Official Journal of the Asian Pacific Society of Respirology
Respirology

ORIGINAL ARTICLE

Incidence and aetiologies of pulmonary granulomatous inflammation: A decade of experience

ALIA NAZARULLAH,[1] ROBERT NILSON,[1] DIEGO JOSE MASELLI[2] AND JAISHREE JAGIRDAR[1]

[1]*Department of Pathology and* [2]*Division of Pulmonary Diseases and Critical Care, Department of Medicine, University of Texas Health Science Center at San Antonio, San Antonio, Texas, USA*

ABSTRACT

Background and objective: **Granulomatous lung disease (GLD) is caused by a wide range of conditions. Often there is a need to correlate pathological findings with clinical, microbiological or radiological data to determine an aetiology. The aim of this study was to determine the different aetiologies of GLD over the past decade.**

Methods: **Among 2228 consecutive lung specimens from 1999 to 2011, 226 cases (10.1%) were positive for GLD. One hundred ninety patients were retrospectively reviewed and diagnoses were assigned based on availability of histological/clinical/microbiological correlation.**

Results: **A confident, probable and uncertain diagnosis was made in 68.4%, 13.2% and 18.4% patients. The aetiologies comprised infectious, non-infectious and uncertain in 54.7%, 26.8% and 18.4% patients. Mycobacterial infections constituted 27% of all patients, and included atypical, tuberculous and unclassified mycobacteria in order of frequency. Acid-fast bacilli (AFB) were visualized in tissue sections in 29% cases and cultured in 73% cases. Fungal infections comprised 27% of all cases, which included *Coccidioides*, *Cryptococcus*, *Aspergillus* and *Histoplasma* in order of frequency. Fungi were visualized in tissue sections with Gomori methenamine silver (GMS) stain in 83% patients and cultured in 52% cases. Sarcoidosis was the major non-infectious aetiology, constituting 21% of all patients. Necrosis in granulomas was associated with the presence of infection ($P < 0.001$).**

Conclusions: **The aetiology in necrotizing GLD with negative AFB and GMS stains is most likely infectious due to atypical mycobacteria. Coccidioidomycosis was the most common fungal infection. The aetiology in non-necrotizing GLD is most likely non-infectious, probably sarcoidosis.**

Key words: coccidiomycosis, granuloma, lung, mycobacteria, sarcoidosis.

Correspondence: Jaishree Jagirdar, Department of Pathology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78229, USA. Email: jagirdar@uthscsa.edu

Received 8 April 2014; invited to revise 5 May 2014; revised 30 July 2014; accepted 20 August 2014 (Associate Editor: Toby Maher).

SUMMARY AT A GLANCE

The incidence and aetiologies of GLD were evaluated over a 10-year period, providing further epidemiological data on a disease caused by multiple pathologies and with a certain aetiology often undetermined. Infectious aetiologies (atypical mycobacteria, coccidiodes) were more common and presented with necrosis. The most common non-infectious cause was sarcoidosis.

Abbreviations: AFB, acid fast bacilli; EBB, endobronchial biopsy; GLD, granulomatous lung disease; GMS, Gomori methenamine silver; HIV, human immunodeficiency virus; PPD, purified protein derivative; TBB, transbronchial biopsy.

INTRODUCTION

Granulomatous lung disease (GLD) is caused by a wide range of conditions. A detailed history of exposures is fundamental in GDL and has been found pivotal to reach a precise diagnosis.[1] Nevertheless, often there is a need to correlate history and pathological findings with clinical, microbiological or radiological data to determine an aetiology. It is critical to reach the precise diagnosis because the treatment for GLD may differ significantly, ranging from induced immunosuppression (i.e. sarcoidosis) to aggressive antibiotic therapy (i.e. tuberculosis). A certain diagnosis is often not reached; therefore, epidemiological data may be useful to inform clinical management decisions.

Many good review articles exist that emphasize histomorphological evaluation in establishing the correct diagnoses.[2–4] However, there is surprisingly sparse literature regarding the incidence of different aetiologies of GLD. Apart from Mukhopadhyay *et al.* and Woodard *et al.*, studies have limited their survey to specific subsets, that is, cases seen in consultation practice, surgically excised pulmonary granulomas and solitary necrotizing granulomas.[5–9] Even though making a diagnosis usually rests on histomorphology and ancillary techniques, knowing the likelihood of

Table 1 Classification of diagnoses

Disease	Confident	Probable	Uncertain
Infectious aetiology	• Positive cultures • Visualization of microorganisms in tissue section • Positive antigen/antibody detection with consistent clinico-pathological setting	• Clinical suspicion • Previous history of infection • Consistent histology	• Negative cultures • No visualization of microorganisms • Negative antigen/antibody • No diagnosis was favoured
Sarcoidosis	• Compatible histological, radiological and clinical findings • Negative cultures • No visualization of microorganisms	• Compatible histological, radiological and clinical findings • No microbiological data available	• As above

encountering different aetiologies of pulmonary granulomatous processes based on geographical areas and immune status of patient could be helpful in guiding a focused workup and treatment, especially when there is paucity of clinical findings.

The aim of this study is to correlate clinical, histological and microbiological data and establish the incidence of various aetiologies of GLD in a consecutive, in-house and single institution material in San Antonio, Texas. We hypothesized that the aetiologies of GLD follow specific distributions and patterns, and knowledge of these may aid the clinician to reach the diagnosis with a higher degree of certainty.

METHODS

This study was approved by the Institutional Review Board. Surgical pathology reports in the electronic database (CoPath, Cerner) of the Department of Pathology were searched for keywords granuloma, granulomas, granulomata, granulomatosis and granulomatous in combination with the keyword lung. Patients before mid-1999 had inconsistent microbiological data, and hence, we limited our study to in-house patients from 1 August 1999 to 1 March 2011.

Patient records, radiological imaging and microbiological results were reviewed for each patient, when available. The clinical information was compared with the surgical pathology reports to confirm final diagnoses in retrospect. A single pulmonary pathologist was used to maintain consistency in terminology and to avoid inter-observer differences in reporting reviewed slides. Diagnoses were categorized as 'confident', 'probable' or 'uncertain', based on the degree of certainty. Infectious entities listed as 'confident' had either microorganisms in tissue section, positive culture, positive serology or positive antigen detection in a consistent clinical-pathological setting. 'Probable' infectious diagnoses rested on clinical suspicion, supported by positive purified protein derivative (PPD) test or previous history of infection and consistent histology (Table 1). To be listed as 'confident', a diagnosis of sarcoidosis required compatible histological, radiological and clinical findings in conjunction with negative cultures. When clinical follow-up or microbiology data were lacking, diagnosis of sarcoidosis was recorded as 'probable'. The category of 'uncertain' diagnoses comprised cases where a broad differential existed, with no particular diagnosis favoured (Table 1). The category of 'incidental' was delineated for those findings without any clinical significance or that did not require any further treatment (i.e. small cholesterol granulomas).

Clinical records were reviewed to assess evidence of immunocompromise and underlying lung disease. Immunocompromise was further divided into two different categories, 'overt' and 'possible'. The former included entities such as human immunodeficiency virus (HIV)/acquired immune deficiency syndrome, autoimmune collagen vascular diseases with steroid treatment, malignancy treated by chemotherapy, interferon-treated hepatitis C and previous organ transplant requiring immunosuppressive drugs. Diabetes and substance abuse (alcohol, illicit drugs, etc.) were considered possible risk factors for immunosuppression. Underlying lung diseases included chronic obstructive pulmonary disease, asthma, untreated lung neoplasm, cystic lung disease and interstitial lung disease.

Granulomatous inflammation was classified histopathologically as necrotizing or non-necrotizing. Special histochemical stains used to identify infectious organisms were Fite and Ziehl–Neelsen stains for acid fast bacilli (AFB) and Gomori methenamine silver (GMS) stain for fungi.

RESULTS

The inclusion criteria were met by 2228 reports concerning lung specimens. Two hundred tweny-six out of 2228 (10.1%) specimens were found positive for GLD. Excluded reports had specimens with findings 'suggestive' of granuloma (5/34), more than one specimen from the same patient (8/34) or findings of granulomatous disease considered incidental (21/34).

The included 190 cases consisted of 59% men (112/190) and 41% women (78/190) with a median age of 52 years (range 10–86 years). A confident, probable and uncertain clinico-pathological diagnosis was

Table 2 Aetiologies of granulomatous lung disease

Diagnosis	Total cases (%)	Confident diagnosis (%)	Probable diagnosis (%)
Infectious aetiology	104(54.7)	94(49.4)	10(5.3)
Mycobacterial infection	50	45	5
Tuberculous	15	15	0
Non-tuberculous	23	21	2
Unclassified†	12	9	3
Coccidioidomycosis	18	18	0
Cryptococcosis	7	7	0
Histoplasmosis	6	6	0
Aspergillosis	4	4	0
Zygomycososis	4	4	0
Actinomycosis	3	3	0
Pseudallescheriasis	2	0	2
Pneumocystis jirovecii	2	0	2
Nocardiosis	1	1	0
Unclassified fungal infection†	3	3	0
Coccidioidosis and aspergillosis	2	2	0
Mycobacterial infection and cryptococcosis	1	1	0
Mycobacterial infection and aspergillosis	1	0	1
Non-infectious aetiology	51(26.8)	36(19)	15(7.8)
Sarcoidosis	39	31	8
Drug-induced lung injury	5	2	3
Methotrexate	2	1	1
Sirolimus	1	1	0
Everolimus	1	0	1
Montelukast	1	0	1
Drug-induced sarcoidosis	1	1	0
Rheumatoid nodule	1	1	0
Granulomatosis with polyangiitis (GPA)	1	0	1
Crohn's disease-associated lung disease	1	0	1
Intravenous drug abuse (talcosis)	1	0	1
Hypersensitivity pneumonia	2	1	1
Uncertain	35(18.4)	N/A	N/A
Total	190	130(68.4)	25(13.2)

Number in (%) indicates percentage of total number of cases.
† The mycobacterial and fungal infections in this category are unclassified due to absence of culture but presence in tissue.

made in 68.4% (130/190), 13.2% (25/190) and 18.4% (35/190) patients, respectively (Table 2). Considering the largest diagnostic tissue provided for each patient, the specimens consisted of 111 transbronchial biopsy (TBB), endobronchial biopsy (EBB) or core biopsies, 26 pneumonectomies, 25 wedge or excision biopsies, 17 partial or complete lobectomies, 6 autopsies and 5 fine-needle aspirations.

Aetiologies

Of the total 190 patients, the aetiologies were concluded to be infectious, non-infectious and uncertain in 54.7% (104/190), 26.8% (51/190) and 18.4% (35/190) patients, respectively.

In four patients, two coexisting infectious organisms known to cause granulomatous inflammation were found. Hence, these cases will occur twice when specific infectious agents are listed.

One hundred four of the 190 cases were found to have an infectious aetiology to GLD. Mycobacterial aetiology were identified in 52/104 patients. Nearly half (23/52) of the mycobacterial infections were classified as non-tuberculous/atypical mycobacteria, and 15/52 patients were classified as tuberculous based on culture. Fourteen of the 52 cases were unclassified mycobacteria due to negative/absent cultures and no definite histopathological characteristics. Among the patients categorized as mycobacterial aetiology, AFB were identified in tissue sections in 29% (15/52) patients and cultured in 73% (38/52) cases. Other means of diagnosis included visualization in smears only, positive PPD and previous history of infection (Table 3).

Fungal organisms were the cause of the granulomatous inflammation in 52/190 patients. *Coccidioides* dominated the spectrum of fungal aetiologies (20/52), followed by *Cryptococcus* (8/52), *Aspergillus* (7/52), *Histoplasma* (6/52), *Zygomyces* (4/52), *Pseudallescheria* (2/52) and *Pneumocystis* (2/52). Due to negative culture, serology and antigen detection in combination with uncertain morphologic

Table 3 Methods of diagnosis in cases with infectious aetiologies

Infectious agent	Total cases	Visualized by special stains (%)	Visualized and culture negative (%)	Culture positive (%)	Other means of diagnosis† (%)
Mycobacteria	52	15 (29)‡	6 (12)‡	38 (73)‡	8 (15)‡
Tuberculous	15	3	0	15	0
Non-tuberculous	23	8	0	23	0
Unclassified	14	6	6	0	8
Fungal organisms	52	43 (83)§	22 (42)§	27 (52)§	3 (6)§
Aspergillus	7	6	5	2	0
Coccidioides	20	17	7	11	2
Cryptococcus	8	8	4	4	0
Histoplasma	6	5	3	2	1
Zygomyces	4	1	0	4	0
Pseudallescheria	2	2	0	2	0
Pneumocystis jirovecii	2	1	0	2	0
Unclassified	3	3	3	0	0
All non-mycobaterial bacteria	4	1 (25)¶	1 (25)¶	2 (50)¶	1 (25)¶
Actinomyces	3	1	1	1	1
Nocardia	1	0	0	1	0

† Other means of diagnosis include visualization on smear, serology/antigen detection.
‡ Per cent of all cases of mycobacteria.
§ Per cent of all cases of fungal organisms.
¶ Per cent of all cases of non-mycobacterial bacteria.

features, the fungal organism could not be specified in three cases. Among the patients with fungal aetiology, the organisms were visualized in tissue sections with histochemical stains in 83% (43/52) of patients and cultured in 52% (27/52) cases. Forty-two per cent (22/52) of the patients with fungal aetiology were visualized in tissue but had negative cultures (Table 3).

Only 4/190 patients had a bacterial aetiology other than mycobacteria. These consisted of three cases of actinomycosis and patient of nocardiosis. The organisms were visualized in tissue in one patient and cultured in two cases (Table 3).

The four patients with co-infections included aspergillosis with coccidioides (two cases), mycobacteria with aspergillosis and mycobacteria with cryptococcosis.

Fifty-one of the 190 patients were considered to have a non-infectious aetiology. All patients, except two patients of hypersensitivity pneumonia, corresponded to either pulmonary manifestation of systemic disease or drug-induced lung injury. Sarcoidosis was the most common aetiology in the non-infectious category constituting 39/51 patients. The second most frequent diagnosis in this category was drug-induced lung disease (5/51) with causative agents being methotrexate (two patients), sirolimus (one patient), everolimus (one patient) and montelukast (one patient). One patient of interferon-induced sarcoidosis was found and listed separately, as it fell in the grey zone between sarcoidosis and drug-induced lung disease. Single patients of other specific diagnosis made up the remainder of this group (Table 2).

In 35/190 patients, no specific diagnoses were favoured clinically or histopathologically, leaving a broad list of differential diagnoses. Twenty-two of the 35 cases with uncertain aetiology had non-necrotizing granulomas, while 10/35 patients had necrotizing granulomas. The remaining 3/35 patients could not be classified based on necrosis as slides were irretrievable. Twelve of the 35 cases with uncertain aetiologies had history of overt or probable immunocompromise.

Immunosuppression and underlying lung disease

A majority of all patients either had overt immunocompromise (55/190), possible immunocompromise (28/190) or underlying lung disease (42/190), leaving 62/190 of patients without significant past medical history and 3/190 where no clinical history was available (Table 4). A higher proportion of patients without significant past medical history were seen in the non-infectious group, had newly diagnosed sarcoidosis and were otherwise healthy.

The most frequent underlying lung diseases were chronic obstructive lung disease (30/42) and interstitial lung disease (7/42). Underlying lung disease was most often seen in the uncertain and infectious aetiologies than the non-infectious aetiology.

Patients with infectious aetiologies of GLD were slightly more likely to be overt or possibly immunosuppressed compared with patients with non-infectious or uncertain diagnoses. In HIV-positive patients (13/190), mycobacterial infection was the most common aetiology found and comprised nearly half (6/13) of these patients.

Necrosis in granuloma

Among all patients with GLD, 42% (80/190) were necrotizing granulomas and 55% (104/190) were

Table 4 Underlying lung disease and factors causing immunosuppression

	Infectious (%)	Non-infectious (%)	Uncertain (%)	Total (%)
Overt immunosuppression	31 (30)†	16 (31)‡	8 (23)§	55 (29)¶
Status post organ transplantation	14	1	2	17
Collagen vascular disease	3	12	0	15
HIV	12	0	1	13
Chemotherapy for cancer	2	2	5	9
Interferon treated Hepatitis C	0	1	0	1
Possible immunosuppression	19 (18)†	5 (10)‡	4 (11)§	28 (15)¶
Diabetes	7	4	3	14
Substance abuse	8	1	1	11
Diabetes and substance abuse	4	0	0	4
Underlying lung disease	26 (25)†	4 (8)‡	12 (34)§	42 (22)¶
COPD	20	3	7	30
ILD	2	0	5	7
Lung cancer (no therapy)	2	0	0	2
Cystic lung disease	1	0	0	1
Asthma	1	1	0	2
No known risk factor	26 (25)†	26 (51)‡	10 (29)§	62 (33)¶
Past medical history irretrievable	2 (2)†	0	1 (3)§	3 (2)¶
Total	104	51	35	190

† Per cent of all infectious patients;
‡ Per cent of all non-infectious patients;
§ Per cent of all uncertain patients;
¶ Per cent of all patients
COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; ILD, onterstitial lung disease.

Table 5 Necrotizing versus non-necrotizing granulomatous disease

Aetiology	Cases (%)	Necrotizing granuloma (%)	Non-necrotizing granuloma (%)
Infectious	104 (55)	69 (36)	32 (17)
Mycobacterial	50	34	16
Coccidioides	18	9	9
Cryptococcosis	7	4	3
Histoplasmosis	6	5	1
Aspergillus	4	4	0
Others	19	13	3
Non-infectious	51 (27)	1 (0.5)	50 (26.5)
Sarcoidosis	39	0	39
Drug induced†	6	0	6
Others	6	1	5
Uncertain	35 (18.5)	10 (5)	22 (11.5)
Total	190	80 (42)	104 (55)

Number in (%) indicates percentage of total number of cases. Three per cent of patients could not be classified based on necrosis as slides were irretrievable.
† Drugs include methotrexate, sirolimus, everolimus and montelukast.

non-necrotizing granulomas (Table 5). The remaining 3% (6/190) of specimens could not be categorized because slides were irretrievable. Specimens with infectious aetiology showed necrotizing granulomatous inflammation in a majority (69/104) of cases. Among the cases with non-infectious aetiologies, non-necrotizing granulomas were seen in 50/51 cases. Conversely, excluding uncertain aetiologies, all except one of the cases with necrotizing granulomas was of infectious aetiology. Rheumatoid nodule was the only case in the non-infectious aetiology to show necrotizing granulomatous inflammation. Necrosis in granulomas was found to have a statistically significant association with the presence of infection ($P < 0.001$).

DISCUSSION

The main findings of this study revealed that mycobacterial infections were the most common cause for GLD, with nearly half of these classified as

non-tuberculous mycobacteria. The most common fungal pathogen identified was coccidiomycosis. The most common non-infectious aetiology found was sarcoidosis.

This is one of the largest single institution surveys of incidence of different aetiologies of pulmonary granulomatous inflammation. Only two comparable studies have previously been done.[5,6] In concordance with the results of Woodard *et al*. and Mukhopadhyay *et al.*, infection and sarcoidosis were the two most common aetiologies of pulmonary granulomatous inflammation in our study.[5,6] Infection was the most common cause of GLD encountered in our study (54.7% of all cases) and the study by Woodard *et al*. (54% of all cases), while it was the second most common aetiology in the study by Mukhopadhyay *et al*. (28% of all cases).[5,6] Mycobacteria and fungi dominated the aetiologies of infectious diseases in the above studies.

Mycobacterial disease made up for 27% of all our patients, while Woodard *et al*. reported an incidence of 20% pulmonary mycobacterial infection, all tuberculous.[6] The difference reflects the sharp increase in diagnosed atypical mycobacterial disease in post-HIV era and decline of tuberculosis since the mid-1990s in United States.[10,11] Surprisingly, Mukhopadhyay *et al.*, with specimens collected during 2000–2010, found only 8% incidence of mycobacterial infections in US institutions and 19% in non-US institutions, which was not consistent with our results.[5] This difference may be due to a higher local incidence and that our institution is a regional referral centre and has a lung transplant programme.

Fungal infections comprised almost half of all infectious aetiologies and a quarter of all cases. Being endemic in the South-West Texas region, *Coccidioides* was the most commonly diagnosed fungal organism.[12] *Histoplasma*, endemic in midwest and northeast United States, was the causative agent in a handful of cases.[13] The rest of the fungal organisms are ubiquitous. The spectrum of fungal infections in our study was different from previous studies, reflecting the fact that incidence of fungal infections is heavily influenced by geographic location.[5,6] In the study by Mukhopadhyay *et al.*, 19% of total cases in United States were of fungal aetiology, the majority being *Histoplasma* (47% of fungal infections), with all patients hailing from *Histoplasma*-endemic areas in midwest and northeast United States.[5] In the study by Woodard *et al.*, fungal infections comprised 30% of all cases, with the majority also being *Histoplasma* (62% of fungal infections), and was based in North Carolina, another endemic area for *Histoplasma*.[6]

Excluding uncertain aetiologies, all patients with necrotizing granulomatous disease, except one, were found to have an infectious aetiology, with statistical significance. This finding is especially important, as it helps pathologists and clinicians narrow down the differential diagnosis based on identifying necrosis histologically, without preceding clinical or microbiological information.

Only 1/3 of patients finally diagnosed as mycobacterial infection had organisms visualized in the tissue, while 2/3 were positive by culture, underscoring the value of culture in patients suspected of mycobacterial aetiology. This finding is in concordance with previous studies, where 62–65% of mycobacterial infections were grown in culture and only 30–31% were visualized in tissue.[5,6]

In contrast, fungal organisms were visualized histologically in over 4/5 of our patients with fungal aetiology. This is similar to earlier findings, where among all patients with fungal aetiology, over 60% were visualized in tissue sections.[5]

Sarcoidosis dominated the spectrum of non-infectious granulomatous disease, comprising 20% of all patients. This finding is consistent with preceding studies that revealed an incidence of sarcoidosis of 22–31%.[5,6]

The next frequent aetiology in the non-infectious category was pulmonary manifestations of prescription drugs. Medications like methotrexate and sirolimus are known to cause granulomatous interstitial pneumonitis resembling sarcoidosis.[14] There was one patient of α-interferon-induced sarcoidosis with lung involvement. The appearance/reactivation of sarcoidosis with interferon therapy is described in the literature and may involve multiple organ systems including lungs.[15]

There are limitations of this study that deserve mention. The study carries the inherent pitfalls of a retrospective design. Nevertheless, it remains one of the largest series published to date evaluating the aetiologies of GLD. Because the study was carried out in a single site geography likely influenced the results. It is possible that the incidence of mycobacterial infections and sarcoidosis in other geographic regions, where health-care and ethnic differences exist, might defer from our results. Despite this, previous studies are consistent with our findings.[5,6] The diagnosis of 'probable' infection partly relied on a histological diagnosis and may have affected the classification of these patients. Nevertheless, these patients had other characteristics (i.e. history, clinical suspicion and other positive testing) that supported the diagnosis of an infection, but it remains possible that misclassification occurred. Another limitation is that diagnoses obtained from TBB and EBB may have been partially limited by the size of the specimen and the blinded manner in which they were obtained. It is also possible that the granulomatous process itself might have eradicated causative microorganisms. Finally, although controversial, many experts require clinical evidence of sarcoidosis in at least two organs necessary for a diagnosis of sarcoidosis. Nevertheless, in this series, the diagnosis of sarcoidosis was supported by clinical and radiological findings of sarcoidosis in conjunction with negative microbiological testing.

GLD continues to be a diagnostic challenge. Even after careful clinical and patholgical re-examination, a cause can be established in only 60% patients.[16] At our institution, a lung specimen with a necrotizing granulomatous inflammation is most likely to be infectious, probably atypical mycobacterial or coccidioidomycotic. In a case of non-necrotizing GLD, the aetiology is likely to be non-infectious, probably sarcoidosis. In a necrotizing granuloma with

negative AFB and GMS stains, the aetiology is more likely to be due to atypical mycobacteria and less likely due to *Mycobacterium tuberculosis*. Diagnostic yield is better on cultures for mycobacterial infections than special histochemical stains on tissue, whereas for fungal infections, more than 80% of patients have organisms visible in tissue sections. Further studies are needed in different geographic regions to better understand the spectrum of GLD.

REFERENCES

1 Müller-Quernheim J, Gaede KI, Fireman E, Zissel G. Diagnoses of chronic beryllium disease within cohorts of sarcoidosis patients. *Eur. Respir. J.* 2006; **27**: 1190–5.
2 Adams DO. The granulomatous inflammatory response. A review. *Am. J. Pathol.* 1976; **84**: 164–92.
3 El-Zammar OA, Katzenstein AL. Pathological diagnosis of granulomatous lung disease: a review. *Histopathology* 2007; **50**: 289–310.
4 Marinelli WA, Davies SF. Granulomatous diseases of the lung that mimic respiratory infections. *Semin. Respir. Infect.* 1988; **3**: 181–202.
5 Mukhopadhyay S, Farver CF, Vaszar LT, Dempsey OJ, Popper HH, Mani H, Capelozzi VL, Fukuoka J, Kerr KM, Zeren EH *et al*. Causes of pulmonary granulomas: a retrospective study of 500 cases from seven countries. *J. Clin. Pathol.* 2012; **65**: 51–7.
6 Woodard BH, Rosenberg SI, Farnham R, Adams DO. Incidence and nature of primary granulomatous inflammation in surgically removed material. *Am. J. Surg. Pathol.* 1982; **6**: 119–29.
7 Hutton Klein JR, Tazelaar HD, Leslie KO, Colby TV. One hundred consecutive granulomas in a pulmonary pathology consultation practice. *Am. J. Surg. Pathol.* 2010; **34**: 1456–64.
8 Segal EL, Starr GF, Weed LA. Study of surgically excised pulmonary granulomas. *J. Am. Med. Assoc.* 1959; **170**: 515–22.
9 Ulbright TM, Katzenstein AL. Solitary necrotizing granulomas of the lung: differentiating features and etiology. *Am. J. Surg. Pathol.* 1980; **4**: 13–28.
10 Falkinham JO 3rd. Epidemiology of infection by nontuberculous mycobacteria. *Clin. Microbiol. Rev.* 1996; **9**: 177–215.
11 Oren E, Winston CA, Pratt R, Robison VA, Narita M. Epidemiology of urban tuberculosis in the United States, 2000–2007. *Am. J. Public Health* 2011; **101**: 1256–63.
12 Kirkland TN, Fierer J. Coccidioidomycosis: a reemerging infectious disease. *Emerg. Infect. Dis.* 1996; **2**: 192–9.
13 Kauffman CA. Histoplasmosis: a clinical and laboratory update. *Clin. Microbiol. Rev.* 2007; **20**: 115–32.
14 Flieder DB, Travis WD. Pathologic characteristics of drug-induced lung disease. *Clin. Chest Med.* 2004; **25**: 37–45.
15 Fantini F, Padalino C, Gualdi G, Monari P, Giannetti A. Cutaneous lesions as initial signs of interferon alpha-induced sarcoidosis: report of three new cases and review of the literature. *Dermatol. Ther.* 2009; **22**(Suppl. 1): S1–7.
16 Mukhopadhyay S, Wilcox BE, Myers JL, Bryant SC, Buckwalter SP, Wengenack NL, Yi ES, Aughenbaugh GL, Specks U, Aubry MC. Pulmonary necrotizing granulomas of unknown cause: clinical and pathologic analysis of 131 patients with completely resected nodules. *Chest* 2013; **144**: 813–24.

