SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2016; 33; 59-65

Papular sarcoidosis of the knees. A frequent form of presentation of systemic sarcoidosis

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Abstract. *Background:* In recent years we have observed with increasing frequency granulomatous papular lesions involving the knees, for which we proposed the term papular sarcoidosis of knees. *Objectives:* To evaluate the clinicopathological features of papular sarcoidosis of the knees. *Methods:* Patients with papular lesions of the knees and histopathologically sarcoid granulomas were included in the study. Systemic sarcoidosis was investigated in all cases. Clinical charts were retrospectively retrieved. Biopsy specimens were evaluated under polarized light to detect foreign bodies. *Results:* Fifty-three patients fulfilled inclusion criteria. In 36 cases systemic sarcoidosis was diagnosed and these cases were considered as papular sarcoidosis of the knees. Foreign particles were observed in 21 of these 36 patients. In only 9/36 patients did the activity of systemic disease persist over two years. In 17 cases systemic sarcoidosis could not be demonstrated during follow-up. *Conclusion:* Papular sarcoidosis of the knees can be considered a relatively frequent form of cutaneous sarcoidosis usually present at the beginning of the disease that can be useful for the diagnosis of sarcoidosis. It is mainly observed in acute forms of sarcoidosis and can be considered a sign of good prognosis. *(Sarcoidosis Vasc Diffuse Lung Dis 2016; 33: 59-65)*

Key words: sarcoidosis, skin, papules, papular sarcoidosis, knees, foreign bodies

Introduction

Sarcoidosis is a multisystem granulomatous disease of unknown etiology that predominantly involves the lungs, mediastinal lymph nodes, eyes and skin. Less frequently it can also affect the liver, spleen, parotid glands, and other organs (1). The cutaneous lesions observed in patients with systemic sarcoidosis are classified into specific and nonspecific according to the presence or not of histopathologically sarcoid granulomas (2). Specific skin lesions are especially important because when present a simple skin biopsy may be of great value as a minor-invasive procedure for the diagnosis of systemic disease.

A few years ago we observed that a significant proportion of our patients with systemic sarcoidosis had papular lesions on the knees for which we proposed the term papular sarcoidosis of knees (3). Since then we have reviewed all our patients with systemic sarcoidosis and erythematous-brownish papules of the knees that histologically showed sarcoid granulomas to better analyze the clinicopathological features of papular sarcoidosis of the knees. We also studied those patients with papular lesions on the knees clinically and histologically indistinguishable from papular sarcoidosis of the knees who, during the clinical follow-up, did not develop systemic sarcoidosis.

Received: 24 February 2015
Accepted after revision: 18 June 2015
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Methods

Patients with papular lesions on the knees that histologically showed sarcoid granulomas diagnosed in the Department of Dermatology of Bellvitge Hospital between 1980 and 2014 were included in the study. This is a universitary hospital providing tertiary health care to a population of about 1 million people. In all cases the presence of systemic sarcoidosis was investigated. The diagnosis of systemic sarcoidosis was performed according to the following criteria: compatible clinical and radiographic appearance; histological demonstration of noncaseating granulomas in one or more tissues with stains and culture negative for mycobacteria and fungi; and the exclusion of other granulomatous diseases. Investigations included clinical history and physical examination, ophthalmological examination, chest radiography, standard haematological and biochemistry profiles (including serum calcium level, hepatic enzymes, renal function tests and serum ACE level), tuberculin skin test, and pulmonary function tests (forced vital capacity and carbon monoxide diffusing capacity). Gallium-67 scan and computed tomography of the chest were carried out according to clinical criteria. Biopsies were taken where possible. Those patients with papular lesions on the knees that histologically showed sarcoid granulomas that could not be initially diagnosed with systemic sarcoidosis were followed-up to detect the possible involvement of other organs and thus diagnose sarcoidosis. Other ancillary tests were ordered according to clinical findings. The medical records of the patients were reviewed to analyze the radiological stage at diagnosis, the presence of erythema nodosum (EN), the coexistence with of other forms of specific cutaneous sarcoidosis, the presence of foreign bodies in the skin biopsy, the persistence of disease activity for over two years and the need for treatment with systemic corticosteroids. Data were introduced in a database and analyzed with SPSS 17.0 for Windows.

Results

A total of 53 patients were included in the study. They were 46 women and 7 men with a mean age of 49.94 years (SD 11.78). All patients were Caucasian except two women from Morocco. All patients showed a discrete number of papules of granulomatous appearance grouped on the knees, sometimes showing a linear arrangement (Figure 1). Histopathologically all patients had non-necrotic epithelioid cell granulomas with scarse or absent lymphoid rim (Figure 2 A). In 29 cases foreign bodies were observed within the granulomas (Figure 2 B). Twenty patients had EN. Fifteen of 53 patients had recurrent outbreaks.

In 36 patients the diagnosis of systemic sarcoidosis was confirmed. The clinical features of these patients are shown in table 1. The remaining 17 patients, with clinically and histologically indistinguishable cutaneous lesions, failed to demonstrate evidence of systemic sarcoidosis during a mean follow-up of 97.41 months (table 2). The 36 cases with systemic sarcoidosis correspond to 31 women and 5 men with a mean age of 49.08 years (SD 12.49). The cutaneous lesions of the knees were bilateral in 24/36 cases, linearly arranged in 28/36, and with foreign bodies in the skin biopsy in 21/36. Eight patients also showed other forms of specific cutaneous sarcoidosis (4 plaques and 4 subcutaneous sarcoidosis). EN was diagnosed in 18/36 patients. Twelve of 36 patients had recurrent outbreaks of cutaneous lesions on the kneees. In 31/36 patients cutaneous lesions and systemic sarcoidosis were diagnosed simultaneously, in 3/36 patients systemic sarcoidosis was diagnosed previously, and in the remaining two patients systemic sarcoidosis was confirmed 6 and 8 months after diagnosis of skin lesions. Twenty-one of 36 patients had radiographic stage I at diagnosis, 8 stage II, 3 stage III and 4 stage 0. Only 9 of 36 patients required systemic treatment with corticosteroids and in only 9 patients did the activity of systemic disease persist over two years. The papular lesions persisted a median time of 6.44 months. However they were less persistent in patients with EN (3.59 vs 9 months, Mann-Whitney test p=0.003) and in patients with radiological stage I compared with the rest of patients (4.20 vs 9.27 months, p=0.038).

The 17 cases without confirmed systemic sarcoidosis correspond to 15 women and 2 men with a mean age of 51.76 years (SD 10.22). The cutaneous lesions of the knees were bilateral in 9 cases, linearly arranged in 13, and with foreign bodies in the skin biopsy in 8. Four patients also showed other granulomatous cutaneous lesions (4 plaques with histopathologically sarcoid granulomas). Two patients

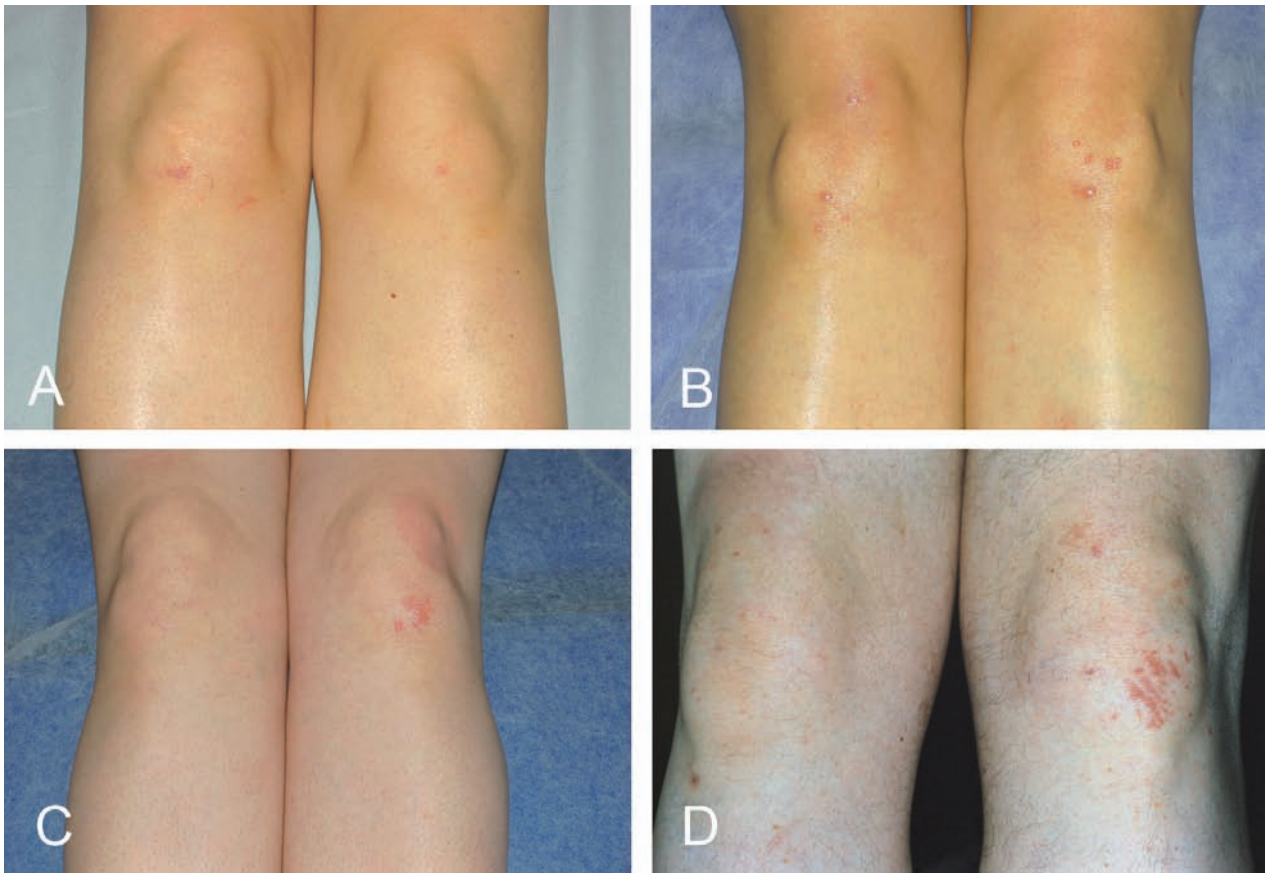

Fig. 1. Papular sarcoidosis of the knees. **A, B,** Multiple erythematous-brownish papules grouped on both knees of two female patients with systemic sarcoidosis. **C,** Granulomatous-appearing papules limited to the left knee in a female patient with systemic sarcoidosis. **D,** Papules with linear arrangement limited to the left knee of a male patient without confirmed systemic sarcoidosis

had EN. Three patients had recurrent outbreaks of their papular lesions of the knees. The papules persisted a median time of 6.93 months.

Discussion

All patients described in the present study presented erythematous-brownish papules of the knees that histopathologically showed sarcoid granulomas in the upper dermis. The clinical picture, the histopathological features, and the presence of foreign bodies in a high proportion of patients drew a very uniform clinicopathological picture for which we proposed the name of papular sarcoidosis knees (3). Since then several cases have been reported with this terminology (4, 5).

To date we have collected a total of 53 patients with these clinicopathological features. In 36 of our patients the diagnosis of systemic sarcoidosis was confirmed through the demonstration of other organ involvement. We consider that only these 36 cases can be considered papular sarcoidosis of the knees. The remaining 17 patients had no evidence of sarcoidosis during follow-up. We name these patients with sarcoid granulomas limited to the skin with the term sarcoid skin reaction. These cases without proven sarcoidosis may simply represent a local sarcoid reaction but should be followed clinically since two of our patients developed systemic sarcoidosis subsequently in the follow up. No clinical or histopathological features were able to predict the presence of systemic sarcoidosis in our 53 patients. It is being debated how many organs need to be involved to diagnose sarcoidosis (6). The presence of sarcoid granulomas is no rarely observed in the skin and these lesions may be clinically and histopathologically indistinguishable from cutaneous involvement

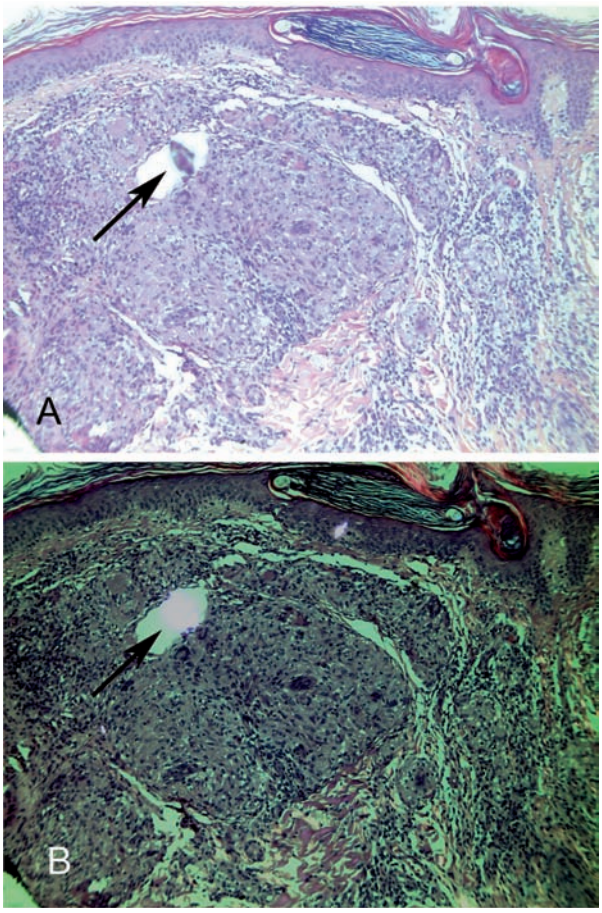

Fig. 2. Papular sarcoidosis of the knees. **A,** Sarcoid granulomas in superficial dermis (Hematoxylin-eosin stain; original magnification X100). **B,** Foreign bodies inside a granuloma under polarized light (Hematoxylin-eosin stain; original magnification X100)

by sarcoidosis. For this reason, we believe that when analyzing a patient with sarcoid granulomas in the skin, more than one organ involvement should be documented to achieve a diagnosis of sarcoidosis.

The 36 patients with papular sarcoidosis of the knees showed a discrete number of papules of granulomatous appearance grouped on the knees, sometimes showing a linear arrangement. Fifteen patients also had EN. In most cases the papules were not previously detected by the patients and were discovered by the physician on physical examination. None of our patients had noticed inoculation of exogenous material into the skin. The lesions usually lasted several months and then spontaneously disappeared in parallel with the normalization of the chest x-ray, usually in less than a year (mean time 6.44 months).

Until recently it was considered that the presence of polarizable foreign material inside of sarcoid granulomas excluded the diagnosis of sarcoidosis. However, the presence of foreign bodies has been detected in a significant proportion of granulomatous skin lesions of patients with systemic sarcoidosis (22-24%) (7,8). It has been suggested that these foreign bodies could provide a stimulus for granuloma formation in patients who are currently developing systemic sarcoidosis, thus favoring or determining the location of lesions (7-10). In 21 of our 36 patients with papular sarcoidosis of the knees the presence of foreign bodies was demonstrated (58.33%). The knees are frequently exposed to minimal trauma that can introduce exogenous particles into the dermis. Moreover, the tendency toward linear arrangement of the papules may be related to the inoculation of foreign material by a previous linear traumatism, possibly produced months or years earlier. The absence of scar tissue in histological samples of papular sarcoidosis of the knees suggests that the predilection of sarcoidosis to involve old scars may be due to accidental inoculation of antigens or other foreign particles by the traumatism, rather than by the scar tissue alone.

Several types of specific cutaneous lesions of sarcoidosis with prognosis significance have been described. Maculopapular lesions are often associated with acute forms of sarcoidosis (2, 11-13). Plaque-type lesions are more commonly associated with persistent and chronic forms of the disease (2, 11-16). Lupus pernio is associated with extremely chronic forms of sarcoidosis and is one of the markers of chronic fibrotic disease (12, 17). Most cases of papular sarcoidosis of the knees are associated with acute forms of sarcoidosis with less than 2 years of persistence of disease activity and they therefore can be considered as a sign of good prognosis in sarcoidosis.

A total of 116 patients with systemic sarcoidosis and different clinical forms of granulomatous cutaneous lesions have been diagnosed in our Hospital. So, papular sarcoidosis of the knees has been observed in 31% of our patients with specific cutaneous involvement of sarcoidosis. Because of small lesions of papular sarcoidosis of the knees may go unnoticed, we believe that this type of lesion would be observed in a higher proportion of patients with sarcoidosis if they were systematically examined. In these pa-

Table 1. Data of the patients with papular sarcoidosis of the knees and confirmed diagnosis of systemic sarcoidosis

Nº	Age	Sex	Bilateral	Linear	Duration lesions (months)	Recurrent	EN	Foreign bodies	Present at debut of sarcoidosis	RX stage	Extrathoracic organs involved	>2 years	Cortico steroids
1	44	F	+	+	6	+	+	+	+	1	-	-	+
2	53	F	+	+	3	+	+	+	-	1	Lymphatic glands, liver	+	-
3	55	F	-	+	2	+	+	-	+	1	-	+	-
4	33	F	+	+	N/A	N/A	+	-	+	1	N/A	N/A	N/A
5	33	F	-	-	2	N/A	+	+	+	1	Hypercalcemia	-	-
6	57	F	+	-	6	-	+	-	+	1	Anterior uveitis, parotid gland	-	-
7	53	F	+	+	3	+	+	+	+	1	-	-	-
8	53	F	+	+	1	-	+	+	+	0	Anterior uveitis	-	-
9	31	F	+	+	2	+	+	+	+	1	Spleen	-	-
10	56	F	+	+	36	-	-	-	+	2	Lymphatic glands, bone	+	+
11	74	F	+	+	4	N/A	+	+	+	2	Muscular	-	-
12	67	F	+	+	6	-	-	-	+	1	Spleen	-	-
13	39	F	-	+	3	-	+	+	+	1	Anterior uveitis, liver	-	+
14	53	F	+	+	5	-	+	+	+	1	-	-	-
15	27	F	-	+	2	+	+	+	+	1	-	-	-
16	30	F	+	-	9	+	-	+	+	0	Liver	+	-
17	55	F	+	-	7	-	+	N/A	+	1	-	-	-
18	50	F	+	+	4	-	-	+	+	3	-	+	+
19	51	F	-	-	1	-	+	+	+	1	-	-	-
20	57	F	-	-	3	+	-	N/A	+	1	-	-	-
21	58	M	-	+	6	-	-	+	+	2	-	+	+
22	66	F	+	-	6	-	-	-	+	0	Oral mucosa, conjuctival	-	-
23	53	F	+	+	6	-	-	-	+	3	-	-	-
24	50	F	+	+	4	N/A	-	+	+	1	-	-	-
25	58	F	-	+	6	+	+	+	+	1	Liver	-	-
26	61	F	+	-	5	+	-	-	-	1	Neurosarcoidosis, posterior uveítis, conjunctival	+	+
27	22	M	+	+	6	-	-	+	+	2	Liver, spleen	-	-
28	44	F	+	+	5	-	+	+	+	1	-	-	-
29	58	M	+	+	15	-	-	-	+	2	Liver	+	+
30	43	F	-	+	23	-	-	+	+	2	-	-	-
31	53	M	+	+	12	-	-	+	+	2	-	-	-
32	49	F	+	+	6	-	-	+	+	2	-	N/A	+
33	46	M	-	+	10	-	-	-	+	1	Liver	N/A	-
34	29	F	-	+	1	-	-	-	-	2	Salivary gland, conjunctival	+	+
35	38	F	+	+	4	-	-	-	+	0	Conjunctival	N/A	-
36	68	F	-	+	3	+	+	-	+	1	-	-	-

N/A, not available

Table 2. Data of the patients with papules on the knees and sarcoid granulomas in whom the diagnosis of systemic sarcoidosis could not be confirmed during follow-up

Nº	Age	Sex	Bilateral	Linear	Duration lesions (months)	Recurrent	EN	Foreign bodies
1	51	M	-	+	6	-	-	+
2	66	F	+	-	6	N/A	-	-
3	31	F	+	+	9	-	-	+
4	72	F	-	+	5	-	+	+
5	60	F	+	+	8	-	-	+
6	43	F	+	+	10	-	-	-
7	37	F	+	+	6	+	-	-
8	54	F	+	+	12	-	-	-
9	53	F	-	-	N/A	-	-	-
10	52	F	-	-	9	-	-	-
11	59	F	-	+	9	-	-	+
12	56	F	+	+	3	+	-	-
13	59	F	-	+	6	N/A	-	+
14	48	F	-	+	3	-	+	-
15	42	M	-	+	5	-	-	+
16	47	F	+	+	7	+	-	-
17	50	F	+	-	4	N/A	-	+

N/A, not available

tients, the easy accessibility of papular sarcoidosis of the knees allows for histological confirmation of the disease avoiding invasive diagnostic procedures. Moreover, physical examination of patients with EN should include inspection of the knees to detect possible underlying sarcoidosis.

Papular lesions of the knees and histopathologically sarcoid granulomas in which the diagnosis of systemic sarcoidosis cannot initially be confirmed should be considered as a sarcoid reaction limited to the skin. However, patients should be clinically followed up to detect the possible involvement of other organs and to confirm the diagnosis of sarcoidosis.

In summary, papular sarcoidosis of the knees may be considered a relatively frequent form of cutaneous involvement in systemic sarcoidosis with prognostic significance. It is mainly observed in acute forms of sarcoidosis and can be considered a sign of good prognosis. Moreover, papular sarcoidosis of the knees is usually present at the beginning of the disease and can be useful for the diagnosis of sarcoidosis.

References

1. Hunninghake GW, Costabel U, Ando M, et al. ATS/ERS/WASOG Statement on sarcoidosis. Sarcoidosis, Vasc, Diffuse Lung Dis 1999;16:149-73 / Am J Respir Crit Care Med. 1999; 160: 736-55.
2. Mañá J, Marcoval J, Graells J, Salazar A, Peyrí J, Pujol R. Cutaneous involvement in sarcoidosis. Relationship to systemic disease. Arch Dermatol 1997; 133: 882-888.
3. Marcoval J, Moreno A, Mañá J. Papular sarcoidosis of the knees: a clue for the diagnosis of erythema nodosum-associated sarcoidosis. J Am Acad Dermatol 2003; 49: 75-8.
4. Choi HJ, Oh SH, Chang SE, Moon KC. Papular sarcoidosis limited to the knees: a clue for systemic sarcoidosis. Int J Dermatol 2006; 45: 169-70.
5. Pitarch G, García-Melgares ML, Martínez A, Febrer I. Sarcoidosis cicatrizal y sarcoidosis popular de las rodillas. Piel 2006; 21: 111-112.
6. Judson MA, Baughman RP. How many organs need to be involved to diagnose sarcoidosis?: An unanswered question that, hopefully, will become irrelevant. Sarcoidosis Vasc Diffuse Lung Dis 2014; 31: 6-7
7. Kim YC, Triffet MK, Gibson LE. Foreign bodies in sarcoidosis. Am J Dermatopathol 2000; 22: 408-412.
8. Marcoval J, Mañá J, Moreno A, Gallego I, Fortuño Y, Peyrí J. Foreign bodies in granulomatous cutaneous lesions of patients with systemic sarcoidosis. Arch Dermatol 2001; 137: 427-30.
9. Walsh NMG, Hanly JG, Tremaine R, Murray S. Cutaneous sarcoidosis and foreign bodies. Am J Dermatopathol 1993; 15: 203-207.
10. Val-Bernal JF, Sanchez-Quevedo MC, Corral J, Campos A. Cutaneous sarcoidosis and foreign bodies. An electron probe roentgenographic microanalytic study. Arch Pathol Lab Med 1995; 119: 471-474.

11. Marcoval J, Mañá J, Rubio M. Specific cutaneous lesions in patients with systemic sarcoidosis: relationship to severity and chronicity of disease. Clin Exp Dermatol 2011; 36: 739-44.
12. Sharma OP. Cutaneous sarcoidosis: clinical features and management. Chest 1972; 61: 320-325.
13. Veien NK, Stahl D, Brodthagen H. Cutaneous sarcoidosis in caucasians. J Am Acad Dermatol 1987; 16: 534-540.
14. Hanno R, Callen JP. Sarcoidosis: a disorder with prominent cutaneous features and their interrelationship with systemic disease. Med Clin North Am 1980; 64: 847-866.
15. Olive KE, Kataria YP. Cutaneous manifestations of sarcoidosis: relationship to other organ systemic involvement, abnormal laboratory measurements, and disease course. Arch Intern Med 1985; 145: 1811-1814.
16. Callen JP. Relationship of cutaneous sarcoidosis to systemic disease. Clin Dermatol 1986; 4: 46-53.
17. James DG. Dermatological aspects of sarcoidosis. QJM 1959; 28: 109-124.