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Predictive value of C-reactive protein and clinically relevant baseline variables in sarcoidosis

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Abstract. *Background:* This study aims to examine the predictive and prognostic implications of C-reactive protein (CRP) and clinically relevant baseline variables in determining treatment indication and disease progression in a large clinical cohort of patients with stable sarcoidosis. *Methods:* A retrospective observational study of 328 sarcoidosis patients attending a regional tertiary referral centre over a 26-year period was performed. Clinical, biochemical, radiological and physiological data were analysed according to a clinically relevant dichotomous cutpoint of CRP. Multiple models of logistic regression were used to determine independent predictors of outcome as defined by indication for treatment with corticosteroids, radiological deterioration and physiological progression. *Results:* 328/409 (80.2%) sarcoidosis patients had baseline serum CRP measured and were suitable for inclusion. Baseline CRP was elevated in 154 (47%). 178 (54.3%) were prescribed corticosteroid treatment during the disease course. Physiological deterioration was demonstrated in 48 (14.6%) patients and radiological progression in 59 (17.9%) patients. High baseline CRP was strongly associated with Lofgren's syndrome (p=<0.001) and reduced FVC% predicted (p=0.012). High CRP was found to be a negative predictor of radiological progression (p=0.046). In a sub-analyses of patients without Lofgren's syndrome (n=223), patients with high baseline CRP were almost twice as likely to receive corticosteroid treatment, OR 1.89 (95% CI 1.04-3.55). Low baseline DLCO% independently predicted the need for corticosteroid treatment (p=<0.001) and physiological decline (p=0.045). *Conclusions:* Elevated baseline CRP in sarcoidosis is associated with a good prognosis and is a negative predictive indicator of radiological progression. In patients without Lofgren's syndrome, high CRP and low DLCO% at presentation may identify a subset of patients more likely to develop physiological progression who may benefit from early systemic treatment. *(Sarcoidosis Vasc Diffuse Lung Dis 2016; 33: 331-340)*

Key words: sarcoidosis, C-reactive protein (CRP), predictive value, progression

Introduction

Sarcoidosis is a systemic, inflammatory, granulomatous disease of unknown aetiology (1). The prevailing hypothesis is that the disease occurs due to an altered or incomplete immune response to an autoantigen or granulomatous pathogen that is inhaled into the lung of genetically susceptible hosts (1). Sarcoidosis is associated with considerable phenotypic diversity with the potential for numerous sites of organ involvement and varying levels of disease activity, making severity and progression difficult to assess (2). Diagnosis relies on the presence of compatible clinical, radiological and histological findings with the exclusion of other well-known causes of granuloma formation (3). Adequate markers to determine

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predictors of treatment and disease progression in sarcoidosis are currently lacking (4).

C-reactive protein (CRP) is an acute-phase protein synthesised by hepatocytes in response to tissue damage or inflammation (5). CRP is a frequently used marker of inflammation in the clinical setting due to its feasibility and cost-effectiveness. Elevated CRP is a significant predictor of clinical response in a wide range of inflammatory conditions (6-9). In chronic obstructive pulmonary disease (COPD), high CRP is associated with poor lung function and smokers (10, 11). In sarcoidosis, baseline CRP is elevated in approximately 20-60% of patients (12, 13). The majority of studies assessing CRP in sarcoidosis have focussed on monitoring disease activity rather than predicting disease response (14, 15). One study investigating the prognostic value of baseline CRP in chronic sarcoidosis patients receiving immunomodulator therapy showed that patients with elevated baseline CRP had more severe disease than those with lower baseline levels. CRP was confirmed to be a predictor of response to immunosuppression in this patient cohort (16).

Few large-scale studies have looked at predictive indicators of treatment or disease progression in sarcoidosis since the introduction of CRP as a routine marker of inflammation (17-21). The present retrospective observational cohort study aims to provide this data using a comprehensive electronic database in a well-defined cohort of Irish sarcoidosis patients over a 26-year follow-up period. The primary study objective was to evaluate the utility and practical application of a single baseline serum CRP concentration in predicting the need for first-line treatment with corticosteroid therapy. The secondary objectives were to determine the utility of baseline CRP in predicting disease progression as defined by physiological deterioration and radiological progression, and to determine other prognostic factors that may be associated with a poorer outcome in sarcoidosis.

Methods

Study population

All patients with a confirmed diagnosis of sarcoidosis attending Galway regional tertiary referral centre between 1983 and 2009 were identified from the sarcoidosis database. The database holds information pertaining to numerous epidemiological and clinical parameters including gender, age at diagnosis, ethnic origin, symptoms at presentation, standard haematological, biochemical and bronchioalveolar lavage fluid (BALF) profiles, biopsy-confirmation and yield, extent of extra-pulmonary involvement, baseline and follow-up pulmonary function and radiological staging, systemic treatment received and follow-up duration.

The diagnosis of sarcoidosis was based on consistent clinical and radiological features with histological confirmation according to the American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and Other Granulomatous Disorders (ATS/ERS/WASOG) guidelines (22). Histological confirmation consisted of the presence of non-caseating granulomas on biopsy specimens of the pulmonary parenchyma, lymph nodes, skin, parotid glands or elsewhere.

Clinical features at initial presentation including symptoms of respiratory impairment, constitutional symptoms and extra-pulmonary manifestations (dermatological, ocular, rheumatologic, endocrine, cardiac and neurological involvement) were recorded. Baseline haematological and biochemical indices at presentation including haemoglobin (Hb), white cell count (WCC) and differential, platelets, bone profile, liver and renal function, erythrocyte sedimentation rate (ESR) and CRP were recorded. Serum angiotensin-converting enzyme (ACE) was not routinely recorded in this patient cohort due to previous studies suggesting a limited role in diagnosis and monitoring of sarcoidosis (23-25). Measurements of 24-hour urinary calcium and BALF CD4:CD8 ratio were also included where measurements were taken.

Pulmonary function tests (PFTs) were performed at presentation and subsequent follow-up visits allowing calculation of Forced Expiratory Volume (FEV1), Forced Vital Capacity (FVC), FEV1/FVC ratio, Total Lung Capacity (TLC) and the diffusion capacity for carbon monoxide (DLCO) using a Sensormedics V-Max 22 device. Values were expressed as percentage predicted for age, sex, and height employing European Respiratory Society (ERS) reference ranges. All PFTs were carried out by pulmonary physiologists trained according to the recommendations of the ERS (26).

Chest radiography (CXR) was performed in all patients at presentation, with each individual case reported by a consultant radiologist at the time of scanning, and subsequently scored by an individual respiratory physician according to modified Scadding criteria (17). The chest radiographs were classified as stage 0, no abnormality; stage 1, hilar adenopathy only; stage 2, hilar adenopathy and parenchymal abnormalities; stage 3, parenchymal abnormalities only; and stage 4, pulmonary fibrosis. Radiographs were repeated annually for the first three years with ongoing annual radiographs if disease progression was evident.

The extent of extrapulmonary involvement was defined by the ACCESS (A Case-Control aEtiologic Study of Sarcoidosis) assessment instrument which defines criteria for definite, probable and possible involvement of fifteen organs or organ systems (27). Individuals with definite or probable involvement, as defined by these criteria, were considered to have organ involvement at that site.

In terms of systemic corticosteroid therapy, the decision to treat patients was made by the consultant respiratory physician responsible for the individual patient based on the following clinical criteria: presence of disabling or distressing symptoms of sarcoidosis of the upper or lower respiratory tract; disfiguring cutaneous sarcoidosis unresponsive to topical steroid or chloroquine therapy; diffuse myalgia or arthralgia unresponsive to non-steroidal anti-inflammatory drug therapy; diffuse lymphadenopathy; ocular manifestations unresponsive to topical steroid therapy, and patients with cardiac or neurological involvement. Confirmation of symptoms was sought from physical examination, relevant imaging, PFTs and biochemical laboratory testing. However, radiographic findings, lung function, or biochemical markers alone were not sufficient indication for corticosteroid treatment in the absence of compelling symptoms.

Corticosteroid treatment was initiated at a dose equivalent to 20 mg of prednisolone daily; higher doses were used infrequently if lower doses were found to be inadequate. Steroid therapy was usually continued for approximately 1 year, followed by slow weaning over several months to the equivalent of 5 mg of prednisolone daily. Only when symptoms were stable with this dose was steroid therapy discontinued.

Evaluation of indication for treatment

Indication for treatment was defined as need for corticosteroid treatment throughout the duration of follow-up. First-line treatment with corticosteroids was deemed sufficient in line with general treatment consensus (12, 28). Patients receiving alternatives to corticosteroids were included up to the point of commencing second-line therapy. Subgroup analyses of patients receiving second-line immunosuppressive therapy was not performed due to small patient numbers.

Evaluation of disease severity

Pulmonary disease severity is usually evaluated by PFTs and chest radiography. However, previous studies have shown only a weak correlation between lung function and chest radiographic disease in sarcoidosis (22, 29). In this study, therefore, we performed separate analysis of physiological deterioration and radiological stage.

Physiological deterioration was defined as detection of a significant decline in PFT parameters as per Hunninghake criteria (defined according to Hunninghake criteria as >15% reduction in baseline FEV1% and/or >10% decline in baseline DLCO%) (30). Radiological progression was defined as increased Scadding stage with parenchymal involvement over follow-up. This was divided into three groups: patients who improved (A), patients who stayed the same (B) and patients who deteriorated (C) from baseline Scadding CXR stage.

Statistical analysis

Demographic variables and baseline characteristics were summarised by the arbitrarily and prospectively chosen dichotomous cutpoint of baseline serum CRP (<6 vs. >6 mg/dL). This cutpoint was chosen based on the normal range provided by our regional laboratory (Beckman Instruments Inc., Galway, Ireland), whereby values less than or equal to 6 mg/L are considered normal. This cutpoint has been used to assess predictive and prognostic implications of CRP in other chronic inflammatory diseases in Ireland (31).

Analyses were conducted using R software (version 2.12.0) and Minitab V16. Simple descriptive statistics of mean and standard deviation were used

for continuous data, and frequencies and percentages for categorical data. Comparisons between CRP groups were performed using t-tests for continuous variables and chi-squared tests for categorical variables. A p-value <0.05 was considered to be statistically significant.

Logistic regression models were fitted to determine if CRP was a good predictor of the primary and secondary outcomes. Variables with few patient numbers were excluded from analysis due to convergence problems in the logistic models. The full model with all presenting characteristics was fitted first and then stepwise logistic regression was performed to choose the most parsimonious set of predictors for the outcomes of interest. The odds ratio (OR), 95% confidence interval and p-value were computed for each of the presenting predictors.

The reporting of this observational study conforms to the recommendations of STROBE (32).

Results

328/409 (80.2%) of sarcoidosis patients had baseline CRP and were suitable for inclusion. Baseline and demographic variables of patients, stratified by CRP, are presented in table 1. Both groups were of similar size with no significant differences between age, gender, smoking status or follow-up duration. FEV1%, FVC% and DLCO% were significantly lower in the high CRP group indicating reduced lung function (p=0.035, 0.005 and 0.007 respectively). FEV1/FVC ratio was not statistically significant. A significantly higher proportion of Lof-

Table 1. Presenting clinical, physiological and radiological characteristics of sarcoidosis cohort stratified by baseline CRP level

	CRP<6	CRP>6	Total	p-value
n	175	153	328	
Male gender	89 (50.9)	77 (50.3)	166 (50.6)	0.924
Age in years, Mean (SD)	38 (12.6)	36.4 (11.6)	37.2 (12.2)	0.248
Lofgren's syndrome	45 (25.7)	60 (39.2)	105 (32.0)	**0.009**
Smokers	100 (57.5)	89 (58.2)	189 (57.6)	0.898
Serological markers, Mean (SD)				
ESR	15.2 (10.0)	26.5 (24.6)	20.4 (19.1)	**<0.001**
WCC	6.7 (2.1)	7.9 (3.2)	7.2 (2.7)	**<0.001**
Lymphocytes	1.2 (0.5)	1.3 (0.5)	1.2 (0.5)	0.351
Eosinophils	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.796
Platelets	268.9 (67.6)	313.0 (108.0)	289.4 (91.3)	**<0.001**
Lung function tests, Mean (SD)				
FEV1 %	93.5 (16.4)	89.2 (18.3)	91.5 (17.4)	**0.026**
FVC	99.6 (15.0)	94.6 (16.7)	97.3 (16.0)	**0.005**
FEV1/FVC	78.9 (8.3)	79.4 (9.2)	79.1 (8.7)	0.585
DLCO	87.9 (17.2)	82.9 (16.5)	85.6 (17.0)	**0.007**
Scadding chest radiograph staging				0.834
Stage 0	2 (1.1)	2 (1.3)	4 (1.2)	
Stage 1	100 (57.1)	78 (51.0)	178 (54.3)	
Stage 2	63 (36.0)	62 (40.5)	125 (38.1)	
Stage 3	8 (4.6)	8 (5.2)	16 (4.9)	
Stage 4	2 (1.1)	3 (2.0)	5 (1.5)	
Extrapulmonary features	55 (31.4)	35 (22.9)	90 (27.4)	0.083
Mean (SD) follow-up, months	57.6 (74.4)	58.6 (69.2)	58.1 (71.9)	0.907
n (%) treated with steroids	90 (51.4)	88 (57.5)	178 (54.3)	0.270
n (%) with Physiological Deterioration	50 (16.7)	50 (18.3)	48 (17.5)	0.718
n (%) with Radiological Progression				0.159
A	62 (35.4)	62 (40.5)	124 (37.8)	
B	74 (42.3)	71 (46.4)	145 (44.2)	
C	39 (22.2)	20 (12.9)	59 (17.9)	

ESR= erythrocyte sedimentation rate, WCC= white cell count, FEV1% = forced expiratory volume in 1 second, FVC = forced vital capacity, DLCO = diffusion lung capacity of carbon monoxide. A-p-value of <0.05 is considered statistically significant

gren's syndrome was noted in the high CRP group (p=0.009), suggesting high CRP is associated with this acute form of sarcoidosis.

Of the 328 patients in the study, 178 (54.3%) patients were prescribed corticosteroid treatment. 48 (14.6%) patients were found to have physiological deterioration. 124 (37.8%) patients had improved Scadding stage on further imaging, with no change in 145 (44.2%) patients and radiological progression in 59 (17.9%).

The full binary logistic model for baseline CRP with presenting characteristics is shown in table 2(a) and the stepwise regression model in table 2(b). Lofgren's syndrome and FVC% were the best explanatory factors of CRP levels (p=<0.001 and 0.012 respectively, table 2(a)). High baseline CRP was 1.4 to 3.9 times more likely to occur in the presence of Lofgren's syndrome, and patients with high baseline CRP were more likely to have reduced baseline FVC%.

BAL CD4:CD8 at presentation was only available in n=81 patients and was significantly associated with age at diagnosis, high WCC, low FVC% and low DLCO% (p=0.003, <0.001, 0.015 and 0.013). There were no significant associations with CRP or Lofgren's syndrome. High BAL CD4:CD8 was found to be significantly associated with need for corticosteroid treatment (p=0.028) but not with physiological or radiological progression.

Results of further logistic regression analyses looking at the primary and secondary outcomes of the study are summarised in tables 3, 4 and 5.

In terms of predicting indication for treatment with systemic corticosteroids, high Scadding CXR classification, low DLCO%, low FEV1% and extrapulmonary involvement at presentation were found to be the best set of presenting characteristics to predict need for corticosteroid treatment (p=0.013, 0.007, <0.001 and 0.018 respectively, table 3(b)). CRP was not found to be a significant predictor of treatment (p=0.531, table 3(a)).

Analyses of disease progression based on physiological deterioration showed reduced baseline DLCO% to be associated with an increased risk of pulmonary function decline (p=0.045, table 4(b)). CRP was not found to be a significant predictor of physiological deterioration (p=0.901, table 4(a)).

Smoking status, Lofgren's syndrome, CRP, ESR, FEV1% and baseline Scadding CXR were found to best predict radiological progression (p=0.028, 0.002, 0.046, 0.015, 0.038 and 0.008 respectively, table 5(b)). Interestingly, high CRP was noted to be a negative predictor of radiological progression with the odds on radiological deterioration significantly

Table 2. Results of logistic regression analyses according to CRP

Presenting characteristics	Regression coefficient			
	p-value	OR	95% CI	Significance
(a) Results of binary logistic regression analysis of all presenting characteristics with baseline serum CRP				
Age	0.541	0.99	0.97-1.01	NS
Lofgren's syndrome	**0.004**	2.26	1.29-3.95	S
FEV1%	0.774	1.00	0.98-1.03	NS
FVC%	0.134	0.98	0.95-1.01	NS
DLCO%	0.173	0.99	0.97-1.00	NS
Scadding chest radiograph staging				
1	0.429	0.36	0.03-4.5	NS
2	0.541	0.45	0.04-5.71	NS
3	0.637	0.52	0.04-7.74	NS
4	0.745	0.59	0.03-13.56	NS
Extrapulmonary involvement	0.348	0.78	0.46-1.32	NS
(b) Results of stepwise logistic regression analysis of presenting characteristics with baseline serum CRP				
Lofgren's syndrome	**<0.001**	2.31	1.40-3.81	S
FVC%	**0.012**	0.98	0.96-1.00	S
DLCO%	0.140	0.99	0.97-1.00	NS

FEV1% = forced expiratory volume in 1 second, FVC = forced vital capacity, DLCO = diffusion lung capacity of carbon monoxide. A-p-value of <0.05 is considered statistically significant.

Table 3. Results of logistic regression analyses for the primary outcome indication of systematic corticosteroid treatment

Presenting characteristics	Indication for treatment			
	p-value	OR	95% CI	Significance
(a) Results of binary logistic regression analysis of all presenting characteristics with systematic corticosteroid treatment				
Females	0.304	1.41	0.73-2.70	NS
Age	0.712	1.00	0.98-1.03	NS
Smokers	0.150	1.49	0.87-2.55	NS
Lofgren's syndrome	0.303	0.71	0.37-1.36	NS
CRP	0.531	0.83	0.47-1.48	NS
ESR	0.332	1.01	0.99-1.02	NS
WCC	0.275	1.07	0.95-1.19	NS
Haemoglobin	0.943	0.99	0.79-1.24	NS
Platelets	0.864	1.00	0.99-1.00	NS
FEV1%	0.061	0.97	0.94-1.00	NS
FVC%	0.820	1.00	0.96-1.03	NS
DLCO%	**0.042**	0.98	0.96-0.99	S
Scadding chest radiograph staging	**0.027**	1.93	1.08-3.45	S
Extrapulmonary involvement	**0.025**	1.98	1.09-3.62	S
(b) Results of stepwise logistic regression analysis of presenting characteristics and systematic corticosteroid treatment				
FEV1%	**<0.001**	0.96	0.95-0.98	S
DLCO%	**0.007**	0.98	0.96-0.99	S
Scadding chest radiograph staging	**0.013**	1.96	1.16-3.33	S
Extrapulmonary involvement	**0.018**	1.99	1.12-3.51	S

CRP = C-reactive protein, ESR= erythrocyte sedimentation rate, WCC= white cell count, FEV1% = forced expiratory volume in 1 second, FVC = forced vital capacity, DLCO = diffusion lung capacity of carbon monoxide. A-p-value of <0.05 is considered statistically significant.

Table 4. Results of logistic regression analyses for the secondary outcome of prediction of physiological deterioration

Presenting characteristics	Physiological deterioration			
	p-value	OR	95% CI	Significance
(a) Results of binary logistic regression analysis of all presenting characteristics with prediction of physiological deterioration				
Female	0.818	1.11	0.46-2.65	NS
Age	0.507	1.01	0.98-1.04	NS
Smokers	0.708	0.87	0.42-1.81	NS
Lofgren's syndrome	0.141	0.48	0.18-1.28	NS
CRP	0.901	0.95	0.44-2.06	NS
ESR	0.928	1.00	0.98-1.02	NS
WCC	0.419	1.06	0.92-1.23	NS
Haemoglobin	0.144	0.82	0.62-1.07	NS
Platelets	0.742	1.00	1.00-1.01	NS
FEV1%	0.344	1.02	0.98-1.07	NS
FVC%	0.260	0.97	0.93-1.02	NS
DLCO%	0.078	1.02	1.00-1.05	NS
Scadding chest radiograph staging	0.087	2.01	0.90-4.47	NS
Extrapulmonary involvement	0.826	1.09	0.50-2.41	NS
(b) Results of stepwise logistic regression analysis of presenting characteristics and prediction of physiological deterioration				
Lofgren's syndrome	0.100	0.48	0.20-1.15	NS
Haemoglobin	0.055	0.79	0.63-1.00	NS
DLCO%	**0.045**	1.02	1.00-1.08	S
Scadding chest radiograph staging	0.072	1.99	0.94-4.19	NS

FEV1% = forced expiratory volume in 1 second, FVC = forced vital capacity, DLCO = diffusion lung capacity of carbon monoxide. A-p-value of <0.05 is considered statistically significant.

Table 5. Results of logistic regression analyses for the secondary outcome of prediction of radiological deterioration

Presenting characteristics	Radiological progression			
	p-value	OR	95% CI	Significance
(a) Results of logistic regression analysis of all presenting characteristics with prediction of radiological deterioration				
Female	0.866	0.95	0.49-1.81	NS
Age	0.446	0.99	0.97-1.01	NS
Smokers	**0.024**	0.52	0.30-0.92	S
Lofgren's syndrome	**0.001**	0.34	0.18-0.65	S
CRP	**0.035**	0.53	0.30-0.96	S
ESR	**0.043**	1.02	1.00-1.03	S
WCC	0.310	1.06	0.95-1.20	NS
Haemoglobin	0.728	0.96	0.77-1.20	NS
Platelets	0.359	1.00	1.00-1.01	NS
FEV1%	0.079	0.97	0.94-1.00	NS
FVC%	0.684	1.01	0.97-1.04	NS
DLCO%	0.230	1.01	0.99-1.03	NS
Scadding chest radiograph staging	**0.004**	2.39	1.31-4.36	S
Extrapulmonary involvement	0.122	1.62	0.88-2.99	NS
(b) Results of stepwise logistic regression analysis of presenting characteristics and prediction of radiological deterioration				
Smokers	**0.028**	0.54	0.31-0.94	S
Lofgren's syndrome	**0.002**	0.40	0.22-0.72	S
CRP	**0.046**	0.59	0.34-0.94	S
ESR	**0.015**	1.02	1.00-1.03	S
FEV1%	**0.038**	0.98	0.96-1.00	S
Scadding chest radiograph staging	**0.008**	2.16	1.22-3.82	S
Extrapulmonary involvement	0.156	1.55	0.85-2.83	NS

CRP = C-reactive protein, ESR= erythrocyte sedimentation rate, WCC= white cell count, FEV1% = forced expiratory volume in 1 second, FVC = forced vital capacity, DLCO = diffusion lung capacity of carbon monoxide. A-p-value of <0.05 is considered statistically significant.

decreasing with increasing CRP (OR 0.59, 95% CI 0.34-0.94).

Sub-analyses of patients with (n=105) and without Lofgren's syndrome (n=223) was performed to determine if there were any significant differences between the different presentations of sarcoidosis. In patients with Lofgren's syndrome, low DLCO was found to be the only predictor of indication for corticosteroids (p=0.048). Female gender and low FVC% at presentation were significantly associated with physiological deterioration (p=0.022 and 0.038 respectively). Female patients with Lofgren's syndrome were almost 4 times more likely to experience physiological deterioration compared to male patients with Lofgren's syndrome, OR 3.88 (95% CI 1.08-20.55). High CRP was found to be a negative predictor of physiological deterioration (p=0.048) in Lofgren's syndrome. There were no significant predictors of radiological deterioration in patients with Lofgrens's syndrome.

In patients without Lofgren's syndrome, low baseline DLCO%, low FEV1%, extrapulmonary involvement and high baseline CRP were the best predictors of corticosteroid treatment (p=0.021, 0.031, 0.020 and 0.045 respectively). It is interesting to note that high CRP was not found to predict corticosteroid treatment when the entire population was included whereas in patients without Lofgren's syndrome, those with a patients with a high baseline CRP were twice as likely to receive corticosteroid treatment, OR 1.89 (95% CI 1.04-3.55). Although gender did not reach statistical significance at p=0.082, females were much more likely to receive corticosteroid treatment than males, OR 1.84 (95% CI 0.94-3.01). There were no significant predictors of physiological deterioration. High CRP remained a negative predictor of radiological deterioration (p=0.009) with smoking status the only other predictor of radiological deterioration (p=0.034) in this subgroup.

Discussion

This is one of the largest clinical studies investigating the influence of predictive outcomes of CRP in a well-defined homogeneous population of

sarcoidosis patients. High baseline CRP was strongly associated with the presence of Lofgren's syndrome, reduced baseline FVC% and reduced baseline DLCO%. Reduced DLCO% was found to be a significant independent predictor of indication for corticosteroid treatment and physiological decline on logistic regression analysis. Sub-analyses in patients without Lofgren's syndrome showed high baseline CRP and low DLCO% to be significant predictors of indications for corticosteroid treatment. Importantly, this is the first study to show a negative correlation of baseline CRP with radiological progression, suggesting that patients with high CRP at presentation are less likely to progress to severe disease, particularly if timely treatment is given.

The association between elevated CRP and Lofgren's syndrome has been well described (36, 37). Rothkrantz-Kos et al. previously investigated the usefulness of inflammatory markers to predict physiological impairment in sarcoidosis (29). The authors found that mean CRP concentrations of stable or progressive disease did not differ significantly from their control group and postulated that the acute phase response can be expected only in patients with active, as opposed to severe disease, including those with Lofgren's syndrome. Since patients with Lofgren's syndrome are known to have the best prognosis, Drent et al. speculated that an acute phase response may be beneficial in overcoming the still unknown cause of sarcoidosis (33).

Differential activation of inflammatory pathways by Lofgren's syndrome and less acute forms of the disease may influence the value of CRP as a prognostic marker in sarcoidosis. No previous studies have assessed the difference in CRP in the different presentations of sarcoidosis. It would be interesting to observe if and when CRP levels return to normal in Lofgren's disease, or if continuous or sustained elevation in CRP may predict disease progression in a subpopulation of chronic sarcoidosis patients with more extensive and severe disease.

In the present study, high CRP was found to inversely correlate with FVC% and DLCO% on univariate and multivariate analysis. FVC% and DLCO% are the most common indicators of pulmonary function impairment as they provide information on the actual state of the lungs, indicating mutually restrictive and/or obstructive pulmonary function abnormalities in sarcoidosis (22). Even when chest radiography is normal, FVC% or DLCO% may be reduced in 15-25% and 25-50% of patients, respectively (34, 35).

Several studies have demonstrated low DLCO% in sarcoidosis patients to be associated with alterations in exercise, including excessive ventilation to oxygen consumption, oxygen desaturation and widened alveolar-arterial oxygen gradients (36-41). In a recent study in stable COPD patients, CRP was noted to be inversely correlated with the partial pressure of oxygen and six-minute walk test distance. Koechlin et al. also demonstrated an inverse correlation of CRP levels with endurance time and Broekhuizan et al. found CRP levels to increase in patients with poor exercise capacity (42, 43). Given the correlation between high CRP and reduced DLCO% in the current study, it would be interesting to determine if high CRP may also be a marker of exercise capacity in these patients.

Elevated CRP levels may reflect skeletal muscle dysfunction as a direct consequence of the systemic effects of chronic respiratory disease or may be the result of an independent process that contributes to the systemic inflammatory load (44, 45). The high CRP levels associated with Lofgren's syndrome could perhaps reflect systemic muscle inflammation manifest as arthralgia in this acute form of sarcoidosis. Drent et al. showed an association with fatigue and elevated CRP levels, with patients suffering from fatigue shown to be more limited by dyspnoea, reduced exercise capacity and muscle pain than their counterparts (46). This finding was not confirmed in our study with extra-pulmonary manifestations being more likely to occur in those with lower CRP levels. This may be explained by the fact that fatigue per se was not included in the analysis of extra-pulmonary involvement as the ACCESS assessment instrument does not incorporate fatigue as one of its fifteen components of organ involvement.

Previous studies in sarcoidosis and other respiratory conditions have demonstrated higher CRP levels in smokers compared with non-smokers (47, 48). Many studies looking at inflammatory markers in BALF have subsequently excluded smokers from their analysis. However, this association was not significant in the present study and no differences were observed when comparing current-smokers verses ex-smokers verses non-smokers. This leads us to believe that smoking is unlikely to be an initial trigger

in the cascading inflammatory process underlying sarcoidosis and provides us with a strong argument to develop and institute therapies aimed at decreasing the inflammatory state independent of smoking cessation. Ziegenhagen et al. evaluated the role of BALF and serological parameters in predicting the severity of newly-diagnosed sarcoidosis patients. No differences were found in the BALF or serological parameters between smokers and non-smokers (47). Furthermore, in this study, smoking was not found to be a predictor of indication for treatment with steroids on multiple logistic regression analysis. However, smoking status was noted to have an independent effect on radiological progression. This may be explained by the persisting low level of inflammation that tends to occur in smokers which may adversely affect alveolar inflammation and subsequent progression of disease (48).

The retrospective nature of this study may have some inherent limitations. Firstly, not all information could be obtained despite attempts to retrieve missing data hence such patients were excluded from analysis. The initial univariate analysis is perhaps limited by stratification according to the arbitrarily chosen CRP cutpoint of 6 g/dL as per local laboratory guidelines. Our study also used standard rather than high-sensitivity CRP assays which may be less sensitive and less specific and therefore may not provide the same results if a high-sensitivity assay had been used. However, the standard CRP assay is used in clinical practice and is a feasible, easily reproducible and relatively inexpensive test that can be used at a practical level. Given that the data presented reflects the clinical practice of a regional tertiary referral centre for sarcoidosis in Ireland and extends over a prolonged period, there is likely to be heterogeneity in corticosteroid prescribing between clinicians. This may bias the results of the treatment outcome as a subpopulation of patients who were treated with corticosteroids may have achieved spontaneous remission of their disease even without treatment.

The study is also limited given the lack of serial CRP measurements and subsequent inability to determine concordance between CRP at baseline and throughout the disease course. Analysis of serial CRP would provide greater reliability and validity regarding its prognostic value in determining disease progression and treatment indication. Clarifying the effectiveness and diagnostic accuracy of CRP by applying ROC curve analysis or by determining the sensitivity and specificity of CRP as a predictive marker would have added to the validity of these results.

Conclusion

An abnormally elevated baseline CRP occurred in 46.6% of our population consistent with previously published data. High baseline CRP was associated with the presence of Lofgren's syndrome and reduced FVC% and DLCO% at presentation. In patients without Lofgren's syndrome, high CRP and low DLCO% at presentation may identify a subset of patients more likely to develop physiological progression who may benefit from early systemic treatment. This should be considered when CRP levels are measured. Although there may be a role for high CRP as a negative predictor of radiological progression, a normal CRP does not seem to rule out sarcoidosis or exclude clinically significant disease limiting the predictive utility of CRP in diagnosis or disease progression. Further prospective, longitudinal studies incorporating serial CRP measurements may improve the predictive utility of this marker in a subset of patients with high CRP and low DLCO at presentation.

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