EDITORIAL

THE "MYSTERY" OF CUTANEOUS SARCOIDOSIS: FACTS AND CONTROVERSIES

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The reason why the cutaneous form of sarcoidosis is well known in the literature is because of its spectrum of manifestations granting it the fame of a Great Imitator. The mystery shrouding the pathogenesis of this rare cutaneous disease is still there (in spite of the fundamental progress of the various diagnostic methods in current day medicine). The production of the morphological substrate – the epithelioid cell granuloma – which is considered to be characteristic of skin sarcoidosis, could, however, also be the end result of a reaction to i) various specific infectious agents such as Leishmaniasis cutis, coccidioidomycosis, etc., ii) certain residual bacterial or other mycobacterial antigens which, at the moment of setting the diagnosis are - by definition - non-infectious but still immunogenic, as well as iii) different tumor antigens in lesional tissue or other location. Often, differentiating between sarcodiosis and a sarcoid-like reaction, based on the updated criteria for cutaneous sarcoidosis, is problematic to downright impossible. A future characterization of the genetic signature of the two conditions, as well as the implementation of additional mandatory panels for i) the identification of certain infectious or ii) non-infectious but immunogenic and iii) tumor antigens in the epithelioid cell granuloma (or in another location in the organism), could be a considerable contribution to the process of differentiating between the two above-mentioned conditions. This will create conditions for greater accuracy when setting the subsequent therapeutic approaches.

Key words: sarcoidosis, sarcoid like reaction, genetic signature, bacterial antigens, tumor antigens

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Sarcoidosis is a multisystemic granulomatous disorder of unknown origin that develops in genetically predisposed individuals in response to as yet undefined antigens (1). Ethnicity has an impact on the risk for developing the disease, and seems to have an influence on its manifestations and course (1). The present chapter contains an update on the current knowledge about cutaneous sarcoidosis, including pathogenesis (namely the influence of the genetic background), clinical features, diagnosis and treatment.

Pathogenesis of cutaneous sarcoidosis (CS)

CS is a granulomatous disorder that can develop either as a part of a multisystemic disease, most often in association with pulmonary sarcoidosis, or can be restricted to the skin (2). Although there are some specific data about the pathogenesis of CS, to a large extent much of what is known about the cutaneous form of the disease is extrapolated from studies on the pathogenesis of sarcoidosis in other organs, namely the lung (2). The difficulty in understanding the pathogenesis of this disease can be attributed to the elusive causative agent, the lack of a universally accepted animal model, and the protean manifestations of the disease with large variations in different populations and ethnic groups (2, 3).

It is exactly the presence of certain bacterial or viral antigens in the lesions with epitheloid cell granulomas which raises the question of whether the case at hand is a true case of sarcoidosis as an autonomous disease or rather a certain type of sarcoid reaction (2).

The currently accepted model is that sarcoidosis is a disease triggered by certain environmental factors in genetically predisposed individuals (1). The environmental factors described as potential causes of sarcoidosis include a large list of antigens that may be derived from infectious agents (e.g. Mycobacteria, Propionibacteria, viruses), inorganic compounds (e.g. zirconium, aluminium and occupational exposures) (4, 5). The association between sarcoidosis and certain neoplasms is also interesting, noting that it has been increasingly recognised (6). The immense diversity of possible triggering antigens makes us wonder, in fact, if we are actually dealing with a single disease or, instead, with several different diseases that represent a reaction pattern to many different antigens (2). In other words, one may question at some point, whether sarcoidosis is actually an autonomous disease or if, in alternative, we are dealing with sarcoid-like reactions to numerous diverse antigenic stimuli (2). Differentiating between sarcoidosis as an autonomous disease and sarcoid-like reactions requires considerable effort and is not always easy (2). The epithelioid-cell granuloma is not equivalent to sarcoidosis since it may be identified in a number of infectious and non-infectious disorders, including neoplastic diseases (2). At the current state of knowledge, accurate distinction between different causes of epithelioid cell granulomas is in many cases not possible (2). Sarcoid-like reactions may be grouped generally into several subtypes (2). The differentiation between each one of them requires a certain combination of diagnostic tests, whose objective is to exclude or detect the presence of an infectious, tumoral or immunogenic antigen on the one hand, and to characterize the genetic profile of the affected patients (for example, sarcoidosis-specific genes) on the other (2). Only thus may one accurately differentiate between the two above-described pathologic processes.

Another intriguing point of debate is the mechanism by which the different antigens trigger the formation of granulomas in the tissue (2). One interesting hypothesis is that sarcoidosis may be the result of an autoimmune response due to cross-reactivity between the triggering antigens and self-antigens through a mechanism of molecular mimicry (1). For example, this mechanism has been hypothesized as probably implicated in sarcoidosis in relation to *Mycobacterium tuberculosis* heat shock proteins (7).

The exact sequence of events through which the triggering antigens lead to the formation of granulomas are already understood, although not completely (2).

The problems related to the clarification of the pathogenetic concept regarding the patients described in the literature as suffering from skin sarcoidosis, are also due to the fact that sarcoid-like granulomas are also observed in i) infectious diseases, such as deep mycosis and cutaneous leishmaniasis; ii) reaction to non-infectious but probably still immunogenic agents, which may be identified in the lesional

Table I. *Regional and ethnic variability of cutaneous sarcoidosis (CS).*

Country	Ethnicity	Predominant type of CS	References
Denmark	Caucasians	Plaques, annular lesions	Veien et al. 1987
India	Indian	Combination of multiple papules, nodules and plaques	Mahajan et al. 2007
Japan	Japanese	Scar sarcoidosis, papules, nodules	Mizuna 2011
Nigeria	Africans	Scar sarcoidosis	Olumide et al. 1989
Portugal	Mostly Caucasians	Nodular plaques, papules	Mangas et al. 2006
Singapore	Mixed - mainly Indian & Chinese	Papules, nodules, plaques, and scarring alopecia	Chong et al. 2005
South Africa	Black Africans	Nodules, plaques	Jacyk 1999
South Korea	Korean	Nodular plaques, papules	Jung & Roh 2011
Taiwan	Taiwanese	Papules, nodules, large plaques	Chao et al. 2000
Tunisia	North-Africans	Papules (micronodular lesions)	Khaled et al. 2008
USA, West coast	Mixed, mainly African-Americans	Erythema nodosum, papules, plaques	Sharma 1972
USA, South Carolina	African-Americans	Papular, hypopigmented macules	Minus & Grimes 1983

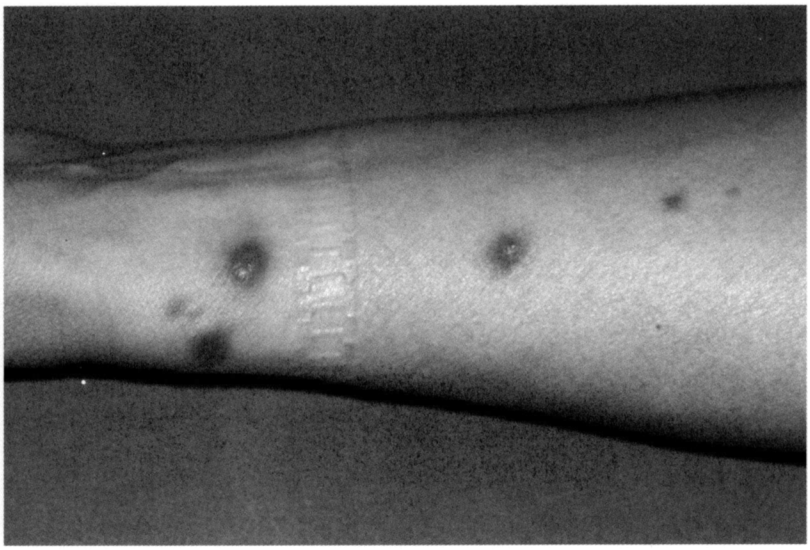

Fig. 1. *Papulo-nodular lesions. Disseminated papular lesions in a sporotrichoid pattern.*

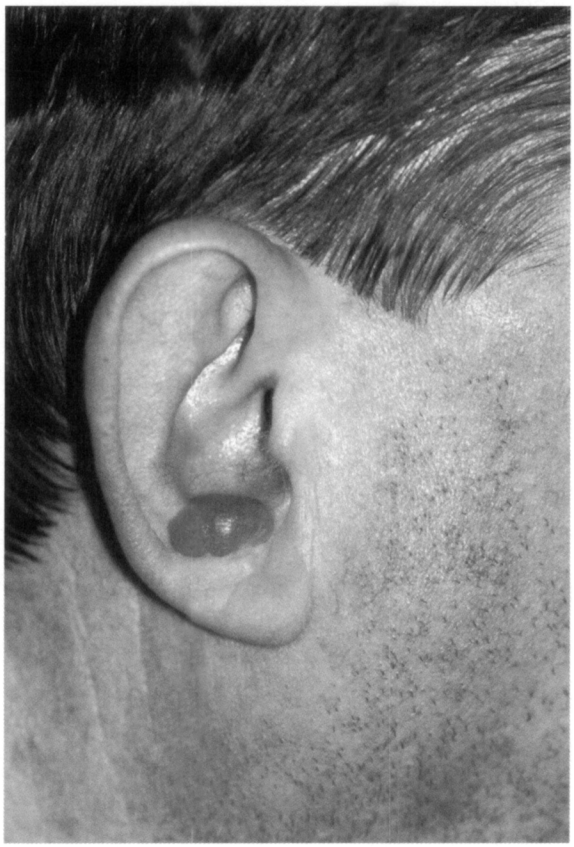

Fig. 2. *Nodular lesion on the anti-helix.*

tissue with the help of various additional techniques – for example, non-tuberculous mycobacteria or *Propionibacterium* acnes and iii) strictly sterile granulomas with no data on any infectious and non-infectious but immunogenic agents (2). In substance, the sterile granulomas can also be the result of a type of reaction to i) antigens, localized in the tissue, or ii) tumor antigens of remote location, which may have generated a reaction based on the phenomenon of molecular mimicry (2). If we are dealing with sarcoidosis or with a sarcoid-like reaction is, quite often, a "no answer" question (2).

Granuloma formation depends on the development of a predominantly TH1 immunological response (5). Sarcoidosis is characterized by an immune paradox, in the fact that although there is an increased immunological response in the tissues affected, characterized by activation of T-cells expressing predominantly TH1 cytokines, there is on the other hand peripheral blood lymphopenia and cutaneous anergy to tuberculin and other skin tests (5). Several cell types play an important role in granuloma formation, namely lymphocytes, monocytes/macrophages and dendritic cells (1).

T-cells secrete TH1 cytokines, such as interleukin (IL)-2 and interferon (IFN)-γ (2). More recently,

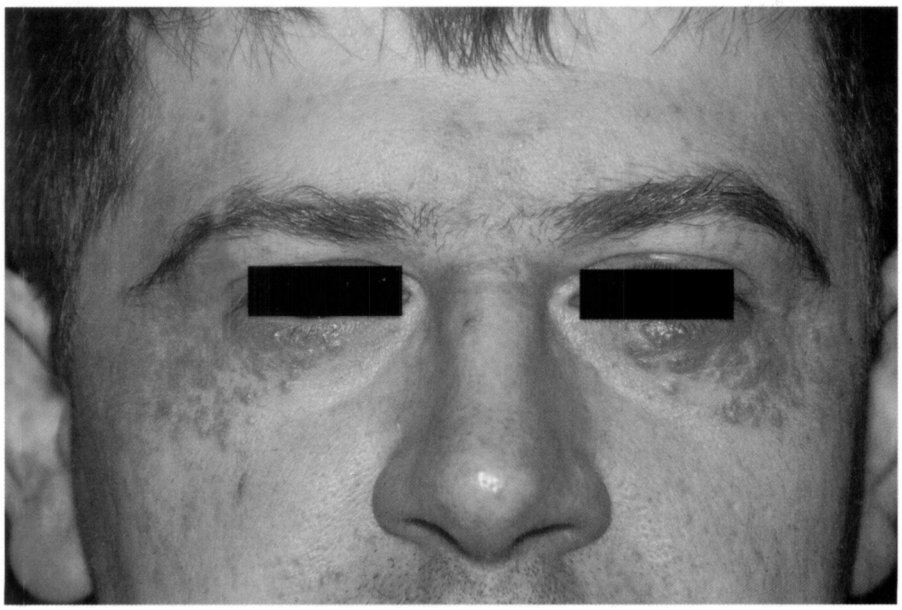

Fig. 3. *Small papules. Periocular lesions reminiscent of Demodex folliculorum folliculitis, periocular rosacea or lupus milliaris disseminatus faciei.*

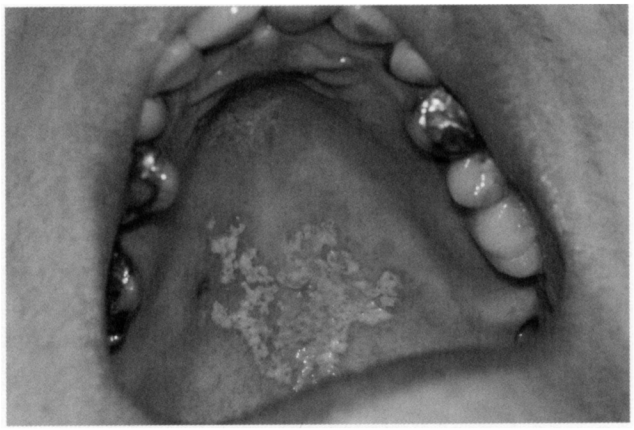

Fig. 4. *Ulcerative lesions. Erosions on the hard palate suggesting lichen planus or autoimmune bullous dermatoses.*

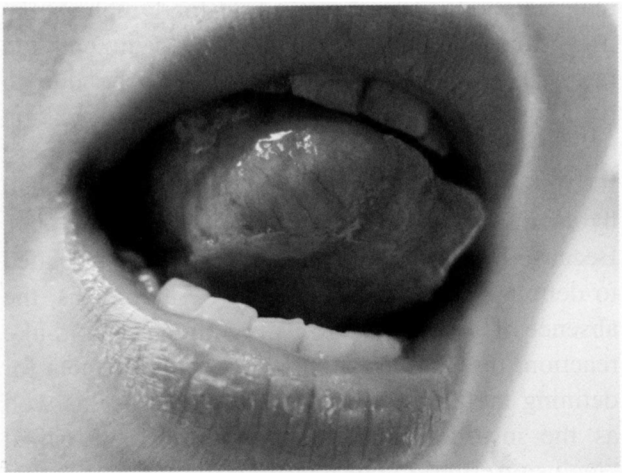

Fig. 5. *Sarcoidosis plaque of the tongue.*

the proinflammatory cytokine IL-17 has also been identified as having a potential role in the formation of pulmonary granulomas. In addition, there is some speculation about participation of CD4+T cells producing IL-17 in CS as well (8). Certain subsets of TH1 T-cells seem to play a part, although their role is less well understood: such is the case of CD4+CD25+FOXP3+ T-cells, which represent a regulatory subset with inhibitory function. Although not entirely explained within the context of granuloma formation, their action is pointed as a possible explanation, at least in part, for the phenomenon of cutaneous anergy observed in sarcoidosis patients (3).

Monocytes and their tissue counterpart, the macrophages, are the main cell type entering the composition of the typical "naked" granuloma (3, 4). It is well known that their role is far from being limited to the effector/phagocytic function, as they also function as an extremely active source of cytokines that play an important role in the immune response, including IL-1, tumor necrosis factor (TNF)-a, IL-15, IL-18 and transforming growth factor (TGF)-b, among others (3, 4).

Lastly, dendritic cells are potent antigen presenting cells (APC), and are increasingly recognised as playing an important role in the pathogenesis of sarcoidosis, namely due to their capacity of inducing TH1-driven immune responses (3-5). Dendritic cells have been identified in the cutaneous lesions of sarcoidosis, although they have also been described in the lung and lymph nodes (3, 4). Dendritic cells were shown to have an aberrant phenotype in sarcoidosis, and their dysfunction is likely to be an adjunct contributor to the anergic state observed in these patients (3, 4).

More recently, the role of innate immunity has also been hypothesized to be important in immunopathogenesis of sarcoidosis. For example, it has been demonstrated that toll-like receptors (TLR), namely TLR-2 may play an important part in the pathogenesis of sarcoidosis through interaction with serum amyloid A protein (9). It has also been hypothesized that bacterial and viral antigens may contribute to the pathogenesis of sarcoidosis through interaction with TLRs (2). The activation of these receptors leads to downstream cascades resulting in activation of inflammatory pathways, such as mitogen-associated protein kinases and nuclear factor k B (NF-kB) pathways (2, 10).

Genetics

The genetics of sarcoidosis are not precisely elucidated at present, but they are certainly complex and are believed to result from the interplay of several genes (2). The phenotypic variability in the manifestations of sarcoidosis and the predilection for certain forms of presentation according to the geographic region and ethnicity, certainly contribute to the difficulty in clarifying the exact weight of genetics in the pathogenesis of the disease (2). Clarification of specific genotypic signatures in sarcoidosis and in sarcoid-like reactions would

certainly help in our understanding of these diseases and in their distinction from each other, which is at present a very difficult, or even impossible, task in some instances (2). Numerous candidate genes have been studied as having a potential role in sarcoidosis and, not surprisingly, most of these genes are related to the regulation of the immune response (1, 3, 4).

One of the strongest genetic associations has been found with butyrophilin-like 2 gene (BTLN-2), which is located in the MHC region in the short arm of chromosome 6 (4). The product of this gene is a protein that seems to act as a co-stimulatory molecule that downregulates T-cell function (4). Thus, an abnormality in protein function may result in an increased immune response due to aberrant T-cell activation (4). Genetic predisposition for sarcoidosis has also been linked to certain polymorphisms in MHC molecules, which seem to modulate the phenotype of the disease, including its severity and chronicity (1). Genetic predisposition for sarcoidosis has been linked to the DRB locus in the HLA II class region and to HLA-B*07 in the HLA class I region, among others (11, 12). As suggested by previous studies, the variable distribution of HLA alleles between different ethnic groups may also explain differences in clinical phenotype and course between patients of different ethnicity (13, 14). For instance, DRB1*0301 allele is strongly associated with Löfgren's syndrome and erythema nodosum in Dutch and Croatian patients. Such a phenotype is unknown among Japanese patients who lack the allele (15, 16).

Epidemiology and diagnosis

The incidence of sarcoidosis varies greatly between ethnicities and regions (number per 100,000 inhabitants and year): 1.4 in Japan, 20 in the UK, 60 in Sweden, and 107 in Black Americans (17). CS occurs in about one-third of patients with systemic sarcoidosis. Diagnosis can be suspected by familial background, clinical history, and physical examination (5, 18). Diascopy reveals an apple jelly color in typical lesions (5). Histopathological examination is an important adjunct to the diagnosis, showing sarcoidal-type granulomas in case of specific cutaneous involvement by the disease (18). On the other hand, non-specific manifestations, like erythema nodosum, will not show cutaneous involvement by sarcoidal granulomas. Through its easy accessibility, skin sampling for histopathological analysis offers considerable advantages compared to other affected organs (18).

Diagnostic imaging is challenging for radiologists because signs of sarcoidosis may easily mimic other diseases such as neoplasms or tuberculosis. To exclude a systemic form of sarcoidosis, X-ray of the chest should be carried out. In addition, to exclude an active or latent tuberculosis an Interferon Gamma Release Assay (IGRA), e. g. the Quantiferon Gold Assay, might be helpful for some patients.

Laboratory investigations demonstrate antinuclear antibodies in about one-third of patients. Serum angiotensin-converting enzyme levels are raised mainly in CS associated with systemic manifestations. The same is true for lymphopenia, hypercalcemia and elevated blood sedimentation rate (5). Hypercalcemia is thought to be due to parathyroid hormone-independent 1-hydroxylation of 25-hydroxyvitamin D within sarcoid granulomas. It is noteworthy that hypercalcemia can be aggravated by intense exposure to ultraviolet radiation (17). Because of the currently existing problems related to defining the cutaneous form of sarcoidosis, the absence of a precise classification of the sarcoid like reaction, the absence of specific genetic panels for defining the type of the reaction or disease as well as the insufficient classification of the so-called "inclusion criteria", one may draw the conclusion that the epidemiological data on cutaneous sarcoidosis, and sarcoidosis in general, should be reconsidered in view of their precise determination (2).

Histopathology

The hallmark of CS is the presence of well circumscribed non-caseating epitheloid granulomas in the dermis (18). The granulomas are also called "naked" since lymphocytes are usually scanty, and plasma cells are typically absent (18). Lymphocytes may be seen at the periphery of granulomas or scattered within them, but they are typically sparse. Multinucleated giant cells of the Langhans type may contain either eosinophilic asteroid bodies or basophilic laminated Schaumann bodies, although these are not sensitive or specific findings (5, 18). It is important to note, however, that the variability in the histopathological manifestations of sarcoidosis

can be considerable (somewhat paralleling its protean clinical manifestations), and occasionally the findings are unusual, by showing, for example, focal necrosis in the centre of granulomas, a heavier lymphocytic infiltrate, an interstitial pattern, adnexotropism, neurotropism, involvement of the subcutaneous fat, epidermal hyperplasia or a lichenoid pattern, just to mention some of the more frequent variations (19, 20).

Clinical manifestations and differential diagnosis

CS is a great imitator in dermatology (5). Early recognition of the disease plays an important role as a visible clue to systemic disease (18).

CS can be subdivided into specific and nonspecific cutaneous lesions. In about 80% of patients CS precedes systemic sarcoidosis or develops at the same time (21). Papules are the most common presentation of CS (5). They can be of variable size and usually have a brownish pigmentation in light skin, but red and violaceous papules may also occur (Figs. 1, 2). The papules are often seen on the face, which raises differential diagnosis with perioral dermatitis, tinea faciei, cheilitis granulomatosa, cutaneous Crohn's disease, granuloma faciale, lymphocytoma cutis (Lyme borreliosis), lupus vulgaris, lupus miliaris disseminatus faciei, lupus erythematosus, lymphomas (18) (Fig. 3). Papules are the common type of scar sarcoidosis (Fig. 3) after tattooing (22). Scar sarcoidosis has been observed after herpes zoster infection as a form of Wolf's isotypic response (23).

Specific lesions also include patches that may become hypopigmented in darker skin types (24). Here, vitiligo and leprosy represent important differential diagnoses (18). Histopathology is paramount in achieving a correct diagnosis in these cases (18).

Subcutaneous nodules are another possible manifestation. Rheumatoid nodules and xanthomas are among the differential diagnoses (18).

Plaques develop as larger, flat-topped indurated lesions of varying color. Scaling and central atrophy sometimes suggest other dermatoses like chronic discoid lupus erythematosus, granuloma annulare, psoriasis, discoid eczema, syphilis, mycosis fungoides, tinea corporis, leishmaniasis, non-tuberculous mycobacteriosis of the skin, tuberculosis cutis serpiginosa, and lichen planus (5, 18). Plaque-type sarcoidosis shows an association with cardiac involvement as demonstrated by 18F-fluorodeoxyglucose positron emission tomography-computed tomography (25).

A specific and characteristic cutaneous manifestation is lupus pernio – a marker of chronic disease. These chronic reddish or bluish lesions are located at the tip and the alar rims of the nose. The differential diagnosis includes rhinophyma, perniosis, lupus erythematosus, lymphomas and cutaneous angiosarcoma among others (18).

Scarring may be a feature of CS affecting the scalp. It also leads to alopecia (26). Accordingly, other types of scarring and non-scarring alopecias should be considered in the differential diagnosis of scalp sarcoidosis (26).

CS may be ulcerated or may develop in pre-existing chronic ulcers such as leg ulcers.

Rare manifestations include ichtyosiform lesions of the lower legs, subcutaneous nodules, atrophic plaques, morphea-like lesions, verrucous lesions, and erythroderma (5, 26, 27).

Papules, nodules, plaques and ulcers have been described as specific manifestation of sarcoidosis on the oral mucosa including sometimes the tongue (Figs. 4, 5) (28).

Nails can also be affected (5). The nail apparatus may be involved primarily as in sarcoid trachyonychia or secondarily due to underlying bone involvement (29). The differential diagnosis includes primary diseases of the nails and ungual manifestations of systemic diseases (30).

Erythema nodosum is the most common nonspecific skin lesion in sarcoidosis (5). It is considered as a hypersensitivity reaction that manifests with tender and painful nodules due to an inflammatory process centred in the subcutaneous tissue (5). The predilection site is the pretibial region of the lower legs. It is part of Löfgren's syndrome together with bilateral hilar lymphadenopathy, fever, and polyarthralgia (5). Histology typically shows a septal panniculitis with an inflammatory infiltrate whose composition varies according to the time in the evolution of the lesion sampled (31). Although in late stages in the course of the lesions one may see the so-called Miescher's granulomas, epithelioid granulomas of the sarcoidal type are not a feature

of erythema nodosum. A major clinical differential diagnosis is erythema induratum Bazin, which has predominant involvement of the calves (5).

Small nerve fibre neuropathy may be a symptom of sarcoidosis, although the mechanism is not well understood. Aδ and unmyelinated C fibres are affected. The major symptom is neuropathic pain (32).

Clinical presentation and histopathology are the mainstays of differential diagnosis. Tuberculin skin test is usually negative in CS. Depending on the individual situation, the investigations need to be completed by special stains in histopathology such as Ziehl-Neelsen (to differentiate it from mycobacterial infections), Giemsa stain (to exclude leishmaniasis), Warthin-Starry stain (to rule out bacillary angiomatosis), mycobacterial polymerase-chain reaction (in case of tuberculosis, leprosy or atypical mycobacteriosis are suspected), or laboratory investigations to exclude certain infectious (e. g. syphilis) or autoimmune diseases (5).

Regional and ethnic variability of cutaneous sarcoidosis

The genetic background explains much of the observed differences in incidence but seem to affect also the type of cutaneous manifestations of this disease (Table I). In Indian patients, the angiotensin converting enzyme status affects the development and course of systemic sarcoidosis. People with a deletion/deletion (DD) allele, for instance, have an Odd's ratio of 9.0 for developing sarcoidosis (33). Ethnicity seems to have a more profound affect on symptomatology of sarcoidosis than region. On the other hand, genetic predisposition seems to be realized only in the context of a relevant exposure to environmental stimuli (1).

Whereas worldwide papular lesions seem to be the most common, in some parts of the world, like Nigeria and India, scar sarcoidosis seems to be the leading cutaneous manifestation (34, 35). Erythema nodosum is relatively common among Caucasians but rare in Asians

Treatment

A stepwise approach to patient care is appropriate, and potent topical corticosteroids (e.g. clobetasol) or repeated intralesional injections of triamcinolone (3-10 mg/mL) may be all that is needed in mild skin-limited disease (36).

In more advanced cases, systemic corticosteroids may be necessary at a dose of 1 mg prednisolone equivalent/kg body weight/day (5). Cutaneous sarcoidosis responds better to corticosteroids than systemic disease.

The antimalarials hydroxychloroquine or chloroquine are an alternative to systemic corticosteroids with an upper limit of daily dosages of 6.5 and 3.5 mg/kg body weight, respectively, to avoid ocular adverse events. Low-dose methotrexate 15-20 mg/ week followed by 5 mg folic acid the next day, minocycline 200 mg/d or allopurinol 100-300 mg/d have been used as well (5). Antimalarial drugs, azathioprine, tetracyclines, and methotrexate are contraindicated in pregnant and lactating women (37). Thalidomide, although effective, is not available in several countries including Germany. It has teratogenic effects and needs strict contraception in female patients.

Mizoribine at a daily dose of 150 to 300 mg with monitoring of serum concentrations 2 h after administration between 3 to 6 μg/ml has been reported to be effective in CS associated with cutaneous vasculitis (38). Fumaric acid, approved in Germany and Switzerland for psoriasis seems also to be an option for recalcitrant CS (39).

Isotretinoin, 0.5-2 mg/kg/day, has been used successfully in a handful of reported cases. However, the teratogenic potential of isotretinoin is often prohibitive considering that the primary demographic group likely to develop sarcoidosis is women of childbearing potential (40).

During the last decade, TNF-α inhibitors like infliximab and adalimumab have been used, whereas etanercept was ineffective (40). Tuberculosis screening is a precaution since activation of tuberculosis due to TNFa-inhibitors is a serious adverse event (40).

Photochemotherapy with 8-methoxypsoralen and long-wave ultraviolet irradiation (PUVA) have been used for generalized CS. Lasers and photodynamic therapy showed efficacy in limited disease, particularly in lupus pernio (41, 42). UVA-1 therapy was successful in limited papular CS (43).

Standard therapy for erythema nodosum is systemic corticosteroids combined with compression

bandages and rest. Non-steroidal anti-inflammatory drugs may be helpful for pain control (40).

A most important issue is the regular follow-up of sarcoidosis patients.

Outlook

Currently we hold some understanding of the mechanisms behind the pathogenesis of sarcoidosis, but some facts still need much further investigation. The better understanding of the genetic background and all the factors influencing the phenotype and course of the disease sarcoidosis and sarcoid-like reactions will also likely help in the establishment of more appropriate therapies in CS, namely targeting its molecular mechanisms.

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