DOI: 10.1111/j.1468-3083.2009.03396.x JEADV

REVIEW ARTICLE

Sarcoidosis of the skin – A dermatological puzzle: important differential diagnostic aspects and guidelines for clinical and histopathological recognition

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Abstract

Sarcoidosis of the skin may have an extremely heterogeneous clinical presentation, so that the definitions of 'great imitator' and 'clinical chameleon' have long been used.

There is, in fact, a large group of skin diseases that can enter the differential diagnosis with cutaneous sarcoid manifestations, either clinically or/and pathologically. As the clinical consequences and the prognosis of these groups of diseases are often very different, it is important to correctly plan the diagnostic workup.

The diagnostic process in this case often presents a challenge as no single test is sufficiently specific, so that a certain diagnosis can be only made in the presence of a compatible clinical and radiographic picture, along with histopathological evidence of non-necrotizing, epithelioid cell granulomas, and exclusion of other potential aetiologies.

For practical reasons, four main groups of skin conditions capable of mimicking sarcoidosis can be identified: (i) transmissible, infectious diseases; (ii) allergic and immunological manifestations of various aetiologies; (iii) granulomatous diseases of various aetiologies; and (iv) lymphomas and pseudolymphomas.

The aim of this article is to describe the main clinical and histopathological findings of such disease entities, and to discuss the role of those features (morphological, pathological and laboratory) that can help distinguish them from sarcoidosis of the skin.

Received: 6 January 2009; Accepted 23 June 2009

Keywords

differential diagnosis, *Leishmania*, leprosy, lupus, sarcoidosis

Conflicts of interest

None declared.

Introduction

Skin sarcoidosis is a disease of undetermined aetiology.[1,2] Although it is a relatively frequent disease for Afro-Americans living on the territory of the Caribbean region, as well as for Swedes, Irishmen and other ethnic groups, the reasons of its phenotypic manifestations are poorly known.[1,3–5] Besides the skin, sarcoidosis can affect any other organ and is capable of imitating a variety of diseases; consequently, in dermatology it is often called 'The Great Imitator'[1,6] or a 'clinical chameleon'.[1] The clinical morphology of cutaneous sarcoidosis may vary within a wide range. Consequently, to diagnose it is not always easy (Table 1).

Hence, the conclusion can be reached that, in case of suspicion of some cutaneous forms of sarcoidosis, the histopathology should play an important role in the diagnosis. The microscopic findings in cases of sarcoidosis include a characteristic, non-caseating granulomatous reaction (Fig. 1a–d) or the non-specific reaction of erythema nodosum.[1,7,8] Having in mind, however, that many diseases show sarcoidal granulomatous reactions but have a completely different pathogenesis, the application of certain auxiliary diagnostic methods is often necessary.[9,10]

Sarcoidosis as a systemic disease can involve any organ or tissue, even though lung and intrathoracic lymph nodes are the most

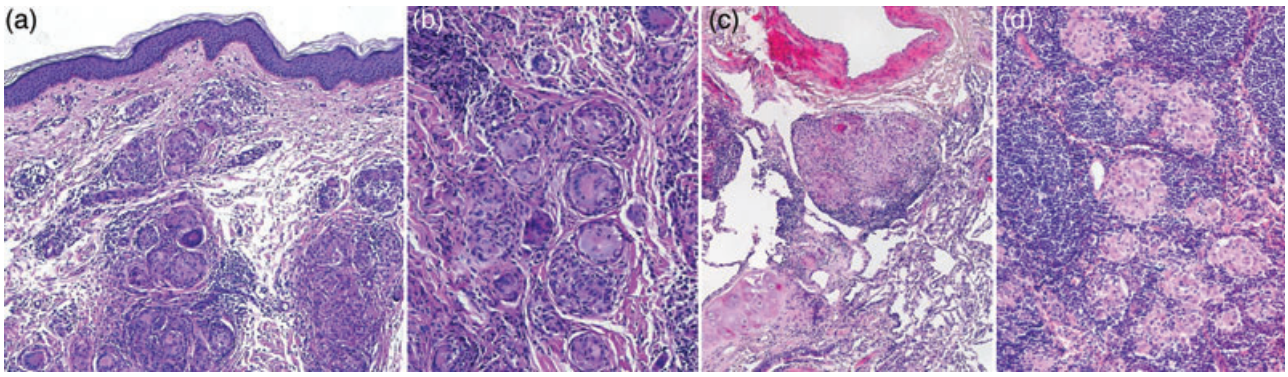

Figure 1 (a) Cutaneous sarcoidosis (haematoxylin and eosin (H&E) staining). Low-power view with dermal infiltration of nests and clusters of non-caseating epitheloid granulomas surrounded by only weak inflammation. (b) Cutaneous sarcoidosis (H&E staining). High-power view with multinucleated giant cells and histiocytic cells. (c) Pulmonal sarcoidosis (H&E staining). Low-power view of a transbronchial biopsy with non-caseating epitheloid granuloma in between a bronchus and pulmonal artery with weak accompanying inflammation. (d) Sarcoidosis within a lymph node (H&E staining). Low-power view representing numerous non-caseating epitheloid granulomas.

Table 1 Cutaneous lesions able to mimic sarcoidosis of the skin either clinically or/and pathologically

	Morphological mimickers of cutaneous sarcoidosis	Histological mimickers of cutaneous sarcoidosis
Group 1 Diseases of transmissible nature	Erythema induratum Bazin, papulonecrotic tuberculid, tuberculosis cutis luposa, leprosy lesions, secondary and tertiary syphilids, tubero-serpiginous syphilids, tubero ulcero-serpiginous syphilids, dermatophytosis, leishmaniasis cutis, bacillary angiomatosis	Lichen scrophulosorum, tuberculosis cutis miliaris disseminate, tuberculosis fungosa serpiginosa, tuberculosis miliaris ulcerosa mucosae et cutis, tuberculosis cutis luposa, leprosy lesions, leishmaniasis cutis (not always)
Group 2 Allergic and immunological manifestations of vague aetiologies	Atopic dermatitis, psoriasis vulgaris, erythema nodosum, pernions, erythema annulare centrifugum, chronic discoid lupus erythematosus, subacute cutaneous lupus erythematosus	–
Group 3 Granulomatous diseases of unclear entity	Granuloma annulare, lipoidic necrobiosis, lichen nitidus, necrobiotic xanthogranuloma, lupoid rosacea, perioral dermatitis, facial eosinophilic granuloma, lupus miliaris disseminatus faciei	Granulomatosis disciformis Miescher Lupoid rosacea
Group 4 Pseudolymphomas and lymphomas	Lymphoma and pseudolymphoma of B- and T-cellular type	–
Group 5 Other/rare forms of cutaneous sarcoidosis	Lichenoid sarcoidosis, keloidal sarcoidosis	–

frequently affected.[1,3,11] The diagnostic process is in this case often a challenge as no single test is sufficiently specific, so that a certain diagnosis can be only made in the presence of a compatible clinical and radiographic picture, along with histopathological evidence of non-necrotizing, epithelioid cell granulomas, and exclusion of other potential aetiologies (Fig. 1a–d).[1]

In this scenario, the recognition of skin lesions may be crucial as they provide both a visible clue to the diagnosis, and an easily accessible site for histopathological confirmation of the clinical suspicion.[1,4,7,12] Cutaneous involvement occurs in up to one third of sarcoid patients, and may be extremely heterogeneous in terms of morphology, extent, evolution (self-limited vs. chronic forms), clinical relevance and response to treatment.[1,8,9,13,14] Most authors tend to divide cutaneous manifestation of sarcoidosis into specific and non-specific types, the latter (i.e. erythema nodosum) occurring in association with systemic sarcoidosis but lacking the specific, non-necrotizing granulomas on biopsy.[10,15–17]

From a practical point of view, a dermatologist can face two possible situations, leading to different pathways, in the management of sarcoidosis patients:

1) A patient with unknown sarcoidosis seeks medical attention for the presence of skin lesions. In such a case, the dermatologist is the one who has the chance to raise the clinical suspicion, which is sometimes difficult as the clinical lesions may assume a wide array of morphologies. Histopathology plays a key role in this case, but the pathologist cannot diagnose sarcoidosis in isolation,

as sarcoidal granulomas have no unique pathological features to differentiate them from other granulomas (statement on sarcoidosis AJRCCM 1999; 160: 736–755). A multidisciplinary approach aimed towards determining the likelihood of a diagnosis of sarcoidosis (after careful evaluation of clinical, radiological and pathological findings) and establishing a follow-up programme is recommended for patients with suggestive skin biopsy findings (statement on sarcoidosis AJRCCM 1999; 160: 736–755). A follow-up programme will be of particular importance for those patients in whom the skin involvement precedes the systemic manifestations of the disease.

2) A patient with known sarcoidosis is referred for the diagnostic evaluation of a skin lesion/s. In this case, the dermatologist is asked to determine the nature of the lesion, and to discuss with the referring physician the therapeutic options.

The aim of this article is to highlight the main clinical and histopathological differential diagnoses of cutaneous sarcoidosis, and to discuss the role of auxiliary methods that may contribute to the solution of the diagnostic dilemma. The clinical morphology of lesions in dermatology is not always decisive, so a careful evaluation of all parameters is frequently necessary.[1,15]

This article focuses on four basic categories of disease, some of which imitate sarcoidosis of the skin both clinically and histopathologically. These are: transmissible diseases, allergic and immunological diseases, granulomatous diseases of uncertain aetiology, and lymphomas or pseudolymphomas. The role of several important auxiliary methods contributing to diagnostic precision is also discussed.

Aetiopathogenetic aspects

The aetiopathogenetic factors in sarcoidosis are, at present, not completely clear.[1] A key role has been attributed to different virological, bacterial and chemical agents.[16]

The importance of human herpesvirus 8 (HHV-8) in cutaneous sarcoidosis has yet to be clarified.[18,19] Interferon therapy and the hepatitis-C viral infections also probably play some role regarding the manifestations of the disease, and the crucial factor is felt to be the disturbance of internal homeostasis and consequent antigenic mimicry.[1,20] A possible role for Epstein–Barr or Coxsackie B viruses has been discussed but not proven.[21]

Similarly, bacteria and related infectious agents, including *Propionibacterium acnes*, *Yersinia enterocolitica*, *Chlamydia pneumophila*, *Borrelia burgdorferi* and *Mycoplasma* species, have been implicated. However, their roles as epigenetic factors, or factors influencing the phenotypic manifestations of cutaneous sarcoidosis, are still disputable.[21] The detection of mycobacterial DNA in sarcoid lesions in some patients is surprising, and imposes the obligatory exclusion of any active, systemic or post-primary cutaneous forms of tuberculosis.[21–24] It is clearly important that these and other infectious diseases be excluded, as there would be potential worsening of the patient's general status where corticosteroids or immunomodulators are to be employed as forms of therapy.

In addition, the importance of some metals in the development of sarcoidosis, such as beryllium, zirconium, titanium and aluminium, is not clear.[1]

Group 1: Diseases of transmissible nature

Many cutaneous lesions from other diseases are able to mimic sarcoidosis of the skin either clinically or/and pathologically (Table 1).

This group includes eight basic diseases, each of which may have different clinical manifestations, that can imitate cutaneous sarcoid lesions.[25,26] A correct diagnosis is crucial to avoid dissemination in the skin area and/or involvement of distant organs or tissues.

1. Sarcoidosis vs. tuberculosis

There are different forms of cutaneous tubercular reactions, and each of them can mimic certain 'sarcoid clinical variants'.

1.1 Hyperergic forms of skin tuberculosis

Lichen scrofulosorum can, to some extent, mimic small disseminating nodular sarcoidosis.[27]

The papulonecrotic tuberculid can resemble a disseminated ulcerative form of sarcoidosis in patients with weakened T-cellular immunity.

Erythema induratum Bazin is a hyperergic form of post-primary tuberculosis, where the lesions are located in the area of the dorsal part of the shin.[1] There is no clinical difference between this disease and the ulcerative localized form of sarcoid. Sarcoidosis of the skin, however, only rarely occurs in this area. Women predisposed to acrocyanosis and cutis marmorata livedoides/telangiectatica congenita are also predisposed to sarcoidosis of the skin.[1,28,29] For diagnosis, it is important to determine not only the histopathological picture, but also to detect mycobacterial DNA by the polymerase chain reaction (PCR) method in lesional tissue.[1]

The tuberculin reaction in patients with hyperergic form of sarcoidosis is strongly positive, while the Ziehl–Neelsen staining is negative, to (sometimes) slightly positive.[1,29]

The histopathology of any one of the hyperergic forms differs from the histopathology of sarcoidosis. In the case of erythema induratum Bazin, the histopathological correlate is granulomatous lobular panniculitis, frequently accompanied by vasculitis.[1]

In cases of papulonecrotic tuberculid, lymphocytic vasculitis predominates, accompanied by tuberculoid infiltrates.[1,30]

Lichen scrofulosorum shows Langhans-type giant cells, tuberculoid infiltrates and necrosis.[31,32] It is important for the patients that a blood test for interferon be performed, in order to find/exclude any active systemic form of tuberculosis (pulmonary or gastrointestinal) with further appropriate use of scheduled polychemotherapy.

A distinction from polyarteritis nodosa, which can be associated with cryoglobulinaemia, paraproteinaemia, *Streptococcus* infection or tumours, is also important.

1.2 Anergic forms of skin tuberculosis

The anergic forms of tuberculosis can also mimic disseminated or localized cutaneous forms of sarcoidosis. These forms are scarce and mainly diagnosed in Third World countries. It is difficult to find and diagnose such cases in Europe, although sporadic cases have been described in Bulgaria and Romania.

Variant forms include tuberculosis cutis miliaris disseminata, tuberculosis fungosa serpiginosa and tuberculosis miliaris ulcerosa mucosae et cutis. These occur within the framework of inoculation in cases of active tuberculosis (gastrointestinal or pulmonary) in adults having a weakened immune system or in young children whose immune protective mechanisms are underdeveloped.[29,31–34]

Clinically, tuberculosis cutis miliaris disseminata does not differ from the small-papular disseminated ulcerative, the benign miliary lupoid or the small disseminated nodular forms of sarcoidosis.[35] However, there are few clinical similarities between the other two forms and the different cutaneous forms of sarcoidosis.

An important feature of the disseminated forms of tuberculosis is the patient's generally debilitated status, as well as low-grade fevers and night sweats, which are not observed in localized and disseminated forms of cutaneous sarcoidosis.

The tuberculin reaction in the anergic forms is negative, while PCR-DNA in lesional skin is strongly positive,[34] as is staining for organisms using the Ziehl–Neelsen method.[31,32,34,36,37] The histological analysis shows tuberculoid granulomas with, or more frequently, without caseous necrosis. The distinction from sarcoidosis is straightforward if the above-mentioned diagnostic panels are observed.

1.3 Allergic forms of cutaneous tuberculosis

To classify the lesions, the allergic forms of cutaneous sarcoidosis including lupus vulgaris (or tuberculosis cutis luposa) are the most problematic (Fig. 2). This is a post-primary form of tuberculosis that can be developed not only per continuitatem, at a distant site from the primary focus of infection, but also after subsequent exogenous inoculation.[38] The tuberculin test is positive, and Ziehl–Neelsen staining is often negative.[39] Lesions resemble those of the subcutaneous nodular exudative or plaque-like forms of sarcoidosis. Caseous granulomatous reactions and tuberculoid granulomas can be found.[40] By diascopy, small lupus nodules are observed in the form of 'apple or orange jelly' types (Fig. 2).[1,39,41] Once the diagnosis is proven, the use of polychemotherapy is recommended, as the risk of malignant transformation and mutilating (lupus vulgaris mutilans) symptoms is high.[38,39]

The atypical mycobacterioses, including those due to *Mycobacterium marinum*, *M. abscessus* and *M. ulcerans*, are less commonly included in the differential diagnosis of sarcoidosis, but they must not be completely excluded.[42,43] The morphology of any single lesion must be carefully observed. Newly generated keloidal formations with perilesional localization must be histologically analysed.

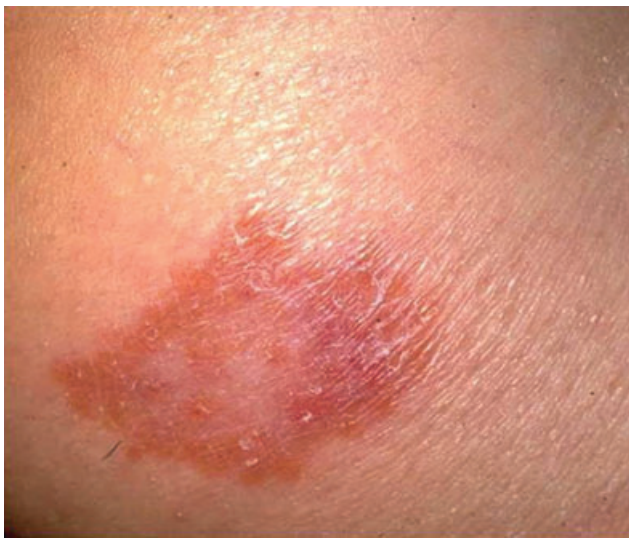

Figure 2 Erythematous plaque-like form of lupus vulgaris. Under pressure through a magnifying glass, the characteristic 'apple jelly' lupoid aspect is observed.[1]

2. *Sarcoidosis vs. leprosy*

Sarcoidosis of the skin vs. lepromatous leprosy and tuberculoid leprosy

From a differential-diagnostic point of view, consideration should be given to forms of lepromatous leprosy and tuberculoid leprosy. This disease was known in the past under the names of Hansen or Zaraath disease (biblical name of the disease).[44] Transmission takes place directly from ill persons or by direct contact with, or consumption of, underdone species of armadillos infected by *Mycobacterium leprae*.

Today, this disease can be transmitted through the nine-banded armadillo in the State of Louisiana, USA. It is observed among certain at-risk groups, including hunters and illegal meat middlemen.[44,45]

About 10–15 million people suffer from leprosy worldwide. In 2006, the WHO had reported approximately 300 000 new leprosy infections. The incubational period lasts between 3 and 20 years, and its clinical manifestations are largely determined by the status of a patient's T-cell immunity.[40]

An obvious key feature in distinguishing lesions caused by mycobacteria from sarcoidosis is that Ziehl–Neelsen and Fite–Faraco staining of sarcoid skin lesions is negative, while those, induced by *Mycobacterium leprae* and *Mycobacterium tuberculosis* are often positive.[40,44,45] The differentiation of *Mycobacterium leprae* from *Mycobacterium tuberculosis* can be achieved by applying silver nitrate; *Mycobacterium leprae* shows light, while *Mycobacterium tuberculosis* shows dark, staining with this method.[1,46] The most sensitive but not always accessible method to demonstrate *Mycobacterium leprae* in lesional (nasal) mucosa is through detection of mycobacterial DNA by PCR methods.[46]

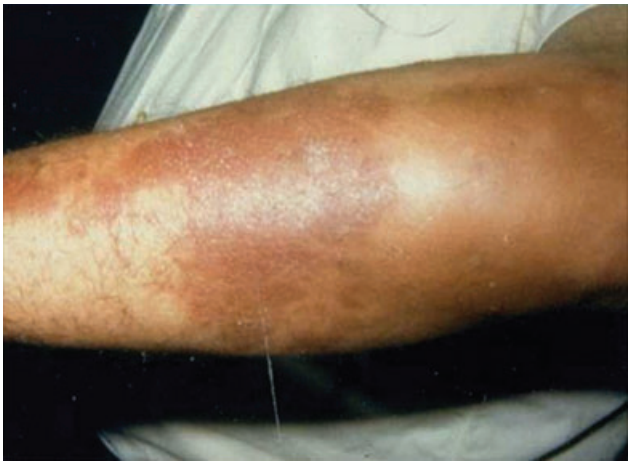

Figure 3 Patient with disseminated cutaneous lepromatous leprosy and initial systemic amyloidosis of inflammatory type, proved by biopsy of the anal mucosa.

The lepromatous form of the disease clinically manifests as localized or disseminated plaque-like hyperpigmented lesions, which cannot be easily clinically distinguished from localized, disseminated and confluent plaque-like forms of sarcoidosis of the skin (Fig. 3).[46–48] Leprosy can also imitate the disseminated plaque-like or ulcerative cutaneous form of sarcoidosis. Frequently, these forms of leprosy have an unfavourable prognosis due to the patients' poor T-cellular immunity.[47,48]

Accordingly, the solid or dense staining of entire bacteria in lesional tissue of such cases typifies active and transmissible forms of leprosy.[46]

In the case of disseminated forms of the disease, known as Lucio–Latapí or lazarine leprosy, the risk of disseminated generalized infection with secondary amyloidal disease of AA-type (inflammatory type) is high.[45,46,48] The most frequent cause of death in such patients is terminal renal insufficiency. Additionally, the adrenal glands, thyroid glands and the liver can be also affected.[46] Systemic involvement can be derived directly from bacteraemia (e.g. transmissible hepatitis, glomerulonephritis, iridocyclitis, leprous panophthalmia), but can also result from a systemic form of amyloidosis.[45,46]

Histopathologically, granulomas are found in patients suffering from tuberculoid leprosy, a form of the disease characterized by well-developed cell-mediated immunity to the causative organism. Due to this fact, it is difficult to distinguish tuberculoid leprosy lesions from cutaneous sarcoidosis by haematoxylin and eosin staining alone. In addition, the Fite–Faraco stain is also often negative. In such cases, indirect methods can be used to evaluate the granulomas. For example, the finding of degenerated, S100 positive nerve elements within granulomas correlates with the neurotropic nature of the granulomas in tuberculoid leprosy. In addition, a dense reticulin meshwork is often observed in sarcoidal granulomas but is notably less prominent in the granulomas of tuberculoid leprosy.

The lepromin skin test of the patients is highly positive, and a reaction of the type of erythema nodosum leprosum is very probable. Reactions of this kind are mostly manifested during the application of initial therapy, more rarely they are spontaneous or appear during the lepromin test.[45] Nowadays, lepromin test is not recommended and it is substituted by the above-mentioned diagnostic methods.

In Europe, tuberculoid or the so-called non-infective forms of leprosy are observed most commonly. However, rare forms of lepra indeterminata and dimorphic leprosy can be imported from the respective 'predisposed geographic regions', such as Central Africa, India and China.[47,48]

The differentiation of leprosy from sarcoidosis in eastern Europe is, unfortunately, often neglected. Generally, this leads to the incorrect diagnosis of sarcoidosis and to the use of immunosuppressive therapy. In that respect it leads to the transformation of tuberculoid to lepromatous leprosy, generalized bacteraemia, and also to the development of systemic amyloid disease. The risk of development of renal insufficiency is high, requiring haemodialysis and transplantation, worsening drastically the patient's quality of life.[45–47] The most accessible method to prove the presence of amyloid disease of the systemic type is biopsy of the anal mucosa.

3. Sarcoidosis of the skin vs. secondary and tertiary syphilis of the skin

Late forms of syphilis, including secondary and tertiary syphilis, represent a serious problem in differential diagnosis. Although they will hardly escape dermatologist's experienced eyes notice, secondary and tertiary syphilids can clinically cause difficulties for the diagnosis. Disseminated secondary papular syphilids or papulonecrotic forms of lues maligna (in the case of innate or acquired deficiencies in T-cellular immunity) resemble to some extent the small disseminated, erythematous confluent and localized nodular/ulcerative forms of sarcoidosis, as well as the lesions of benign miliary tuberculid and bacillary angiomatosis.[49]

Tubero-serpiginous or tubero-ulcero-serpiginous syphilids are often clinically confused with tuberculosis cutis colliquativa, sporotrichosis, actinomycosis or lupus erythematosus profundus. Rarely, these forms of syphilis can also raise the possibility of ulcerative, plaque-like, infiltrative or subcutaneous nodular forms of sarcoidosis.[49]

Besides the standard serological tests of these relatively late forms of syphilis, Treponema pallidum-DNA detection by PCR in lesional skin and 19S-FTA abs IgM testing of serum can help to insure a correct diagnosis.[46]

4. Sarcoidosis of the skin vs. dermatophytosis of the skin with circinate or papulosquamous configurations

Skin infections caused by anthropophilic and zoophilic dermatophytes display heterogeneous clinical morphologies. In many

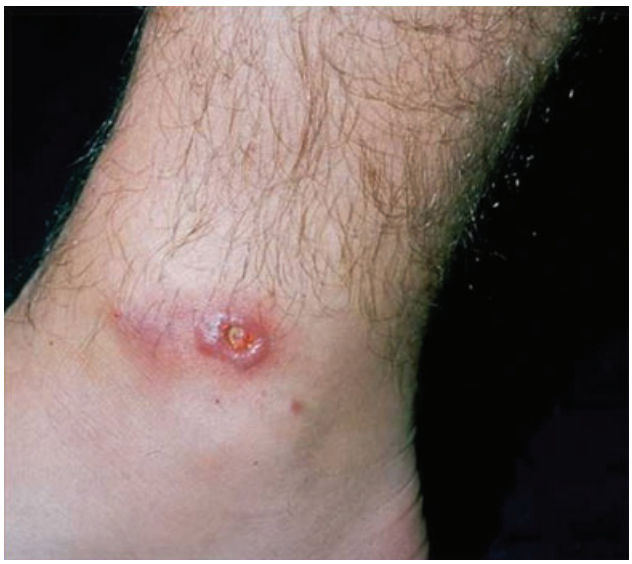

Figure 4 Localized ulcerative form of leishmaniasis of the skin following bites from *Phlebotomus* sp. during a stay in Ethiopia. In the ulcerative form of sarcoidosis, the lesions do not have an indurated border. The same is true of leishmaniasis. The keloidal aspect of the edge can also be interpreted as a rare secondary manifestation of cutaneous sarcoidosis in the area of new or old scars. This imposes the need for histopathological appraisal of the lesions, both to exclude leishmaniasis and the 'specific histological form' of sarcoidosis.

cases of tinea corporis (profunda), papulosquamous or annular/polycyclic configurations prevail.[50] It is not always possible to distinguish these lesions from acrally localized ichthyosiform, confluent erythematous or circinate annular forms of sarcoidosis.[1,51] Important auxiliary methods helping to clarify the origin of lesions include study of skin scrapings (potassium hydrochloride or calcofluor preparations), mycological culture, and PAS or Groccot staining of tissue samples. *Trichophyton rubrum, Trichophyton violaceum, Trichophyton verrucosum, Trichophyton interdigitale* (formerly *Trichophyton mentagrophytes)* and *Epidermophyton floccosum* are considered to be the most frequent aetiological agents.[50]

5. Sarcoidosis of the skin vs. hyperergic and anergic forms of leishmaniasis of the skin

5.1 Normoergic reactions

Localized forms of leishmaniasis cutis are the most frequent (Fig. 4).[52] The organisms are transmitted by *Phlebotomus* vectors that are capable of freely penetrating through widely used mosquito nettings. These vectors transmit *Leishmania* organisms in their promastigote form, about 10–15 microns long and 2–3 microns wide.

The amastigote form of leishmaniasis settles in the human body after biting. The clinical manifestations of leishmaniasis cutis cannot always be distinguished from cutaneous sarcoidosis, even in locations where leishmaniasis is common.[52,53] To prove that patients have resided in regions endemic for leishmaniasis, such as Mexico, the Amazon, Ethiopia, India, Nepal, China, Brazil, Bolivia (South Europe and North Africa) and the territory of the former socialist republics (USSR), is often problematic.[53,54] Intact immunity is most frequent among patients with localized skin lesions of leishmaniasis.[52–54] The affected persons show positive Montenegro reactions, positive Giemsa staining and from high to average high titres of antibodies in the serum.[55] Isolation on special culture media is recommended. The main agents of the lesions are *Leishmania* minor, *Leishmania* major, *Leishmania infantum* and *Leishmania aethiopica*, known also as Old World leishmaniasis.

5.2 Hyperergic form of reaction

Both hyperergic and anergic generalized forms of leishmaniasis create more frequent differential diagnostic problems.[56,57]

The hyperergic recurring or persisting form clinically resembles small disseminated nodular sarcoidosis, lichen scrofulosorum and dermatophytid.[57]

This imposes the application of the respective additional 'diagnostic panels' in order to exclude the aforesaid diseases. The intracutaneous leishmania antigen test (Montenegro test) is strongly positive. The titre of circulating serum antibodies is high, and Giemsa staining can be both positive and negative.[52–54] Isolation on special selective media, such as Novy-McNeal-Nicolle/Adler medium is possible and recommended.[52,53] The amplification test, on hamsters or humans, is not routinely practised nowadays, but it provokes a disseminated generalized form of leishmaniasis in rodents. If the diagnosis is not clear and a generalized skin reaction is present, the amplification test can significantly facilitate the diagnosis.

5.3 Anergic forms of reaction

The anergic forms of leishmaniasis are chiefly caused by *Leishmania aethiopica* and *Leishmania brasiliensis,* and their cutaneous manifestation is most frequently, the diffuse cutaneous form of leishmaniasis.[52]

Clinically, one observes non-ulcerating nodules and plaques tending towards confluence and the formation of small satellite nodules in the immediate vicinity of the primary lesions. The Montenegro reaction is negative, Giemsa staining is strongly positive, the titre of the antibodies in the serum is low to negative, and the amplification test and the isolation of leishmania in culture are positive.[52,57,58] Clinically, the lesions resemble the plaque-like confluent disseminating or localized forms of sarcoidosis or the lazarine form of leprosy of the Lucio–Latapí type.[57,58] The histopathology is not typical and shows lymphocytes, histiocytes (macrophages), granulocytes, plasma-cell infiltrates and, partially, tuberculoid granulomas.

In the presence of differential diagnostic difficulties in some of the localized forms, observed in Brazil or Mexico and other regions (due to infections by *Leishmania aethiopica* or *L. brasiliensis* – so-called espundia), the diagnosis can be made more precise by

the additional application of monoclonal antibodies against amastigotes in lesional tissue[52,53].

6. Sarcoidosis of the skin vs. bacillary angiomatosis

Bacillary angiomatosis can be difficult to differentiate from small papular localized or disseminated sarcoidosis. Its distinction from localized papular, partially ulcero-necrotic syphilids is also problematic. The aetiological agent is *Rochalimaea (formerly Bartonella) quintana or Rochalimaea henselae.*[59] *Demonstration of these bacteria is accomplished by its cultivation in special media or, directly, by Warthin–Starry staining.*[60] *An important clinical feature is the angiomatous nature of the nodules. The most specific and certain proof that the infection is present is based on PCR detection of bacterial DNA in lesional skin.*[59–61]

Group 2: Allergic and immunological manifestations of diverse aetiologies

Sarcoidosis of the skin vs. diseases of immunological and infectious-allergic nature: differential diagnosis

Diseases of immunological and infectious-allergic nature can induce localized or generalized sarcoid-like cutaneous lesions.[1] They include atopic dermatitis, psoriasis vulgaris, erythema nodosum, perniosis and erythema annulare centrifugum.[1] Sarcoid-like cutaneous lesions are also clinically observed in certain forms of lupus erythematosus.

2.1 Localized/disseminated sarcoidosis of the skin vs. psoriasis vulgaris of chronic stationary plaque-like and erythrodermic types. The isolated subungual form of sarcoidosis vs. psoriasis

The cutaneous form of sarcoidosis was described in 1877 for the first time by the surgeon Hutchinson as a 'papillary form of psoriasis'.[16] The erythrodermic form of sarcoidosis is extremely rare and histopathologically shows the specific sarcoidal granulomas.[1] The differentiation from psoriasis is important. Attention must be paid to the anamnesis and the genetic disposition of the patients, as well as to the evolution of lesions over time.[1]

The geographical or polycyclic annular form of psoriasis is relatively easy to distinguish from the polycyclic annular or circinate skin lesions of sarcoidosis. However, when lesions reach a large size, tend towards confluence or develop infiltrative features, biopsy is recommended.

Isolated forms of sarcoidosis with subungual localization and onycholysis are very rare. Sarcoidal granulomas with epitheloid and giant cells are found histopathologically. The occasional demonstration of the subungual form of sarcoidosis in patients with psoriasis would be extremely unlikely, but possible.

2.2 Sarcoidosis of the skin vs. atopic dermatitis

As noted above, the cutaneous form of sarcoidosis can rarely manifest as erythroderma. It must therefore be distinguished not only from erythrodermic psoriasis but also from atopic dermatitis with erythroderma.[1] The details provided by the patient's history, the clinical picture, the family history and the presence of type 1 hypersensitivity to certain airborne and alimentary allergens, are very important to establishing a correct diagnosis.[1] To this end, it is recommended that one obtain the respective skin and blood tests. The determination of total IgE in serum is obligatory if atopic dermatitis is suspected.[1,16] Histopathologically, epidermal spongosis is found, and sarcoidal granulomas are absent.

2.3 Sarcoidosis of the skin vs. erythema annulare centrifugum vs. erythema nodosum vs. chilblains (perniosis)

The circinate small-papular and large plaque-like disseminated, partially annular forms from erythema annulare centrifugum, could be wrongly interpreted as sarcoidosis of the skin.[62] The aetiology of this poly-aetiological, probably allergic reaction to infection is not completely clear.[63,64] It is observed in various malignancies, as well as in streptococcal infections, active tuberculosis, genital or anal candidosis, fungal infections of the skin (dermatophytosis), lumbricosis, food allergies, paraproteinaemias, as a reaction to medications, and in lupus erythematosus.[65,66]

The annular, polycyclic aspect of the lesions suggests the possibility of an annular granulomatous disease.

The histopathological picture in erythema annulare centrifugum is that of a dense, superficial and deep dermal, perivascular infiltrate (sometimes described as 'coat-sleeved') comprised mainly of lymphocytes but also including macrophages (histiocytes) and occasional eosinophils.[65,66] Significant thickening of the vascular endothelium is observed. The epitheloid and giant cells so characteristic for the 'specific lesions' of cutaneous sarcoidosis are not observed.[62]

Erythema nodosum plays an important role in the diagnosis of sarcoidosis. Most dermatologists consider it as a 'non-specific histological and clinical form' of cutaneous sarcoidosis.[1]

It can also represent a cutaneous manifestation of sarcoidosis in the form of the so-called Löfgren syndrome. Besides the presence of erythema nodosum, bilateral hilar adenopathy and pains in the joints are characteristic (immunological version of erythema nodosum).[67,68]

The cutaneous findings in Crohn's disease and chronic ulcerative colitis are identical.

However, erythema nodosum can also result from exposure to medications (contraceptives, salicylates, sulfonamides) or infectious agents. Infections due to *Toxoplasma, Streptococcus pyogenes, Yersinia enterocolitica*, dermatophytes and infections by *Chlamydia trachomatis* serotype L1–L3 have been described as possible triggers of erythema nodosum.[67–69] Erythema nodosum lesions are also observed in cat scratch disease.

Perniosis (chilblains) is the result of functional peripheral vascular disease in patients with impaired digital circulation.[70] Patients with acrocyanosis and cutis marmorata are predisposed.[70,71]

Bullous and ulcerative forms of chilblains are rare, but they have been described in the literature.[72] Histopathologically, fibrosing inflammation in the corium, vascular dilatation, necrosis and/or subepidermal blistering, and infiltrates composed of lymphocytes and macrophages are observed.[72] The occurrence of chilblains in the legs can mimic the erythema nodosum that accompanies Löfgren syndrome.

When present on the dorsal part of the fingers, chilblain lupus should also be considered.[71,72] From the differential diagnostic point of view, chilblains must be differentiated from other forms of vasculopathy.[72] The determination of antithrombin III, protein C, factor V Leiden mutation, antiphospholipid antibodies with their respective subfractions (anticardiolipin and antiphospholipid), lupus anticoagulant, cryoglobulins, cryofibrinogen and paraproteins is indispensable.

2.4 Sarcoidosis of the skin vs. chronic discoid lupus erythematosus

According to Otto Braun Falco, the chronic discoid form of lupus erythematosus is characterized by three basic clinical features: atrophy, erythema and keratosis.[73] It is often localized to the facial area, the scalp and the lower neck. In time, it can lead to mutilating scars.[73]

Ulcerative lesions in the nasal area are not rare. In the initial stage, when keratoses are absent, the lesions can be similar to the ulcerative form of sarcoidosis or to ulcerating lupus pernio.

Regarding the cicatrizing forms of alopecia, in addition to chronic discoid lupus erythematosus and lichen planopilaris, sarcoidosis of the scalp must not be excluded.[1,74]

Early forms of chronic discoid lupus erythematosus emphasize the clinically erythematous nature of the lesions.

2.5 Sarcoidosis of the skin vs. subacute cutaneous lupus erythematosus

The subacute cutaneous form of lupus erythematosus shows a similar clinical picture to sarcoidosis, whether papulosquamous, purely erythematous or polycyclic/annular.[73,75,76] This frequently creates serious differential diagnostic problems.

The papulosquamous forms of sarcoidosis, already known since Hutchinson's time (1877), are difficult to discern.[1,73] They were at one time known as 'papillary psoriasis' of the skin.[1] The polycyclic/annular and erythematous forms of subacute cutaneous lupus erythematosus are mostly symmetrically localized in the area of the back and lower neck.[73] Clinically, the differentiation of the circinate forms of sarcoidosis from those in subacute cutaneous lupus erythematosus, as well as from granuloma annulare and erythema annulare centrifugum, is difficult and sometimes impossible.[73] It is necessary and even indispensable to take skin biopsy and to perform serological tests and comprehensive diagnostics. The purpose is to exclude systemic involvement in patients with cutaneous lupus erythematosus.

The subacute form of lupus erythematosus can also manifest as erythema in the area of the nasolabial folds or adjacent skin.[75,76] Lesions may be confined to the tip of the nose. In early stages, atrophy and keratosis are absent, and this makes the differentiation from lupus pernio in young women more difficult (Fig. 5).

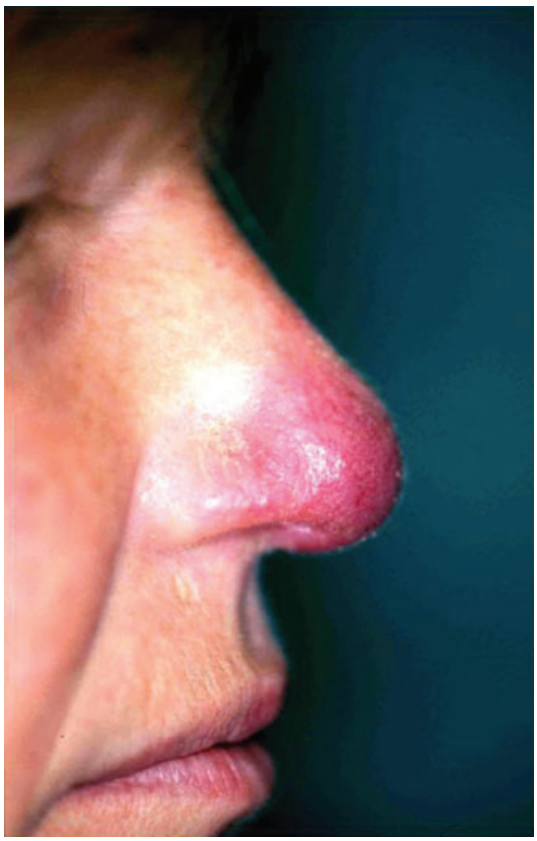

Figure 5 Lupus pernio in a young female patient. Erythemas of the nasal area, particularly in young women, should raise the possibility of lupus pernio in addition to the cutaneous form of lupus erythematosus.

In some patients with cutaneous lupus, acrocyanosis in the nasal area leads to an incorrect diagnosis, such as granulosis rubra nasi, erythematotelangiectatic rosacea or Raynaud's phenomenon or disease.[1]

Group 3: Sarcoidosis of the skin vs. granulomatous diseases of unclear aetiology

The variegated palette of this group includes diverse diseases whose aetiopathogenesis is still a mystery. It comprises granuloma annulare, necrobiosis lipoidica, rheumatoid nodules, lichen nitidus, necrobiotic xanthogranuloma (Fig. 6), granuloma faciale, lupoid rosacea, lupoid perioral dermatitis and the pseudotuberculoid response, lupus miliaris disseminatus faciei.

3.1 Sarcoidosis of the skin vs. granuloma annulare

The localized form of granuloma annulare can show some resemblance (due to its circinate configuration) to the polycyclic/annular form

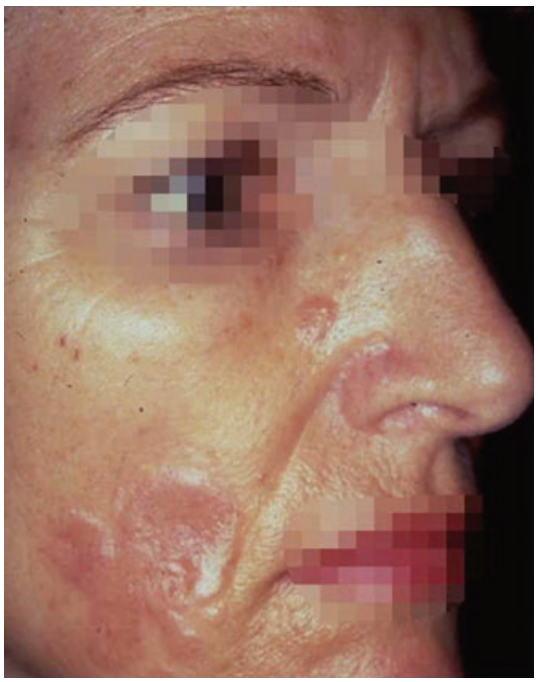

Figure 6 Necrobiotic xanthogranuloma is rarely diagnosed clinically. The lesions have a plaque-like configuration that suggests the possibility of plaque-like cutaneous sarcoidosis or granuloma faciale. Depending on the morphology of the lesions, the differential diagnosis may be even more extensive.

of sarcoidosis. The infiltrative character of the lesions is common to both diseases. In addition, the erythematous disseminated form of sarcoidosis of the skin is often compared to the disseminated form of granuloma annulare.[77]

Perforating localized and generalized granuloma annulare can imitate the ulcerative localized or generalized forms of sarcoidosis of the skin.[78,79]

In the case of granuloma annulare, necrobiosis (degeneration of collagen, non-typical for sarcoid lesions), palisaded arrangements of macrophages (histiocytes) and perivascular lymphocytic infiltrates are observed.[77] The epithelioid and giant cells characteristic for sarcoidosis are usually not observed.

3.2 Sarcoidosis of the skin vs. necrobiosis lipoidica

Necrobiosis lipoidica is a granulomatous cutaneous disease that shows diverse clinical presentations.[80] Patients with diabetes mellitus and beta-lipoproteinaemia of the familial type are generally predisposed to this disease.[80]

The localized form of this disease manifests unilaterally or bilaterally over the pretibial regions. This form shows plaque-like lesions that tend towards ulceration. In these cases, the differentiation from granuloma annulare and sarcoidosis is made both clinically and histopathologically. Strongly expressed necrobiosis, with palisaded arrangements of histiocytic infiltrates and giant cells, is observed in the dermis.

Examples of disseminated macular necrobiosis lipoidica and forms localized to the forehead and scalp are diagnostically problematic.[81,82]

The differentiation of disseminated erythematous sarcoidosis from chronic and progressive granulomatosis disciformis of Miescher is also difficult. In the case of this cutaneous variant, patients do not have diabetes mellitus or systemic beta-lipoproteinaemia. Tuberculoid granulomas are found histopathologically. To differentiate this condition from certain cutaneous forms of tuberculosis is not always easy.

3.3 Sarcoidosis of the skin vs. rheumatoid nodules

Rheumatoid nodules are observed in approximately 20% of patients suffering from rheumatoid arthritis.[83,84] They are localized not only to cutaneous and subcutaneous tissues, but can also be found in the heart, lungs, pericardium, myocardium, larynx, eyes, nose and peritoneum.[83,84]

In the case of nodules with subcutaneous localization, the subcutaneous nodular form of sarcoidosis is also a diagnostic possibility. For this reason, biopsy studies are recommended, as well as a complex appraisal of all existing serological, microbiological and clinical findings.

3.4 Sarcoidosis of the skin vs. lichen nitidus

Lichen nitidus is a granulomatous disease of unknown aetiology. Clinically it manifests in the form of small lichenoid papules in the genital skin or elsewhere.[85,86] On clinical grounds, the small papular disseminated form of sarcoidosis could be considered. Microscopically, lymphohistiocytic infiltrates and giant cells are found in lichen nitidus, often confined to a single dermal papilla. Necrobiosis or tuberculoid infiltrates are absent.[85] The prognosis for the patient is good.

Due to their typical morphology and frequent localization to the genital area, these lesions should seldom be clinically confused with the small papular form of sarcoidosis.

3.5 Sarcoidosis of the skin vs. necrobiotic xanthogranuloma

Necrobiotic xanthogranuloma affects adult patients.[87] Lively debates are held with respect to its association with paraproteinaemia, Hodgkin's disease and infections by human T-cell lymphotropic-1 viruses.[87,88] The assertions of different authors in the literature are controversial.[87-89] Besides the skin, other organs can also be affected.

The cutaneous manifestations of this disease can affect the face, neck, thorax and proximal portions of the extremities, and consist of plaques and nodules that frequently ulcerate.[87,88] In the differential diagnosis, one must consider plaque-like or ulcerative-plaque-like forms of cutaneous sarcoidosis.

The histopathology of a typical lesion shows pronounced necrobiosis, xanthogranulomatous infiltrates, epithelioid and foam

cells, and giant cells of Touton and foreign-body types.[89] Lipid vacuoles, not typical for sarcoidosis, are also found.[89]

3.6 Sarcoidosis of the skin vs. lupoid rosacea

Some specific forms of rosacea, such as erythematous and papular rosacea, rosacea conglobata and lupoid rosacea, can be clinically interpreted as small papular or plaque-like forms of sarcoidosis.[90,91]

Other considerations include lupus pernio or the butterfly erythema of systemic lupus erythematosus. Routine histopathology, direct and indirect immunofluorescence, and determination of several immunological parameters, such as ANA, ENA, complement components C3 and C4, dsDNA antibodies, Sm-Ag, antiphospholipid antibodies and U1-RNP-Ag, are obligatory.

3.7 Sarcoidosis of the skin vs. lupoid perioral dermatitis/perioral dermatitis with atypical localization

The lupoid form of perioral dermatitis is characterized by succulent single papules and/or papular plaques that, if pressed and seen through a magnifying glass, demonstrate lupoid infiltration and histopathologically show tuberculoid granulomas.[92,93]

It is not clear if the equivalent of this disease is lupus miliaris disseminatus faciei. The different localization of the two diseases would be one argument against this thesis. It is important to exclude the post-primary and active systemic forms of cutaneous tuberculosis.

The small papular lesions of perioral dermatitis, together with their partial periocular localization, can be confused with the localized papular form of sarcoidosis, leading to differential diagnostic problems.

In the case of perioral dermatitis with periocular localization, histopathological study of a skin biopsy is indispensable. The differentiation from lichen nitidus and severe forms of seborrheic dermatitis is also very important.

3.8 Sarcoidosis of the skin vs. granuloma faciale

Granuloma faciale is a rare skin disease and its origin is not yet clear. It clinically manifests in the form of confluent, brownish-yellow to orange infiltrative plaques.[94,95] This lesional morphology makes differentiation from lupus vulgaris, sarcoidosis of the skin and leprosy difficult. Histopathologically, eosinophilic and neutrophilic leucocytes, adipocytes, macrophages and plasma cells are observed, separated from the overlying epidermis by a grenz zone of uninvolved collagen.[94,95] The specific microscopic findings facilitate the differentiation from sarcoidosis.

3.9 Sarcoidosis of the skin vs. granulomatous reactions – pseudotuberculoid response/lupus miliaris disseminatus faciei

Pseudotuberculids, such as lupus miliaris disseminatus faciei, are not clinically different from small papular sarcoidosis. A slightly lichenoid aspect to the lesions also can be noted. Histopathologically, they show tuberculoid granulomas, and no *Mycobacterium tuberculosis*-DNA can be detected by PCR in lesional skin.[96,97] Ziehl Neelsen staining is negative, and the tuberculin test can be slightly positive to negative.[96,97] Systemic tuberculosis generally cannot be demonstrated. Radiology of the lungs, blood testing for interferon or attempts to isolate *Mycobacterium tuberculosis* from morning urine or by aspiration of gastric juice are recommended.[1]

Group 4: Sarcoidosis of the skin vs. pseudolymphomas or lymphomas

Lymphomas and pseudolymphomas can play an important role in the differential diagnosis of sarcoidosis of the skin. The correct clinical identification of the lesions is not always possible, and this necessitates the use of various auxiliary techniques.

4.1 Sarcoidosis of the skin vs. pseudolymphomas

Sometimes it is difficult to distinguish pseudolymphomas of the skin from the true lymphomas, as well as from certain forms of sarcoidosis. The pseudolymphomas and lymphomas of the skin have both B- and T-cell characteristics.[98] T-cell forms of lymphoma and pseudolymphoma are the more frequent.[98]

One of the most frequent forms of pseudolymphoma is lymphadenosis benigna cutis or so-called lymphocytoma of B-cell type.[98] The majority of lymphocytomas has to be considered as Lyme borreliosis at stage 1. Clinically, lymphadenosis benigna cutis manifests as solitary or disseminated small papules or as a localized lupoid form. The latter shows lupoid infiltrates under pressure through a magnifying glass, which inevitably suggests the possibility of lupus vulgaris.

Its differentiation from the small disseminated, solitary small-papular and plaque-like forms of sarcoidosis is also difficult.[99] It is important to perform histopathological and immunohistochemical studies, and also to apply certain molecular biological techniques in order to determine the possible clonality of the infiltrate.[98,99]

Pseudolymphomas of the B-cell type are problematic when the distribution of cutaneous infiltrates is symmetrical. Sometimes these are wrongly interpreted as the rare Brocq–Pautrier angiolupoid variant of sarcoidosis, which has a chronic, infiltrative appearance. This form frequently relapses after discontinuation of therapy with local corticosteroids.[1] Under pressure through a magnifying glass, the characteristic 'apple jelly' lupoid infiltrate is observed.[1]

True cutaneous B-cell lymphomas are rare, but when they occur they commonly present as solitary nodules or plaques.[9]

In the case of persistent arthropod reactions, angiolymphoid hyperplasia with eosinophilia, and lymphocytic infiltration of the skin of Jessner–Kanof, an acute erythematous form of sarcoidosis could be considered.

In cases of drug-induced erythroderma, the acute, generalized erythematous form of sarcoidosis would be quite possible.[1] However, epidermotropism is absent from the infiltrates in lesional tissue. Therefore, histopathology is indispensable. A determination regarding possible clonality of the infiltrate provides key clinical information.

4.2 Sarcoidosis of the skin vs. lymphomas

The initial stages of T-cell lymphomas can frequently lead to differential diagnostic problems in the distinction from the localized erythematous form of sarcoidosis.

During the stages of suberythroderma and erythroderma of T-cell lymphomas, there is little likelihood of confusion with the disseminated confluent erythematous form of sarcoidosis. However, it is not impossible.[1]

In the case of lymphomas at initial stage: Ia/Ib, small papules or plaques with variable localization are observed.[100,101] Histopathological and immunohistochemical testing, as well as determination of clonality, is of prime importance and contribute to the differentiation of T-cell lymphomas from disseminated confluent erythematous and localized cutaneous forms of sarcoidosis.[100,101]

Epidermotropism is not characteristic of B-cell lymphomas. They are mostly located in the dermis and subcutis in the form of nodules of violet to vermillion color.[102] They would not be confused with the plaque-like form of sarcoidosis.[1]

5. Other rare forms of sarcoidosis of the skin

Sarcoidosis can arise in the area of old scars, and therefore the clinical differentiation from uncomplicated scars may be practically impossible.[103] With chronicity, the lesions gradually acquire a lichenoid gloss and brownish colour.

Lichenoid versions of sarcoidosis have also been described in the literature.[104,105] Persistence and/or alteration in colour of old hypertrophic scars, or the appearance of spontaneous keloids, should bring to mind the possibility of a rare form of cutaneous sarcoidosis.[106] In such cases, histopathological testing is indispensable. The exclusion of systemic involvement in those with cutaneous sarcoidosis is also essential.

Conclusions

1. The polymorphic clinical picture of patients affected by sarcoidosis frequently is the reason lesions are interpreted as rosacea, perioral dermatitis, granuloma annulare, etc.[103,107] This way, the potential for incorrect diagnosis and therapy is present, resulting in progression of cutaneous to systemic disease. Some authors think that, in 20–30% of cases, cutaneous sarcoidosis precedes systemic involvement.[1]
2. In the course of time, with persisting inflammation, patients develop systemic amyloidosis of inflammatory type, leading to sedimentation of SAA (AA) protein in the tissues and organs.[108,109] SAA- protein is synthesized in the liver and belongs to the alpha-1-globulin fraction. It is precipitated in the liver, adrenal glands, gastrointestinal tract, central nervous system and kidneys.[108,109] One of the major complications, arising because of the precipitation of SAA amyloid in the kidneys, is the development of terminal renal insufficiency. To prove the SAA-type of amyloidosis, it is necessary to perform a rectal and/or cutaneous biopsy.[109]
3. It is also important to know if, under the clinical and histopathological guise of sarcoidosis, there is not in fact a disease of transmissible nature, such as tuberculosis, leprosy or leishmaniasis. Where this possibility disregarded, and therapy using local and/or systemic immunomodulators/immunosuppressants employed, progression and dissemination of the infection could be the result.
4. The clarification of the clinical morphology of the lesions and of the sarcoid-like cutaneous lesions is extremely difficult. The cutaneous form of sarcoidosis may rightfully be called a 'clinical chameleon'.

This review offers a simplified method of making the diagnosis, by dividing the differential diagnosis into four basic groups, including the respective subgroups.

In this way, using the morphology of the lesions, the physician should be better able to narrow the possible differential diagnoses.

Acknowledgments

No sources of funding were used to assist in the preparation of this review. The author has no conflicts of interest that are directly relevant to the content of this review.

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