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Evidence for association between sarcoidosis and pulmonary embolism from 35-year record linkage study

In the last year, we have observed large pulmonary embolisms (PEs) in four of 85 patients that attended the Oxford Sarcoidosis Clinic. In addition, we note a few case reports of PEs and unprovoked thrombotic events in patients with sarcoidosis (only one referenced here),¹ leading us to question if, compared with normal populations, patients with sarcoidosis have a higher risk of developing PE.

To explore this possibility, we performed a retrospective cohort analysis using data from the well-established Oxford Record Linkage Study.² This is a database of statistical records, spanning 35 years, of all hospital admissions (including day cases) to National Health Service (NHS) hospitals, and all deaths, regardless of where they occurred, in defined populations within the former Oxfordshire NHS region. The database and methods used for studying disease associations have been described² and can also be found in the Supplementary data. The sarcoidosis cohort (n=1002) was assembled by identifying admissions during the study period where sarcoidosis was recorded as the principal diagnostic reason for admission. The reference cohort (n=526 107) comprised patients admitted for the first time for various medical and surgical conditions as the principal diagnosis³ (see table 1). The disease and reference cohorts were matched by age, gender, year of first admission and district of residence.

Within these cohorts, we searched the database for any subsequent NHS hospital care for, or death from, (1) PE and (2) other cardiovascular disorders (CVDs) (see table 1). In subset analyses, we applied an age restriction of 65 for the sarcoidosis and reference cohort to minimise confounding co-morbidities. We also re-analysed the data excluding patients who presented with PE or

Table 1 Occurrence of PE compared with other cardiovascular events in patients admitted to hospital with sarcoidosis, compared with a reference cohort

Outcome	Observed	Expected	RR	Lower CI	Upper CI	p Value
All ages						
AAA	2.00	2.70	0.75	0.09	2.72	0.69
CHD	44.00	43.80	1.00	0.73	1.35	0.98
Heart Failure	21.00	11.80	1.78	1.10	2.72	0.01
MI	33.00	28.60	1.15	0.79	1.62	0.41
PE	14.00	7.30	1.92	1.05	3.23	0.01
DVT	5.00	5.00	1.00	0.32	2.34	1.00
Strokes excluding SAH	21.00	18.30	1.15	0.71	1.76	0.53
SAH	2.00	2.20	0.91	0.11	3.31	0.90
Under 65 years						
AAA	2.00	2.60	0.78	0.09	2.82	0.72
CHD	36.00	37.80	0.95	0.67	1.32	0.77
Heart Failure	18.00	8.20	2.22	1.31	3.51	0.00
MI	25.00	23.90	1.04	0.68	1.54	0.83
PE	13.00	6.60	1.98	1.05	3.39	0.01
DVT	5.00	4.10	1.23	0.40	2.88	0.65
Strokes excluding SAH	17.00	12.60	1.35	0.79	2.17	0.22
SAH	2.00	2.00	1.02	0.12	3.72	0.98
All ages excluding DVT and PE diagnosed within first year of admission						
AAA	2.00	2.60	0.77	0.09	2.78	0.95
CHD	42.00	41.90	1.00	0.72	1.36	0.99
Heart Failure	20.00	11.30	1.78	1.09	2.75	0.01
MI	32.00	27.20	1.18	0.81	1.67	0.35
PE	12.00	6.50	1.87	0.96	3.27	0.03
DVT	4.00	4.50	0.89	0.24	2.29	0.82
Strokes excluding SAH	20.00	17.00	1.18	0.72	1.82	0.47
SAH	1.00	2.00	0.50	0.01	2.80	0.48

Patients in the reference cohort were drawn from a group who were admitted to hospital with squint, otitis media, haemorrhoids, deflected septum, nasal polyps, impacted tooth, ingrowing toenail, bunions, sebaceous cyst, superficial injury and appendicectomy.

AAA, abdominal aortic aneurysm; CHD, coronary heart disease; DVT, deep vein thrombosis; PE, pulmonary embolism; RR, rate ratio; SAH, subarachnoid haemorrhage.

other CVDs within a year of the index admission to reduce any surveillance bias (see Supplementary data).

Rate ratios were calculated, comparing rates of PE or other CVDs in the sarcoid cohort with rates in the reference cohort. The CI for the rate ratio and χ^2 statistics for its significance were calculated as previously described.² Further description is provided in the Supplementary data.

The risk of PE was significantly higher in sarcoidosis patients (rate ratio 2.0, 95% CIs 1.1 to 3.4, for the under 65 year olds, table 1). We also found an increased risk of heart failure but the risk of other CVDs was not significantly increased. A similar profile was found after excluding cases of CVD and PE in the first year, and where no age restrictions were applied (see table 1).

Our observation comes from a well-established epidemiological data set comprising large numbers collected over a long period of time (1963–1998), in a defined population. The data set was collected by a team trained in the coding of clinical data. The population is stable, with respect to migration, forming a homogenous cohort, and has a standardised mortality ratio of 85, indicating a relatively healthy population. One limitation is the

lack of scope for validation. We know little about the patients other than their International Classification of Diseases (ICD) codes (eg, sarcoidosis, PE). We have no data on diagnostic criteria, or potential confounding factors—for example, corticosteroid treatment for sarcoidosis, smoking status and other risk factors for thrombosis. In addition, these are hospitalised patients, and many sarcoidosis patients are not admitted even when the disease is active. One caveat is that this was probably not always the case, particularly early on during the cohort period when patients may have been admitted for Kveim testing.

Our data show that the incidence of heart failure was also higher than expected in the sarcoidosis group. It is known that as many as 25% of patients with sarcoidosis have cardiac involvement in which sudden cardiac death and congestive cardiac failure are features.⁴ It may be that in the cohort of patients with disease severe enough to require admission there is a greater degree of systemic involvement, in which cardiac manifestations are present.

The cause for this potential increase in risk of PE is speculative, but could include use of corticosteroids, hitherto unrecognised

presence of procoagulant factors (macrophages and activated leucocytes are known to increase activation of thrombin and fibrin formation) and co-existence of sarcoidosis and antiphospholipid syndrome.⁵ Antiphospholipid antibodies occur in 2–5% of the general population, but in up to 38% patients with sarcoidosis, correlating with poorer prognosis.⁵

Overall, our findings would be viewed as hypothesis generating, providing a platform for further study, and supportive of the anecdotal observations made in our Sarcoidosis Clinic. Despite the limitations discussed above, PE should be considered in patients with sarcoidosis when there is sudden deterioration in dyspnoea.

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► Additional data are published online only. To view these files please visit the journal online (<http://thorax.bmj.com>).

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Chemotherapy should not be withheld from patients with an indwelling pleural catheter for malignant pleural effusion

A 1–12% rate of pleural infection has been observed in patients with an indwelling pleural catheter (IPC) to manage malignant pleural effusion (MPE), leading to concern that systemic chemotherapy may increase infection risk.^{1–5} This study aimed to determine whether chemotherapy increases the infection rate in patients with an IPC.

Data were collected from a prospectively maintained database, hospital notes and electronic records in a tertiary centre. All patients who had an IPC inserted between May 2006 and January 2010 to treat an MPE without pleural infection at the time of insertion were included. Pleural infection was defined as satisfying all of the following criteria: (1) positive pleural fluid culture; (2) symptoms of infection; and (3) treatment with antibiotics.

Eighty-two IPC placements in 78 patients with an MPE were included (table 1). Malignancies included breast cancer (n=21), mesothelioma (n=18), non-small cell lung cancer (n=13) and adenocarcinoma of unknown origin (n=8). Of 44 patients who received systemic chemotherapy (including cytotoxic chemotherapy and targeted therapies), 23 had an IPC during chemotherapy (table 1) (see online supplement for details of chemotherapy regimens). On average, patients had 2.5 cycles of chemotherapy with an IPC present (range 1–7 cycles). None of these 23 patients had WHO grade III or IV toxicities. Ten patients developed neutropenia at some point during their chemotherapy, of whom three had an IPC present at that time. In all cases neutropenia lasted <1 week and none of these patients developed infections.

Seven patients (9%) developed pleural infections, only one of whom was receiving chemotherapy (sunitinib) during the time the IPC was present. There was no difference in infection rate between those who received chemotherapy while the IPC was

present and those who did not (Fisher exact test, p=0.667). Of the other six, three had previously received chemotherapy, one had chemotherapy after treatment of the infection and two never received chemotherapy.

Nine (11%) other patients had a positive pleural fluid culture (four during chemotherapy) without symptoms of infection and not requiring antibiotics. Five of these patients had subsequent negative pleural fluid cultures without antibiotic treatment. This may have been due to colonisation or contamination.

A range of organisms were identified, with *Staphylococcus aureus* the most common in cases of infection (three cases of infection, one of colonisation) and coagulase-negative *Staphylococcus* the most common in colonisation (one infection, five colonisation).

The median time the IPC was present was 71 days (range: 6–711). Twenty-nine IPCs (35%) were removed prior to death. Although the no chemotherapy group appear to have a shorter IPC duration than the chemotherapy group, this was because of a higher mortality in the no chemotherapy group. The median time from IPC insertion to infection was 103 days (range 40–206). In the three patients who developed infection following previous chemotherapy, the time from last dose of chemotherapy to infection was 301 days (range 90–639).

These results show that systemic chemotherapy did not increase risk of pleural infection in this cohort of patients with IPCs. We conclude that an IPC is not a contraindication to chemotherapy.

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Table 1 Patient demographics

	Systemic chemotherapy while IPC in situ	No systemic chemotherapy while IPC in situ
Number	23	59
Mean age (years)	60	67
Males:females	11:12	34:25
Median duration IPC was in situ (days) (range)	84 (11–487)	66 (6–711)
Median duration IPC was in situ in patients in whom IPC was removed prior to death	84 (11–239)	82 (30–711)
No. of patients who died with IPC in situ (%)	13 (57%)	40 (68%)
Average time patient received chemotherapy while IPC was in situ (days) (range)	68 (11–208) (~2.5 cycles)	—
Pleural infections	1 (4%)	6 (10%)
Colonisation of IPC	4 (17%)	5 (8%)

IPC, indwelling pleural catheter.