

The importance of non-necrotising granulomatosis

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Abstract

Objective: The diagnosis of non-necrotising granulomatosis (NNG) is very frequent in clinical practice. There are few studies, however, within the spectrum of pathologies that cause NNG; consequently, except for sarcoidosis, little information is available. The objective is to determine the prevalence of sarcoidosis, autoimmune diseases and other entities in NNG.

Methods: We collected all pathological reports with a diagnosis of non-necrotising granulomatosis from 1 January 2010 to 31 December 2014 in the Clinical University Hospital of Santiago de Compostela, Spain.

Results: A total of 290 tissue samples from 207 patients were reviewed. Of these patients, 50.7% were women, with a mean age of 51.2 years. The origins of the samples were: skin 32.9%, lymph nodes 26.6%, transbronchial biopsy 14.5%, lung 5.8% and others 20.2%. Final diagnoses were: sarcoidosis 59.9%; infectious diseases 7.7%, including tuberculosis 4.0% and non-tuberculous mycobacterial infection 1.4%; foreign body granulomatosis 6.3%; neoplasms 5.9%; autoimmune disease 3.1% and others 4.0%. A diagnosis was not determined in 5.9% patients.

Conclusion: The prevalence of sarcoidosis in NNG is over 50%, while autoimmune disease prevalence is considerably lower (3.1%), with Wegener granulomatosis being the most commonly reported. The most frequent alternative diagnosis was infectious disease, mainly tuberculosis.

Keywords: Infection, sarcoidosis, cancer, granulomatosis

Introduction

The diagnosis of non-necrotising granulomatosis (NNG) is very frequent in clinical practice but rarely reported. Granulomatous inflammation is a variant of chronic inflammation characterized by the presence of granulomas, sometimes showing central necrosis. Granuloma formation is typically part of a type IV, T cell-mediated hypersensitivity reaction. This is an inflammatory reaction mediated by CD4 + T lymphocytes (delayed type hypersensitivity), in which the cytokines produced by T lymphocytes induce an inflammation that can be chronic, destructive and associated with the activation of macrophages that lead to the formation of granulomas [1-3]. In the presence of NNG, physicians usually focus their attention on sarcoidosis, but there are many other conditions that can be included within this histological diagnosis, including infectious diseases, drugs, and systemic

illnesses such as autoimmune diseases and malignancy [4-7]. Unfortunately, there are few studies concerning the spectrum of pathologies that cause an NNG pattern; consequently, except for sarcoidosis [8-10], little information is available [4,11]. This etiological diversity determines the need for careful patient examination to reach a precise diagnosis.

The aim of this study is to find the prevalence of sarcoidosis and autoimmune diseases in NNG. We also describe disorders causing or associated with NNG in our institution.

Material and methods

The pathological reports of all tissue samples described as NNG inflammation from 1 January 2010 to 31 December 2014 in the Clinical University Hospital of Santiago de Compostela were reviewed. Socio-demographic, analytical and pathological charac-

teristics were gathered. These patients were followed and a final diagnosis was made. Only those patients with histologically confirmed NNG were included in the study.

This study was conducted in accordance with the principles of the Declaration of Helsinki [12] in full conformity with Spanish regulations. Ethical approval was given by the Research Ethics Committee of our institution, and informed consent has been obtained.

Results

A total of 290 tissue samples from 207 patients were included in the period studied. In 79 cases there were two or more histological samples from the same patient. Representative histological images of NNG can be seen in **Figure 1**. Overall, 50.7% of patients were women, with a mean age of 51.2 years. Clinical and epidemiological characteristics, including the origin of the samples and the final diagnosis are shown in **Table 1**. Skin, lymph nodes, transbronchial biopsy and lung were the origins of the most commonly involved samples. Sarcoidosis (**Figures 1A-1C**) was the most common final diagnosis (in more than 50% of cases), followed by infectious diseases (**Figure 1D**), half of which corresponded to tuberculosis. Only 6 patients were diagnosed with autoimmune disease, with Wegener granulomatosis as the most frequently reported autoimmune disease. In 12 patients, no final diagnosis was found.

Discussion

Non-necrotising granulomatosis is a frequent histological finding in clinical practice [7]. Granulomatous inflammation

Table 1. Clinical and epidemiological characteristics of patients.

Characteristic (n=207)	No. (%)
Age (year, mean)	51.23
Gender	
Male	102 (49.3)
Female	105 (50.7)
Sample origin	
Skin	68 (32.9)
Lymph nodes	55 (26.6)
Transbronchial biopsy	30 (14.5)
Lung	12 (5.8)
Others	42 (20.2)
Final diagnosis	
Sarcoidosis	124 (59.9)
Infectious diseases	16 (7.7)
Tuberculous infection	8
Nontuberculous infection	3
Foreign body granulomatosis	13 (6.3)
Neoplasms	12 (5.9)
Autoimmune disease	6 (3.1)
Wegener granulomatosis	2
Chronic polyarticular arthritis	1
Autoimmune hepatitis	1
Systemic lupuserythematosus	1
Alopecia	1
Rosacea	3 (1.4)
Crohn disease	2 (0.9)
Cheilitis	2 (0.9)
Amyloidosis	1 (0.5)
No diagnosis found	12 (5.9)

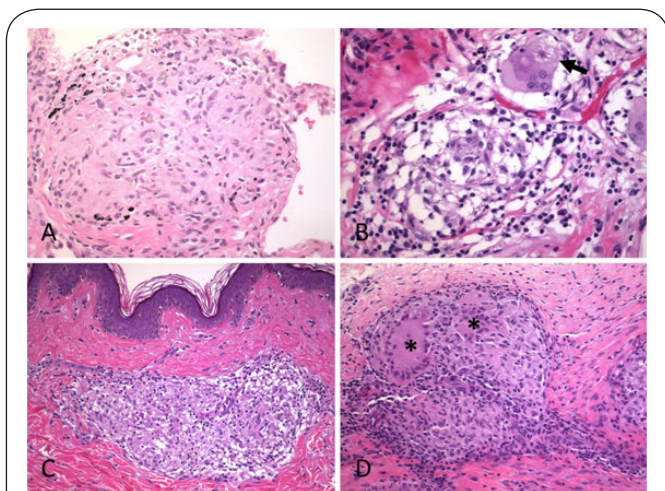


Figure 1. Non-necrotizing granulomatosis in tissue samples. Pulmonary sarcoidosis (**A** and **B**). In some granulomas small aggregates of black anthracotic pigment can be seen in the cytoplasm of some histiocytes (**A**). An asteroid body can be appreciated (arrow) in a giant cell associated with a granulomatous formation in pulmonary sarcoidosis (**B**). Cutaneous non-necrotising granulomas in sarcoidosis (**C**). Granulomas without necrosis in synovial membrane due to mycobacterium marinum infection; multinucleated giant cell histiocytes can also be seen (asterisks) (**D**).

is a special pattern of delayed type hypersensitivity reaction mediated by T lymphocytes. In response to different stimuli, dendritic cells release cytokines that cause CD4 + T lymphocytes to transform into T_H1 effector cells, which in turn, secrete several cytokines (mainly interferon gamma [IFN γ]) responsible for granuloma formation. Under the influence of IFN γ and other cytokines, activated macrophages (epithelioid cells) fuse to form giant cells [1,2]. Granuloma is called the aggregate of epithelioid cells, which usually includes multinucleated giant cells, generally surrounded by a lymphocyte collar (**Figure 1**). Immune granulomas are a consequence of various agents that induce a persistent immune response mediated by T lymphocytes as it is not possible to easily eliminate the causative agent. Granulomas associated with some specific germs (for example, Mycobacterium tuberculosis) are usually accompanied by a central area of caseic-looking necrosis (granulomatous inflammation with caseous necrosis) [3]. The combination of granulomatous changes, stellate necrosis with neutrophils and few giant cells is characteristic of cat scratch disease, although similar changes may occur in atypical mycobacteriosis, and tularemia [7]. Granulomas due to schistosome infection involve T_H2 lymphocytes, and therefore the presence of eosinophils is very striking [13]. The typical microscopic lesion of sarcoidosis is a small granuloma mainly composed of epithelioid cells, with scattered lymphocytes

and Langhans' giant cells. In sarcoidosis, necrosis is either absent or limited to a small fibrinoid focus, and the Langhans' giant cells are smaller than those seen in tuberculosis [7,9]. Non-specific inclusions such as asteroid bodies (Figure 1B), Schaumann bodies, and calcium oxalate crystals can be seen in the cytoplasm of giant cells in sarcoidosis [7]. Occasional non-necrotising granulomas with dense chronic inflammatory infiltrate can be seen in the intestine wall of patients with Crohn's disease [14]. A noncaseating granulomatous inflammation can also be seen in tuberculosis, atypical mycobacteriosis, fungus diseases, leprosy, syphilis, leishmaniasis, Hodgkin's lymphoma, berylliosis, in lymph nodes draining a carcinoma, as well as other conditions [3,7,8,10,15]. Granulomatous formations that have had more evolution time usually appear surrounded by a ring of fibroblasts and connective tissue [2].

Foreign body granulomas, however, are a different pathological situation since they are non-immunogenic responses around materials of sufficient size to prevent phagocytosis by a macrophage; these materials are usually easily identifiable in microscopic examination [2,16].

For all these reasons, the diagnosis of NNG is often considered to be inconclusive for pathologists. As a consequence, in a case of NNG, only when the other etiological possibilities have been excluded and the clinical picture is characteristic, will a diagnosis that is compatible with sarcoidosis be justified [7,9]. Due to the fact that the different cases of NNG are associated with a wide range of etiologies, the appropriate treatment depends on the identification and elimination of the underlying cause. The clinical presentation is often nonspecific and there are few studies within the spectrum of pathologies that cause NNG [4,6,11,17]. The most common causes include sarcoidosis and infections [6]. Although the majority of studies focus on lung involvement [5,18], up to 20% of cases in our series came from other origins.

Given that the most usual approach to diagnosis relies on the differentiation between sarcoidosis and infection, it is also very important to submit a part of the biopsy sample for microbiological analysis. In our study infectious disease was found in 16 patients, most of them due to tuberculous infection. At the same time, as other authors have also reported, potentially fatal diseases such as a malignancy can also occur [18-20]. In the present series, neoplasms were detected in 12 patients. An accurate assessment of lesions can be made by joining the differential diagnoses generated by clinical, microbiological and histological features as well as the anatomic location of the lesion [ungprasert, judsonarber]. Frequently, the precise cause of NNG cannot be established from the outset; diagnostic difficulties arise from inadequate biopsy specimens and from a lack of clinico-pathological correlation. So it is important to follow-up patients, never hesitating if necessary to repeat the biopsy for an accurate diagnosis. In fact, in our study, two or more histological samples were obtained from the same patient in 79 cases.

Although the main limitation of this study is the retrospective

design which could compromise the accuracy of some clinical data included, our article summarises the most frequent etiologies of NNG in our institution. We find that the diagnosis of NNG should prompt an investigation of possible treatable causes or associated conditions. For the optimal management of patients, we emphasise the importance of considering a differential diagnosis generated by both the histological features as well as the clinical characteristics.

Conclusions

The prevalence of sarcoidosis in NNG is over 50%. Autoimmune disease prevalence is considerably lower, however, with Wegener granulomatosis being the most frequently reported. Infectious diseases are the most frequent alternative diagnosis, mainly tuberculosis, but it is important to keep the possibility of malignancy in mind. An accurate diagnosis is possible in the majority of cases. Thus, due to diversity of forms and causes of NNG, there is a need for careful patient examination to verify the final diagnosis.

List of abbreviations

NNG: non-necrotising granulomatosis

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	VAC	BS	JMCT	AGQ
Research concept and design	✓	✓	✓	✓
Collection and/or assembly of data	✓	✓	✓	✓
Data analysis and interpretation	✓	✓	✓	✓
Writing the article	✓	✓	✓	✓
Critical revision of the article	✓	✓	✓	✓
Final approval of article	✓	✓	✓	✓
Statistical analysis	✓	✓	✓	✓

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References

1. James DG. **A clinicopathological classification of granulomatous disorders.** *Postgrad Med J.* 2000; **76**:457-65. | [Article](#) | [PubMed Abstract](#) | [PubMed FullText](#)
2. Kumar V, Abbas AK and Aster JC. **Diseases of the immune system.** 10th Ed. In: **Robbins Basic Pathology.** 2018; 121-88.
3. de Martino M, Lodi L, Galli L and Chiappini E. **Immune Response to Mycobacterium tuberculosis: A Narrative Review.** *Front Pediatr.* 2019; **7**:350. | [Article](#) | [PubMed Abstract](#) | [PubMed FullText](#)
4. Woodard BH, Rosenberg SI, Farnham R and Adams DO. **Incidence and nature of primary granulomatous inflammation in surgically removed material.** *Am J Surg Pathol.* 1982; **6**:119-29. | [Article](#) | [PubMed](#)
5. Hutton Klein JR, Tazelaar HD, Leslie KO and Colby TV. **One hundred consecutive granulomas in a pulmonary pathology consultation practice.** *Am J Surg Pathol.* 2010; **34**:1456-64. | [Article](#) | [PubMed](#)
6. Mukhopadhyay S, Farver CF, Vaszar LT, Dempsey OJ, Popper HH, Mani H, Capelozzi VL, Fukuoka J, Kerr KM, Zeren EH, Iyer VK, Tanaka T, Narde I,

- Nomikos A, Gumurdulu D, Arava S, Zander DS and Tazelaar HD. **Causes of pulmonary granulomas: a retrospective study of 500 cases from seven countries.** *J Clin Pathol.* 2012; **65**:51-7. | [Article](#) | [PubMed](#)
7. Arber DA. **Lymph nodes.** 11th Ed. In: Goldblum JR, Lamps LW, McKenney JK, Myers JL(Eds.). **Rosai and Ackerman's Surgical Pathology.** 2018; 1530-631.
8. Cunningham JA. **Sarcoidosis.** *PatholAnnu.* 1967; **2**:31-46.
9. Ungprasert P, Ryu JH and Matteson EL. **Clinical Manifestations, Diagnosis, and Treatment of Sarcoidosis.** *Mayo Clin Proc Innov Qual Outcomes.* 2019; **3**:358-375. | [Article](#) | [PubMed Abstract](#) | [PubMed FullText](#)
10. Judson MA. **The diagnosis of sarcoidosis.** *CurrOpinPulm Med.* 2019; **25**:484-96.
11. Nazarullah A, Nilson R, Maselli DJ and Jagirdar J. **Incidence and aetiologies of pulmonary granulomatous inflammation: a decade of experience.** *Respirology.* 2015; **20**:115-21. | [Article](#) | [PubMed](#)
12. **General Assembly of the World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects.** *J Am Coll Dent.* 2014; **81**:14-8. | [PubMed](#)
13. Ariyaratne A and Finney CAM. **Eosinophils and Macrophages within the Th2-Induced Granuloma: Balancing Killing and Healing in a Tight Space.** *Infect Immun.* 2019; **87**. | [Article](#) | [PubMed](#)
14. Hong SW, Yoon H, Shin CM, Park YS, Kim N, Lee DH and Kim JS. **Clinical Significance of Granulomas in Crohn's Disease: A Systematic Review and Meta-analysis.** *J Gastroenterol Hepatol.* 2019. | [Article](#) | [PubMed](#)
15. Fontenot AP. **Immunologic Effects of Beryllium Exposure.** *Ann Am Thorac Soc.* 2018; **15**:S81-S85. | [Article](#) | [PubMed Abstract](#) | [PubMed FullText](#)
16. Rolim LSA, Barros C, Pinheiro JC, PT DEO, LB DES and Santos PPA. **Analysis of nine cases of oral foreign body granuloma related to biomaterials.** *J Biosci.* 2019; **44**. | [Pdf](#) | [PubMed](#)
17. Terziroli Beretta-Piccoli B, Mainetti C, Peeters MA and Laffitte E. **Cutaneous Granulomatosis: a Comprehensive Review.** *Clin Rev Allergy Immunol.* 2018; **54**:131-146. | [Article](#) | [PubMed](#)
18. Pisani RJ and DeRemee RA. **Clinical implications of the histopathologic diagnosis of pulmonary lymphomatoid granulomatosis.** *Mayo Clin Proc.* 1990; **65**:151-63. | [Article](#) | [PubMed](#)
19. McGrath LA, Mudhar HS, Sheard R, Spiteri-Cornish K, Winder S, Rundle P and Rennie IG. **Paraneoplastic Granulomatous Vitritis: Elaboration of 8 Cases.** *Ophthalmol Retina.* 2019; **3**:589-596. | [Article](#) | [PubMed](#)
20. Krvavac A, Munzer K, Miller A, Poddar N, Jamkhana Z and Patolia S. **The concurrence of granulomatous inflammation in intrathoracic lymph nodes with regional metastasis from primary lung cancer in surgically resected specimens.** *Adv Respir Med.* 2018; **86**:215-219. | [Article](#) | [PubMed](#)

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