Granulomatous Lung Diseases: A Retrospective study of Differential Diagnosis and CT Features

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Aims and objectives

Granulomatous Lung Diseases (GLD) comprises a wide range of infectious and non-infectious pathologies that present the same pattern of chronic inflammatory response [1]. The granulomas emerge after an attempt of the cellular immune response to contain an agent of difficult eradication. Histologically, granulomas consist of an aggregation of macrophages that transform into epithelioid cells, surrounded by monocytes - mainly lymphocytes [2].

Mycobacterial and fungal infections are the most common infectious causes of GLD, including tuberculosis (TB), nontuberculous mycobacteriosis, Histoplasma, Cryptococcus, Coccidioides, Blastomyces and Aspergillus [2].

Non-infectious GLD might be the result of several different physiopathological conditions [3], including inflammatory diseases, such as sarcoidosis; exposure related lung diseases, such as hypersensitivity pneumonitis; vasculitis, most commonly granulomatosis with polyangiitis; autoimmune disorders, such as rheumatoid nodules; and also associated with malignancies [2, 4]. Granulomatous inflammation has been occasionally found associated with some neoplastic diseases, including lung cancer, and is usually attributed to a 'sarcoid reaction', although some authors also suggest a possible correlation with a previous granulomatous lung infection, specially in endemic areas [5, 6].

Finally, there are granulomatous lesions of uncertain etiology, comprising a group known as Granulomatous Lesions of Unknown Significance - GLUS. This term was used for the first time in 1990 to designate biopsies whose results contained epithelioid granulomas without a definitive cause, even after subsequent investigation [7].

The incidence of GLD vary according to geographical location and ethnical features of the population, which might influence not only the occurrence of infectious GLD but also non-infectious causes, including exposure related GLD and autoimmune diseases.

Imaging findings of GLD might be much similar despite the cause, but particularities of each etiology influence the radiological features and corroborate when a confident pathological diagnosis is not possible.

This study aimed to outline the incidence of the etiologies of biopsy proven GLD in a tertiary hospital in Sao Paulo, Brazil, as well as its correlation with the imaging findings.
Methods and materials

Patient population:

In this retrospective study, all 994 consecutive lung biopsies performed between January 2013 and December 2017 in our institution, a tertiary hospital located in Sao Paulo, Brazil, were retrieved from hospital records. All samples were collected by intra-operative biopsy, bronchoscopy with transbronchial biopsy or percutaneous CT-guided needle biopsy.

This study was approved by institutional and national ethics committees. Due to the retrospective nature of the study, the informed consent was not necessary.

The inclusion criteria was the existence of granulomatous lesions in the pathology report (88 of 994 patients). Patients without chest CT previous to biopsy were excluded and the final study population was 75 patients (Fig. 1).

Data acquisition:

Demographic and pathologic data of all cases were reviewed and collected (C.V.O.). Two radiologists (each one with 1 year experience in chest radiology), blinded to the etiology of the GLD, reviewed the Chest CT of all patients and classified the imaging features of each case (D.R. and M.B.R.). A third radiologist (chest specialist with 10 years experience) reviewed all cases of disagreement to reach a consensus (H.J.L.).

Data analysis:

The CT findings were categorized by the main radiological pattern: consolidation, ground-glass opacity, mass, nodular or micronodular. Micronodular pattern was subcategorized into random, perilymphatic or centrilobular. Other analyzed CT features included: associated findings (cavity, mediastinal/hilar lymphadenopathy, pleural effusion), distribution (focal, multifocal or diffuse), location (right, left or both lungs) and specific affected pulmonary lobes.

Statistical analysis:

Categorical data were represented by absolute (n) and relative (%) frequency, and contingency matrices were analyzed by Pearson's chi-squared test. A risk # # 5% for type I error and risk # # 20% for type II error was considered for the present study. P-value of less than 0.05 was considered statistically significant.
Fig. 1: Study population diagram. Retrospective study of consecutive lung biopsies performed between January 2013 and December 2017.

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Results

The study population of 75 cases consisted of 49.3% men (37/75) and 50.7% women (38/75). The median age was 59 (range 18-96). The majority of samples were obtained by CT-guided biopsy (47/75, 62.7%), 23 (30.7%) by intra-operative biopsy and five (6.7%) were acquired by bronchoscopy.

Etiology

The table below summarizes the etiologies of GLD in our study population. Infection was the most common cause of GLD (47/75, 62.7%), non-infectious causes occurred in 13.3% (10/75) and GLUS corresponded to 24% (18/75) of the cases. Among infectious causes of GLD, the great majority was fungal or mycobacterial, led by *Histoplasma capsulatum* (27/75, 36%) (Fig. 2A) and *Mycobacterium tuberculosis* (7/75, 9.3%) (Fig. 2B). Unclassified mycobacterial infection represented 6.7% of cases (5/75). Other fungal infections included *Paracoccidioidomycosis* (3/75, 4.0%), *Aspergillosis* (3/75, 4.0%) and *Cryptococcosis* (1/75, 1.3%). Only one case of parasitic infection occurred, represented by *Paragonimiasis*. Among non-infectious causes, sarcoidosis occurred in 4 cases (5.4%) (Fig. 2C) and granulomatous inflammation associated with cancer occurred in 6 cases (8.0%). Other non-infectious causes did not occur in our study population.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Total cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious</td>
<td>47 (62.7)</td>
</tr>
<tr>
<td>Fungal</td>
<td>34</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td>27</td>
</tr>
<tr>
<td>Paracoccidioidomycosis</td>
<td>3</td>
</tr>
<tr>
<td>Aspergillosis</td>
<td>3</td>
</tr>
<tr>
<td>Cryptococcosis</td>
<td>1</td>
</tr>
<tr>
<td>Mycobacteriosisis</td>
<td>12</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>7</td>
</tr>
<tr>
<td>Unclassified</td>
<td>5</td>
</tr>
<tr>
<td>Paragonimiasis</td>
<td>1</td>
</tr>
<tr>
<td>Non-infectious</td>
<td>10 (13.3)</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>4</td>
</tr>
<tr>
<td>Cancer associated with GI</td>
<td>6</td>
</tr>
<tr>
<td>GLUS</td>
<td>18 (24)</td>
</tr>
</tbody>
</table>
Total 75 (100)

(%) = Percentage of total number of cases

Gi = Granulomatous Inflammation

GLUS = Granulomatous Lesions of Unknown Significance

**Table - Etiology of Granulomatous Lung Diseases**

**Chest CT Findings**

The main radiological pattern, location and distribution, as well as associated imaging findings are summarized in Table 1.

The nodular pattern was the commonest CT finding overall (49/75, 65.3%), the second was centrilobular micronodules (9/75, 12%), followed by consolidation (7/75, 9.3%) and mass (6/75, 8.9%) (Fig. 3).

The majority of cases had unilateral pulmonary findings (59/75, 78.7%), more commonly in the right side (31/75, 41.3%). Two-thirds of the cases showed a focal lesion on chest CT (50/75); multifocal (20/75, 26.7%) and diffuse (5/75, 6.7%) distribution of lesions were less common.

Among associated findings, hilar or mediastinal lymphadenopathy occurred respectively in 16% (12/75) and 10.7% (8/75) of the cases; pleural effusion (8/75) and cavitation (8/75) also occurred in 10.7% of cases (Fig. 4).

Nodular pattern was the most common imaging feature in Histoplasmosis cases (25/27, 92.6%), whereas it occurred in half of cases (24/48) of GLD of other causes (p<0.05). None of the cases of Histoplasmosis presented micronodules or ground glass opacities as the main patterns. Cavitation also was not present in any case. Regarding distribution of the lung lesions, all cases except one (26/27, 96.3%) were focal in Histoplasmosis, while in other causes of GLD focal distribution occurred in 50% (24/48) of cases (p<0.05) (Table 2).

Among patients with tuberculosis, the second etiology of GLD in our study population, the most common imaging pattern was centrilobular micronodules (3/7, 42.9%), significantly more frequent than in other causes of GLD (6/68, 8.8%). Cavitation also was highly suggestive of mycobacterial infection, occurring in 57.1% (4/7) of cases of tuberculosis, compared to only 2 cases (2.9%) of all other causes of GLD, considering that one of these 2 cases occurred in a patient with unclassified mycobacteriosis (Tables 3 and 4).
All 4 cases of sarcoidosis had multifocal distribution and patterns varied between consolidation, nodular and perilymphatic micronodules. Mediastinal or hilar lymphadenopathy occurred in majority of cases.
Fig. 2: Histopathological features of Granulomatous Lung Diseases. A. Histoplasmosis. GMS (400x): necrotizing granulomatous inflammation with Histoplasma capsulatum yeasts (green arrows) in a VATS lung biopsy. B. HE (50x): necrotizing granulomatous inflammation in a lung biopsy of a patient with tuberculosis. C. HE (50x): non necrotizing granulomatous inflammation in a lung biopsy of a patient with sarcoidosis.

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Fig. 3: Axial CT images of patients with different granulomatous lung diseases showing the main radiological patterns.

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**Fig. 4:** Chest CT images of patients with different granulomatous lung diseases showing the main associated findings.

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Table 1: Chest CT features of granulomatous lung diseases. GI = Granulomatous Inflammation GLUS = Granulomatous Lesions of Unknown Significance

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**Table 2:** CT findings in patients with and without Histoplasmosis.

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**Table 3:** CT findings in patients with and without Tuberculosis.

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Table 4: CT findings in patients with and without Mycobacteriosis (Tuberculosis and Unclassified Mycobacteriosis).

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Conclusion

Despite considered a high TB burden country by World Health Organization [8], in our study, held in one single tertiary hospital located in Sao Paulo, Brazil, Histoplasma infection was more frequent than tuberculosis among biopsy proven GLD. Mukhopadhyay et al [9] reviewed the causes of GLD in 7 different countries, including Brazil. On this study population, tuberculosis occurred in 13 of 50 cases of GLD from Brazil (26.0%), and none of the Brazilian cases was due to histoplasmosis, which was diagnosed exclusively in the USA. The study of Nazarullah et al [10] reviewed GLD diagnosed in a single institution in San Antonio, Texas, and also demonstrated predominance of mycobacterial infection, with nearly half classified as non-tuberculous mycobacteria. One possible reason for the significant difference in the incidence of mycobacterial infection in our study population might be the fact that samples other than lung biopsy, such as sputum or bronchoalveolar lavage, were not included in our study. It also suggests that possibly only minority of cases of tuberculosis and other mycobacteriosis have been diagnosed by lung biopsy.

Centrilobular micronodules and cavitation are typical imaging features of tuberculosis and were significantly more common in TB and all mycobacterial infections compared to other causes of GLD in our study.

The nodular pattern and focal distribution were the commonest CT features in overall patients, which can be explained by the crescent indication of lung biopsies for investigation of indeterminate solitary pulmonary nodules suspected for malignancy [11]. Histoplasma infections presents the same predominant imaging features on CT and should be considered a differential diagnosis in the investigation of solitary pulmonary nodules in asymptomatic patients, specially when neoplasms are of low probability or discarded and pathology suggests granulomatous disease [12].
References


