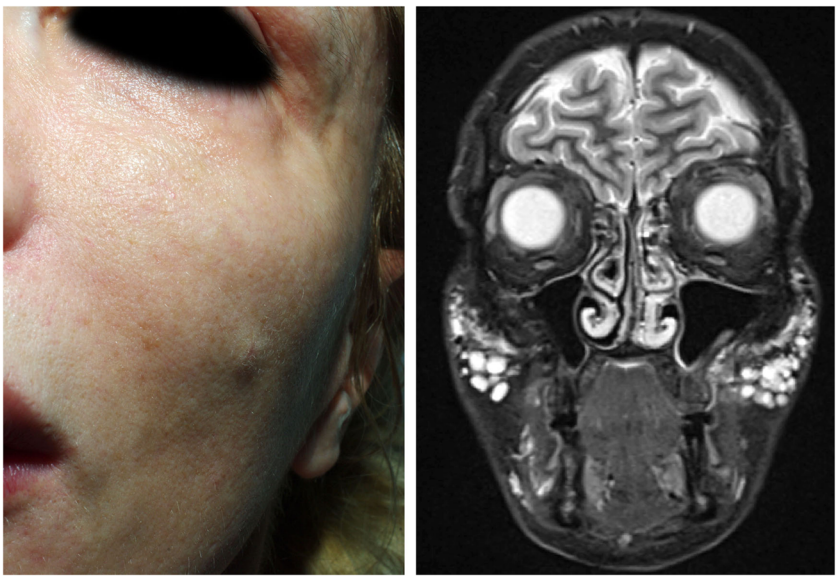

Fig. 7 Granuloma on filling product; note the hypersignal of the cheeks on the MRI indicating the tissue inflammatory reaction

or/and intramuscular meglumine antimoniate or sodium stibogluconate antimony [69–71]. Second-line therapies are azoles (fluconazole or itraconazole), intravenous or intramuscular pentamidine isethionate, cryotherapy, thermotherapy, and doxycycline [72]. Third-line options are miltefosine, intralesional zinc sulfate, pentoxiphylline, PDT, CO_2 laser, paromycin ointment, amphotericin B, topical imiquimod, and direct current electrotherapy [72].

Cutaneous atypical mycobacteria infections have heterogeneous clinical appearance, including nodules, papules, plaques, pustules, abscess, and ulcers [73]. *Mycobacterium* (*M.*) *marinum* is the most commonly involved strain. It causes skin and soft tissue infections after exposure to aquatic environments or marine animals. Thus, *M. marinum* infection is also known as "fish tank granuloma." Patients typically show clusters of nodules, ulcers, or verrucous plaques that may spread from the arms or legs in a sporotrichoid pattern (Fig. 9) [74]. The diagnosis is made by culture or PCR of a skin biopsy specimen. It is a rare disease and evidence-based therapeutic recommendations are missing. The most widely used treatments are minocycline, doxycycline, clarithromycin, rifampicin, and co-trimoxazole. Additional options are azithromycin or combinations of antimicrobial drugs: clarithromycin + ethambutol, ciprofloxacin + clarithromycin, or rifabutin + clarithromycin + ciprofloxacin. Third-line options are surgery, PDT, cryotherapy, or infliximab, in addition to antibiotic drugs in order to reduce the inflammatory reaction [75–77]. *M. chelonae* is a rapidly growing mycobacterium that causes dark red nodules and, occasionally, abscesses. The infection is related to skin wounds due to penetration procedures such as injection, liposuction, acupuncture, tattoos, and rarely catheter injection (Fig. 10). Lesions are localized and occur after an incubation lasting 1 to 6 months [78]. Surgical incision and drainage of the abscess in combination with antibiotics (clarithromycin, azithromycin, and clarithromycin as part of dual or triple therapy with ciprofloxacin, tobramycin, or tigecycline) are essential for the treatment [79, 80].

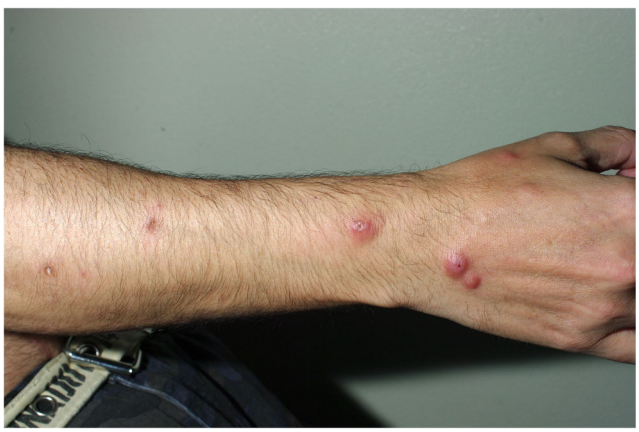

Fig. 9 *Mycobacterium marinum* infection in an aquarist with the typical sporotrichoid pattern on the right upper limb

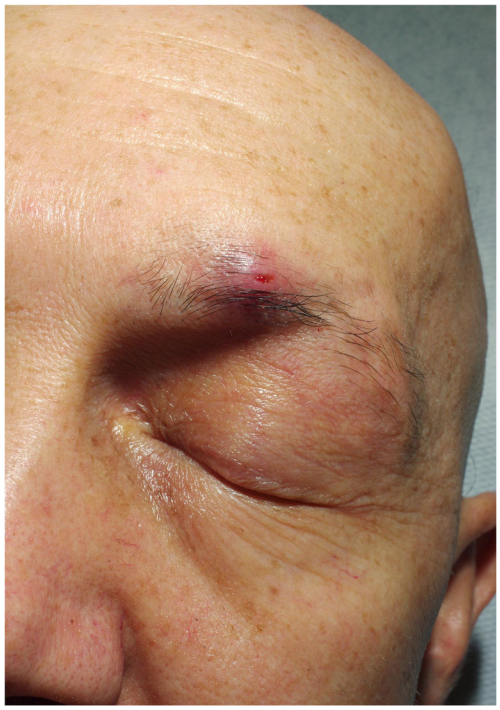

Fig. 10 *Mycobacterium chelonae* granuloma of the eyebrow in a patient who received intralesional corticosteroid injections for alopecia areata

Disseminated Cutaneous Granulomas

Disseminated cutaneous granulomas can be divided into infectious and non-infectious forms.

Infectious Forms

Infectious disseminated cutaneous granulomas are mainly systemic infections. Almost all infectious agents that can induce granulomas may be responsible for mucocutaneous disease [81]. The skin lesions do not have a specific clinical pattern, and the general context will guide the diagnosis, as well as specific tissue analysis. The most sensitive PCR techniques might sometimes be positive. Among many infectious agents (Table 2), mycobacteria are the most frequently involved ones. In tuberculosis and leprosy, there is either a true skin infection or tuberculids, which are regarded as a cutaneous hypersensitivity reaction to *Mtb* or *Mycobacterium leprae* linked to the release of antigen by an internal mycobacteria infectious focus [82]. Skin tuberculids lesions are not contagious. Tuberculosis patients with skin tuberculids have a high degree of tuberculin sensitivity. The clinical manifestations of tuberculosis tuberculids are erythema nodosum, erythema induratum of Bazin, papulonecrotic tuberculids, lichen scrofulosorum

Table 2 The most common infectious diseases causing disseminated cutaneous granulomatosis

Bacterias	Viruses	Parasites	Fungi
Mycobacteria	HIV	Bilharzia	Candidiasis
Tuberculosis	HBV, HCV	Toxocarose	Aspergillosis
Atypical mycobacteria	EBV	Toxoplasmosis	Cryptococcosis
Leprosy	CMV	Leishmaniasis	Histoplasmosis
Others			
Syphilis			
Listeriosis			
Salmonellosis			
Donovanose			
Brucellosis			
Pasteurellosis			
Yersiniose			
Nocardiose			
Bartonella henselae			
Tularemia			
Whipple			

HIV human immunodeficiency virus, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *EBV* Epstein-Barr virus, *CMV* cytomegalovirus

(Fig. 11), and lupus miliaris disseminates facei, whose differential diagnosis is granulomatous rosacea [83].

Leprosy is also a mycobacterial infection with particular clinical features that will not be detailed here.

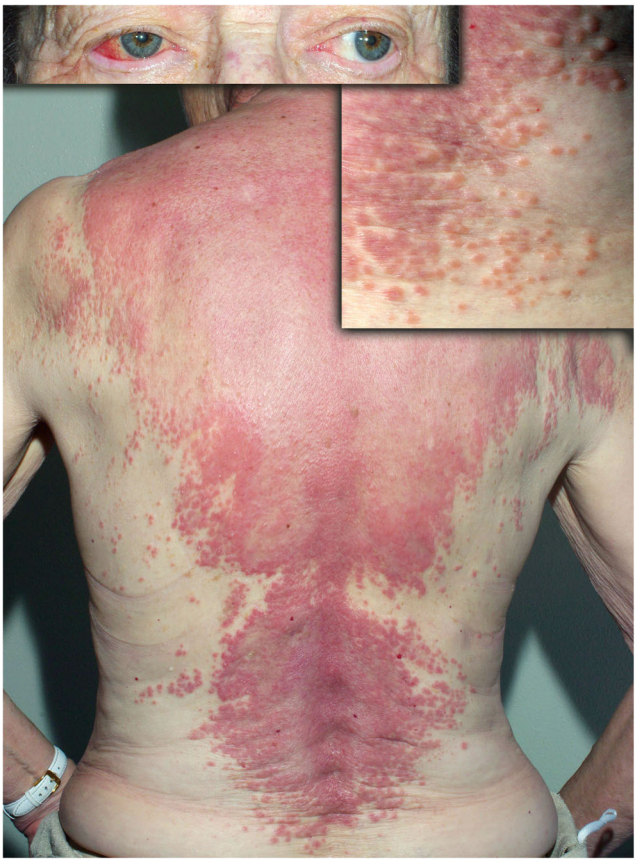

Fig. 11 Disseminated granulomatous reaction lichen scrofulosorum type in a patient treated for lymph node tuberculosis; the patient developed at the same time a granulomatous uveitis of the right eye

Non-infectious Forms

There are many etiologies of non-infectious disseminated cutaneous granulomas and they can be divided into several subgroups (Table 3). Only sarcoidosis and interstitial granulomatous dermatitis will be discussed in this section.

Sarcoidosis

Sarcoidosis is a chronic inflammatory disease that can affect several organs. Concerning the skin, we distinguish non-specific cutaneous manifestations, such as erythema nodosum, which has been recently reviewed in this Journal [84], from specific manifestations characterized histologically by the presence of non-caseous granulomas [85]. These specific manifestations occur in 10–40% of sarcoidosis patients and are frequently observed at the onset of the disease. They may precede systemic signs from 6 months to up to 3 years [3, 86]. The risk of developing systemic sarcoidosis in patients with disease limited to the skin is unknown. Cutaneous sarcoidosis is also known as one of the "great imitators" in dermatology, together with syphilis and malignant melanoma [87–89].

Although the histopathological features are similar, clinical manifestations of sarcoidosis-specific cutaneous lesions vary widely [90]. They are usually asymptomatic [88–90]. The most frequent and characteristic forms are:

Maculo-papular Lesions The papules are commonly red-brown to purple, slightly infiltrated and measure less than 10 mm. They are mostly located on the face with palpebral, periorbital, and nasolabial folds involvement. In some cases, papules may extend or coalesce to form either annular lesions or plaques. They are rather associated to acute forms of sarcoidosis and disappear generally without leaving a scar [88–90].

Plaques These rounded or oval, red-brownish lesions are usually indurated, and their size may vary from some millimeters to several centimeters in diameter (Fig. 12). Plaques have a predilection for the limbs, back, face, and scalp causing sometimes cicatricial alopecia. They are rather associated with chronic forms of sarcoidosis and are more likely to persist or recur, sometimes healing with a permanent scar [88–90].

Nodules These lesions appear as non-tender, firm, mobile, subcutaneous nodules ranging from 0.5 to 2 cm in diameter.

Table 3 The main etiologies of non-infectious disseminated cutaneous granulomatosis

Systemic inflammatory diseases
Sarcoidosis
Connective tissue disease, lupus erythematosus, rheumatoid arthritis (interstitial granulomatosis dermatitis)
Inflammatory bowel disease, autoimmune hepatitis
Neoplasia
Lymphoma:
Cutaneous: mycosis fongoides T cell lymphoma (granulomatous) Systemic: Hodgkin, non-Hodgkin
Myelodysplastic syndrome Solid tumors: lung, breast, uterus, prostate
Metabolic
Diabetes, dyslipidemia, dysthyroïdia
Toxic
Drugs: antihypertensives, hypolipemic agents, topiramate, gold, allopurinol
Immunotherapy and growth factors: interferon α, G-CSF, anti-TNF-α, IFN-α
Immunodeficiency
Congenital: common variable immunodeficiency, Wiskott-Aldrich syndrome (among others)
Acquired: iatrogenic
Idiopathic

G-CSF granulocyte-colony stimulating factor, *TNF* tumor necrosis factor, *IFN* interferon

Their number ranges from one to one hundred. Small nodules are sometimes eruptive (Fig. 13) and may take a chronic course. Large nodules are more frequent and appear purplish or brownish red (Fig. 14). Lesions are located deep in the dermis and subcutaneous tissue of the extremities and trunk, less frequently of the face or head. They are more common on the forearms, where they tend to coalesce to form linear bands, although they have also been reported on the fingers. In contrast to erythema nodosum, subcutaneous nodules are typically painless; in addition, the skin color is usually normal and they persist longer [88–90].

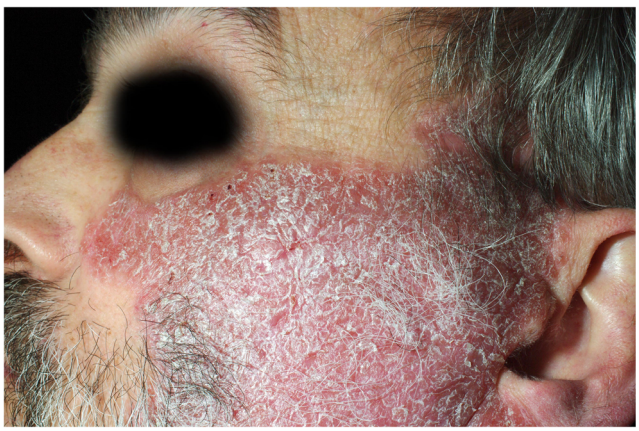

Fig. 12 Erythematous scaling sarcoidosis plaque of the face

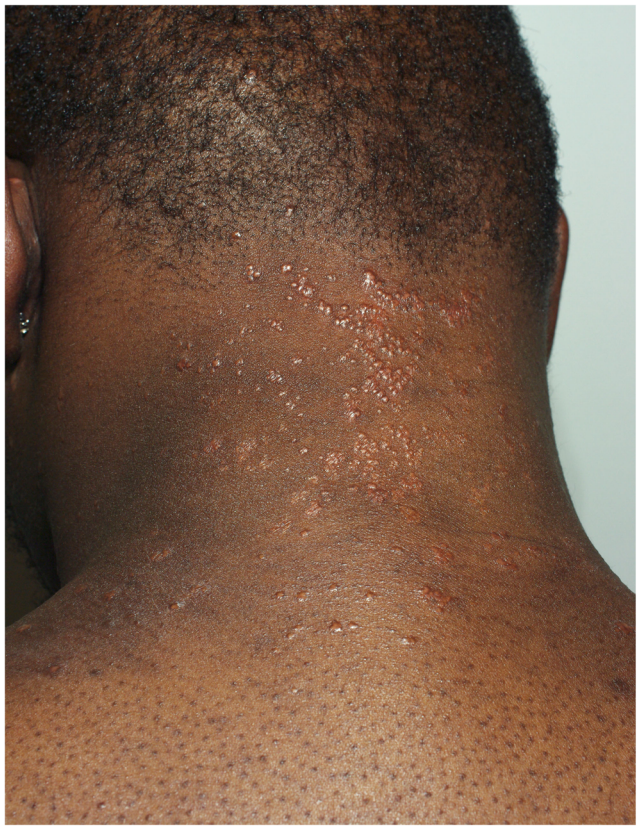

Fig. 13 Sarcoidosis with small nodules on the neck

Diffuse Infiltrating Forms The most characteristic form in this subgroup is "lupus pernio" which resembles a cold-induced change. This is an indolent, red-purple or violaceus, indurated skin lesion that may affect the cheeks, nose, lips, and ears mostly in black Caribbean women over 40 years of age; the frequency in the Caucasian population varies according to the series [89, 91–96]. The lesions can range widely from small rounded to exuberant plaques covering the cheeks and nose, becoming very disfiguring. Scaly desquamation may be observed, and erosions can occur. The lesions can erode into the cartilage and bone [97] and are regarded as an ominous sign reflecting chronicity and poor prognosis. Frequently, there is a concomitant involvement of the upper respiratory tract and, in aggressive cases, ulcerations in the nasal mucosa may occur [98].

Scar Sarcoidosis The presence of sarcoid granulomas in scar tissue is a relatively common cutaneous manifestation of sarcoidosis. Erythematous infiltration of old scars (sometimes more than 20 years old) or tattoos is a very characteristic feature of sarcoidosis, which in these cases has often visceral involvement. Scars thicken and/or become red-brownish to purplish and indurated (Fig. 15).

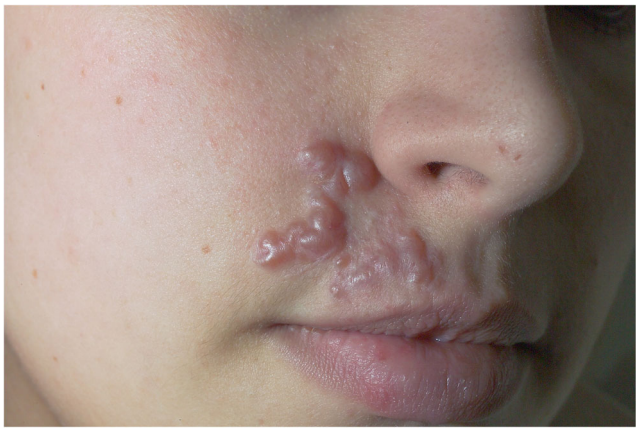

Fig. 14 Purplish red nodular sarcoidosis lesions of the face

The diagnosis of cutaneous sarcoidosis is based on clinical presentation, histological criteria, and exclusion of other cutaneous granulomatosis [85]. The cutaneous disease is not correlated to the severity of the systemic involvement, which is the key prognostic factor.

Treatment of cutaneous sarcoidosis depends on the extension and the type of lesions. First-line therapies are topical or intralesional corticosteroids, systemic corticosteroids, chloroquine or hydroxychloroquine, and methotrexate [99, 100]. Second-line treatments are mycophenolate mofetil, infliximab, minocycline, and doxycycline [101–105]. Except for apremilast, leflunomide, thalidomide, chlorambucil, and azathioprine, the third-line treatments are mostly reported in anecdotal cases: allopurinol, quinacrine, fumaric acid esters, PUVA, PDT, isotretinoin, topical tacrolimus, pentoxifylline, adalimumab, dapsone, laser, and surgery [106–111].

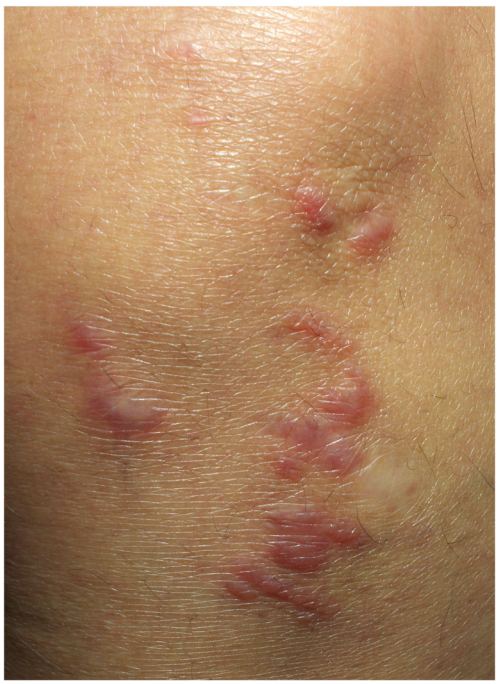

Fig. 15 Scar sarcoidosis: erythematous infiltration of an old scar

Interstitial Granulomatous Dermatitis

This rare dermatitis was first described by Ackerman and colleagues in 1993 [112]. Although the original manifestation has been described as subcutaneous linear nodules, also known as rope sign, later reports showed a quite heterogeneous clinical spectrum ranging from hyperpigmented, erythematous papules (Fig. 16), subcutaneous plaques, and annular lesions to firm red-purplish nodules. The lesions are usually asymptomatic, but can be slightly pruritic or painful. The histopathological examination confirms the diagnosis and is characterized by a dense and diffuse interstitial infiltrate in the reticular dermis, composed of histiocytes in a palisade arrangement, sometimes with necrobiosis of collagen and with neutrophils and eosinophils. Interstitial granulomatous dermatitis has been associated with various systemic diseases, including autoimmune diseases such as rheumatoid arthritis (the most common), scleroderma, or lupus erythematosus [113]. Recently, a case has been reported in association with primary biliary cholangitis [114]. However, other etiologies have been described in isolated cases including malignancy [115] or drugs [116]. The most frequent drugs involved are anti-hypertensives, such as the angiotensin-converting-enzyme inhibitors, calcium channel blockers, beta blockers, diuretics, and hypolipidemic agents, anticonvulsants, antihistaminics, and TNF-α blockers [117].

The therapy of choice is not well-defined. A spontaneous resolution may occur within weeks to months, but relapses are possible. Therapeutic options are potent topical or systemic corticosteroids, non-steroidal anti-inflammatory agents, methotrexate, hydroxychloroquine, cyclosporine A, dapsone, and,

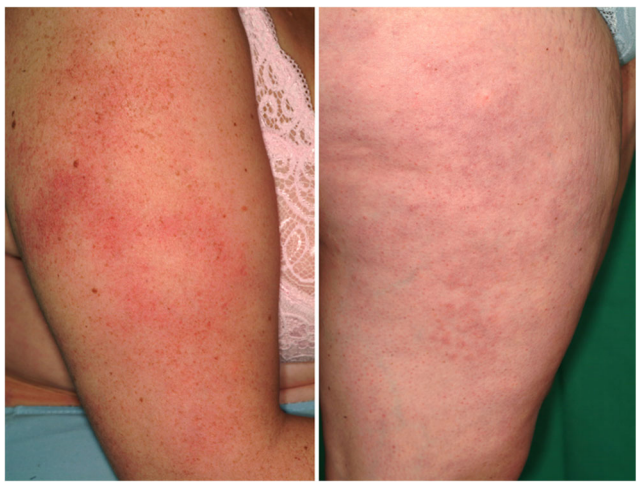

Fig. 16 Hyperpigmented, erythematous papules of the right arm and thigh in a patient with interstitial granulomatous dermatitis associated with lupus erythematosus

Table 4 Workup in case of cutaneous granulomatous lesions

Diagnostic confirmation	-Clinical -Histological with cutaneous biopsy -Culture (bacteria, mycobacteria) -Preservation of a frozen fragment for PCR (mycobacteria or clonality detection)
Etiology	Medical history: Comorbidities (autoimmune disease, diabetes, immunosuppression) Drugs Foreign body Water exposure Physical examination: Clinical signs of associated diseases Laboratory testing: Complete blood count, ESR, CRP, creatinin, calcemia, liver enzymes, LDH, glycemia, glycated hemoglobin, cholesterol, triglycerides, TSH Serum proteins electrophoresis ANA, rheumatoid factor, angiotensin converting enzyme. Serology for HIV, syphilis, B and C hepatitis Interferon-gamma release assays for tuberculosis Radiological tests: Chest X-ray, abdomen and pelvis ultrasound
Unclear ethiology	Regular follow up

PCR polymerase chain reaction, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *LDH* lactate dehydrogenase, *TSH* thyroid stimulating hormone, *ANA* anti-nuclear antibody

for difficult-to-treat cases, TNF-α inhibitors or tocilizumab have been tried [33, 43, 118–120].

Diagnostic Work up

Since cutaneous granulomatosis are a heterogeneous group of reactive dermatoses with multiple ethiologies, they are frequently difficult to diagnose in clinical practice. We suggest a minimal work-up in disseminated forms (Table 4) looking for an infectious, metabolic, or inflammatory origin. This assessment has to be adapted and supplemented according to the clinical presentation and anamnestic data.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Informed Consent When necessary, informed consent has been collected from patients.

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