Chapter 45
Sarcoidosis

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45.1 Introduction

Sarcoidosis is a multiorgan noninfectious granulomatous disease which can manifest in the integumentary system in a variety of ways, one of the most common being a maculopapular, acneiform facial eruption. Although sarcoidosis is generally categorized as a pulmonary disease, it involves the skin in approximately 25–30 % of cases. The etiology of sarcoidosis remains unknown. The polymorphic cutaneous lesions are grouped into specific and nonspecific lesions. The characteristic histological finding in sarcoidosis, the noncaseating granuloma, is present in the specific lesions of cutaneous sarcoidosis, including macules, papules, plaques, subcutaneous nodules, infiltrative scars, and lupus pernio. The nonspecific lesions of cutaneous sarcoidosis, such as erythema nodosum (EN), calcifications, erythema multiforme, and clubbing, lack this feature. Sarcoidosis is a diagnosis of exclusion based on a combination of clinical, histological, and radiographic evidence. Since cutaneous sarcoidosis is frequently present at the onset of systemic disease, the dermatologist is often the first health-care provider to evaluate the patient. Biopsy-proven cutaneous sarcoidosis warrants a further workup for systemic disease. Corticosteroids are the mainstay of treatment for symptomatic sarcoidosis, followed by antimalarial and immunosuppressive medications.

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45.2 Background

There are many theories surrounding the etiology of sarcoidosis, but the cause(s) of the disease is still unknown. A multicenter trial of over 700 patients, entitled "A Case Control Etiologic Study of Sarcoidosis (ACCESS)," was unable to identify a specific antigen in sarcoidosis but did establish an increased risk of the disease with exposure to mold and musty odors, agricultural chemicals and aerosols, and insecticides [1]. In sarcoidosis, normal tissue function is disrupted by noncaseating granulomas. The formation of the noncaseating granuloma begins with macrophages and dendritic cells (antigen-presenting cells) using class II major histocompatibility (MHC) complexes to present an unknown antigen(s) to CD4+ T cells [2]. Through interactions with the MHC and costimulatory molecules, the T cell becomes activated and ignites a T_H1 inflammatory response. The T cells release IL-2 and IFN-γ to recruit additional T cells, as well as stimulate macrophages to produce TNF-α, leading to the differentiation of macrophages into epithelioid cells and formation of multinucleated giant cells [2].

In the United States, there are two peaks for sarcoidosis, in people between 25 and 35 years and in women between 45 and 65 years [3]. Sarcoidosis is more common in African Americans (although all races can be affected), and this group is more likely to present with advanced disease and have a poorer prognosis [4]. The highest incidence of disease in the United States in African American women in their fourth decade of life [3]. Sarcoidosis persists as a progressive disease in 30 % but has a mortality of less than 5 % [5]. The most common causes of death are progressive pulmonary fibrosis or other pulmonary or cardiac complications [4]. The first-degree relatives of people with sarcoidosis are at a 5-time increased risk for developing the disease [6]. Recent research has proposed certain genetic susceptibilities associated with the disease. An increased risk of sarcoidosis is associated with HLA-DRB1 and a splice site mutation in the gene butyrophilin-like 2 (BTNL2) [7].

45.3 Clinical Presentation

Cutaneous sarcoidosis is a clinically polymorphic disease. Many atypical presentations of cutaneous sarcoidosis have been reported, including but not limited to ichthyosiform, ulcerative, erythrodermic, hypopigmented, photo-distributed, verrucous, morpheaform, and lichenoid sarcoidosis [8]. Maculopapular eruptions are the most common specific lesion and tend to occur on the head, neck, perioral region, eyelids, and nasolabial folds. The papules are usually small (3–5 mm), monomorphic, and flesh-colored without epidermal change. The papules may also be red, violaceous, or hyperpigmented, and groups of papules may coalesce into annular lesions or plaques. This presentation of sarcoidosis may present similar to other acneiform eruptions of the face (Figs. 45.1 and 45.2). The differential diagnosis includes acne,

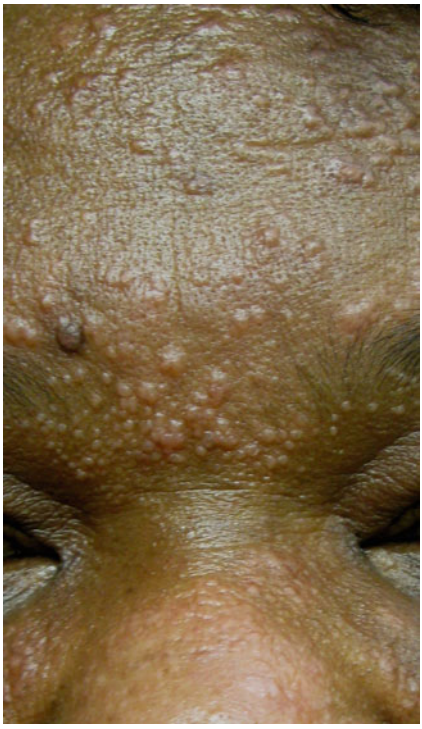

Fig. 45.1 Papular sarcoidosis in the T zone

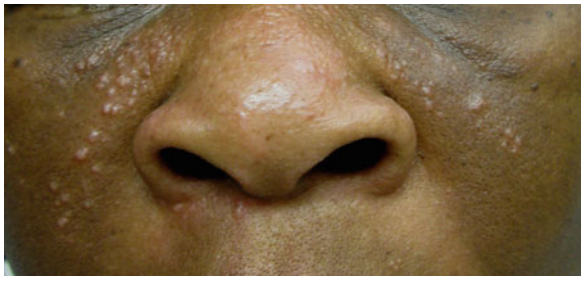

Fig. 45.2 Papular sarcoidosis of the malar checks

rosacea, granulomatous periorificial dermatitis, and granulomatous rosacea. Sarcoidosis differs from acne vulgaris in that there is no comedonal component and lesions are not pustular in nature. The majority of the time the difference can be determined clinically but biopsy can easily distinguish these entities. Although maculopapular sarcoidosis may not seem significant, Mana [9] reported a series in which four out of 14 patients with maculopapular lesions developed chronic cutaneous, pulmonary, or ocular sarcoidosis [9].

45.4 Workup

The diagnosis of sarcoidosis requires careful integration of clinical, radiographic, and histological information, as well as the exclusion of other granulomatous diseases. Evaluation begins with a thorough history and physical examination focusing on the skin, lungs, heart, eyes, lymph nodes, and nervous system. When sarcoidosis is suspected, the skin is often the most accessible and least invasive option available for obtaining a biopsy. If the biopsy reveals noncaseating granulomas, the stains and tissue cultures must be negative for infectious agents, such as Mycobacteria, fungi, leishmaniasis, and syphilis, and foreign body granulomas must also be excluded [9]. When a diagnosis of cutaneous sarcoidosis is suspected, the patient needs to be evaluated for systemic sarcoidosis. This will require consultation with several specialty physicians.

Evaluation for pulmonary sarcoidosis begins with a chest radiograph and pulmonary function tests. Pulmonary manifestations are present in approximately 90 % of patients with sarcoidosis. The radiograph most commonly reveals bilateral hilar lymphadenopathy, but may also show infiltrates or fibrosis, while the pulmonary function tests may demonstrate a restrictive pattern with decreased diffusing capacity [10, 11]. High-resolution computed tomography (CT) of the chest is not usually indicated, but can be used to further evaluate patients with atypical chest radiographs [10]. Cardiac sarcoidosis is initially evaluated by electrocardiogram and echocardiogram [10]. Heart failure or symptoms such as palpitations and syncope are only present in 5 % of patients and usually indicate advanced disease [12]. Cardiac magnetic resonance imaging (MRI) is a specific but not sensitive test for detecting structural cardiac disease [12]. Ocular sarcoidosis most commonly presents as uveitis, but can ultimately result in blindness, thus a complete ophthalmologic evaluation is recommended [10]. Neurosarcoidosis is present in up to 15 % of patients with systemic disease [8]. Evaluation may include radiographs of the skull, electroencephalography, CT scan, and/or MRI of the central nervous system [8].

In addition laboratory testing includes complete blood counts, liver and kidney function tests, serum calcium level, creatinine kinase and aldolase, and urinalysis. The serum angiotensin-converting enzyme (SACE) level is increased in 60 % of patients with sarcoidosis, but it is neither sensitive nor specific, and can be elevated in common diseases, such as diabetes and osteoarthritis [4, 9].

45.5 Treatment

There is no FDA-approved treatment for sarcoidosis, and there is limited evidence-based medicine regarding the treatment of cutaneous sarcoidosis [13]. In terms of cutaneous sarcoidosis, corticosteroids (oral and intralesional) are the mainstay of treatment [14, 15]. Corticosteroids provide anti-inflammatory and immunosuppressive effects,

theoretically decreasing granuloma formation [16]. The dosing ranges and schedules of corticosteroids are highly variable, and there is not adequate evidence supporting their use for cutaneous sarcoidosis [11]. Historically, oral prednisone has been reported as effective for cutaneous sarcoidosis, but randomized controlled trials are needed [14, 17, 18]. Given the extensive side effects of systemic corticosteroids, they are generally only used for expansive disfiguring cutaneous lesions after local steroids have failed [3]. Corticosteroids must be tapered slowly over weeks to months to avoid disease flares.

Hydroxychloroquine is an antimalarial agent which is thought to work by decreasing antigen presentation by APCs, resulting in decreased T-cell activation and decreased granuloma formation [19]. The efficacy of antimalarials in cutaneous sarcoidosis has been reported since the 1960s, but there have not been any randomized controlled trials for this indication [20, 21]. More recent studies have reported regression of cutaneous sarcoidosis with hydroxychloroquine (2–3 mg/kg/day for up to 12 weeks) [22] or chloroquine (500 mg daily for 14 days, then 250 mg for long-term maintenance) [23]. Antimalarial medications require frequent eye exams (at least yearly) for ototoxicity. Methotrexate, a dihydrofolate reductase inhibitor, has emerged as a second-line treatment for cutaneous sarcoidosis, typically prescribed at doses of 10–30 mg/week [16]. Webster [24] reported clearing of refractory cutaneous sarcoidosis in three patients with 15 mg/week for up to 11 months [24]. Baughman [25] reported improvement in 16 out of 17 patients treated with methotrexate over a period of 2 years and with average doses of 28 mg/week [25]. Minocycline (200 mg/day) has been reported in one open prospective study of 12 patients with refractory cutaneous sarcoidosis, with 8 patients experiencing complete regression and 2 with partial regression after 12 months, but with 3 suffering relapse of disease after stopping this therapy [26].

Other medications that have been reported for the treatment of sarcoidosis include pentoxifylline [27], thalidomide [28–32], allopurinol [33, 34], isotretinoin [35, 36], infliximab [37, 38], adalimumab [39], azathioprine [40], cyclophosphamide [40], cyclosporine [41], chlorambucil [42, 43], leflunomide [44, 45], and melatonin [46], but randomized controlled trials are needed to evaluate these treatments. Non-pharmaceutical options include lasers, dermabrasion, excision, and phototherapy (PUVA, UVB, and photodynamic therapy).

45.6 Conclusion

Sarcoidosis is a systemic disease affecting multiple organ systems. Cutaneous lesions may be mistaken for acne but can be distinguished based on the lack of comedones and the distinct histological appearance. Prompt diagnosis is important, as the skin may be a presenting sign of widespread disease. Multiple therapies are effective, and patients often require oral medications for internal disease as well as topicals for cutaneous lesions.

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