

Lung granuloma: A clinicopathologic study of 158 cases

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Abstract:

BACKGROUND AND AIMS: A granuloma is a common pathological diagnosis in lung biopsies and is caused by a variety of etiologies. The aim of this study was to assess the etiology and frequency of different cases of lung granulomas.

METHODS: The medical records of all patients who had lung granulomas between 2005 and 2013 were retrospectively reviewed. Based on the histological features of the granulomas, along with the clinical, laboratory, and radiological findings, an attempt was made to identify the etiology of the granuloma in each case.

RESULTS: A total of 158 patients with lung biopsy specimens showing lung granulomas were identified. The histological findings revealed necrotizing granulomas in 92 (58%) of the cases and nonnecrotizing granulomas in 66 (42%). A definite etiology was determined in 133 cases (84%), whereas in 26 cases (16%), the etiology could not be identified despite an extensive workup. Infection was the most frequent cause of granuloma, accounting for 105 cases (66%). Mycobacterial tuberculosis (TB) was the type of infection that caused the largest number of granulomas, and was responsible for 100 cases (63%). Among the noninfectious etiologies of lung granuloma, sarcoidosis was the most common cause, accounting for 20 (13%) of the cases.

CONCLUSIONS: Mycobacterial TB and sarcoidosis are the most common causes of lung granulomas in our region. In a substantial proportion of cases, the cause may not be identified despite an extensive workup.

Keywords:

Lung granuloma, mycobacterial tuberculosis, necrotizing granulomas, nonnecrotizing granulomas, sarcoidosis

A granuloma is a common pathological diagnosis obtained from lung biopsies and lung resection specimens characterized histologically by aggregates of epithelioid histiocytes (macrophages)^[1,2] and classified either as necrotizing or nonnecrotizing based on the presence or absence of necrosis.

A variety of etiologies are associated with lung granulomas. Necrotizing lung granulomas have been reported, mostly in association with infection. In particular, mycobacterial and fungal infections are the

most common etiologies.^[2-4] Noninfectious causes of necrotizing granulomas include granulomatosis with polyangiitis (Wegener's granulomatosis), allergic angiitis and granulomatosis (Churg-Strauss syndrome), necrotizing sarcoid granulomatosis, rheumatoid nodule, and bronchocentric granulomatosis.^[5] Nonnecrotizing lung granulomas, on the other hand, occur mostly in sarcoidosis.^[2-5] Other causes associated with nonnecrotizing lung granulomas include infections, chronic hypersensitivity pneumonitis, lymphoid interstitial pneumonia, aspiration pneumonia, chronic granulomatous disease, common variable immunodeficiency, Crohn's disease,

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berylliosis, drug abuse (talc granulomatosis), and drug reactions.^[5] In a substantial percentage (8%–42%) of cases, the cause may not be determined even with extensive workup.^[2-6] Such cases are labeled “granulomas of unknown etiology.”

A few previous studies have reported the causes of lung granuloma.^[3-9] Apart from three studies that reported the incidence of different etiological causes of lung granuloma,^[3,4,7] most other studies have been limited to a subset of cases related to solitary necrotizing granulomas,^[6] surgically excised granulomas,^[9] or granulomas seen in consultation practice.^[8] A study by Mukhopadhyay *et al.*, which included cases of lung granuloma from different geographical settings, reported that infection and sarcoidosis are the most common causes of granulomatous inflammation in lung biopsies, with significant geographical differences in the incidence of mycobacteria and fungi.^[3] The aim of this study was to assess the etiology and frequency of different causes of lung granuloma from lung biopsies at King Abdulaziz Medical City-Riyadh (KAMC-R) in Saudi Arabia using an integrative approach including histopathology, clinical findings, and microbiological data.

Methods

From January 2005 to December 2013, the pathology laboratory database at KAMC-R was reviewed to identify all pathology reports showing lung granulomas. The medical records of these patients were reviewed. Nonrespiratory specimens were excluded from the study. Demographic, clinical, microbiological, and radiological findings were collected.

A granuloma was histopathologically defined as a compact aggregate of histiocytes (epithelioid cells) with or without giant cells. Granulomas were further categorized as necrotizing or nonnecrotizing based on the presence or absence of necrosis.^[1,2] The lung biopsy specimens were obtained through transbronchial and endobronchial biopsies, computed tomography (CT)-guided core biopsies, or surgical specimens. A chest pathologist (HB) who was blinded to the clinical diagnosis examined all histological slides. Based on the histological features of the granuloma, along with the clinical, laboratory and radiological findings, an attempt was made to identify the etiologic cause in each case. Infectious etiology was diagnosed based on positive stains and/or microbiological cultures, or on the response to empirical anti-tuberculosis (TB) therapy in cases of high probability of TB based on clinical and radiological findings. Sarcoidosis was diagnosed based on a combination of compatible clinical and radiological findings, consistent histology, and the absence of bacterial or

fungal infections. Medical records, including response to specific therapy, improvement in clinical conditions, and radiological findings were reviewed for follow-up visits and final diagnoses. If the available data did not lead to an etiological diagnosis, or in the case of a lack of favorable response following the specific therapy or changed therapy during the course of disease, the granuloma was classified as a granuloma of unknown etiology. The study was approved by the Institutional Review Board of the National Guard Health Affairs, Riyadh, Saudi Arabia. All the data were anonymized and pooled for retrospective analysis.

Results

A total of 158 patients with lung biopsy specimens showing lung granulomas were identified in our pathology laboratory database during the study period, 2005–2013. The lung samples were obtained through transbronchial biopsy in 128 cases (82%), CT-guided core biopsies in 30 cases (19%), and surgical specimens in 63 cases (40%).

Baseline characteristics for these 158 patients included a mean age of 47 ± 19 years; and 50% male patients) [Table 1]. All patients presented with at least one of the following symptoms: cough ($n = 102$, 65%), fever ($n = 77$, 49%), dyspnea ($n = 70$, 44%), weight loss ($n = 53$, 34%), night sweats ($n = 31$, 20%), chest pain ($n = 23$, 15%), and hemoptysis ($n = 10$, 6%). The most frequent chest radiological abnormalities

Table 1: Demographic and clinical characteristics of patients with granuloma (n=158)

Patients characteristic	n (%)
Age (years), mean±SD	47±19
Male, sex	80 (50)
Symptoms	
Cough	102 (65)
Fever	77 (49)
Dyspnea	70 (44)
Weight loss	53 (34)
Night sweats	31 (20)
Chest pain	23 (15)
Arthralgia/arthritis	11 (7)
Hemoptysis	10 (6)
Skin rash	5 (3)
Radiological features	
Lymphadenopathy	89 (56)
Parenchymal	
Airspace	75 (47)
Nodular	42 (27)
Interstitial	29 (18)
Mass/nodules	19 (12)
Cavity	11 (7)
Pleural effusion/thickening	50 (32)

SD=Standard deviation

were alveolar/airspace opacities ($n = 75$, 47%), multiple nodular opacities ($n = 42$, 27%), interstitial changes ($n = 29$, 18%), mass/nodules ($n = 19$, 12%), and lung cavity ($n = 11$, 7%). Other associated chest radiological features included lymphadenopathy ($n = 89$, 56%) and pleural changes ($n = 50$, 32%) [Table 1].

Histologic findings revealed necrotizing granulomas in 92 cases (58%) and nonnecrotizing granulomas in 66 cases (42%). A definite etiology was determined in 133 cases (84%), whereas in 26 cases (16%), no etiology could be identified. Infection was found to be the most frequent cause of all types of granulomas, and was responsible for 105 cases (66%) [Table 2].

The leading etiology for necrotizing granulomas was TB infection 75 (82%). Less common underlying etiologies of necrotizing granulomas included sarcoidosis (three cases; 3%), as well as other infections (nontuberculous mycobacteria, fungal), granulomatosis with polyangiitis (Wegener's granulomatosis), and rheumatoid arthritis, (one case each, 1.0%). Unknown etiologies were encountered in 9 (10%) of the necrotizing granuloma cases [Table 2].

TB infection 25 (38%) and sarcoidosis 17 (26%) were the most common etiologies for nonnecrotizing granulomas. Less common causes of nonnecrotizing granuloma were fungal infections (two cases; 3%), hypersensitivity pneumonitis (two cases; 3%), drug reaction (two cases; 3%), and foreign body (one case; 1%). Unknown etiologies were encountered in 17 (26%) of the nonnecrotizing granuloma cases [Table 2].

Discussion

The present study assessed the causes of lung granulomas in pathological specimens in a single referral tertiary center. Consistent with previous studies, lung granulomas are associated with a variety of etiologies. In this study, infections and sarcoidosis are the most

common cause, and are responsible for about 80% of the cases. Previous studies similar to ours also report that infection and sarcoidosis account for the majority of lung granulomas.^[3-9]

Infectious agents are responsible for a substantial number of lung granulomas. In our study, infection, represented 66% of the cases; this similar to previous reports which showed that infection was the most common cause of granuloma, responsible for 28%–55% of all cases.^[3-9]

Mycobacterial and fungal infections were reported to cause the largest numbers of lung granulomas.^[3,4,7] In our study, mycobacterial TB was responsible in about 63% of the cases. In contrast, previous studies have shown a lower incidence of mycobacterial tuberculous infection and a higher number of the nontuberculous mycobacterial and fungal infections, likely reflecting variation due to geographical location and the prevalence of mycobacterial TB.^[3,4] Nazarullah *et al.* reported that among 190 cases with lung granulomas, mycobacterial infection was responsible for 27% of all cases including 7% with mycobacterial TB,^[4] whereas Mukhopadhyay *et al.* reported that among 500 cases of lung granulomas from seven countries there was an 8% incidence of mycobacterial infections (included 0.5% of TB) in USA and 19% (included 9% of TB) outside USA.^[3] Fungal infections were encountered less frequently as a cause of lung granuloma, and were responsible for about 2% of lung granuloma cases in our study. This is similar to the rate reported by Mukhopadhyay *et al.* from outside USA, where fungal infections were responsible for about 4% of all lung granuloma cases. In contrast, higher rates are reported from USA, where fungal infection represents 19%–27% of all causes of lung granulomas.^[3,4]

Among the noninfectious etiologies of lung granuloma, sarcoidosis is the most common cause, accounting for 13% of the cases; this is lower than the rates reported from the previous studies cited above, which reported that sarcoidosis accounts for 20%–31% of all cases.^[2-9]

Table 2: Frequencies of various etiologies of granulomas in biopsy and resected specimens

	All ($n=158$), n %	Necrotizing granulomas ($n=92$), n %	Nonnecrotizing granulomas ($n=66$), n %
Infectious	105 (66)	78 (85)	27 (41)
TB	100 (63)	75 (82)	25 (38)
Nontuberculous mycobacterial	2 (1)	2 (2)	-
Fungal	3 (2)	1 (1)	2 (3)
Noninfectious	53 (34)	14 (15)	39 (59)
Sarcoidosis	20 (13)	3 (3)	17 (26)
Hypersensitivity pneumonitis	2 (1)	-	2 (3)
Drug reaction	2 (1)	-	2 (3)
Granulomatosis with polyangiitis	1 (1)	1 (1)	-
Rheumatoid arthritis	1 (1)	1 (1)	-
Foreign body	1 (1)	-	1 (1)
Unknown etiology	26 (16)	9 (10)	17 (26)

TB=Tuberculosis

A substantial number of lung granulomas remain without definitive etiologies despite extensive workup. Previous studies reported that the etiology of pulmonary granulomas remains unknown in 8%–41% of the cases.^[2-9] In the present study, 26 (16%) cases were labeled as unknown etiology even after thorough clinical, radiological, and microbiological correlation. In a study of 500 granulomatous lung diseases, 210 (42%) were reported to be of unknown etiology.^[3] Ulbright and Katzenstein reported that, in a study of 86 necrotizing granulomas of the lung presenting as single nodules, the etiology in 22 cases (26%) was undetermined.^[6] In another study reported by Mukhopadhyay *et al.* among a series of 131 cases of surgically resected pulmonary necrotizing granulomas that were unexplained at the time of the initial histological diagnosis, 52 cases (40%) remained unexplained even after extensive review.^[10] Among 190 cases of granulomatous lung disease, Nazarullah *et al.* reported that 18% of the cases were of uncertain etiologies.^[4] Many hypotheses have been proposed to explain this inability to arrive at a definitive diagnosis in many cases of lung granuloma, especially in the case of necrotizing granuloma where infections are by far the most common cause. These include lack of isolation and detection of the organisms causing the granuloma due to low numbers of these organisms in the tissue samples either due to the presence of only a few organisms in the biopsied samples or due to the elimination of organisms by the inflammatory process. In addition, the small size of biopsy samples submitted for pathological analysis may influence the ability to make a definitive diagnosis. Favorable outcomes, in terms of clinical improvement and radiological resolution, or stabilization of radiological findings, have been reported in many cases, even if no treatment was given.^[6,10]

The present study had several limitations that warrant consideration. First are limitations that are inherent in the retrospective design. In addition, the present study was performed in a single tertiary referral center which may have introduced referral bias and may not accurately represent the incidence of different causes of lung granuloma in the population or in other geographical areas. Other potential limitations of our study include the use of different methods to obtain the lung samples, which may have influenced the identification of different causes of lung granulomas. This may lead to misclassification of some cases as “granuloma of unknown etiology.” However, even with large samples obtained by surgical methods, previous studies reported that the etiology cannot be determined in 25%–40% of the cases.^[6,10] In addition, using molecular methods such as polymerase chain reaction to identify organisms for tuberculous mycobacteria are limited to the tissue submitted in recent years; these methods

may increase the yield to identify organisms present in small numbers in the tissue and lead to an increase of the number of cases with specific diagnosis. Nevertheless, many cases of lung granuloma remain without obvious etiology, despite thorough clinical, histological, and microbiological correlations even in current era. Despite these limitations, this study represents the only study of lung granuloma in our region and one of the few largest studies published to date assessing the cause of lung granulomas.

Conclusions

The present study was the first conducted in our region and one of the few largest studies published to date that assessed the cause of lung granuloma. The study demonstrated that mycobacterial TB and sarcoidosis are the most common causes of lung granulomas. We found that in a substantial proportion of cases with lung granuloma, the cause may not be identified despite extensive workup.

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Conflicts of interest

There are no conflicts of interest.

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