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Recurrence of Löfgren's syndrome 32 years later. A case report and review of the literature

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To the Editor

The most typical form of acute sarcoidosis is Löfgren's syndrome (LS), characterized by the association of erythema nodosum and/or periarticular ankle inflammation with bilateral hilar lymphadenopathy (BHL). LS is usually a self-limiting disease and commonly resolves spontaneously within the first year (1,2). Recurrence of sarcoidosis following complete remission without treatment and after a prolonged time of inactivity is a very unusual clinical event. It has been described to be more frequent in patients with LS, and only a few cases have been reported in the literature (3-6). Herein, we report an additional case of a patient with recurrence of LS 32 years after the initial presentation, which is, to our knowledge, the longest disease-free interval for a recurrence reported in the literature.

In March 1984, a 23-year-old woman was admitted to our hospital because of a 3-week history of erythema nodosum. A chest radiograph showed right paratracheal and BHL and gallium-67 lung scan showed a lambda pattern. Pulmonary function tests and serum angiotensin-converting enzyme (SACE) level were within the normal range. The tuberculin skin test (PPD, 5TU) was negative. A muscle biopsy showed the presence of non-caseating epithelioid granulomas consistent with sarcoidosis. Thus, the patient was diagnosed with LS. Erythema nodosum disappeared with non-steroidal anti-inflammatory drugs and mediastinal lymphadenopathy was resolved in 6 months without treatment. From 1984 to 2016, the patient remained asymptomatic and in several controls the chest radiograph was normal. In April of 2016, the patient presented again with erythema nodosum and periarticular ankle inflammation. A chest radiograph showed BHL, which was confirmed by thoracic CT. Pulmonary function tests and SACE level were within the normal range. A diagnosis of recurrent LS was performed. Erythema nodosum did not improve under treatment with non–steroidal anti-inflammatory drugs. Prednisone, 30 mg daily, were administered resulting in a prompt disappearance of symptoms. Prednisone was tapered and discontinued 3 weeks later. In October 2016, the chest radiograph showed complete remission of BHL.

Recurrence of sarcoidosis, defined as the reappearance of disease following complete spontaneous remission without treatment is extremely unusual. Recurrence after complete remission has to be differentiated from relapse, which means recrudescence of latent disease during the reduction of corticosteroid dose or within few months after the suppression of treatment (7). Recurrent sarcoidosis has been described to be more frequent in Löfgren's than in non-LS patients. In this article, we report a patient with LS who, after a spontaneous remission, presented a recurrence of LS 32 years later. To our knowledge,

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Table 1. Recurrence of Löfgren's syndrome in the literature. Adapted from Mañá, et al 2003.

Author/ Year	Age/ Gender	Presentation/Recurrence/ CXR stage/Extrathoracic involvement/Positive biopsy	Time of active /inactive disease	Time of follow-up (months)
Löfgren 1953	35/F	P/1/Constitutional symptoms	3/ 12	
		R1/1/EN/Lung, bronchial mucosa	4/12	35
		R2/1/EN, scar sarcoidosis	4/-	
Symmons 1980	46/M	P/2/Asymptomatic	Several months/108	
		R1/1/EN, scar sarcoidosis, constitutional symptoms/Skin	4/-	120
MacFarlane 1981	36/F	P/1/EN	19/187	
		R1/2/EN/Skin	25/18	258
		R2/2/EN	9/-	
Johard 1993	24/F	P/2/EN/Mediastinal lymph node	24/61	
		R1/2/EN	11/-	96
	51/F	P/1/EN, scar sarcoidosis/Skin	7/20	
		R1/2/EN, scar sarcoidosis, cough	11/30	68
		R2/2/EN, scar sarcoidosis, cough	NR/-	
	40/M	P/1/EN/Kveim	24/12	
		R1/0/EN, skin papules/Skin	12/6	108
		Relapse/2/EN, skin papules	54/-	
Mañá 2003	39/F	P/2/EN	12/45	
		R1/2/EN, skin papules, sc nodules/Skin, Kveim	6/43	282
		R2 /2/Subcutaneous nodules/Skin	6/148	
		R3/2/EN, skin papules/Skin	12/10	
	57/F	P/2/EN/Gastrocnemius muscle	12/54	
		R1/2/EN	4/32	
		R2/1/EN	6/89	213
		R3/1/EN, skin papules/Skin	4/12	
	53/F	P/1/EN/Liver	4/10	
		R1/0/Status epilepticus/Kveim	3/67	136
		Relapse/1/EN	4/36	
		R2/1/EN	8/4	
	34/F	P/2/EN/ Gastrocnemius muscle, Kveim	14/96	
		R1/2/Cutaneous plaques/Skin	24/23	253
		R2/1/Cutaneous plaques, asthenia, CNS involvement/Skin	96/0	
	25/F	P/2/EN/ Gastrocnemius muscle	12/52	
		R1/1/EN	6/40	120
		R2/1/EN	3/7	
	24/F	P/1/Periarticular ankle inflammation	4/39	
		R1/0/Cutaneous plaques/Skin	3/12	58
	47/F	P/1/EN/Kveim	8/17	
		R1/1/EN, skin papules/Skin	3/32	60
	38/F	P/1/EN/Scalene lymph node	12/168	
		R1/1/EN, scar sarcoidosis/Skin	12/14	206
	21/F	P/1/EN/Liver	6/223	
		R1/0/Scar sarcoidosis/Skin	5/16	250
	29/F	P/1/EN/Kveim	6/49	
		R1/1/EN, skin papules/Skin	3/12	70
	49/F	P/1/EN	6/50	
		R1/1/EN, skin papules/Skin	6/6	68
	51/F	P/1/EN	15/30	
		R1/1/EN, skin papules/Skin	4/12	61
	39/F	P/1/EN	3/54	
		R1/ EN	3/12	72
	44/F	P/1/ EN/Scalene lymph node	8/58	
		R1/1/EN	4/109	179
	37/M	P/1/EN	10/159	
		R1/1/EN	6/6	181
	27/F	P/1/EN	8/42	
		R1/1/EN, skin papules/Skin	2/-	52

Gender: F (female)/ M (male).P= Presentation. R1= 1 st recurrence. R2=2nd recurrence. R3= 3rd recurrence. CXR: Chest radiograph. EN=Erythema nodosum.

this case constitutes the longest disease-free interval of recurrent sarcoidosis reported so far. Very few cases of recurrence of LS have been reported in the literature (table 1). Löfgren (1), in his series of 212 patients, reported one patient that presented with constitutional symptoms, and recurred twice as LS respectively 12 and 30 months after the initial presentation. Symmons and Woods (3), described a case that presented as asymptomatic stage 2 on chest radiograph and recurred with LS 10 years later. McFarlane (4), reported another patient with three episodes of LS, in an overall period of 21 years. Johard and Eklund (5), described three patients with LS, one patient with one recurrence and two patients with two, all as LS, that occurred in a period between 6 and 9 years. In 2003, our group conducted a previous study to evaluate recurrent sarcoidosis in a cohort of 472 patients. We observed 17 patients suffering from 24 recurrences. All the patients but one presented with LS, and 17 out of 24 episodes of recurrence were as LS as well. The disease-free interval without treatment ranged from 10 months to 17 years (6).

LS usually has a good prognosis, with complete remission within two years in more than 90% of cases (2,8). However, in some cases the disease may become chronic or may recur many years later (1,2). LS has been reported to be more frequent in white young women from the northern European countries, Ireland and Spain, whereas it is uncommon in the black race (2). These differences may be related to genetic factors. In European studies, HLA-DRB1*0301 haplotype and CCR2 chemokine receptor gene were identified as genetic risk factors for LS and predictors of good prognosis (9,10). Although LS can occur at any time of year, a seasonal cluster has been described in the spring months, suggesting that an environmental factor may play a role in the etiology of the disease (2). Therefore, the interrelation between genetic host susceptibility and environmental factors that may act as a trigger of the disease is crucial in the development of sarcoidosis. We hypothesized that a re-exposure to or re-infection by an extrinsic antigen might precipitate the phenomena of recurrence in individuals genetically predisposed to LS. A flare-up of LS 32 years after the initial presentation strongly reinforces this hypothesis.

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