Causes of pulmonary granulomas: a retrospective study of 500 cases from seven countries

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ABSTRACT

Background The frequencies of various causes of pulmonary granulomas in pathological material are unknown, as is the influence of geographical location on aetiology. The aim of this study was to identify the causes of pulmonary granulomas in pathological specimens, to define their frequencies, and to determine whether these causes vary by geographical location.

Methods 500 lung biopsies and resections containing granulomas were reviewed retrospectively by expert pulmonary pathologists from 10 institutions in seven countries. Fifty consecutive cases from each location were assigned a diagnosis based on histological features and available clinical/microbiological data.

Results A specific cause was identified in 58% of cases (290/500), most commonly sarcoidosis (136, 27%) and mycobacterial or fungal infections (125, 25%). Mycobacteria were identified in 19% of cases outside the USA versus 8% within the USA. In contrast, fungi accounted for 19% cases in the USA versus 4% in other locations. Fungi were mostly detected by histology, whereas most mycobacteria were identified in cultures. In 42% of cases (210/500) an aetiology could not be determined.

Conclusions Across several geographical settings, sarcoidosis and infections are the most common causes of pulmonary granulomas diagnosed in pathological specimens. Fungi are more commonly identified than mycobacteria in the USA, whereas the reverse is true in other countries. A definite aetiology cannot be demonstrated in more than a third of all cases of pulmonary granulomas, even after histological examination. These findings highlight the need to submit material for histology as well as cultures in all cases in which granulomatous disease enters the differential diagnosis.

Granulomatous inflammation is a common finding in lung biopsies and resections. It is surprising, therefore, that there are few data regarding the frequencies of various aetiologies of granulomatous inflammation in the lung. Large-scale series incorporating clinical/microbiological data are particularly lacking, most previous histological studies having focused on specific entities rather than the full spectrum of causes of granulomatous lung disease. Although a few studies have included cases of different aetiologies, they have been restricted to specific subsets such as solitary necrotising granulomas,[1] surgically excised granulomas[2] or granulomas seen in consultation practice.[3]

Another gap in our understanding of granulomatous lung disease is the absence of published data regarding the spectrum of causes of granulomatous lung disease in different geographical settings. It is conceivable that the causes of pulmonary granulomas could vary by geography depending on the prevalence of different infections in different locations. A comprehensive list of aetiologies derived from several geographical settings would be of value to physicians in a greater variety of locations worldwide than information obtained from a single institution/location.

With this background in mind, the aim of our study was to identify the causes of pulmonary granulomas in pathological specimens from a variety of geographical settings in order to determine whether the causes of pulmonary granulomas vary by geographical location. As a corollary, we also sought to quantify the incidence of granulomas of unknown aetiology in these locations.

METHODS

Five hundred cases of granulomatous lung disease were retrospectively reviewed by pathologists from 10 centres in seven countries, including one each in Austria, Brazil, India, Japan, Scotland (UK), Turkey and four in the USA. All but one of the contributing pathologists are members of the Pulmonary Pathology Society, and have subspeciality training and/or expertise in pulmonary pathology. Cases of pulmonary granulomas were identified by searching the pathology archives of each institution. Fifty consecutive, in-house, single-institution cases of granulomatous lung disease were contributed by each pathologist. In order to facilitate comparison, the time period from which the cases were selected was limited to any period between the years 2000 and 2010, the precise start date being left up to each contributor. The period over which 50 consecutive cases of pulmonary granulomas were diagnosed varied from 1 to 6 years (mean 2.8 years; median 2.5 years). All available slides (H&E and special stains for organisms such as Ziehl–Neelsen or Grocott methenamine silver) were reviewed in each case. Overall, special stains for organisms

were performed in 435/500 (87%) cases (mean number of blocks stained 1.04, median 1, range 1–5). In the majority (350/500, 70%), one tissue block was stained with special stains for organisms.

Inclusion criteria

The study was restricted to lung biopsies and resections, including transbronchial and endobronchial biopsies, CT-guided core biopsies, surgical biopsies (wedge biopsies/resections, open or video assisted), lobectomies and pneumonectomies. Glass slides were reviewed by pathologists to confirm the presence of granulomatous inflammation. 'Granuloma' was defined as an organised collection of histiocytes. Cases were assigned a diagnosis by each contributor based on pathological findings and any available data from microbiological cultures, serologies and/or clinical studies collected retrospectively from available medical records. Two pulmonologists (LTV and OJD) reviewed clinical data from their institutions as well as clinical data collected by other participants.

Exclusion criteria

Cytology specimens (fine-needle aspirates, bronchial washings/brushings, bronchoalveolar lavage) and autopsies were excluded. Cases seen in consultation were also excluded in order to avoid referral bias and to allow the cases to be truly representative of disease frequencies in the region of origin.

Diagnostic criteria

Cases were classified as infections if organisms were demonstrated on histological specimens or identified in cultures. Paracoccidioidomycosis was diagnosed on the basis of serological studies. As mycobacteria cannot be speciated in histological specimens, the differentiation of *Mycobacterium tuberculosis* from non-tuberculous mycobacteria was based on cultures and rarely on species-specific PCR studies performed on biopsied lung tissue. In cases in which mycobacteria were identified in pathological specimens but cultures were not performed, not available or negative, the organisms were categorised as mycobacteria of unknown type. In cases with documented infection, clinical data from seven centres (all four US centres, Scotland (UK), Brazil and Japan) was reviewed and patients were classified as immunosuppressed (HIV/AIDS, other immunodeficiency disorder, organ transplant, chemotherapy, corticosteroid therapy), indeterminate (malignancy, diabetes mellitus, sarcoidosis, chronic alcoholism, debilitated patient with abnormally low body mass index $<20\ kg/m^2$) or immunocompetent (absence of the above factors). A diagnosis of sarcoidosis was based on a combination of compatible clinical and radiological findings, consistent histology and negative histological stains and/or microbiological cultures. Other specific diagnoses were based on standard histological and clinical criteria as outlined in earlier reviews.[4–6] Cases that lacked clinical, microbiological or histological evidence of a specific aetiology were classified as granulomatous inflammation of unknown aetiology. No patient-identifying information was shared between participants. Institutional review boards (IRB) or equivalent bodies from all contributing institutions approved the study or exempted it from review (corresponding author IRB: IRB for the Protection of Human Subjects; exempt number: 40-09). Statistical analysis was performed using web-based open-access software (http://statpages.org/ctab2x2.html). Discrete variables were analysed using Fisher's exact test. A p value (two-tailed) of less than 0.05 was considered significant.

RESULTS

Demographic data and immune status

The study population consisted of 500 patients (263 men, 237 women; male:female ratio 1.1:1) ranging in age from 2 to 88 years (mean 51.8, median 51.5). Four were under 18 years of age and 14 were over 80 years old. Detailed clinical information was available in 300 cases (200 USA, 50 Scotland (UK), 50 Japan). In these patients, cultures of one or more respiratory tract specimens were available in 76% (228/300) and cultures of biopsied lung tissue were available in 30% (91/300). Information regarding immune status was known in 107 patients with granulomatous infections (USA 55, Scotland (UK) 11, Brazil 24, Japan 17). Of these, only seven (7%) were overtly immunosuppressed (four chemotherapy, one HIV/AIDS, one idiopathic lymphopaenia, one corticosteroids). Twenty-six (24%) were classified as indeterminate (18 malignancy, three diabetes mellitus, two chronic alcoholism, two sarcoidosis, one debilitated with abnormally low body mass index). The remaining 74 (69%) patients had no history of immunosuppression and were therefore presumed to be immunocompetent.

Specimen types

Transbronchial biopsies (258/500, 51%) and surgical biopsies (wedge biopsies/resections, 148/500, 30%) comprised the majority of specimens, followed by CT-guided core biopsies (45, 9%), lobectomies (28, 6%), endobronchial biopsies (16, 3%), bilobectomies (three, 0.6%) and pneumonectomies (two, 0.4%).

Specific causes of granulomatous lung disease

Table 1 shows the incidence of various causes of granulomatous lung disease identified in this study. Details regarding the number of cases from each site are provided in table 2. A specific diagnosis was made in 58% of cases (290/500), the majority consisting of sarcoidosis (136/500, 27%) or infections (125/500, 25%) (figure 1A–D). Hypersensitivity pneumonitis (extrinsic allergic alveolitis) accounted for 3.4% of cases (17/500) (figure 1E) and Wegener granulomatosis for 1% (five/500) (figure 1F). All other diagnoses accounted for fewer than 1% of cases each.

The relative yield of cultures and histology in the diagnosis of granulomatous infections is shown in table 3. Overall, cultures

Table 1 Incidence of various causes of granulomatous lung disease in lung biopsies and resections

	No of cases (%)		
	USA (n=200)	Non-US (n=300)	Total (n=500)
Specific diagnoses	**133 (67)**	**157 (52)**	**290 (58)**
Sarcoidosis	61 (31)	75 (25)	136 (27)
Infection	55 (28)	70 (23)	125 (25)
Hyersensitivity pneumonitis (EAA)	11 (6)	6 (2)	17 (3.4)
Wegener granulomatosis	2 (1)	3 (1)	5 (1.0)
Aspiration pneumonia	2 (1)	0 (0)	2 (0.4)
Lymphoma or LIP	1 (0.5)	1 (0.3)	2 (0.4)
Churg–Strauss syndrome	0 (0)	1 (0.3)	1 (0.2)
ANCA-associated disease*	1 (0.5)	0 (0)	1 (0.2)
Rheumatoid nodule	0 (0)	1 (0.3)	1 (0.2)
Unknown aetiology	**67 (33)**	**143 (48)**	**210 (42)**

*ANCA-positive disease that did not fit with either Wegener granulomatosis or Churg–Strauss syndrome.
ANCA, antineutrophil cytoplasmic antibody; EAA, extrinsic allergic alveolitis; LIP, lymphoid interstitial pneumonia.

Table 2 Granulomatous lung disease: diagnoses in each geographical location (figures refer to number of cases)

	SYR	SCT	CLE	HER	UK	AUS	JPN	TUR	BRZ	IND
Specific diagnoses	**31**	**34**	**37**	**31**	**42**	**23**	**34**	**18**	**31**	**9**
Infection	10	17	15	13	11	7	17	2	24	9
Sarcoidosis	18	9	19	15	22	15	16	16	6	0
Hypersensitivity pneumonitis (EAA)	1	5	3	2	6	0	0	0	0	0
Wegener granulomatosis	0	1	0	1	1	1	0	0	1	0
Aspiration pneumonia	1	0	0	1	0	0	0	0	0	0
Lymphoma or LIP	1	0	0	0	1	0	0	0	0	0
Churg–Strauss syndrome	0	0	0	0	1	0	0	0	0	0
ANCA-associated disease*	0	1	0	0	0	0	0	0	0	0
Rheumatoid nodule	0	0	0	0	0	0	1	0	0	0
Unknown aetiology	**19**	**16**	**13**	**19**	**8**	**27**	**16**	**32**	**19**	**41**
Total	**50**	**50**	**50**	**50**	**50**	**50**	**50**	**50**	**50**	**50**

*ANCA-positive disease that did not fit with either Wegener granulomatosis or Churg–Strauss syndrome.
ANCA, antineutrophil cytoplasmic antibody; AUS, Graz, Austria; BRZ, São Paulo, Brazil; CLE, Cleveland, Ohio, USA; EAA, extrinsic allergic alveolitis; HER, Hershey, Pennsylvania, USA; IND, New Delhi, India; JPN, Toyama, Japan; LIP, lymphoid interstitial pneumonia; SCT, Scottsdale, Arizona, USA; SYR, Syracuse, New York, USA; UK, Aberdeen, Scotland, UK.

and histology were complementary, many cases being positive by both modalities. However, cultures were most useful in detecting mycobacterial infections, whereas histological examination alone was able to identify the vast majority of fungal infections. Table 4 categorises all infections by organism and geographical location. A detailed breakdown of infections diagnosed at each contributing site is shown in table 5. Virtually all granulomatous infections (123/125) were caused by mycobacteria or fungi. In the two remaining cases, two organisms with potential to cause granulomatous inflammation were identified (*Mycobacterium xenopi* and *Aspergillus* in one, *Mycobacterium avium–intracellulare* and *Nocardia* in the other).

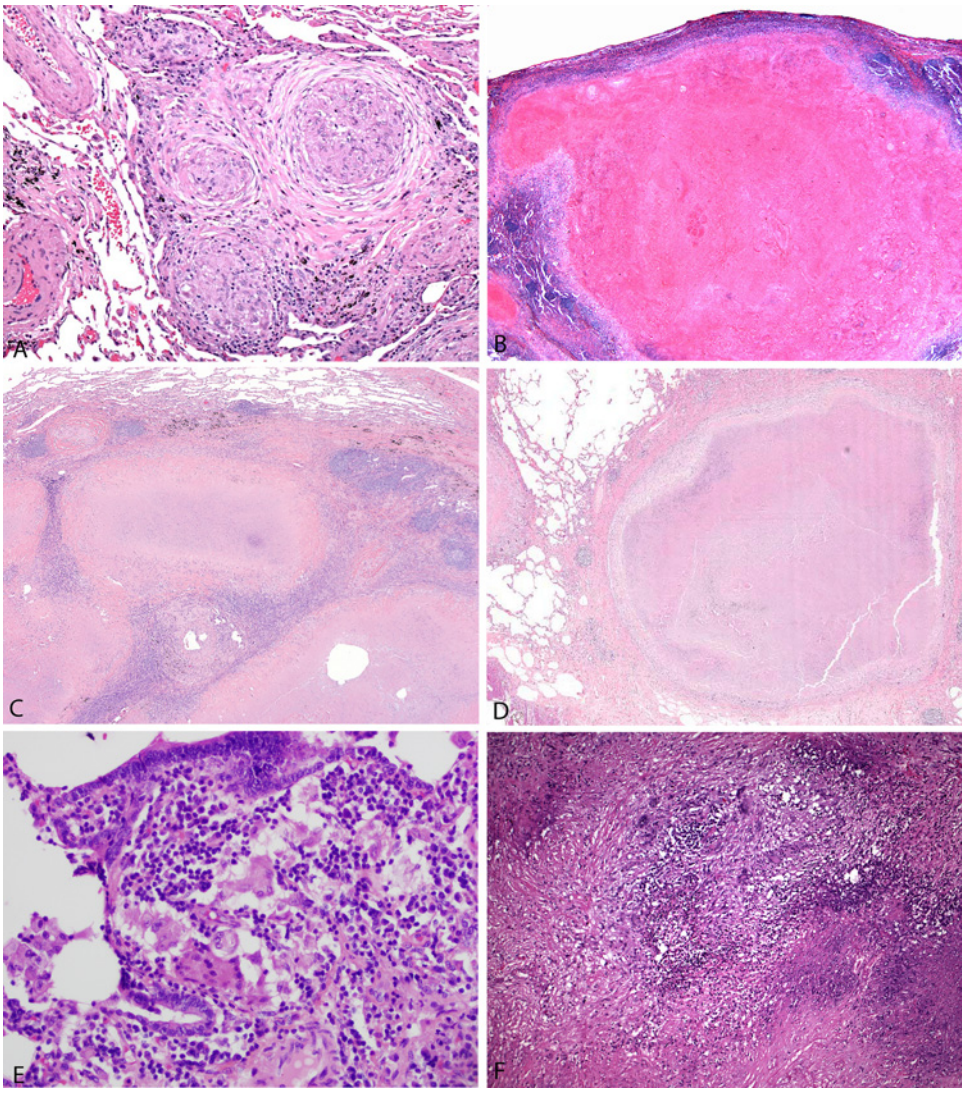

Figure 1 Common causes of granulomatous inflammation in lung biopsies and resections from various geographical settings. (A) Sarcoidosis. Non-necrotising granulomas within the interstitium, some of which are surrounded by concentric layers of fibrosis (40×). (B) Fungal infection (histoplasmoma). Necrotising granuloma with a large area of central necrosis (12.5×). *Histoplasma* yeasts were seen on a silver stain (not shown) within the necrotic area. (C) Fungal infection (coccidioidoma). Mass-like lesion formed by several necrotising granulomas (40×). *Coccidioides* spherules were present within the granulomas. (D) Mycobacterial infection (tuberculosis). Necrotising granuloma in a case from which *M. tuberculosis* was isolated in cultures (40×). (E) Hypersensitivity pneumonitis (extrinsic allergic alveolitis). Tiny, poorly formed non-necrotising granuloma within peribronchiolar interstitium (200×). (F) Wegener granulomatosis. Dirty necrosis surrounded by palisaded histiocytes and multinucleated giant cells (100×). H&E stain, A–F.

Table 3 Comparison of yield of microbiological cultures and histology* for detecting organisms in pulmonary granulomas

Organism	No of cases	Culture data available	Cultures pos, histology neg	Cultures neg, histology pos	Cultures and histology pos
Mycobacteria	**72**	**54**	**32**	**7**	**15**
M tuberculosis	28	28	17	1†	10
Non-tuberculous mycobacteria	21	21	15	1†	5
Mycobacteria, unknown type‡	23	5	0	5	0
Fungi	**51**	**32**	**1**	**25**	**6**
Histoplasma	18	13	0	13	0
Coccidioides	13	11	0	6	5
Cryptococcus	6	4	0	3	1
Paracoccidioides	6§	0	0	0	0
Aspergillus	4	2	1	1	0
Pneumocystis	2	2	0	2	0
Fungus, unknown type	2¶	0	0	0	0
Two organisms	**2**	**2**	**0**	**0**	**2**
Total	**125**	**88**	**33**	**32**	**23**

*Histology includes H&E-stained sections as well as all available special histochemical stains (Ziehl–Neelsen, auramine–rhodamine, Grocott methenamine silver, etc).
†Identified and speciated by mycobacterial genus-specific PCR performed on fresh, unfixed biopsy tissue.
‡Mycobacteria identified by acid-fast stains on histological specimens but not speciated because cultures were negative or not performed.
§All six cases of paracoccidioidomycosis were diagnosed serologically.
¶Fungi identified on histological specimens but not speciated because histological features were non-specific and cultures were not performed.
neg, negative; pos, positive.

Granulomatous lung disease of unknown aetiology

In 42% of cases (210/500), a definite aetiology could not be determined even after histological examination (table 1). In 24% (50/210) of these, cultures of biopsied or resected lung tissue also failed to reveal an infectious aetiology. Table 6 shows the influence of necrosis and specimen type on the ability to obtain a specific diagnosis. Surprisingly, necrotising granulomas yielded a lower proportion of specific diagnoses (107/194, 55%) than non-necrotising granulomas (183/306, 60%), and a specific diagnosis was less likely in excision specimens (98/181, 54%) than in small biopsies (192/319, 60%). Neither of these differences were statistically significant (p=0.308 for the association between necrosis and specific diagnosis; p=0.220 for the association between specimen type and specific diagnosis; Fisher's exact test, two-tailed).

Table 4 Variation in frequency of specific granulomatous infections in different geographical locations

	USA (n=55)	non-US (n=70)	Total (n=125)
Mycobacteria	**16**	**56**	**72**
M tuberculosis	1	27	28
Non-tuberculous mycobacteria	13	8	21
Mycobacteria, unknown type*	2	21	23
Fungi	**38**	**13**	**51**
Histoplasma	18	0	18
Coccidioides	13	0	13
Cryptococcus	4	2	6
Paracoccidioides	0	6	6
Aspergillus	0	4	4
Pneumocystis	2	0	2
Fungal organisms, unclassifiable	1	1	2
Two organisms	**1**	**1**	**2**

*Mycobacteria identified by acid-fast stains on histological specimens but not speciated because cultures were negative or not performed.

Geographical variation in the incidence of granulomatous lung diseases

Both within and outside the USA, sarcoidosis and infection accounted for approximately equal proportions of cases of pulmonary granulomatous inflammation (table 1). In all locations in the USA (except Scottsdale, Arizona), both European nations and Turkey, sarcoidosis outnumbered infections. In Scottsdale, infections (34%) were more common than sarcoidosis (18%). Sarcoidosis and infections accounted for approximately equal numbers of cases in Japan. In India and Brazil, in contrast, infections were diagnosed in far greater numbers than sarcoidosis. There were too few cases of the other specific diagnoses to arrive at any meaningful conclusions regarding geographical variation.

The incidence of sarcoidosis ranged from 12% (Brazil) to 44% (Scotland), excluding cases from India, where no clinical data were available. The incidence of sarcoidosis was slightly higher in the USA (31%) than elsewhere (25%). Within the USA, the incidence of sarcoidosis ranged from 18% (Scottsdale) to 38% (Cleveland, Ohio). Outside the USA, the incidence of sarcoidosis in Austria (30%), Turkey (32%) and Japan (32%) was comparable to US incidence figures, whereas the incidence was markedly higher in Scotland (44%).

In pulmonary granulomas, cultures were more likely to detect mycobacteria than histology, whereas the reverse was true for fungi. Although *Coccidioides*, *Cryptococcus* and *Aspergillus* occasionally grew in cultures from pulmonary granulomas, *Histoplasma* and *Pneumocystis* did not; their detection, therefore, rested entirely on histological examination. Infections showed significant variation by geographical location. While mycobacterial infections comprised only 8% (16/200) of cases in the USA, they accounted for 19% (56/300) of cases in other locations. The contrast was even more striking for *M tuberculosis*, which was identified in only one of 200 cases (0.5%) in the USA (Hershey, Pennsylvania) versus 27 of 300 (9%) from locations outside the USA (13 cases from Brazil, six from Japan, four each from Scotland and Austria). In contrast to the marked geographical

Table 5 Granulomatous lung disease: infections in each geographical location (figures refer to number of cases)

All infections	SYR	SCT	CLE	HER	UK	AUS	JPN	TUR	BRZ	IND
Mycobacteria	**2**	**2**	**5**	**7**	**8**	**5**	**15**	**2**	**17**	**9**
M tuberculosis	0	0	0	1	4	4	6	0	13	0
Non-tuberculous mycobacteria	2	2	4	5	1	0	6	0	1	0
Mycobacteria, unknown type*	0	0	1	1	3	1	3	2	3	9
Fungi	**8**	**14**	**10**	**6**	**2**	**2**	**2**	**0**	**7**	**0**
Histoplasma	5	1	9	3	0	0	0	0	0	0
Coccidioides	1	12	0	0	0	0	0	0	0	0
Cryptococcus	1	1	0	2	0	0	2	0	0	0
Paracoccidioides	0	0	0	0	0	0	0	0	6	0
Aspergillus	0	0	0	0	2	1	0	0	1	0
Pneumocystis	1	0	1	0	0	0	0	0	0	0
Fungal organisms, unclassifiable	0	0	0	1	0	1	0	0	0	0
Two organisms	**0**	**1**	**0**	**0**	**1**	**0**	**0**	**0**	**0**	**0**

*Mycobacteria identified by acid-fast stains on histological specimens but not speciated because cultures were negative or not performed.
AUS, Graz, Austria; BRZ, São Paulo, Brazil; CLE, Cleveland, Ohio, USA; HER, Hershey, Pennsylvania, USA; IND, New Delhi, India; JPN, Toyama, Japan; SCT, Scottsdale, Arizona, USA; SYR, Syracuse, New York, USA; UK, Aberdeen, Scotland, UK.

variation in the frequency of tuberculosis, non-tuberculous mycobacterial infections were encountered both within and outside the USA (all four centres within the USA and three of six non-US centres). The nine mycobacterial infections detected in India were suspected to represent tuberculosis given the high prevalence of tuberculosis in that country, but because culture confirmation was not available we classified them as mycobacteria of unknown type. Similar considerations applied to the cases with mycobacteria of unknown type from Japan (three), Brazil (three) and Turkey (two).

Fungal infections were more common in the USA (38/200, 19%) than in other countries (13/300, 4%). Histoplasmosis and coccidioidomycosis were diagnosed exclusively in the USA. All but one case of histoplasmosis was derived from endemic regions in the midwest and northeast USA. The only case diagnosed in a non-endemic location (Scottsdale, Arizona) involved a patient who resided in an endemic state (Tennessee). Similarly, all except one case of coccidioidomycosis was reported from an endemic area (Scottsdale) in the southwestern USA. The only case reported from a non-endemic area (Syracuse, New York) involved a patient who had previously resided in Arizona. *Cryptococcus* infections were reported from most locations within the USA, as well from Japan. *Paracoccidioides* infections (six cases) were reported exclusively from Brazil.

DISCUSSION

This is the largest and most geographically inclusive study of all-cause pulmonary granulomatous inflammation to date, and the first to analyse the frequencies of granulomatous lung disease in pathological specimens from a variety of geographical settings. Our findings confirm that infection and sarcoidosis are the most common causes of granulomatous inflammation in lung biopsies and resections worldwide, highlight significant geographical differences in the incidence of mycobacteria and fungi in lung granulomas, and provide an estimate of the proportion of cases of granulomatous lung disease in which a definite aetiology cannot be determined even after histological (and in many cases, microbiological) examination.

The high incidence of infections and sarcoidosis is not unexpected and reflects the experience of clinicians and pathologists in daily practice. However, our findings differ in some respects from the few previous studies that have attempted to delineate the aetiologies of pulmonary granulomas. In 1982, Woodard *et al*,[7] using an approach similar to ours, analysed both biopsies and surgical specimens, and found that infections and sarcoidosis were the main causes of pulmonary granulomas. However, their rate of specific diagnoses was higher than ours (81% vs 58%), and the proportion of infections was also higher than in our study (80% vs 25%). The higher rate of specific diagnoses was partly due to the exclusion of secondary and incidental granulomas, which we included in our series. The reason for the higher proportion of infections in their study is unclear, but it may be that the large number of transbronchial biopsies in our series resulted in an excess of cases of sarcoidosis with a relative decrease in infections. Two other histological studies of pulmonary granulomas were restricted to surgically resected cases and excluded small biopsies.[1 2] Ulbright and Katzenstein[1] further restricted their study to necrotising granulomas. Not surprisingly, therefore, those studies contained mostly infections and did not include any case of sarcoidosis. Notably, all three studies cited were carried out in the USA, and therefore reported either a predominance of fungal infections[2 7] or equal numbers of cases of fungal and mycobacterial infection.[1]

The striking geographical variation seen in our study suggests that the frequency of detection of organisms in pulmonary granulomas is largely a function of the infections endemic in the

Table 6 Relationship of type of granuloma and type of specimen to the frequency of specific diagnoses

	Specific diagnoses			Unknown aetiology
	Sarcoidosis No of cases (%)	Infection	Other	
Necrotising granulomas (n=194)	6 (3)	93 (48)	8 (4)	87 (45)
Non-necrotising granulomas (n=306)	130 (42)	32 (11)	21 (7)	123 (40)
Small biopsy (n=319)	122 (38)	60 (19)	10 (3)	127 (40)
Excision (n=181)	14 (8)	65 (36)	19 (10)	83 (46)

region of origin. For example, the high rates of detection of *Histoplasma* in the northeastern and midwestern USA, of *Coccidioides* in the southwest, and of *M tuberculosis* in Brazil mirror endemic infections in those regions. Other noteworthy aspects of the geographical variation seen in this study are the rarity of *M tuberculosis* in pulmonary granulomas in the USA, the absence of *Histoplasma* and *Coccidioides* in pulmonary granulomas outside the USA and the ubiquitous distribution of *Cryptococcus* and non-tuberculous mycobacteria.

Although granulomas of unknown aetiology were not the primary focus of our study, our findings quantitate the extent of this common and vexing problem in routine clinical practice. The surprisingly high proportion (42%) of granulomas of unknown aetiology in this study is most likely due to our strict criteria for classifying diagnoses as 'specific' and the lack of clinical and microbiological information in many cases. Interestingly, neither the presence of necrosis nor the size of the specimen (excision vs small biopsy) had any influence on the proportion of cases of unknown aetiology (table 6). The most likely explanation for both findings is the large number of cases of sarcoidosis, a specific diagnosis that was made predominantly in cases with non-necrotising granulomas diagnosed on small (transbronchial) biopsies. There are several possible explanations why an aetiology is not demonstrable in many cases of granulomatous lung disease, the reasons differing somewhat for infections and non-infectious diseases. In infections, organisms may not be demonstrable for several reasons. First, when small biopsies are used as the diagnostic specimen, the area containing organisms may not be sampled. Second, organisms may be removed or destroyed by the granulomatous response. Third, if organisms are very few in number, they may fall below the detection threshold of conventional histological methods. Fourth, even with a thorough review of tissue samples, organisms may be missed when they are few in number. Finally, if biopsied tissue is not submitted for cultures, which is frequently the case with needle biopsies and incidentally detected lesions, another opportunity for detecting organisms is lost. This last point is worth emphasising. The significant number of cases in our study in which cultures detected organisms (mostly mycobacteria) that were not identifiable by histological examination (table 3) highlights the need to submit biopsied lung tissue for cultures whenever feasible. There are many potential reasons why non-infectious causes of granulomas may be missed. Key histological findings—such as the necrotising vasculitis of Wegener granulomatosis or the lymphangitic distribution of granulomas in sarcoidosis—may not be sampled by small biopsies. Pathologists who lack experience in pulmonary pathology may not look for or appreciate these findings. Potentially diagnostic serological studies such as antineutrophil cytoplasmic antibody (ANCA; for Wegener granulomatosis) may not have been performed. Finally, important pieces of clinical information (such as a history of rheumatoid arthritis, bird exposure or hot tub use) may not have been provided to the pathologist.

The limitations of this study include the non-uniform availability of clinical and microbiological data and the lack of central histological review. Our data, being derived from randomly selected locations, does not provide a perfect measurement of the incidence of granulomatous lung disease in the general population. Within the USA, for example, the southeastern and western states lack representation while histoplasmosis-endemic regions (northeast and midwest) are oversampled. In addition, cases from the USA are overrepresented (four of 10 locations) while regions such as China, Africa, Australia and large regions of the developing world are not represented. Furthermore, as sampling bias is inherent in the design of this pathology-based study, our data may not accurately reflect the incidence of these diseases in the population, because conditions more likely to be biopsied may be overrepresented. Despite these limitations, this series represents the only study of granulomatous lung disease from multiple geographical regions.

In summary, sarcoidosis and infections are the most common causes of pulmonary granulomas in histological material worldwide. Mycobacteria are more commonly identified than fungi in pulmonary granulomas outside the USA, whereas fungi are more commonly found than mycobacteria in pulmonary granulomas in the USA. Sarcoidosis is the most common non-infectious pulmonary granulomatous disease in every geographical location studied. The aetiology of a large proportion of pulmonary granulomas remains unknown even after histological examination, indicating the need for additional research to elucidate the causes and significance of such cases.

Take-home messages

- Sarcoidosis and infections are the most common causes of pulmonary granulomas diagnosed in pathological specimens.
- Fungi are more commonly identified in pulmonary granulomas than mycobacteria in the USA, whereas a mycobacterial aetiology is more common in other countries.
- A definite aetiology cannot be demonstrated in more than a third of all cases of pulmonary granulomas, even after histological examination.
- Clinicians who perform lung biopsies or resections should submit material for histology as well as microbiological cultures in all cases in which granulomatous disease enters the differential diagnosis.

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