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Stage IV sarcoidosis: comparison of survival with the general population and causes of death

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ABSTRACT: The objectives of this study were to compare the survival of sarcoid patients with pulmonary fibrosis with that of the general population and to determine the causes of death and the incidence of evolutive complications.

This retrospective cohort included 142 sarcoid patients in radiographic stage IV (74 males; mean±SD age 48.1±12 yrs). Their survival was compared with that of the general French population, matched for the year and age at diagnosis of stage IV disease, sex and length of follow-up. Expected survival probabilities were calculated year-by-year on the basis of probabilities provided by official demographic data for France. Survival curves were based on the Kaplan–Meier method and compared using the log-rank test.

During the follow-up period (7.1±4.8 yrs), pulmonary hypertension (PH) was observed in 29.7% of cases and aspergilloma in 11.3%. Long-term oxygen therapy was required in 12%. Survival was 84.1% at 10 yrs, which was worse than for the general population (p=0.013). 16 (11.3%) patients died from the following causes: refractory PH (n=5), chronic respiratory insufficiency (n=4), acute respiratory insufficiency (n=2), haemoptysis due to aspergilloma (n=1), heart sarcoidosis (n=1), nocardiosis (n=1) and unknown causes (n=2).

Survival is significantly decreased in stage IV patients. 75% of fatalities are directly attributable to respiratory causes.

KEYWORDS: Mortality, prognosis, pulmonary hypertension, sarcoidosis, stage IV

Although sarcoidosis is generally viewed as a benign disease, its prognosis is highly disparate according to ethnic and genetic factors, initial presentation, organ involvement, and patient source [1–4]. The course is chronic in about a third of cases, with a substantial proportion of patients sustaining permanent sequelae in relation to the development of fibrosis (pulmonary and extrapulmonary) [1, 2]. Up to 9.7% of patients will eventually die from sarcoidosis [1, 2, 4–15]. According to the chest radiographic classification of sarcoidosis, stage IV designates overt pulmonary fibrosis, as judged by the presence of distortion with hilar retraction, bullae, cysts, honeycombing and emphysema [1]. Stage IV is observed in 4.7–15% of patients at presentation [4, 6, 7, 14, 16]. In Europe and the USA, deaths ascribed to sarcoidosis are usually the result of respiratory failure and, less frequently, cardiac or central nervous system involvement [1, 2, 4–7, 10, 14, 17, 18], and stage IV is associated with a worse survival rate [3].

Little has been published on morbidity and mortality resultant from sarcoidosis with pulmonary fibrosis. First, the overall excess of fatalities in sarcoid patients is marginal compared with the general population [18, 19], but no information is available for the subgroup of patients with pulmonary fibrosis. Secondly, the causes of death of these patients are unclear, as is the incidence of complications, such as pulmonary hypertension (PH) and mycetoma formation. Lastly, the benefit of treatment remains uncertain in such a context.

The primary aim of the study was to compare the survival of a large French cohort of sarcoid patients with pulmonary fibrosis with a matched general population. Other objectives were to assess 1) the causes of mortality, 2) the incidence of complications, 3) the effect of therapy and 4) the long-term evolution of pulmonary function.

PATIENTS AND METHODS

This retrospective study received institutional review board approval (Comité de Protection des Personnes ''Ile-de-France X'', Aulnay-sous-Bois, France) and the requirement for informed consent was waived. The study was conducted in a pneumology tertiary care

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centre specialising in sarcoidosis. Sarcoid patients are usually referred to our department for clinical evaluation and/or therapeutic advice. Chest radiography is systematically performed at first admission and then usually repeated every 3–6 months until recovery. In our department, patients with stage IV disease are listed in a database. These patients were reviewed by three of us (A. Nardi, F. Girard and H. Nunes).

Inclusion criteria were as follows: 1) sarcoidosis diagnosis according to the American Thoracic Society (ATS)/European Respiratory Society (ERS)/ World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) statement [1] and 2) radiographic stage IV either at first admission or during follow-up [1]. Chest radiographs were analysed by consensus by one clinician (A. Nardi) and one radiologist (M. Brauner), both of whom are highly experienced in interstitial lung diseases. Stage IV was defined by patent advanced fibrosis with evidence of upper lobe volume loss with hilar retraction with or without masses, coarse linear bands, honeycombing, bullae and emphysema.

Entry in the study (inclusion) was the date of the first evaluation in our department with a chest radiograph demonstrating stage IV. At inclusion, the 142 patients included underwent a full work-up comprising serum angiotensin-converting enzyme (SACE) (n=129), spirometry (n=133), diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) (n=118), room-air blood gases (n=126), high-resolution computed tomography (HRCT) (n=132), bronchoalveolar lavage (BAL) (n=45) and Doppler echocardiography (n=58). During follow-up, patients were followed up with regular visits and investigations at time intervals depending on clinical requirements. During follow-up, 111 patients underwent at least one Doppler echocardiography. PH was defined by an estimated systolic pulmonary artery pressure of >40 mmHg.

The functional effect of therapy was evaluated within 3–12 months for 95 patients, who had their sarcoidosis therapy significantly intensified after inclusion. Improvement was defined as an increase of $\geqslant$10% in % predicted forced vital capacity (FVC) or $\geqslant$15% in $D_{L,CO}$ % predicted from initial values and worsening as a decrease of >10% in FVC or >15% in $D_{L,CO}$. Long-term evolution of pulmonary function tests (PFTs) was evaluated from the test at inclusion to the last available performed test $\geqslant$=12 months after (n=115 for spirometry and n=100 for $D_{L,CO}$).

Statistical analyses were performed using SAS software version 8.1 (SAS Institute Inc., Cary, NC, USA). Data are presented as percentages or as mean$\pm$SD (range). Patients who improved under therapy were compared with those who did not improve using the Chi-squared test or Fisher's exact test for categorical variables, and the unpaired t-test for continuous variables.

Information regarding vital status and causes of death was obtained by reviewing medical records, and by contacting the referral physician and general practitioner. Survival was calculated from inclusion until the end of the follow-up period. Transplanted patients were censored at the date of transplantation. Univariate analysis based on the proportional hazards model was used with the log-rank test. For continuous variables, we chose to divide patients into two groups, one on each side of the median value. All significant parameters were entered into the multivariate Cox proportional hazards model. Results are reported as hazard ratios (HRs) and 95% confidence intervals (CIs).

Survival of patients was compared with the expected survival of the French general population. For that purpose, we used a model constructed according to the stochastic Monte Carlo method [20–22]. Each virtual control (general population) resulted from a random drawing repeated 1,000 times for a final state of living or deceased using the values of survival probability for each year for a given age and sex. Each virtual control was matched with a patient of our cohort of 142 persons, for the same year and age at diagnosis of stage IV, same sex and same length of follow-up. A computer program was designed using Visual Basic (Microsoft® Corp., Redmond, WA, USA). Expected survival probabilities were calculated year-by-year on the basis of probabilities published by the Institut National de la Statistique et des Etudes Economiques (demographic data in France) [23]. Survival curves were based on the Kaplan–Meier method and compared using the log-rank test. For all statistical analyses, $p<0.05$ was considered significant.

RESULTS

Patient characteristics

Among 264 patients identified in the database between April 1986 and May 2006, 142 met the inclusion criteria and 122 were excluded (incomplete medical record: n=37; other radiographic stage after review: n=27; no histological confirmation: n=49; other granulomatous disorder: n=9). The population included 74 males and 31.7% of subjects were black; subjects were mean$\pm$SD 42.3$\pm$13 yrs of age at initial diagnosis of sarcoidosis and 48.1$\pm$12 yrs of age at inclusion. Patients' clinical characteristics are summarised in table 1. PFT findings are presented in table 2. Only four patients showed normal spirometry and $D_{L,CO}$. $D_{L,CO}$ was reduced (<80% pred) in 91.5% of cases. A restrictive pattern (total lung capacity (TLC) <80% pred) was observed in 63.2% of cases, an obstructive pattern (forced expiratory volume in 1 s (FEV_1)/FVC <70%) in 36.1% and a mixed pattern in 19.5%. The results of HRCT, SACE and BAL are presented in table 2.

Complications

Doppler echocardiography was available for 58 patients at inclusion and 15 (25.9%) of them had PH, as defined by an estimated systolic pulmonary artery pressure of >40 mmHg. During the follow-up period, at least one Doppler echocardiography was performed in 111 patients, of whom 33 (29.7%) had PH. Aspergilloma was observed in 16 (11.3%) patients at some point during follow-up. Aspergilloma was defined as a typical fungus ball on HRCT and/or the evidence of a pulmonary cavitary lesion together with *Aspergillus* spp. growth in one respiratory specimen and the presence of precipitins evidenced by immunoelectrophoresis. 10 patients developed both PH and aspergilloma. Pneumothorax occurred in 12 (8.5%) patients and relapsed for four patients. Other complications included tuberculosis (10 patients), *Mycobacterium kansasii* or *Mycobacterium avium* infection (three patients), pneumonia (10 patients), pulmonary embolism (eight patients) and acute respiratory failure requiring admission to an intensive care unit (eight patients). Notably, none developed bronchial carcinoma.

TABLE 1 Clinical characteristics of patients with radiographic stage IV disease

Subjects n	142
Demography[#]	
Males/females	74 (52.1)/68 (47.9)
Age yrs	48.1±12 (15.4–73.7)
Caucasian/black/others	92 (64.8)/45 (31.7)/5 (3.5)
Non-smokers/ex- or current smokers	87 (61.3)/55 (38.8)
Smoking exposure pack-yrs	16.1±14.5 (1–60)
Clinical symptoms[#]	
NYHA functional class I/II/III/IV	19 (13.4)/69.7 (99)/ 13.4 (19)/3.5 (5)
Cough	73 (51.4)
Sputum	26 (18.3)
Haemoptysis	4 (2.8)
Crackles	40 (28.2)
Wheezing	8 (5.6)
Digital clubbing	9 (6.3)
Duration of sarcoidosis yrs	5.8±6.2 (0–27)[+]
Extrarespiratory involvement of sarcoidosis[¶]	
Presence of any type of involvement	106 (74.6)
Median number of involved organs (range)	2 (0–6)
Presence of severe manifestations	44 (31)[§]

Data are presented as n (%) or mean±SD (range), unless otherwise stated. NYHA: New York Heart Association. [#]: at first evaluation with radiographic stage IV; [¶]: at some point of sarcoidosis course; [+]: 39 (27.5%) patients were diagnosed simultaneously with sarcoidosis and radiographic stage IV disease; [§]: severe extrarespiratory manifestations included ophthalmic localisation unresponsive to local therapy in 24 patients, heart involvement in 23, central nervous system involvement in seven and hypercalcaemia in one.

TABLE 2 Pulmonary function tests, serum angiotensin-converting enzyme (SACE), high-resolution computed tomography (HRCT) and bronchoalveolar lavage (BAL) findings at first evaluation with radiographic stage IV disease

Spirometry[#]	
FEV1 mL	1921±631 (660–3520)
FEV1 % pred	63.9±20.7 (21–114)
FEV1/FVC %	73.4±14 (34–99)
FVC mL	2672±857 (740–5330)
FVC % pred	71.6±22.4 (23–137)
TLC mL	4232±1049 (1510–7460)
TLC % pred	73.8±18.6 (34–116)
***D*L,CO**[¶]	
*D*L,CO % pred	56.2±17.8 (18–101)
*K*CO % pred	81.5±20 (31–135)
Room-air blood gases[+]	
P_{a,O_2} mmHg	79.4±11.7 (42–111)
P_{a,CO_2} mmHg	39.7±5.2 (30–79)
SACE level[§]	
⩽1 ULN	52 (40.3)
>1 and ⩽2 ULN	40 (31)
>2 ULN	37 (28.7)
HRCT pattern of fibrosis[ƒ,##]	
Bronchial distortion	85 (64.4)
Linear	27 (20.5)
Honeycombing	15 (11.4)
Unclassified	5 (3.8)
BAL	
Total cell count cells·mm^{-3}	442±62 (28–4000)
Lymphocytes %	29±19.9 (1–73.4)
Lymphocytosis >15%	29 (64.4)
Neutrophils %	16.9±23.8 (0–96)
Eosinophils %	1±1.4 (0–7)

Data are presented as mean±SD (range) or n (%). FEV1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; TLC: total lung capacity; *D*L,CO: diffusing capacity of the lung for carbon monoxide; *K*CO: transfer coefficient of the lung for carbon monoxide (*D*L,CO/alveolar volume); P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension; ULN: upper limit of normal. [#]: n=133; [¶]: n=118; [+]: n=126; [§]: n=129; [ƒ]: HRCT pattern of pulmonary fibrosis according to ABEHSERA *et al.* [24]; [##]: n=132.

Outcome and mortality

Patients were followed for a mean±SD period of 7.1±4.8 yrs after inclusion with a follow-up ⩾5 yrs for 59.7% of patients and ⩾10 yrs for 25.2%. At some point during the course of the disease, 94.4% of patients were given corticosteroids and 37.3% at least one immunosuppressant, while 12% were put on long-term oxygen therapy. At their last visit, 30 (21.1%) patients were no longer receiving specific treatment for sarcoidosis and ''remission'' was noted in 27 (19%) patients. ''Remission'' from sarcoidosis referred to patients with no signs of active extra-respiratory disease, stability on PFTs and chest radiographs, and no relapse during a ⩾6-month observation period without any treatment.

At the end of the study, six patients were lost to follow-up, 122 were alive, five received lung transplants and 16 (11.3%) were dead. By contrast, only four deaths were expected in the general population. Survival was 91.5% at 5 yrs, 84.1% at 10 yrs and 78.1% at 15 yrs, which was significantly poorer than for the general population (HR 3.6, 95% CI 2.9–4.3; p=0.013) (fig. 1).

Fatalities occurred mean±SD (range) 11.9±5.9 (2.6–25.5) yrs after the diagnosis of sarcoidosis and 5.3±3.6 (0.5–14.3) yrs after inclusion, in patients 55.2±12.3 (40.7–82.1) yrs of age. Mortality was caused by refractory PH (five patients), chronic respiratory insufficiency (four patients), acute respiratory insufficiency (unexplained in one patient and as a consequence of lobectomy for aspergilloma in the other) and massive haemoptysis due to aspergilloma (one patient). One patient with severe heart sarcoidosis died of cardiorespiratory failure after the reconstruction of colic continuity. Another patient with moderate PH died of disseminated nocardiosis while receiving corticosteroids and methotrexate. Two patients died of unknown causes.

Univariate analysis

The following parameters at inclusion were significantly associated with a higher risk of death: New York Heart Association (NYHA) functional class (p=0.003), FEV1 <63% pred (p=0.02), FVC <72% pred (p=0.002), TLC <74% pred (p=0.001), *D*L,CO <58% pred (p=0.01) and room-air arterial oxygen tension (P_{a,O_2}) <81 mmHg (p<0.0001) and the presence of PH (p<0.0001). Age (p=0.12), sex (p=0.08), ethnicity (p=0.40), digital clubbing

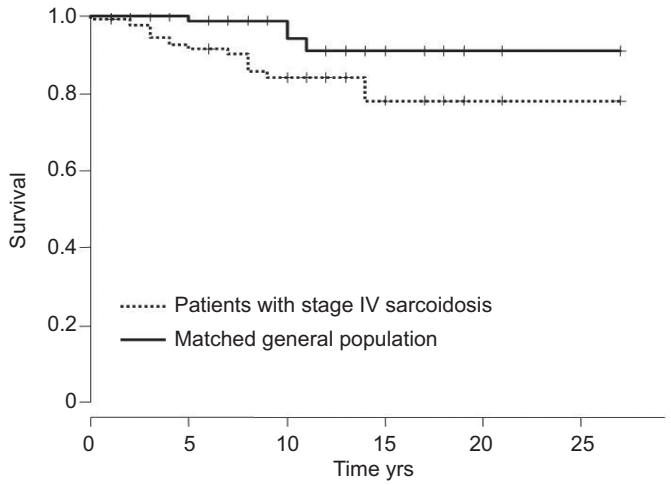

FIGURE 1. Comparison of survival between patients with radiographic stage IV disease and a matched French general population (n=142). Survival of patients was calculated from the date of first evaluation with radiographic stage IV until the end of the follow-up period. +: censored patients. p=0.013.

(p=0.13) and HRCT pattern (p=0.39) were not linked with mortality.

Multivariate analysis

The only independent predictive indicator of mortality was PH (HR 8.2, 95% CI 2.1–31.6; p=0.002).

Effect of therapy

95 (67.4%) patients had their sarcoidosis therapy significantly intensified after inclusion. Treatment consisted of: the initiation or re-introduction of systemic corticosteroids in 39 cases, methotrexate in nine cases, hydroxychloroquine in six cases and azathioprine in one case; an increase of corticosteroid dosage by >10 mg in 19 cases; and the addition of methotrexate to the treatment of 10 patients, hydroxychloroquine in five cases, azathioprine in four cases, thalidomide in one case and mycophenolate mofetil in one case. Evaluation of PFTs within 3–12 months of therapy was available in 57 patients. HRCT (51 patients), SACE (52 patients) and BAL (25 patients) were performed before the initiation of therapy. The recorded outcomes were: improvement (36.8%), stability (50.9%) and worsening (12.3%). Patients who improved were similar to those who did not improve in terms of age, sex, ethnicity, baseline FVC and $D_{L,CO}$, frequency of HRCT honeycombing pattern, increased SACE (15 out of 18 patients who improved *versus* 23 out of 34 of those who did not improve; p=0.376) or alveolar lymphocytosis of >15% (seven out of nine patients who improved *versus* 12 out of 16 patients who did not improve; p=1). The only significant difference between groups was the shorter duration of sarcoidosis before the initiation of therapy in patients who improved under therapy (mean±SD 5.5±5.2 *versus* 9±6.5 yrs; p=0.04).

Long-term functional evolution

Long-term spirometry and $D_{L,CO}$ were available for 115 and 100 patients, respectively, with a mean±SD (range) interval time of 6.2±4.4 (1–20.7) yrs between PFTs. In order to control for the high variability of this interval, the annual variation of FVC and $D_{L,CO}$ was calculated. The variation of FVC was 1.4±6.4 (-18.6–23.4)% predicted per yr and the variation of $D_{L,CO}$ 0.5±9.1 (-36.2–33.9)% pred per yr. At their last visit, PFTs were better in 39.3% of patients, stable in 35.9% and worse in 24.8%.

DISCUSSION

This study reports the largest cohort that deals with the morbidity and mortality of sarcoidosis with pulmonary fibrosis. The main results were as follows: 1) affected patients face a significantly decreased survival, as compared with the general population; 2) mortality is related to respiratory causes in 75% of cases; and 3) morbidity is frequent and often serious. However, 36.8% of patients improved under therapy and despite a highly variable change in individual patients, there was a trend toward stability in long-term pulmonary function.

Despite pulmonary fibrosis being well known to be the major prognostic factor of sarcoidosis in Western countries, the survival of this subgroup of patients has never been specifically estimated, particularly in relation to the general population. In our cohort with a mean±SD follow-up of 7.1±4.8 yrs, the mortality rate was 11.3% and survival was markedly poorer than that of the matched French general population. It is also important to underline that patients died relatively young, with a mean age of 55.2 yrs. Only two studies have previously compared the survival of sarcoid patients with a matched population [18, 19]. In the British study by GRIBBIN *et al.* [19] of 1,019 sarcoid patients identified from a general practice database, survival was significantly worse than for the general population, although the difference was small; however, neither cause-specific mortality nor the severity of sarcoidosis was detailed in that study. In the Danish series of 254 patients with intrathoracic sarcoidosis followed for a median duration of 27 yrs by VISKUM and VESTBO [18], 80 deaths were observed *versus* 65.5 expected, which represented a slight excess mortality during the first 20 yrs but not at the end of follow-up.

The causes of mortality of sarcoid patients with pulmonary fibrosis are unknown. In our study, 75% of patients with stage IV sarcoidosis died as a result of respiratory complications, with PH being directly responsible for mortality in 31.2% and chronic respiratory failure in 25%. Conversely, extrapulmonary sarcoidosis was a contributory cause of death in only one (6.2%) case with heart involvement and immunosuppressant therapy in another (6.2%) who succumbed to a serious infection.

Aspergilloma developed in 11.3% of patients and it was the direct or indirect cause of death in two (12.5%) patients. This complication has been reported in <3% of all sarcoid patients in retrospective series [25, 26]. In a prospective study, aspergilloma, as documented by the finding of serum precipitins or by chest radiograph and/or tomography, occurred in 31.2% of patients with stage III/IV disease (both categories were merged) during a 10-yr period [27]. The lower frequency observed in our study may reflect a more stringent diagnosis or differences in environmental factors.

30% of patients developed PH. PH affects 1–6% of sarcoid patients but it is much more frequent in advanced lung disease. It is well known that the majority of sarcoid patients with PH have evidence of stage IV disease on chest radiography [28, 29].

However, the exact prevalence of this complication in unselected patients with stage IV sarcoidosis has never been established. Indeed, the only available study was conducted by SHORR *et al.* [30] in the US transplant registry, where the reported prevalence was 73.8%. The lower prevalence in our cohort is probably related to differences in patient selection (nontransplant centre *versus* transplant centre) and the technique used for detection (Doppler echocardiography *versus* right heart catheterisation). In our cohort of unselected patients with pulmonary fibrosis, PH was the most robust correlate of mortality, with an 8.1-fold increase in risk of death, as in the study of SHORR *et al.* [31] that originated from a cohort of candidates for lung transplantation with end-stage pulmonary disease. Lung function was also found to be predictive of mortality on univariate analysis, which is consistent with prior studies, including for FVC [5], FEV_1 [18], TLC [18] and P_{a,O_2} [32].

The majority of our patients displayed signs of persistent activity of sarcoidosis, as suggested by increased SACE (59.7% of cases) and lymphocytosis on BAL (64.4% of cases). Interestingly, functional improvement was noted in 36.8% of treated patients. SACE levels and lymphocytosis failed to predict improvement; patients who improved differed from those who did not improve only in their shorter duration of sarcoidosis. In light of these findings, a trial of therapy is warranted early in all patients with pulmonary fibrosis. However, in the study, our treatment decision may have been influenced by the presence of residual activity or the existence of extrarespiratory manifestations, which creates a bias.

Our study had several limitations, mainly related to its retrospective and monocentric nature. First, our department is historically a referral centre for sarcoidosis and one may argue that our results do not apply to all patients with pulmonary fibrosis. This issue has long been debated as far as sarcoidosis is concerned and it is unavoidable. Conversely, our cohort is unique in that it is the largest in the setting of a nontransplant centre. Secondly, patients were not investigated systematically. It is therefore plausible that Doppler echocardiography had been prescribed for sicker patients. Thirdly, the interpretation of chest radiographs is subjective and it is virtually impossible to date the occurrence of stage IV sarcoidosis with precision. It is well-known that the Scadding staging system lacks reproducibility, as recently stressed by BAUGHMAN *et al.* [33]. In that study of 130 patients enrolled in an infliximab trial, there was only fair agreement between two expert radiologists in the original stage of the chest radiograph (weighted kappa 0.43, 95% CI 0.32–0.54). However, it is important to emphasise that the large majority of studies on the prognosis of intrathoracic sarcoidosis have used the Scadding staging system, chest radiography is an easy test to perform and not all sarcoid patients will undergo HRCT to assess pulmonary fibrosis. Fourthly, matching between cases and controls was made on the basis of age and sex, and did not take into account other confounders likely to interfere with mortality, such as smoking habits, ethnicity and socioeconomic status. Nevertheless, there is a well-known strong negative association between cigarette smoking and sarcoidosis [34]. The proportion of black patients was higher than in the French population at large, but ethnicity was not a predictor of mortality. All our patients were covered by health insurance. Finally, the results on predictors of mortality must be interpreted with caution as the number of events was small.

In conclusion, the survival of sarcoid patients with pulmonary fibrosis is significantly decreased, as compared with the general French population. Mortality is related to respiratory causes in a large majority of cases, mainly PH.

STATEMENT OF INTEREST

Statements of interest for M. Brauner and D. Valeyre can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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