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Clinical Features of Skin

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1. Introduction

1.1 Cutaneous sarcoidosis

Sarcoidosis is a multisystem granulomatosis disease of unknown etiology, characterized pathologically by noncaseating granulomas in involved tissues[1,2]. It mainly involves the lungs but may also be associated with systemic manifestations[3]. The disease most commonly affects the lungs, lymph nodes, liver, spleen, phalangeal bones, parotid glands, eyes, and skin[4]. Skin involvement rarely causes significant morbidity or mortality. However, it can adversely affaect a patient's quality of life by causing cosmetic impairment [5].

1.2 History

Sarcoidosis is first described by Sir Jonathan Hutchinson in 1875[6]. In 1889 the dermatologist Besnier described lupus pernio (sarcoidosis of the face) as a variant of cutaneous sarcoidosis. In 1899, Boeck described benign sarcoid and miliary lupoid [4,6].

1.3 Epidemiology

Sarcoidosis occurs worldwide and affects all ages and races. Disease onset is most often in the third decade of life, although a smaller second peak occurs in people older than 50 years[7].

1.4 Etiology and pathogenesis

The cause of sarcoidosis is unknown. It has been suggested that sarcoidosis is a hypersensitivity reaction caused by prolonged exposure to a spesisic antigen[8]. Although a spesific antigen has not yet been identified for sarcoidosis , the immune response which leads to recognizable clinical lesions and functional impairment is of the type 1 variety:elevated IFN gama , IL-2, and Th1 immune regulatory monokine IL2 characterize sarkoidosis[9]. Although mycobacteria have not been identified with traditional methods, mycobacterial DNA has been found in sarcoidal lesions[10]. Infectious agents such as mycobacteria, propionibacterium acnes and Chlamydia have been associated with sarcoidosis[11]. The etiologic role of various chemicals and metals such as beryllium, aluminium, zirconium, and titanium has also been debated. Treatment with interferons can cause a variety of inflammatory conditions, including sarcoidosis[4]. Genetic susceptibility to sarcoidosis has been associated with HLA -1, HLA-B8, and HLA-DR3 alleles[6].

1.5 Cutaneous lesions

Sarcoidosis involves so many organs that it is diffucult to describe all the features. About 40-50% of patients have cutaneous involvement[10]. Lesions are divided into two: specific and nonspecific skin lesions.

Skin lesions that contain typical sarcoid granulomas histologically are classified as specific lesions. Nonspesific skin lesions are those with nondiagnostic inflamatory patterns ;the most common is erythema nodosum. Nonspecific skin lesion lack typical noncaseating granulomas[5].

1.5.1 Specific lesions

The specific lesions of sarcoidosis all contain granulomas histologically, but the clinical appearence of the lesions is inconsistent. Specific lesions of sarcoidosis can present as macules, papules, plaques, nodules, and ulcerations. The involved skin may be skin colored, hyperpigmented, hypopigmented, or violaceous in color. Epidermal changes of the lesions may include atrophy, scaling, telengiectasias, or none at all[5]. Specific sarcoidal lesions most often are found on the head and neck, and but may ocur symetrically or asymmetrically on any part of the skin and mucosa[11].

1.5.1.1 Papules and plaques

The most common presentation is papuler form[4,5,11]. Papules are eleveted skin lesions less than 5mm in size. They have a predilection for the face and especially common around the eyes and on the posterior neck. They may be skin colored, hyperpigmented, erythematous, hypopigmented, violaceous, but clasically they are described as having a yellow–brown hue with an erythematous background. When pressure is applied with a glass slide or a dermoscope the erythematous coloration is mitigated and the yellow-brown color (often described as the color of apple jelly) can be more easily appreciated[4]. The apple jelly appearence and nodules are not pathognomonic for sarcoidosis, as other granulomatous skin conditions, such as lupus vulgaris may exhibit similiar diascopic properties[11].

The plaques form of sarcoidosis is rare and involves the extremities, the face and the corpus[4]. Plaques may arise denova or from a confluence of paules.These lesions are larger than 5mm in diameter [5]. Lupus pernio describes the relatively symmetric, violaceous, indurated plaques that ocur on the nose, ear-lobes, cheeks and digits. This clinical variant of sarcoidosis is distinctive and has been associated with symmetric involvement. Lupus pernio is associated with a higher prevelance of upper respiratory tract disease[11].

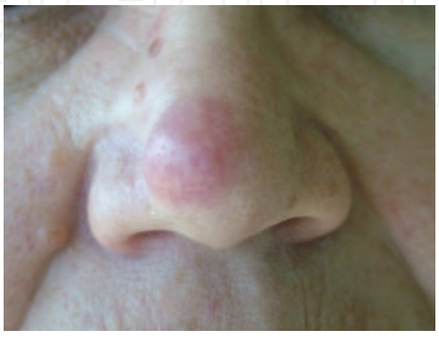

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Fig. 1. Violaceous lupus pernio lesion on the nose

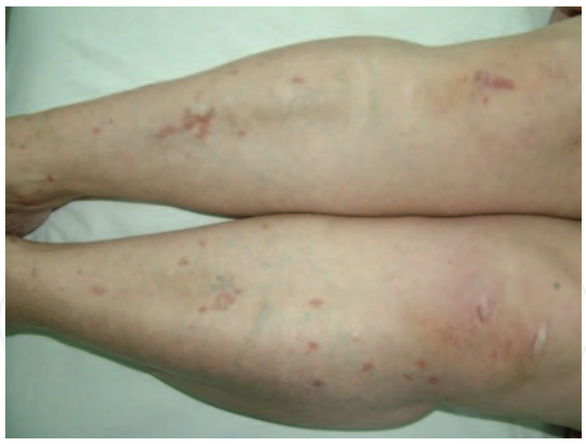

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Fig. 2. Papules and plaques at lower extremity

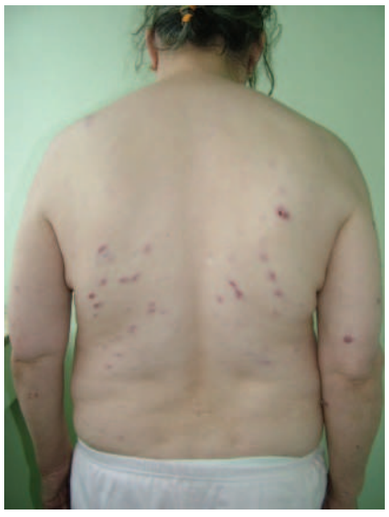

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Fig. 3. Papules and plaques

1.5.1.2 Scar sarcoidosis

Cutaneous sarcoidosis ocuuring in prior scar tisue, at traumatized areas of skin , or around foreign bodies such as tattos is common[5]. Scars become inflamed and infiltrated with sarcoidal granulomas. Inflamation of old scars may paralel or precede systemic disease activity[11]. The presence of foreign body in granuloma does not exclude sarcoidosis entirely. Many cases of scar sarcoidosis are following car accidents in which there is exposure to glass and dirt[11].

1.5.1.3 Scalp

Alopecia occurs with the involvement of the scalp. Scalp sarcoidosis may cause irrversibl cicatricial or noncicatricial sarcoidosis. Biopsy shows noncaseating granulomas. Its reversibility depends on the degree of the destruction of hair folicules [4,11].

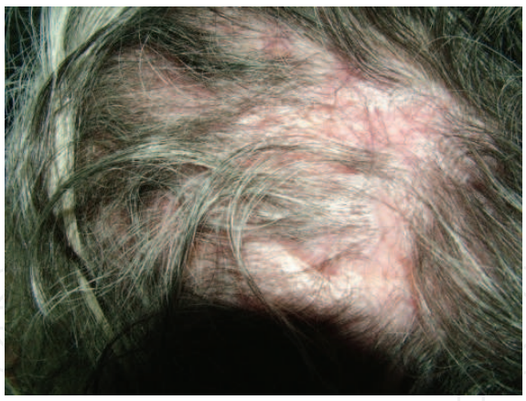

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Fig. 4. Scalp sarcoidosis

1.5.1.4 Nail

Sarcoidal inflammation around the nail matrix or within the distal bones of the digits can cause nail abnormalities[5]. Nail plate deformation and discoloration, clubbing, subungual hyperkeratosis may seen[11]. The incidence of hair and nail involvement is very low [4,11].

1.5.1.5 Mucous membranes

Sarcoidal granulomas may cause papules and plaques of the mucosal membranes and the tongue. Sarcoidosis may cause Mikulicz syndrome[11].

1.5.1.6 Ulcerations

The cutaneos lesions of sarcoidosis very rarely ulcerate. The most common site is the legs[10]. These lesions may mimic other ulcerative conditions such as venous stasis ulcerations, but they have granulomas present histologically[5]. An ulcerated necrobiosis lipoidica diabeticorum must also be considered[10].

1.5.1.7 Subcutaneous nodules

When the sarcoidal granulomas situated in the addipose tissue the skin induces clinically evident subcutaneos nodules and the classic red-brown color may not be seen. Instead the overlying skin may be normal or slightly red [5,10]. Multipl rather than solitary lesions are usually present. This granulomatous panniculitis is known as Darier –Roussy sarcoidosis [5,10].

1.5.1.8 Angiolupoid sarcoidosis (Brocq and pautrier)

This form of cronic cutaneous sarcoidosis is features red Brown papules, nodules, an plaques with prominent telengiectasies that tend to involve the mid face of the women[10]. In such cases, it is important to consider the rare granuloma eosinophlicum faciei as well as pseudolymphoma[5].

1.5.1.9 Macular

Cutaneos sarcoidosis may present as hypopigmented nonelevted areas. This variant is more common in dark skinned patients[5].

1.5.1.10 Additional presentations

Lots of additional prsentations have been reported. These includes erythroderma[12], ichtyosiform[13], rosacea like type[14], psoriasiform[15], morpheaform plaques[16], lichenoid

dermatitis [17], folikülitis like lesions, gyrate erythema, penil and vulvar lesions, palmar erythema, discoid lupus like plaques, lower extremity edema, lesions mimicking polymorphous light eruption[11].

1.5.2 Nonspecific lesions

1.5.2.1 Erythema nodosum

This is the most common nonspecific lesion. In most part of the world , it is necessary to exclude sarcoidosis when erythema nodosum is diagnosed in adults[10]. The lesions of erythema nodosum are tender and found predominantly on the lower extremities as well. The anterior surface of the lower leg is the most common location[5]. The presence of bilateral hiler adenopathy on chest radiograph with erythema nodosum is known as Löfgren syndrome[5].

Other nonspecific lesions are seen very rare. Prurigo nodules, erythema multiforme, lower extremity swelling, Sweet syndrome and pyoderma gangrenosum qualify as nonspecific cutaneous sarcoid lesions[5,11].

1.6 Treatment

The treatment of cutaneous sarcoidosis has been usually derived from agents for pulmonary sarcoidosis[18]. Standard therapeutic interventions for cutaneous sarcoidosis have traditionally included topical, intralesional and systemic corticostreoids, antimalarial drugs, methotrexate, and combinations of these agents[9].

1.6.1 Corticosteroids

Corticosteroid are the worldwide accepted standard treatment of sarcoidosis[9,18, 19]. For the patients with mild limited sarcoidosis the treatment may start with using ultrapotent topical corticosteroids[18]. Intralesional injections have been useful for some cases[18]. The concentration of the corticosteroids selected depends on the firmness and size of the lesion, but most lesions of sarcoidosis may be treated initially with intralesional triamcinolone at concentrations of 3-20 mg/mL repeated every 4 weeks until the lesions have flattened[18]. Adverse effectas are hypopigmentation and atrophy[1,7,8] Systemic corticosteroid theraphy, usually delivered orally , should be reserved for severely disfiguring or destructive lesions, widespread involvement, or lesions that have proved refractory to localized therapy [19]. The dosage of prednisone administered ranges from 40 to 80 mg/prednisone administered ranges from 40 to 80mg/day and is tapered over weeks to months depending on the clinical response [18].

1.6.2 Antimalarial agents

The effectiveness of chloroquine and hydroxychloroquine in sarcoidosis is thougt to be related to the ability of these agents to inhibit antigen processing and presentaion by APCs to CD4 T cells[8]. They have antiinflammatory properties [9,18,19]. The rate of response appears to be higher for cutaneous compared with pulmonary sarcoidosis. These drugs have been widely used for cutaneous sarcoidosis[18]. Maximum oral chloroquine dosage is 3.5 mg/kg/ day and hydroxycholoroquine dosage is 6.5mg/kg/day. Lower dosages are effective and are preferred to maximal dosing [9,18]. The toxicities of antimalarials are nausea, anorexia, dizziness, headaches and blurred vision. Bleaching of the hair, agranulocytosis [9,18,19].

Agranulocytosis is rare but serious complication of theraphy. Potential ocular efffects are the most serious adverse events associated with antimalarial treatment and include the development of corneal deposits of central retinopathy[18].

1.6.3 Methotrexate

Methotrexate is a folate analogue that inhibits dihydrofolate reductase. At high doses methotrexate is antiproliferative , in low doses methotrexate has antiinflammatory properties [19].

The dose of methotrexate is varies. In adults , the average starting dosage is 10 to 15mg a week [18].Hepatotoxicity is the major long-term effect associated with methotrexate , and routine monitoring of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and serum albumine is recomended[9,18,19]. While using methotrexate the patients must be monitored for neutropenia. Methotrexate is cleared with kidneys ; because of this serum creatinine monitoring must be done[18].

Methotrexate is associated with hematologic, gastrointestinal, pulmonary and hepatic toxicities [9,18,19]. Dose dependent toxicities are mucositis, mouth sores, and nausea. These problems can be eliminated by dividing by dividing the dose of methotrexate in half and giving oral folate [9,18,19].

1.6.4 Combination standard theraphy

Antimalarials and corticosteroids can be used in sequence. By this way complications of the long term use can be reduced. Steroids and antinalarials are steroid sparing agents. Both of them can be used in place of steroid or in combination with steroids. Combination therapies have the advantage of decreasing steroid doses[9,18,19] .

1.6.5 Other therapies

Pentoxifylline[20], tetracyclines[21,22], Leflunomide[23], Thalidomide[24], Infliximab[25], Chlorambucil[26], cyclosporin-A [27], allopurinol [28], laser surgery[29] are reported for the treatment of sarcoidosis.

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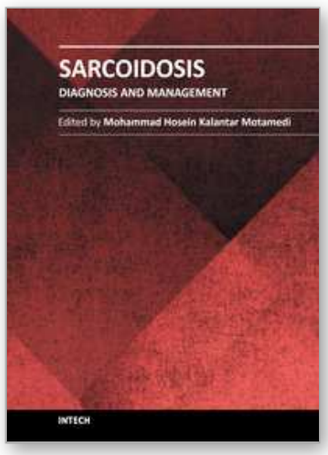

Sarcoidosis Diagnosis and Management

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Sarcoidosis is a type of inflammation that occurs in various locations of the body for no known reason. Normally, when foreign substances or organisms enter the body, the immune system will fight back by activating an immune response. Inflammation is a normal part of this immune response, but it should subside once the foreign antigen is gone. In sarcoidosis, the inflammation persists, and some of the immune cells form abnormal clumps of tissue called granulomas. The disease can affect any organ in the body, but it is most likely to occur in the lungs. It can also affect the skin, eyes, liver, or lymph nodes. Although the cause of sarcoidosis is not known, research suggests that it may be due to an extreme immune response or extreme sensitivity to certain substances. It also seems to have a genetic component as well, and tends to run in families. Sarcoidosis most commonly develops in people between 20 and 50 years of age. African Americans are somewhat more likely to develop sarcoidosis than Caucasians, and females are somewhat more likely to develop sarcoidosis than males. The symptoms of sarcoidosis depend on the organ involved. This book deals with the diagnosis and treatment of this mysterious disease of unknown etiology.

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