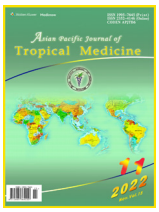

Original Article

Asian Pacific Journal of Tropical Medicine

apjtm.org

doi: 10.4103/1995-7645.361855

Impact Factor: 3.041

Etiology of granulomatous inflammation: A retrospective study of 174 children in a tertiary care center

Ümmühan Çay[1]✉, Derya Alabaz[1], Özlem Özgür Gündeşlioğlu[1], Aysun Hatice Uguz[2], Hande Yanar[2]

[1]*Department of Pediatric Infectious Diseases, Faculty of Medicine, Çukurova University, Adana, Turkey*

[2]*Department of Pathology, Faculty of Medicine, Çukurova University, Adana, Turkey*

ABSTRACT

Objective: To investigate granulomatous inflammation etiology based on clinical history and ancillary tests.

Methods: Children aged <18 years with biopsy proven granulomatous lesions in any tissue specimens between January 2014 and January 2022 were included in the study. The diagnosis was based on the results of immunohistochemical staining, molecular tests, culture, serology, radiological and other auxiliary laboratory tests. Diagnoses were categorized into infectious and non-infectious causes.

Results: In total, 174 patients with granulomatosis inflammation confirmed by histopathology were analyzed. Approximately 59.2% patients were males, and the median age was 4.48 (IQR 2.36-6.39) years (range: 16 months-18 years). The tissues/organs that were most commonly biopsied were lymph node, bone, skin, and lung (51.1%, 17.8%, 9.2%, and 5.7%, respectively). Infectious and non-infectious causes were identified in 73.0% and 12.6% patients, respectively, in terms of granulomatosis inflammation etiology; however, no cause was identified in 14.4% patients. The most common infectious cause was tuberculosis (in 51.7% patients), followed by toxoplasmosis, aspergillosis, mucormycosis, leishmaniasis, and cat-scratch disease (in 8.6%, 5.7%, 1.7%, 1.7%, and 1.1% patients, respectively). The common non-infectious cause was chronic granulomatous disease. Histopathological evaluation revealed granulomatosis inflammation in 33.3% patients, necrotizing granulomatosis inflammation in 30.5% patients, and caseating granulomatosis inflammation in 12.1% patients. When the pathology results of patients with and without tuberculosis were compared, the incidence of caseating granulomatosis inflammation (P=0.003) and necrotizing granulomatosis inflammation (P=0.005) was higher in patients with tuberculosis.

Conclusions: Chronic granulomatous disease is the most common non-infectious cause in children. Moreover, primary or secondary immune deficiencies may cause granulomatosis inflammation, especially in pediatric patients.

KEYWORDS: Granulomatous; Children; Tuberculosis; Chronic granulomatous disease

1. Introduction

Granulomatous inflammation (GI) is a chronic inflammatory reaction of the immune system caused by a foreign agent. Granuloma formation is a distinctive and remarkable response of the

Significance

Pediatric granulomatous diseases include a wide range of diseases from infection to malignancy. In this study, the most common cause of granulomatous inflammation was infections, and the majority were tuberculosis and toxoplasmosis. *Aspergillus* infection was more common in immunocompromised patients. Among non-infectious causes, chronic granulomatous disease was the most common. It should be considered that immunodeficiency may be a primary or secondary cause of granuloma. Caseation and necrosis in granulomatous inflammation is associated with tuberculosis. Detailed definitions of necrosis, classification, and micro granuloma in pathology reports are of great importance in determining the etiology.

✉To whom correspondence may be addressed. E-mail: ucay-1205@hotmail.com

How to cite this article: Çay Ü, Alabaz D, Gündeşlioğlu ÖÖ, Uguz AH, Yanar H. Etiology of granulomatous inflammation: A retrospective study of 174 children in a tertiary care center. Asian Pac J Trop Med 2022; 15(11): 511-517.

Article history: Received 16 August 2022 Revision 10 November 2022
Accepted 23 November 2022 Available online 30 November 2022

immune system. The main cellular element of this inflammation is macrophages; however, other cell types, including T (CD4, CD8) and B cells are also associated with granulomas[1,2]. Granulomas were recognized as a distinct pathological entity approximately 150 years ago, predating the discovery of their component like phagocytes by several decades[3]. It was first discovered in tuberculosis of lungs and was later associated with infectious and non-infectious diseases[3]. GI is a distinctive morphological pattern of chronic inflammation. Some common reaction patterns include necrotizing granulomas, non-necrotizing granulomas, suppurative granulomas, diffuse granulomatous inflammation, and foreign body giant cell reaction[4]. Each pattern is associated with a broad differential diagnosis. Appropriate identification of the tissue reaction pattern narrows the differential diagnosis and subsequently simplifies clinical management. Therefore, detailed pathological identification is crucial for the early diagnosis and treatment initiation of GI.

The occurrence of GI is found across all age groups and at all tissue sites. Granulomatous diseases belong to a large family of granulomatous disorders, which are mostly caused by infections. Apart from infections, autoimmunity, toxicity, allergy, vasculitis, immunological aberrations [*e.g.*, chronic granulomatous disease (CGD)], and neoplastic conditions may cause GI[4,5]. An accurate interpretation of the history and clinical and laboratory findings in addition to the histopathological evaluation of patients with a granulomatous lesion can lead to etiological diagnosis by physicians.

In the present study, pediatric patients with GI confirmed by histopathology were analyzed retrospectively and GI etiological evaluation based on patient history, clinical findings, and supplementary tests is presented.

2. Materials and methods

This single-center, retrospective, observational study was conducted at Çukurova University Medical Faculty, Balcali Hospital, which is a tertiary care children's referral hospital in Turkey. The study was approved by the Clinical Research Ethics Committee of the institute (Dated June 16, 2022;approval No. 125/11).

Children aged <18 years with biopsy proven granulomatous lesions in any tissue specimens between January 2014 and January 2022 were included in the study. Data were extracted using electronic medical records of these patients, which is maintained in the pathology department. Several patient characteristics such as age, gender, previous diseases, biopsied organs and tissues, pathology reports, and final diagnosis were recorded. Patients aged >18 years and those with inadequate clinical data were excluded from the study.

The diagnosis was made based on the results of immunohistochemical staining, molecular tests, culture, serology, radiological and other auxiliary laboratory tests; and it was considered as the definitive diagnosis. Definitive diagnoses were categorized into infectious and non-infectious causes.

Infectious causes were categorized into two groups as tuberculosis (TB) and non-tuberculosis (non-TB). TB diagnosis was made based on TB contact, tuberculin skin test (TST)/interferon-γ release assay (IGRA), clinical, laboratory, and histopathological results. Patients with positive results of acid-fast bacilli or TB-polymerase chain reaction or those with *Mycobacterium tuberculosis* growth in culture were diagnosed as a bacteriologically confirmed TB. Patients with TB contact and TST/IGRA positivity as well as those with clinical, laboratory, and histopathological findings supporting TB without bacteriologically confirmation were diagnosed as clinically diagnosed TB[6].

Statistical Package for the Social Sciences (SPSS) 25.0 package program was used for analyzing the data. Categorical variable were presented as numbers and percentages, whereas continuous variables were presented as mean and standard deviation (median and minimum-maximum, as appropriate). *Chi*-square and Fisher's exact tests were used to compare categorical expressions. Statistical significance level was taken as 0.05 in all tests.

3. Results

During the 8-year period, 186 patients with a pathology report of granulomatosis were admitted to our center. Twelve patients were excluded from the study due to incomplete clinical data. The granulomatous pathology and etiological results of 174 patients were evaluated retrospectively (Figure 1). Approximately 59.2% patients were males, and the median age was 4.48 (IQR 2.36-6.39) years (range: 16 months-18 years). Overall, 20.1% patients were Syrian refugees. The tissues/organs that were most commonly biopsied were lymph node, bone, skin and lung (51.1%, 17.8%, 9.2%, and 5.7%, respectively).

Biopsy samples were most commonly obtained from the cervical and axillary lymph nodes (Table 1). In skin biopsy samples, etiology could be determined based on the pathology results in 9 of 16 patients (TB, 3; leishmaniasis, 3; sarcoidosis, 1; lymphomatoid granulomatosis, 1; and mucormycosis, 1). In bone biopsy samples, etiology could be determined in 26 of 31 patients (TB, 22; CGD, 1; aspergillosis, 1; foreign string, 1;eosinophilic granuloma, 1). The biopsied tissues and organs are shown in Table 1.

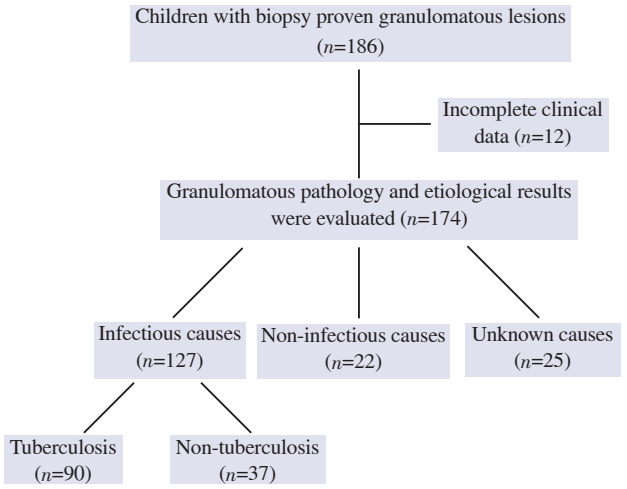

Figure 1. Flowchart of the study.

Table 1. Demographic characteristics of patients and biopsied tissues/organs.

Variable	Data (*n*=174)
Age, year, median (IQR)	4.48 (2.36-6.39)
Gender, *n* (%)	
Male	103 (59.2)
Female	71 (40.8)
Ethnicity, *n* (%)	
Turkish	139 (79.9)
Syrian	35 (20.1)
Organ or tissue, *n* (%)	
Lymph node	89 (51.1)
Bone	31 (17.8)
Skin	16 (9.2)
Lung	10 (5.7)
Gastrointestinal system	8 (4.6)
Ileum	3 (1.7)
Liver	3 (1.7)
Appendix	2 (1.1)
Peritoneum	6 (3.4)
Orbita	5 (2.9)
Pleural	4 (2.3)
Brain	2 (1.1)
Other*	3 (1.7)
Lymphadenopathy, *n* (%)	
Cervical	48 (53.9)
Axillary	18 (20.2)
Submandibular	9 (10.1)
Supracalvicular	5 (5.6)
Inguinal	5 (5.6)
Intra-abdominal	2 (2.2)
Mediastinal	1 (1.1)
Submental	1 (1.1)

*Synovia, mediastinal mass, intra-abdominal mass.

Histopathological evaluation revealed isolated GI in 58 (33.3%), necrotizing GI in 53 (30.5%), suppurative GI in 16 (9.2%), and non-necrotizing GI in16 (9.2%) patients. A total of 21 (12.1%) patients had caseating GI; of these, 16 had isolated caseating GI, 3 had suppurative caseating GI and 2 had necrotizing caseating GI. When the pathology results of etiology unknown, infectious and non-infectious causes were compared, it was observed that the incidence of non-caseating GI (P=0.001) was higher in the non-infectious group than in the infectious and etiology unknown groups. When the TB group was compared with the non-TB group, the incidence of caseating GI (P=0.003) and necrotizing GI (P=0.005) was higher. Contrarily, the incidence of isolated GI (P<0.001) and suppurative GI (P=0.025) were lower in the TB group (Table 2 and 3).

Table 2. Comparison of histopathology results with infectious/non-infectious causes.

Histopathology	Infectious (*n*=127)	Non-infectious (*n*=22)	Unknown (*n*=25)	*P*
Granulomatosis	40 (31.5)	9 (40.9)	9 (36.0)	0.994[a]
Suppurative	12 (9.4)	2 (9.1)	2 (8.0)	0.941[a]
Caseating	15 (11.8)	-	1 (4.0)	0.180[a]
Suppurative caseating	3 (2.4)	-	-	0.606[a]
Caseating necrotizing	2 (1.6)	-	-	0.717[a]
Non-caseating	2 (1.6)	3 (13.6)	-	0.001[b**]
Necrotizing	39 (30.7)	5 (22.7)	9 (36.0)	0.625[a]
Suppurative necrotizing	4 (3.1)	-	-	0.511[a]
Non-necrotizing	10 (7.9)	2 (9.1)	4 (16.0)	0.349[a]
Eosinophilic granuloma	-	1 (4.5)	-	0.013[b*]

*P<0.05, **P<0.001, [a]: *Chi*-square test, [b]: Fisher exact test, -: not found, TB: tuberculosis.

Table 3. Comparison of histopathology results with TB/non-TB.

Histopathology	TB (*n*=90)	Non-TB (*n*=84)	*P*
Granulomatosis	16 (17.8)	42 (50.0)	<0.001[b**]
Suppurative	4 (4.4)	12 (14.3)	0.025[a*]
Caseating	15 (16.7)	1 (1.2)	0.003[b**]
Suppurative caseating	3 (3.3)	-	0.091[a]
Caseating necrotizing	2 (2.2)	-	0.169[a]
Non-caseating	2 (2.2)	3 (3.6)	0.594[a]
Necrotizing	36 (40.0)	17 (20.2)	0.005[b**]
Suppurative necrotizing	4 (4.4)	-	0.051[a]
Non-necrotizing	8 (8.9)	8 (9.5)	0.896[a]
Eosinophilic granuloma	-	1 (1.2)	0.299[a]

*P<0.05, **P<0.001, [a]: *Chi*-square test, [b]: Fisher exact test, -: not found, TB: tuberculosis.

Overall, 20 (95.2%) of 21 patients with caseification were diagnosed with TB. Among 53 patients with necrotizing GI, 73.6% (*n*=39) patients had infectious causes, and 67.9% had TB (*n*=36). Four biopsy samples indicated suppurative necrotizing GI, and all were diagnosed with TB. When the non-TB group with necrotizing GI was examined, two patients with CGDs, one with cat-scratch disease (CSD), one with atypical mycobacteria, one with *Candida*, one with chalazion, one with lymphomatoid granulomatosis, and one with Rosai-Dorfman disease were detected. TB was detected in 50.0% (8 of 16) of the non-necrotizing patients.

Of the 58 patients with isolated GI, infectious causes were identified in 69.0% (*n*=40) patients, and 27.6% had TB (*n*=16). Etiology could not be determined in 15.5% (*n*=9) of these patients. Of the 23 patients with suppurative features (4 with necrosis and 3 with caseification), the etiology was infection in 20 patients and foreign body in 1 patient. The etiology could not be determined in two patients.

The etiological analysis showed infectious causes in 73.0% (*n*=127) and non-infectious causes in 12.6% (*n*=22) patients, and no cause was identified in 14.4% (*n*=25) patients. The most common infectious cause was TB (51.7% patients; *n*=90), followed by toxoplasmosis, aspergillosis, mucormycosis, leishmaniasis, and CSD (8.6%, 5.7%, 1.7%, 1.7%, and 1.1% patients, respectively). The common non-infectious causes were CGD, chalazion, and Crohn's disease (4.0%, 2.3%, and 1.7% patients, respectively) (Table 4).

Table 4. Etiological results of 174 patients with granulomatous inflammation.

Group	Total cases, *n* (%) (*n*=174)
Etiology	
Infectious	127 (73.0)
Non-infectious	22 (12.6)
Unknown	25 (14.4)
Infectious causes	
TB	
Presumed TB	55 (31.6)
Confirmed TB	35 (20.1)
Non-TB	
Toxoplasmosis	15 (8.6)
Aspergillosis	10 (5.7)
Leishmaniasis	3 (1.7)
Mucormycosis	3 (1.7)
Cat-scratch disease	2 (1.1)
Tuleremia	1 (0.6)
Brucellosis	1 (0.6)
Candida	1 (0.6)
Atypical mycobacterium (*Mycobacterium avium*)	1 (0.6)
Non-infectious causes	
Chronic granulomatous disease	7 (4.0)
Chalazion	4 (2.3)
Crohn's disease	3 (1.7)
Foreign body	2 (1.1)
Eosinophilic granuloma	2 (1.1)
Rosai-Dorfman disease	1 (0.6)
Bronchocentric granulomatosis	1 (0.6)
Sarcoidosis	1 (0.6)
Lymphomatoid granulomatosis	1 (0.6)

TB: tuberculosis.

Fifteen patients diagnosed with toxoplasma lymphadenitis had abortive microgranuloma with no necrosis or suppuration. The cervical lymph node, axillary lymph node, and submandibular biopsy samples were obtained from 11, 3, and 1 patient, respectively.

Of the 10 patients with *Aspergillus* spp., 9 had an underlying immunocompromised condition, and the pathology results indicated suppurative GI in 7 and isolated GI in 3 patients (pulmonary, 4; pleural, 1; nasal cavity, 1; vertebra, 1; lymph nodes, 2;brain, 1 patient).

Co-morbid diseases were detected in 22.4% (39/174) patients. The most common co-morbid condition was immunodeficiency 19.0% (33/174) and the most common immunodeficiency was CGD (*n*=16), followed by IL-12Rβ1 deficiency (*n*=6) and severe combined immunodeficiency (SCID: *n*=3) (Table 5). Aspergillosis was detected in eight patients with CGD. Lymph node biopsies were obtained from all six patients with IL-12Rβ1 deficiency (four left axillary and two cervical lymph node biopsies). Based on the results of biopsy and auxiliary tests, one patient was diagnosed with Bacille Calmette-Guérin (BCG)-associated TB lymphadenitis due to the presence of *Mycobacterium bovis*, and IL-12Rβ1 deficiency was subsequently detected. BCG-associated TB lymphadenitis was detected in three patients with SCID. Based on the presence of necrotizing GI in brain biopsy samples and *Candida* growth in culture, the patient was diagnosed with caspase recruitment domain family member 9 (CARD9) deficiency. The co-morbid diseases, biopsied tissues/organs, and the corresponding GI etiologies are presented in Table 5.

Table 5. Relationship of co-morbid diseases and biopsied tissues/organs and etiology.

Co-morbid condition	Organ/tissue	Etiology	Total case, *n* (%), *n*=39
Immunodeficiency			33 (84.6)
CGD	LAP	CGD	3 (7.7)
		Aspergillosis	1 (2.6)
	Bone	CGD	1 (2.6)
		Aspergillosis	1 (2.6)
	Brain	Aspergillosis	1 (2.6)
	Lung	Aspergillosis	4 (10.3)
		CGD	2 (5.1)
	Pleura	Aspergillosis	1 (2.6)
	Mediastinal mass	CGD	1 (2.6)
	Skin mass	CGD	1 (2.6)
IL-12Rβ1 deficiency	LAP	TB**	6 (15.4)
SCID	LAP	TB**	3 (7.7)
CVID	LAP	TB	2 (5.1)
	LAP	TOXO	
Hyper-immunoglobulin M	LAP	Atypical *Mycobacteria**	1 (2.6)
CARD9	Brain	*Candida*	1 (2.6)
Kostmann syndrome	LAP	TB	1 (2.6)
Wiskott-Aldrich syndrome	Skin	Leishmaniasis	1 (2.6)
Undefined	LAP	TB	2 (5.1)
Other diseases			6 (15.4)
Leukemia	LAP	Unknown	3 (7.7)
	Skin	TB	
	Lung	Mucormycosis	
HSCT	Bone	TB	1 (2.6)
Primary hemophagocytosis	Nasal mucosa	Mucormycosis	1 (2.6)
Aplastic anemia	Nasal mucosa	Aspergillosis	1 (2.6)

**Mycobacterium avium*, ***all BCG-associated TB lymphadenitis, LAP: lymphadenopathy, CGD: chronic granulomatous disease, TB: tuberculosis, CARD 9: caspase recruitment domain family member 9, HSCT: hematopoietic stem cell transplantation, CVID: common variable immune deficiency, SCID: severe combined immunodeficiency.

4. Discussion

The most common causes of GI are infections. Similar to adults, mycobacterial infections are common in children with GI, especially in regions where tuberculosis is endemic. However, fungi, parasites, and viruses may also cause GI. There is limited research on this topic. In a study examining children with cervicofacial granulomatous lymphadenitis, non-tuberculous mycobacterial (NTM) infections and CSD were reported as the most common causes[7]. In another study evaluating GI results obtained using fine needle biopsy, *Mycobacterium tuberculosis* complex was found to be the most common infectious cause, followed by atypical mycobacterial species[8]. In the present study, infectious causes were identified in >50% of the patients based on the results of histopathological and auxiliary tests. Contrary to the results of the literature, TB was the most common diagnosis and only one patient was diagnosed with atypical mycobacteria in this study. This may be attributed to the difficulties in diagnosing the current mycobacterial infections, and most of our patients were diagnosed with presumed TB. We believe that there were several NTM infections that we could not identify among these cases. The two most common infectious causes after TB were infections caused by *Toxoplasma* and *Aspergillus* spp.. The most common symptom of acute toxoplasma is cervical lymphadenopathy (LAP). Toxoplasma LAP was detected in 8.6% (n=15) of the patients, and other than cervical lymph nodes, lymphoadenopathies were localized to the axillary and submandibular regions. Eapen *et al*. reported that one of the most important criterion for the detection of toxoplasma lymphadenitis was the presence of microgranulomas[9]. In patients with LAP, in this study, necrosis and suppuration-free granulomas as well as microgranuloma structure observed in pathology results was useful in the diagnosis, which was confirmed by serology.

Cryptococcus neoformans, Histoplasma capsulatum, Coccidioides immitis, Aspergillus, and other invasive fungi can cause GI[4,5]. Patients with GI due to *Aspergillus, Mucor,* and *Candida* were detected in the present study. Invasive fungal infections are more common owing to immunosuppression associated with organ transplantation and malignancy treatment. In addition, the risk of aspergillosis is high in patients with CGD[10]. In the present study, invasive aspergillosis was detected in eight patients with CGD and one patient with aplastic anemia. Biopsy samples obtained from the brain mass revealed necrotizing GI and *Candida* growth in the culture. *Mucor* was detected in two patients with hematological disease. When a granulomatous pathology is detected in patients with risk factors for invasive fungal infection, fungi, especially *Aspergillus*, should be considered, and the case should be evaluated further in detail using immunohistochemical staining as well as culture, molecular, and auxiliary diagnostic tests. Infectious etiology is extremely broad, and microorganisms can be detected based on the above mentioned detailed examinations.

Non-infectious causes, such as leucocyte oxidase defects, vasculitis, immunological aberrations, hypersensitivity pneumonitis, chemicals, and neoplasia, can cause GI[5]. The purpose of granuloma formation is to isolate the antigen in the body and facilitate its elimination. Poor granuloma formation has been shown especially in innate immune defects andresults in dissemination of the antigen to the body[11]. Immunodeficiencies, such as CVID, combined immune deficiencies, and CGD, may present with GI in various organs[12]. Although, granuloma is primarily observed in patients with immunodeficiency, it may also develop secondary to mycobacterial and fungal infections such as *Aspergillus* in these patients. In the present study, patients were diagnosed with CGD after GI detection. In addition, GI due to *Mycobacterium avium* was detected in one patient with hyperimmunoglobulin M, GI due to TB and toxoplasmosis was detected in two patients with CVID, GI due to cutaneous leishmaniasis was detected in one patient with Wiskott-Aldrich syndrome, GI due to TB was detected in one patient with Kostmann disease, and GI due to BCG-associated TB lymphadenitis was detected in three patients with SCID (Table 4). Further, one patient was diagnosed with CARD9 deficiency after granuloma detection and *Candida* growth in culture, and six patients were diagnosed with IL-12Rβ1 deficiency after the detection of BCG-associated TB lymphadenitis, especially in the axillary lymph node. BCG-associated TB lymphadenitis should be considered when left axillary LAP and any form of granuloma are detected, especially in children who have received BCG vaccine. It should be noted that IL-12Rβ1 deficiency may be a major issue underlying GI; therefore, both primary and secondary granulomatous lesions can be observed in immunocompromised patients. Anamnesis and physical examination should be carefully performed in all patients with granulomatous lesions who present with primary immunodeficiency symptoms and a positive family history[12].

Ng *et al*. examined 339 GIs and identified suspected sarcaidosis in 5.6%, foreign body giant cell reaction in 4.7%, carcinoma in 0.9%, and acute lymphoblastic lymphoma/leukemia in 0.3% of the patients as non-infectious causes. Furthermore, one patient had granulomatosis with polyangiitis, one had CGD, and one had chronic sialadenitis[8]. In the present study, the most common non-infectious causes were CGD, chalazion, and Crohn's disease. CGD was the most common non-infectious cause in the present study. Although

sarcoidosis is a common cause of GI after tuberculosis in adults, it is extremely rare in children. In children, CGD is a common non-infectious cause.

Granulomas are histologically categorized as necrotizing or non-necrotizing GI. *Mycobacteria* species are the most common cause of necrotizing GI worldwide[4]. Caseification necrosis is considered pathognomonic for TB[13,14]. In their multicenter GI study, Öztomurcuk *et al.* diagnosed TB in 53.7% of patients with necrotizing GI, 91% of those had caseification, 6.9% had non-necrotizing GI, and 8.6% had non-caseification[15]. In the present study, TB was diagnosed in 67.9% of patients with necrosis and 95.2% of those with caseification. In addition, two patients with caseification necrosis were diagnosed with TB. All patients with suppurative necrosis or caseification were diagnosed with TB. Conditions involving necrosis may include non-TB infections as well as autoimmune/chronic inflammatory diseases and foreign body reactions[4,5,8]. In this study, patients with non-TB necrotizing GI were identified as CSD, *Candida*, NTM, CGD, chalazion, lymphomatoid granulomatosis, and Rosai-Dorfman disease. Further, TB was detected in 50% of patients with non-necrotizing GI. The absence of caseification or necrosis does not rule out the presence of infections, especially TB. This study suggests that detailed definitions of necrosis, caseification, and microgranuloma in pathology reports are of great importance in determining the etiology. Therefore, non-detailed definitions will most likely delay diagnosis.

Although anamnesis, clinical findings, culture test results, serology results, immunohistochemical studies, radiological findings, and evolving molecular techniques are available yet the etiology of GI may remain undetermined. Ng *et al.* examined a large case series and reported that they could not determine GI etiology in 59% of patients[8]. In a study examining pulmonary necrotizing granulomas, it was reported that the etiology could not be determined in 23.1% of patients; however, when these cases were re-evaluated, the etiology was determined in 90.8% patients[16]. In the present study, etiology was undetermined in 14.4% of the patients. This may be attributed to the difficulties in identifying the current infectious agents. In our center, we faced great difficulties in identifying fungi, parasites, or even atypical bacteria such as TB. We believe that aligned re-evaluation of clinical, radiological, laboratory and histological findings will be valuable in identifying the etiology.

This study has some limitations. Our study is a single-center retrospective study. Therefore, multicenter prospective studies are needed. The etiology of several patients could not be determined, and the diagnosis of TB was presumed diagnosis in most patients.

In conclusion, GI includes a large group of diseases. The most common cause of GI is infections, and mycobacteria and toxoplasma should be investigated in the future. *Aspergillus* infection should be considered more frequently in patients with immunosuppression and CGD. Among non-infectious causes in children, unlike adults, CGD should be considered first in the differential diagnosis instead of sarcoidosis. It should be considered that immunodeficiency may be a primary or secondary cause of granuloma. Detailed histopathological identification can help narrow the differential diagnoses. A diagnosis can be made in most patients based on a detailed history, physical examination, and laboratory and histopathological evaluation.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Funding

The authors received no extramural funding for the study.

Authors' contributions

U.C. developed the theoretical formalism, performed the analytic calculations and performed the numerical simulations. U.C, A.H.U and H.Y. contributed to the final version of the manuscript. D.A and O.O.G supervised the project.

References

[1] Pagán AJ, Ramakrishnan L. The formation and function of granulomas. *Annu Rev Immunol* 2018; **36**: 639-665. doi: 10.1146/annurev-immunol-032712-100022.

[2] Patterson KC, Queval CJ, Gutierrez MG. Granulomatous inflammation in tuberculosis and sarcoidosis: Does the lymphatic system contribute to disease? *Bioessays* 2019; **41**(11): e1900086. doi: 10.1002/bies.201900086.

[3] Ramakrishnan L. Revisiting the role of the granuloma in tuberculosis. *Nat Rev Immunol* 2012; **12**(5): 352-366. doi: 10.1038/nri3211.

[4] Shah KK, Pritt BS, Alexander MP. Histopathologic review of granulomatous inflammation. *J Clin Tuberc Other Mycobact Dis* 2017; **7**: 1-12. doi: 10.1016/j.jctube.2017.02.001.

[5] James DG. A clinicopathological classification of granulomatous

disorders. *Postgrad Med J* 2000; **76**(898): 457-465. doi: 10.1136/pmj.76.898.457.

[6] World Health Organization. *Definitions and reporting framework for tuberculosis–2013. 2013. (WHO/HTM/TB/2013.2).* [Online]. Available from: http://apps.who.int/iris/ bitstream/10665/79199/1/9789241505345eng.pdf. [Accessed on 1 August 2022].

[7] Neven Q, Van der Linden D, Hainaut M, Schmitz S. Long-term outcome of surgical excision for treatment of cervicofacial granulomatous lymphadenitis in children. *Eur Arch Otorhinolaryngol* 2020; **277**(6): 1785-1792. doi: 10.1007/s00405-020-05880-5.

[8] Ng DL, Balassanian R. Granulomatous inflammation diagnosed by fine-needle aspiration biopsy. *J Am Soc Cytopathol* 2019; **8**(6): 317-323. doi: 10.1016/j.jasc.2019.07.004.

[9] Eapen M, Mathew CF, Aravindan KP. Evidence-based criteria for the histopathological diagnosis of toxoplasmic lymphadenopathy. *J Clin Pathol* 2005; **58**(11): 1143-1146. doi: 10.1136/jcp.2005.026492.

[10]Segal BH. Aspergillosis. *N Engl J Med* 2009; **360**(18): 1870-1884. doi: 10.1056/NEJMra0808853.

[11]Petersen HJ, Smith AM. The role of the innate immune system in granulomatous disorders. *Front Immunol* 2013; **4**: 120. doi: 10.3389/fimmu.2013.00120.

[12]Rose CD, Neven B, Wouters C. Granulomatous inflammation: The overlap of immune deficiency and inflammation. *Best Pract Res Clin Rheumatol* 2014; **28**(2): 191-212. doi: 10.1016/j.berh.2014.03.006.

[13]Williams GT, Williams WJ. Granulomatous inflammation--a review. *J Clin Pathol* 1983; **36**(7): 723-733. doi: 10.1136/jcp.36.7.723.

[14]Kumar V, Abbas AK, Fausto N, Aster JC. *Robbins and cotran pathologic basis of disease*. Philadelphia: Elsevier Saunders; 2005, p. 82-83.

[15]Öztomurcuk D, Terzi Ö, Demirci C, Kılıçaslan Z. Investigation of granulomatous inflammations in terms of tuberculosis diagnosis: A 5-year multi-center laboratory study. *Turk Thorac J* 2022; **23**(1): 11-16. doi: 10.5152/TurkThoracJ.2022.20314.

[16]Mukhopadhyay S, Wilcox BE, Myers JL, Bryant SC, Buckwalter SP, Wengenack NL, et al. Pulmonary necrotizing granulomas of unknown cause: Clinical and pathologic analysis of 131 patients with completely resected nodules. *Chest* 2013; **144**(3): 813-824. doi: 10.1378/chest.12.

Publisher´s note