Functional and Prognostic Impact of CT Phenotypes in Pulmonary Sarcoidosis—Preliminary Findings of an International Multicentre Study

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Background:

Sarcoidosis is the archetypal multisystem granulomatous disease which, despite its long history, remains poorly understood. Among all organ systems, the lungs bear the brunt and, while the disease course is 'benign' for the majority, a not insignificant minority face considerable morbidity and mortality, not least because of irreversible fibrosis. Computed tomography (CT) has an important role in the diagnosis and monitoring of pulmonary sarcoidosis but the CT manifestations or 'phenotypes' of sarcoidosis vary. The variation in CT features, functional profiles and disease behaviour in patients with sarcoidosis has prompted speculation that sarcoidosis might only be a generic term for different disease processes that happen to share a histopathological lesion, namely the non-caseating granuloma[1].

Objectives:

The exploration of phenotypic separations has the potential to lead to a novel morphological classification in sarcoidosis. The principle aim of this project is to explore the relationships, if any, between CT phenotypes, indices of functional impairment and prognosis in patients with pulmonary sarcoidosis.

Methodology:

Consecutive patients seen in sarcoidosis clinics were retrospectively selected from 3 centres (UK, n=101; Italy, n=47; USA, n=55)(fig.2). 28 were excluded due to poor CT quality. Their CT scans were independently reviewed by 4 radiologists, blinded to clinical data. Observers assigned a dominant phenotype (accounting for >50% of the abnormality) based on those proposed in the Delphi study[2] with a secondary phenotype, if present. Phenotype 15 was assigned to unclassifiable disease on CT. 3 observers completed more detailed quantitative analysis. Lung function tests (performed within 6 months of CT) were reviewed for the UK cohort, and survival data were reviewed for all participants.

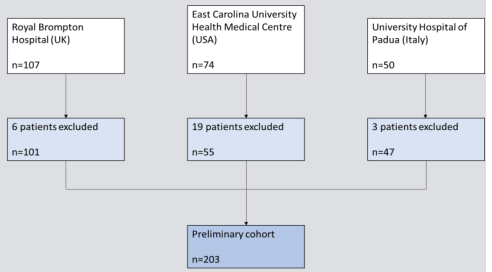

Figure 2: Number of cases collected for the preliminary cohort

CT Phenotypes in Pulmonary Sarcoidosis

A recent large international Delphi study sought the consensus of ~140 experts (respiratory clinicians and radiologists) on recognisable CT phenotypes in patients with pulmonary sarcoidosis[2] (table 1). The Delphi group reached consensus (>70% agreement) over two rounds on seven different CT phenotypes (1-7), broadly divided into those deemed to be inflammatory or non-fibrotic (1-4) and those likely to be fibrotic (5-7). Seven further CT phenotypes (8-14), included in the Delphi statements did not reach consensus.

Table 1:CT phenotypes and descriptors included in the Delphi statements

1	**Multiple mid/upper zone, peribronchovascular, perifissural/subpleural, micronodules, <3mm diameter** *+/- minor component of large nodules, galaxy sign, architectural distortion, upper lobe volume loss*
2	**Multiple mid/upper zone, peribronchovascular, perifissural/subpleural nodules, ≥3mm <3 cm** *+/- minor component of large nodules, galaxy sign, architectural distortion, upper lobe volume loss*
3	**Scattered nodules, ≥3mm <3 cm** *without peribronchovascular, perifissural or subpleural predilection*
4	**Consolidation** *as the predominant CT abnormality*
5	**Bronchocentric reticulation with/without dense opacification WITHOUT cavitation** *+/- minor component of delicate bands of 'loose' reticulation, enlarged peripheral pulmonary arteries ["reversed signet ring sign"], enlarged central pulmonary artery, mosaic attenuation pattern*
6	**Bronchocentric reticulation with/without dense opacification WITH cavitation** *+/- minor component of other features as described for phenotype 5*
7	**Large bronchocentric masses i.e. a PMF-look alike** *with minor components of other features*
8	**Multiple randomly-distributed micronodules, <3mm diameter** *+/- minor component of large nodules, galaxy sign, architectural distortion, upper lobe volume loss*
9	**Scattered large cavitating nodules** *+/- minor component of large nodules, galaxy sign, architectural distortion, upper lobe volume loss*
10	**Ground-glass opacification** *as the predominant CT abnormality*
11	**Mosaic attenuation pattern** *as the predominant CT abnormality*
12	**Interlobular septal thickening** *as the predominant CT abnormality*
13	**Mid/lower zone predominant reticulation, ground-glass opacification and traction bronchiectasis +/- honeycombing** *i.e. resembling UIP, fibrotic NSIP*
14	**Upper zone predominant pleural thickening with sub-pleural consolidation + reticulation +/- upper zone volume loss** *i.e. resembling PPFE*

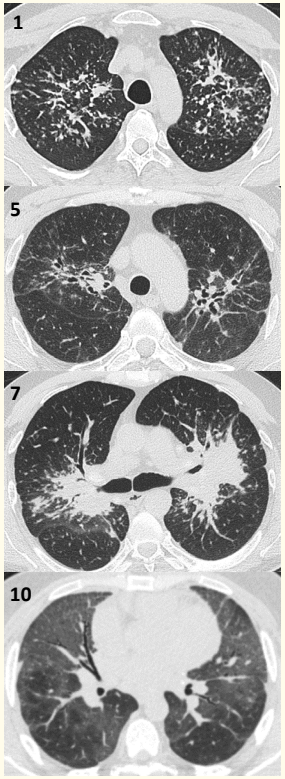

Figure 1: examples of phenotypes 1, 5, 7 and 10

Results:

Demographics/General:

The cohort consisted 112 males and 91 females (median age:53), with 65 black, 119 white and 18 Asian/ mixed/unknown ethnicity participants.

Phenotype 1 was the most prevalent phenotype (22% of all primary phenotype scores)(fig. 3) and more common in white patients than in black (15% vs 5%, p<0.001).

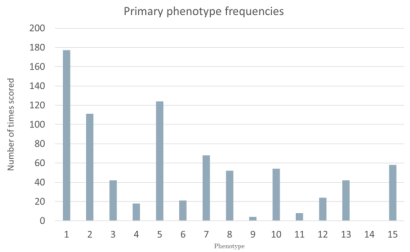

Figure 3: Number of times each phenotypes was scored

Phenotype 7 was more common in men than women (11% vs 5.5%, p<0.001). 12% of smokers were scored with phenotype 12, compared with 2.1% of former smokers and 2.8% of non-smokers (p=0.001). Phenotype 13 was more common in black patients (8.1% vs 3.1%; p<0.001).

The Fleiss' Kappa value for interobserver agreement on the primary phenotype was 0.433 (p<0.001), indicating a moderate level of agreement. When the nodular phenotypes (1, 2, 3, 8 and 9) were grouped, the overall kappa value increased to 0.55 (p<0.001).

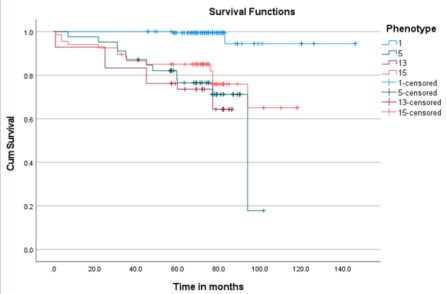

Figure 5: Kaplan Meier survival analysis of phenotypes 1, 5, 13 and 15

Survival:

23 deaths were recorded over the follow up period (average 6 years). Patients scored with 'fibrotic' phenotypes 5 and 13 had poorer survival than those with phenotype 1 (p<0.001)(fig. 5). Unsurprisingly, patients with traction bronchiectasis and honeycombing had poorer outcomes than those without (p<0.001)

Lung function:

Of the UK cohort of patients for which lung function was analysed (n=101), 50% had an obstructive ventilatory defect (n=50), 17% had a mixed defect (n=17), 9% had a restrictive defect (n=9), 20% had an isolated reduction in DLCO (n=20) and 5% had normal lung function (n=5). Phenotype 1 was more commonly associated with an obstructive defect than phenotype 5 (67% vs 37%; p<0.001). Phenotype 5 was associated with restrictive and mixed ventilatory defects in 14% and 23% respectively. The lung function profiles for phenotype 15 (unclassifiable) were fairly homogenous, with obstructive, restrictive, and mixed defects in seen in 31%, 18% and 33% respectively (fig. 4). Reduction in DLCO trended towards phenotype 5, affecting 26%, but this did not meet statistical significance when compared with other phenotypes (p=0.129)

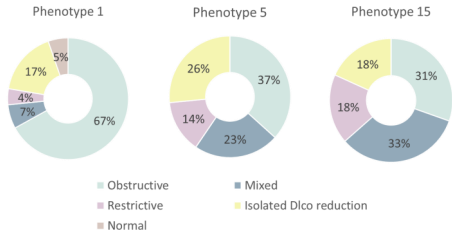

Figure 4: Lung function profiles in patients with phenotypes 1, 5 and 15

The mean overall extent of abnormal lung recorded by 3 observers was correlated with lung function parameters using Spearman correlation coefficients. The overall extent of abnormal lung showed moderate negative correlation with FEV1 (Spearman's correlation coefficient [ρ]=-0.50, p<0.001), FVC (ρ=-0.53, p<0.001), DLCO (ρ=-0.58, p<0.001) and KCO (ρ=-0.40, p<0.001).Correlations between the mean extents of nodules, consolidation and mosaicism with lung function parameters were weak at best, however the mean extent of reticulation showed a strong negative correlation with DLCO (Spearman's ρ=0.63, p<0.001), and ground glass a moderate negative correlation with DLCO (Spearman's ρ=0.40, p<0.001)

Discussion:

To date, there is no accepted CT-based classification in sarcoidosis, however the results of the multinational Delphi study have paved the way for a new morphological classification system that might better explain the observed differences in disease behaviour and prognosis. This preliminary dataset has provided an insight into the more frequently occurring phenotypes. Separations have already been made between these phenotypes regarding their relationships with demographical data, lung function and outcome; specifically, phenotype 1 is more common in white patients than in black, and phenotype 1 is more frequently linked with an obstructive ventilatory defect than phenotype 5. Curiously, despite the association of nodular phenotypes with obstructive ventilatory defects, the extent of nodules observed did not show any significant negative correlation with FEV1; this may indicate that phenotype separations could act as a surrogate marker for microscopic pathophysiological differences amongst patients with sarcoidosis. With regards to outcome, phenotypes 5, 13 and 15 portend a poorer outcome compared to phenotype 1. Expanding the cohort and conducting more detailed statistical analysis (including analysis of serial lung function and serial CT scans) could lay the groundwork for a novel morphological classification in sarcoidosis that offers valuable clinical and research utility.

References: 1. Broos CE, van Nimwegen M, Hoogsteden HC, Hendriks RW, Kool M, van den Blink B. Granuloma formation in pulmonary sarcoidosis. Front Immunol. 2013;4:437 2. Desai SR, Sivarasan N, Johannson KA, George PM, Culver DA, Devaraj A, et al. High-resolution CT phenotypes in pulmonary sarcoidosis: a multinational Delphi consensus study. Lancet Respir Med. 2023