Maculopapular sarcoidosis: the importance of skin signs

Giovanna Galdo,[1] Gelsomina Luongo,[2] Daniela Capacchione,[3] Damiano Abeni,[4] Marta Grimaldi,[5] Luca Fania[4]

[1]Dermatology and Dermosurgery Unit, San Giuseppe Moscati Hospital, Avellino; [2]Department of Pathology, San Giuseppe Moscati Hospital, Avellino; [3]Nuclear Medicine Unit, San Giuseppe Moscati Hospital, Avellino; [4]IDI-IRCCS, Dermatological Research Hospital, Rome; [5]Institute of Dermatology, Università Cattolica del Sacro Cuore, Rome, Italy

Abstract

Sarcoidosis is a multisystem disease that affects the skin in 20 to 30% of cases. Skin findings are often the initial presenting signs, and cutaneous sarcoidosis may appear with a wide variety of lesions; it is often considered an imitator of many other skin diseases. Clinical appearance and specific dermoscopic criteria, confirmed by a typical pathology, may guide to the correct diagnosis. We report the case of a man affected by maculo-papular sarcoidosis on the back, in which the detection of cutaneous lesions was the initial step to determine the systemic nature of the disease.

Introduction

Sarcoidosis is a non-caseating, granulomatous, multisystemic disease affecting mainly mediastinic lymphonodes, lungs, liver, spleen, eyes, muscoloskeletal system, blood, skin, nervous system, heart, periferic lymphonodes, and parotid glands.[1] Sarcoidosis generally affects adults between 20 and 50 years of age, and a second mode occurs in adult between 50 and 65 years of age.[2] Consistently, Afro-American individuals are reported to be more often affected by sarcoidosis. In the United States, it is mainly seen among females. Furthermore, it also seems to be more common in Swedes, Danes, and African-Caribbeans,[3] and among women in Scandinavia and Japan. Children are rarely affected in the pediatric age and a peak is observed at age 13-15 years, with no sex predominance.[4] Many authors assert there is strong evidence of a genetic predisposition to manifest sarcoidosis, marked by a particular human leukocyte antigens allele,[5] in afro-american people as DQB1-0602 or in Caucasian as Butyrophilinlike 2,[6] or by a susceptibility locus as 5q11.2 and by a protective gene on locus 5p15.2.[7] The granulomatous inflammation is due to a dysregulated antigenic response in a genetically susceptible individual as a consequence to an undetermined antigenic exposure. The granuloma is formed by multinucleated giant cells and epithelioid macrophages surrounded by a rim of CD4+ T cells and, less abundantly, by CD8+ T cells as well as B cells.[8] Presence in granulomas of activated macrophages with T cells (with Th1/Th17 response) and their production of cytokines (such as TNF-α, IL-1, IFN-γ, IL-6, IL-12, IL-23, IL-2, IL-15, IL-16, CXCL10, CXCL9) indicate treatment options such as systemic corticosteroids, methotrexate, azathioprine, leflunomide, mycophenolate mofetil, chloroquine and hydroxychloroquine, antitumor necrosis factors, ustekinumab, apremilast, and rituximab.[9-12] Generally, it has a benign clinical course but, sometimes, it presents with a fatal disease leading to death for respiratory failure or cardiac failure when associated with ethnicity (particularly Afro-American and Afro-Caribbean origins), age over 40 years at presentation, lupus pernio, chronic uveitis, sinonasal and osseous localizations, central nervous system involvement, cardiac involvement, severe hypercalcemia, nephrocalcinosis and radiographic stages III and IV.[13] Diagnosis of sarcoidosis is based according to an international consensus statement by 3 criteria: a compatible clinical and radiologic presentation, pathologic evidence of noncaseating granulomas, and exclusion of other diseases with similar findings.[3]

Case Report

A 53-year-old man, with a history of penicillin allergy, lichen ruber planus, and Hashimoto's disease, came to our attention due to itching, erythematous-brownish maculopapular lesions on the back, which had appeared four months earlier. Skin lesions were on the right and left periscapular region, and at the dorsal-lumbar level (Figure 1A,B). The digital epiluminescence polarized light microscope system (DermLite, 3Gen,×20) with immersion oil revealed whitish yellow structureless areas on a yellow-orange background, with peripheral diffuse linear and irregular vessels (Figure 1C). The yellow-to-orange color is typically seen in granulomatous diseases and in the differential diagnosis, we considered cutaneous sarcoidosis, lupus vulgaris, cutaneous leishmaniasis, and xanthomas.

A skin biopsy was performed, and histopathology confirmed the suspected dermoscopic diagnosis of cutaneous sarcoidosis, showing, in the superficial dermis, (hematoxylin and eosin, optical microscope×10) non caseating epithelioid granulomas (Figure 2A) with minimal or absent lymphocytes or plasma cells surrounding the granulomas (naked granuloma). Granulomas did not tend to coalescence and were separated by a thin connective component. The epidermal layer, furthermore, showed absence of dermal papillae and rete ridges, and it appeared thinned. Special stains like Grocott, Ziehl–Neelsen, and periodic acid schiff were negative, as well as tissue cultures for acid fast bacilli and fungal infections.

These findings led us to investigate the case further, to ascertain the presence of systemic disease. Serum angiotensin-con-

Correspondence: Giovanna Galdo, Dermatology and Dermosurgery Unit, San Giuseppe Moscati Hospital, Avellino, Italy.
E-mail: giovannagaldo@libero.it

Key words: sarcoidosis; skin signs; maculopapular lesions.

Contributions: MG, LF, contributed equally to the work.

Conflict of interest: the authors declare no potential conflict of interest.

Funding: none.

Informed consent: written informed consent has been obtained.

Availability of data and materials: data and materials are available by the authors.

Received for publication: 10 July 2022.
Accepted for publication: 14 July 2022.

Licensee PAGEPress, Italy
Dermatology Reports 2023; 15:9561
doi:10.4081/dr.2022.9561

verting enzyme (ACE) levels were elevated (*i.e.*, 82 U/l, normal: 8–52 U/l). Leucocyte typing showed a CD4/CD8 ratio of 3.93 (increased, compared to the normal value of 3.50). Computed tomography of the chest showed multiple enlarged antero-superior mediastinal, prevascular mediastinal left, carinal, and Barety space lymph nodes; in addition, a parenchymal consolidation at the apical segment of the pulmonary right upper lobe was found. Positron emission tomography (PET) confirmed the increase of standard uptake value imaging at the level of the above-mentioned sites (Figure 2B).

Treatment is not indicated for asymptomatic patients with sarcoidosis at stage I or II of the Radiologic Staging of Sarcoidosis (RSS),[14] because spontaneous resolution is common. Our patient started first-line corticosteroid treatment for RSS stage II, as the disease involved both the lungs and the lymph nodes. Treatment was instituted with 37.5 mg of prednisone once a day for ten days, followed by a 20-day progressive dose-reduction of the steroid to reach 17.5 mg daily for ten more days. We observed a complete resolution of the skin lesions, and a marked improvement of the intra-thoracic disease after one month of treatment.

Discussion

Sarcoidosis has multiple skin manifestations. They are divided into specific and aspecific forms. Specific skin sarcoidosis manifestations include papular sarcoidosis, diffuse maculopapular sarcoidosis, plaque sarcoidosis (often evolution of papular sarcoidosis), annular plaque sarcoidosis, subcutaneous sarcoidosis (Darier-Roussy type), lupus pernio, angiolupoid sarcoidosis, tattoo-sarcoidosis, and subungueal sarcoidosis. Uncommon specific cutaneous sarcoidosis findings include: ichthyosiform type, atrophic and ulcerative form, mucosal localization (oral mucosa and pharyngeal mucosa), erythroderma involving large areas of skin with fine superficial scale or mild exfoliative dermatitis, alopecia on the scalp, nail sarcoidosis.[15,16] Therefore, after recognizing that a skin lesion may be a manifestation of sarcoidosis, it is necessary to search in possible systemic involvement and exclude other diseases with the same histology. The differential diagnosis of systemic diseases with granulomas that contain epithelioid and giant cells are tuberculosis, atypical mycobacterial disease, fungal infection (like histoplasmosis and coccidioidomycosis), bartonellosis, toxoplasmosis, brucellosis, sarcoid-like lesions due to cancer or an immunodeficiency or medications, heavy-metal-associated granulomatosis, chronic berylliosis, systemic vasculitis, Crohn's disease, Hodgkin disease and non-Hodgkin's lymphoma.[17]

Sarcoidosis was ascertained in our patient based on the internationally accepted 3 major dignostic criteria: he presented mediastinal lymphadenopathy and parenchymal involvement; histologic confirmation of the presence of non-caseating granulomas in the skin; and exclusion of other causes of granulomatous disorders. We have ruled out other causes of granulomatosis because we did not find blood count abnormalities, no signs of systemic infection, negativity of standard histological stains for fungi and bacteria, negative test of Quantiferon-TB Gold that aids in the detection of Mycobacterium tuberculosis by interferon-gamma (IFN-γ) release assay. ACE levels were increased. We staged the patient by CT and PET total body, we excluded cardiac disease by ECG and echocardiogram, eye involvement by basic eye examination including measurement of visual acuity, pupillary examination, slit lamp examination of the anterior segment of the eye and direct funduscopic examination with visual field, negative creatinine phosphokinase test for muscular involvement.

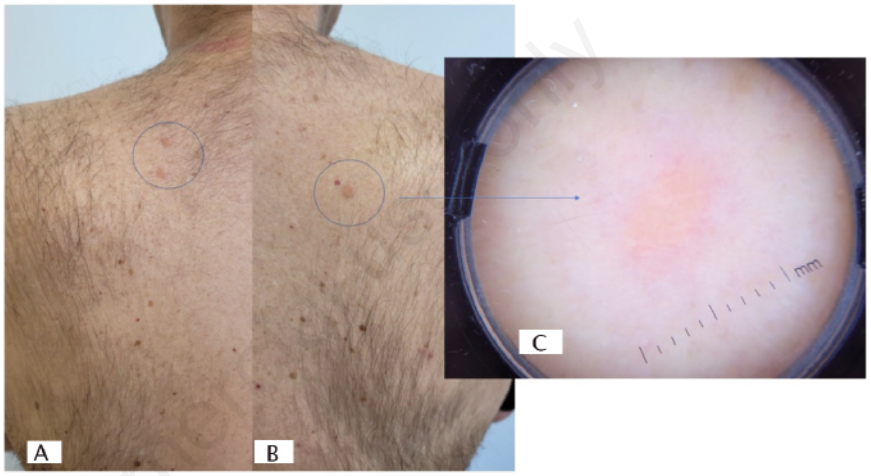

Figure 1. A) Circled skin lesions: erythematous-brownish maculo-papular lesions on the left scapular region; B) Circled skin lesions: erythematous-brownish maculo-papular lesion on the right scapular region; C) DermLite, 3Gen, ×20: dermoscopic findings of the maculo-papular lesion with irregular vessels around a whitish-yellow structureless areas on yellow-orange background.

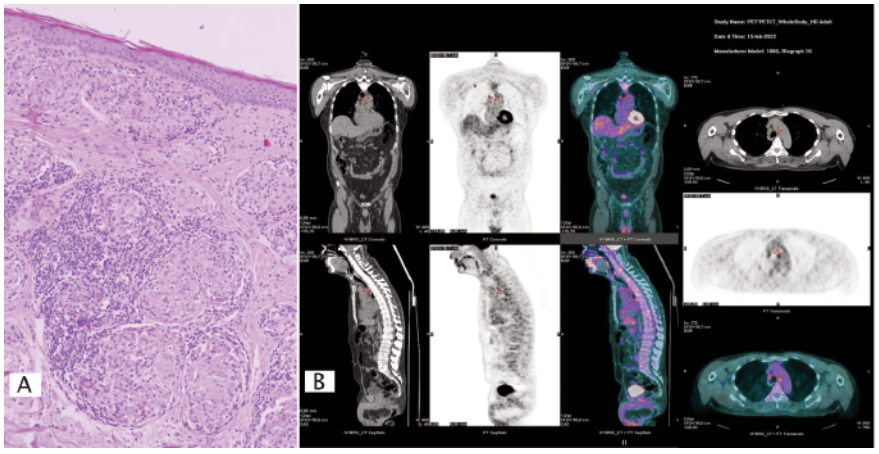

Figure 2. A) Hematoxylin and eosin, optical microscope×10: histological examination - non caseating epithelioid granulomas (naked granuloma) in the superficial dermis and thin epidermal layer without dermal papillae and rete ridges; B) Positron emission tomography - PET: increased standard uptake value (standard uptake value max 4.16) at the apical segment of the pulmonary right upper lobe and in Barety space lymph nodes.

Sarcoidosis with mediastinal lymphadenopathy, parenchymal lung and skin involvement was diagnosed. We began first-line treatment with systemic corticosteroids for II stage of RSS according to the guideline,[13] obtaining a complete remission of cutaneous disease after one month of therapy.

Conclusions

We reported a case of sarcoidosis with maculo-papular skin lesions, mediastinal lymphadenopathy, and parenchymal lung involvement. Skin signs were the first clinical manifestations of the disease. Histological examination of skin lesions is important for the diagnosis of sarcoidosis, but in-depth examination for a possible systemic involvement of the disease is essential for a comprehensive diagnosis.

References

1. Soto-Gomez N, Peters JI, Nambiar AM. Diagnosis and management of sarcoidosis. Am Fam Physician 2016;93:840-8.
2. Hena KM. Sarcoidosis epidemiology: race matters. Front Immunol 2020;11: 537382.
3. Statement on sarcoidosis. Joint statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS board of directors and by the ERS Executive Committee, February 1999. Am J Respir Crit Care Med 1999;160:736-55.
4. Hoffmann AL, Milman N, Byg KE. Childhood sarcoidosis in Denmark 1979-1994: incidence, clinical features and laboratory results at presentation in 48 children. Acta Paediatr 2004;93:30-6.
5. Müller-Quernheim J, Schürmann M, Hofmann S, et al. Genetics of sarcoidosis. Clin Chest Med 2008;29:391-414.
6. Rybicki BA, Walewski JL, Maliarik MJ, et al. The BTNL2 gene and sarcoidosis susceptibility in african americans and whites. Am J Hum Genet 2005;77:491-9.
7. Gray-McGuire C, Sinha R., Iyengar S, et al. Genetic characterization and fine mapping of susceptibility loci for sarcoidosis in African Americans on chromosome 5. Hum Genet 2006;120:420-30
8. Crouser ED, Maier LA, Wilson KC, et al. Diagnosis and detection of sarcoidosis. An official american thoracic society clinical practice guideline. Am J Respir Crit Care Med 2020; 201:e26–51.
9. Gerke AK. Treatment of sarcoidosis: a multidisciplinary approach. Front Immunol 2020;11:545413.
10. Belkhou A, Younsi R, El Bouchti I, et al. Rituximab as a treatment alternative in sarcoidosis. Joint Bone Spine 2008; 75:511–2.
11. Baughman RP, Judson MA, Ingledue R, et al. Efficacy and safety of apremilast in chronic cutaneous sarcoidosis. Arch Dermatol 2012;148:262-4.
12. Judson MA, Baughman RP, Costabel U, et al. Safety and efficacy of ustekinumab or golimumab in patients with chronic sarcoidosis. Eur Respir J 2014;44:1296–307.
13. Tan JL, Fong HK, Birati EY, Han Y. Cardiac sarcoidosis. Am J Cardiol 2019; 123:513-22 .
14. Wu JJ, Schiff KR. Sarcoidosis. Am Fam Physician 2004;70:312-22.
15. Caplan A, Rosenbach M, Imadojemu S. Cutaneous sarcoidosis. Semin Respir Crit Care Med 2020;41:689–99.
16. Haimovic A, Sanchez M, Judson MA, Prystowsky S. Sarcoidosis: a comprehensive review and update for the dermatologist. J Am Acad Dermatol 2012; 66:719.e1-10.
17. Prasse A. The diagnosis, differential diagnosis, and treatment of sarcoidosis. Dtsch Arztebl Int 2016;113:565-74.