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A Clinicopathologic Series of 22 Cases of Tonsillar Granulomas

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Objectives: **Tonsils are uncommonly affected by granulomatous inflammation, often with an obscure cause. This study attempts to elucidate the nature of tonsillar granulomatous inflammation.** ***Design:*** **Retrospective clinicopathologic review.** ***Methods:*** **Twenty-two cases of tonsillar granulomas diagnosed between 1940 and 1999 were retrieved from the files of the Armed Forces Institute of Pathology. H&E slides and a series of histochemical stains were reviewed, and patient follow-up was obtained.** ***Results:*** **There were 11 males and 11 females, aged 7 to 64 years (mean, 29.9 y). Most of the cases presented bilaterally (n = 19) with sore throat, dysphagia, and/or nasal obstruction. The clinical differential included chronic tonsillitis, tuberculosis, nonspecific infection, sarcoidosis, and a neoplasm. Histologically, the granulomas were focal and scattered, or diffuse, identified in the interfollicular zones (n = 16) and/or the germinal centers (n = 13), and occasionally associated with necrosis (n = 6). Based on histochemical and clinical follow-up information, the etiology of the granulomas included sarcoidosis (n = 8), tuberculosis (n = 3), Hodgkin's lymphoma (n = 2), toxoplasmosis (n = 1), squamous cell carcinoma (n = 1), and no specific known cause (n = 7). Twelve patients were either alive at last follow-up or had died with no evidence of disease (mean, 12.4 y), and 9 were either alive at last follow-up or had died with disease (mean, 24.9 y). One patient was alive with unknown disease status (lost to follow-up after 13.3 y).** ***Conclusions:*** **Although a cause for tonsillar granulomas is frequently identified, a number may not develop an identifiable etiology, with the granulomas probably representing an exaggerated immune response to chronic tonsillitis. However, a careful work-up must be conducted to exclude specific causes and avoid clinical mismanagement.** ***Key Words:*** **Tonsil, tonsillitis, granulomatous inflammation, sarcoidosis, infectious disease.**

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INTRODUCTION

Chronic tonsillitis, histologically manifested as follicular hyperplasia, is a common pathological condition that may cause serous otitis media or obstructive sleep apnea as a secondary condition, which necessitates tonsillectomy/adenoidectomy. Granulomatous inflammation of the tonsils is rare, but when present is often part of the presentation spectrum of systemic diseases. Cases of tonsillar enlargement due to sarcoidosis, Crohn's disease, fungal infection, and tuberculosis have been reported in the medical literature, sometimes clinically mimicking neoplasms due to tonsillar enlargement.[1,2] A battery of histochemical stains for organisms is performed by the pathologist, followed by clinical correlation. In the absence of any identifiable cause, a nonspecific diagnosis is rendered. It is unfortunately all too common to append "compatible with sarcoidosis" to the diagnostic line or within a comment, even in the absence of other systemic manifestations. The isolated case reports in the medical literature[2–7] do not help in developing a systematic approach to tonsillectomy specimens with granulomatous inflammation. Therefore, we undertook this study of 22 cases of granulomatous inflammation of the tonsils to determine, where possible, their etiology and to correlate the diagnoses with the eventual clinical outcome.

MATERIALS AND METHODS

Twenty-two cases of tonsillar granulomatous inflammation were retrieved from the Otorhinolaryngic-Head and Neck Registry of the Armed Forces Institute of Pathology, between 1940 and 1999. These 22 cases represented 0.08% (22 of 26,386 cases) of all tonsil and adenoid cases reviewed during the same time period and 0.16% (22 of 13,700 cases) of all non-neoplastic tonsil and adenoid cases reviewed. Fifteen cases were obtained from civilian sources, including university medical centers, community hospitals, and private laboratories, five from military hospitals, and two from Veterans Administration medical centers.

H&E slides from each of the cases were reviewed and evaluated for the presence, distribution, and morphology of the granulomas. Ziehl-Neelsen, Gomori methenamine silver, Warthin-Starry, and Brown-Brenn stains were performed to evaluate the presence of infectious organisms. These stains were repeated for

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each case with available blocks, even when they had been performed at the time of initial consult. Five cases had no accompanying blocks, but lacked only the Warthin-Starry (n = 3) or all of the special stains (n = 2). Clinical follow-up was used to determine the etiologies for these five cases.

Materials within the files of the Armed Forces Institute of Pathology were supplemented by a review of the patients' social demographics, signs and symptoms at presentation, surgical pathology and operative reports, and oral or written communication with the treating physicians. Follow-up data included information regarding laboratory evidence of specific disease, development of subsequent disease, and the current status of the disease and the patient.

RESULTS

Clinical Presentation

A summary of clinical characteristics is presented in Table I. Males were older, averaging 34.0 years at presentation, wheres females averaged 25.9 years. We do not have an explanation for this difference. Fourteen patients were white, seven were black, and one was Hispanic. Most patients presented with a sore throat (n = 12), followed by a mass lesion, dysphagia, and nasal obstruction. Three patients were treated for asymptomatically enlarged tonsils when discovered incidentally during a clinical work-up for unrelated reasons. The managing physicians' clinical impressions (when recorded) included chronic tonsillitis (n = 8), neoplasm (n = 7), sarcoidosis (n = 2), nonspecific infection (n = 2), and singular cases of tuberculosis and Hodgkin's disease. Nineteen cases involved the faucial tonsils, 2 the nasopharyngeal adenoids, and 1 the tonsillar fossa in a patient who had previously had a tonsillectomy. Four of the 19 patients with faucial tonsillar involvement had asymmetrical enlargement and were thought to harbor a neoplasm.

TABLE I.
Clinical Characteristics.

Clinical Characteristic	Tonsillar Granulomas (n = 22)
Sex	
Female	11
Male	11
Age (y)	
Range	7–64
Average	29.9
Women (average)	25.9
Men (average)	34.0
Symptoms at presentation	
Sore throat	12
Mass lesion	3
Dysphagia	2
Nasal obstruction	2
Asymptomatic	3
Location	
Bilateral tonsils	16
Right tonsil	3
Adenoids	3

Macroscopic Findings

The tonsils measured 2.0 to 4.2 cm in greatest dimension (mean, 2.9 cm) and had varying macroscopic appearances from tan-red to yellow-white. The cut surface was described as homogeneous to nodular. In two cases, the crypts were enlarged and contained caseous material.

Microscopic Findings

The granulomatous inflammation was categorized based on distribution (focal, scattered, or diffuse), location (interfollicular or within germinal centers), circumscription (poorly circumscribed, well circumscribed, confluent), and necrosis (present or absent) (Table II). In summary, the majority of the cases (90.9%) showed either scattered or diffuse granulomas, without a specific topographic location; were usually well circumscribed, although dependent on the diagnosis; and were mostly noncaseating (72.7%). Although a few of the cases exhibited the archetypal histomorphology for their respective diagnoses (i.e., noncaseating granulomas with Schaumann or asteroid bodies in sarcoidosis [Fig. 1] or large granulomas with central necrosis in tuberculosis), there was no noteworthy association between the specific granuloma morphology and the underlying pathological process.

The Ziehl-Neelsen stain for acid-fast bacilli was positive in 2 of the 21 cases tested (Fig. 2). Both patients had subsequently developed culture-confirmed tuberculosis (*Mycobacterium tuberculosis*) after the initial evaluation of their tonsillectomy specimens. The remaining histochemical stains performed were negative in all cases tested.

Clinical Management and Patient Outcome

Complete follow-up was obtained in 21 of the cases (Table III). In 14 patients the granulomatous inflammation was secondary to a systemic disease that was known at the time of diagnosis or became manifest at a later time. These diseases consisted of sarcoidosis, tuberculosis, Hodgkin's disease, squamous cell carcinoma of the tonsil,

TABLE II.
Histologic Features of Tonsillar Granulomas.

Feature	n (%)
Distribution	
Focal	2 (9)
Scattered	11 (50)
Diffuse	9 (41)
Location	
Germinal centers	14 (64)
Interfollicular	17 (77)
Circumscription	
Poor	6 (27)
Well	10 (46)
Confluent	6 (27)
Necrosis	
Present	6 (27)
Absent	16 (73)

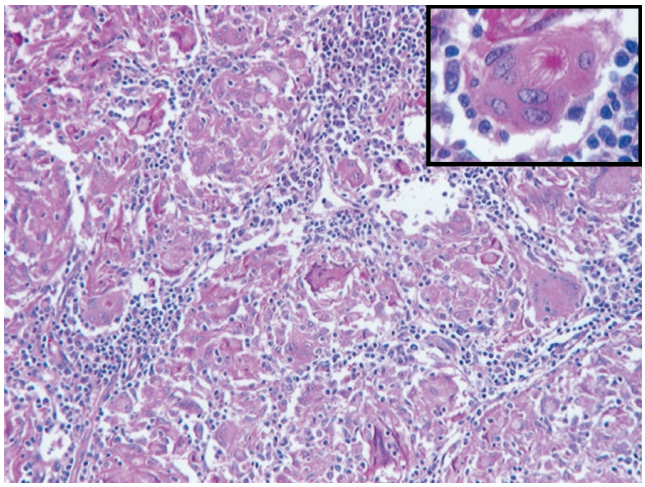

Fig. 1. Tonsillar granulomas in a patient with sarcoidosis. The granulomas are large and confluent with numerous Langhans' multinucleated giant cells, some of which contain asteroid bodies (inset). Original magnification × 200 (inset × 600).

and toxoplasmosis. One patient was initially diagnosed with toxoplasmosis, but has since developed multiple recurrent "masses" in the tonsillar fossa, all interpreted as "atypical lymphocytic infiltrates," without a definitive diagnosis of lymphoma. The patient is otherwise in good health without systemic disease.

Only 7 of 16 patients clinically thought to suffer from sarcoidosis actually had concurrent or developed subsequent clinical or laboratory evidence that supported sarcoidosis as the etiology of their granulomas. Five of the patients had or developed pulmonary disease, one had erythema nodosum and adenopathy, and one had laryngeal sarcoid. Three of the 16 patients clinically thought to have sarcoidosis developed tuberculosis as confirmed by

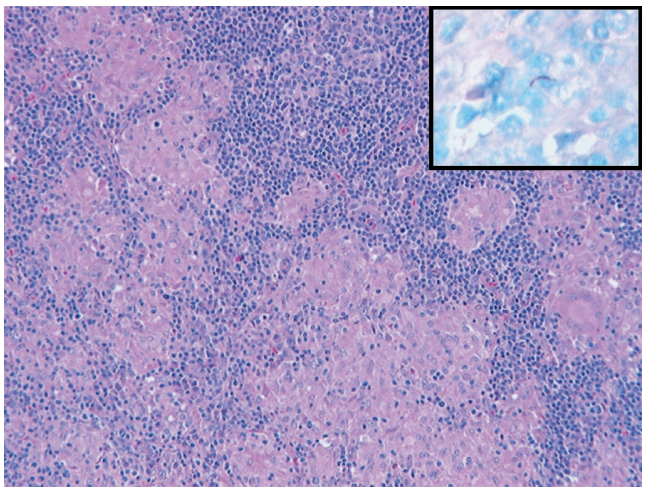

Fig. 2. Granulomatous inflammation in a patient with tuberculosis. Notably, caseous necrosis was absent and the initial stains for acid-fast bacilli were negative, prompting the erroneous diagnosis of sarcoidosis. A repeat Ziehl-Neelsen stain performed for the study was positive, showing an acid-fast beaded bacillus (inset). Original magnification × 200 (inset × 1000).

cultures, two of whom had histologically identifiable acid-fast bacilli. The other died from his extensive pulmonary disease. Of the remaining patients, one had convincing serological evidence for *Toxoplasma gondii* lymphadenitis, one proved to have Hodgkin's disease, and four patients developed no subsequent granulomatous disease.

Six patients died with evidence of disease: four had sarcoidosis, one had tuberculosis, and one had Hodgkin's disease. The patients with sarcoidosis survived for a mean of 43.7 years after the initial diagnosis, and death was usually of an infectious cause not specifically related to sarcoid. The patient with fulminant pulmonary tuberculosis died 1.2 years after tonsillectomy, whereas the patient with Hodgkin's disease died 2.7 years after tonsillectomy. Two patients died with no evidence of their disease—one with Hodgkin's disease (30.3 y) and one with squamous cell carcinoma of the tonsil (6.9 y).

Ten patients are alive at last follow-up with no evidence of disease (mean, 11.2 y). Seven had idiopathic granulomatous inflammation and developed no subsequent disease, two had tuberculosis, and one had toxoplasmosis. Three patients are alive at last follow-up with sarcoidosis (mean, 27.6 y). The remaining patient is alive, without evidence of disease or a specific diagnosis, although an atypical lymphoid infiltrate was present in her most recent biopsy.

DISCUSSION

Granulomatous inflammation is a chronic process that results from the activation of macrophages by antigens that are resistant to cellular digestion. It occurs in numerous settings including infection, most classically by *Mycobacterium tuberculosis*, but also fungi and unusual bacteria; neoplasia, commonly associated with Hodgkin's disease[8–10] but also reported with keratinizing squamous cell carcinoma;[11,12] and foreign body reaction. In addition, a few systemic conditions with poorly understood etiologies, such as sarcoidosis and Crohn's disease,[13] contain granulomatous inflammation as part of their histological spectrum and must be considered when other etiologies have been excluded.

Our series examines the clinicopathologic features of patients who have granulomatous inflammation of their faucial tonsils whose tonsillar histology yields no specific diagnosis at presentation; i.e., negative special stains. Of interest, sarcoidosis accounted for the largest percentage of any diagnosable disease, with 7 of 22 patients exhibiting or developing other supporting signs and symptoms of sarcoidosis. Nevertheless, an equal number of patients developed no further symptomatology, with granulomatous inflammation limited to the tonsils. We were unable to distinguish between these two groups based on histological features alone. However, it may be unwise to label the patients in the latter group with a diagnosis of sarcoidosis based only on their tonsillar pathology. In support of this proposal, the patients who did have sarcoidosis presented with dyspnea, adenopathy, rash, and arthralgia, and only two had a typical clinical presentation of chronic tonsillitis, whereas *all* of the "idiopathic" patients presented with a long history of recurrent or longstanding chronic tonsillitis. Furthermore, the sarcoid group tended

TABLE III.
Patient Follow-up Information.

Patient No.	Age (y)	Sex	Diagnosis	Follow-up (y)	Patient Status
1	12	F	Sarcoidosis	16.2	A, WD
2	19	F	Sarcoidosis	5.3	D, WD
3	23	F	Sarcoidosis	54.0	D, WD
4	24	M	Sarcoidosis	57.0	A, WD
5	28	M	Sarcoidosis	37.3	D, WD
6	40	M	Sarcoidosis	40.0	D, WD
7	62	F	Sarcoidosis	9.7	A, WD
8	7	F	Idiopathic*	17.0	A, NED
9	13	F	Idiopathic	3.0	A, NED
10	15	F	Idiopathic	1.9	A, NED
11	16	M	Idiopathic	19.8	A, NED
12	20	M	Idiopathic	0.1	A, NED
13	21	F	Idiopathic	13.3	A, NED
14	21	F	Idiopathic	1.9	A, NED
15	29	M	Tuberculosis	30.9	A, NED
16	34	M	Tuberculosis	1.2	D, WD
17	41	M	Tuberculosis	24.4	A, NED
18	50	M	Hodgkin's disease	30.3	D, NED
19	55	M	Hodgkin's disease	2.7	D, WD
20	37	M	Squamous cell carcinoma	6.8	D, NED
21	27	F	Toxoplasmosis	15.5	A, NED
22	64	F	Unknown	4.0	A, WD

*Cases listed as idiopathic represent those patients who exhibited no systemic disease and developed none subsequently.

A = alive; NED = no evidence of disease; WD = with disease; D = dead; NED = no evidence of disease.

to be older, age 12 to 62 years (mean, 29.7 y), while the "idiopathic" group tended to be younger, age 7 to 21 years (mean, 16.1 y). Therefore, this idiopathic group may represent a subset of the population that develops a granulomatous response to the usual stimuli for chronic tonsillitis.

The development of head and neck sarcoidosis is well documented in the literature, and occurs in 10% to 15% of patients with sarcoidosis.[14] The eye and/or lacrimal gland is the most common site of involvement in the head and neck, followed by skin, nose, nervous system, larynx, salivary glands, cervical lymph nodes, and middle ear.[15] Tonsillar involvement is exceptional,[7] but occasionally, because of its easy accessibility, random tonsillar biopsies have been advocated to diagnose sarcoidosis—but there is a low diagnostic yield.[16] As reported in our series, tonsillar sarcoidosis composes less than 0.03% of all tonsillectomy cases examined at our institution. Given the referral nature of our practice, the percentage must be even lower in an unselected population. Sarcoidosis of the tonsil may present as a unilateral mass lesion with accompanying cervical adenopathy, producing a clinical scenario suspicious for malignancy,[2,3] similar to sarcoidosis presenting in other otorhinolaryngologic sites.[1] Therefore, histological examination of the tonsil in this clinical setting is mandatory.

Primary tonsillar tuberculosis is a rare entity, but still exists in regions of the world where the overall incidence of tuberculosis is high.[17] Secondary spread to the oropharynx is a rare but described sequela of pulmonary disease.[6] Diagnosis of tonsillar tuberculosis is made by histopathological findings and culture of the organism. The presentation of primary or secondary tonsillar tuberculosis may be difficult to distinguish from sarcoidosis, especially if no acid-fast bacilli are seen or if initial cultures are negative, considering both entities share similar features: pulmonary disease, adenopathy, and granulomatous inflammation. Therefore, it is imperative to try to make a definitive diagnosis, since the potential treatment could be more harmful than inaction (i.e., giving corticosteroids to a patient with tuberculosis).

Our three patients with tuberculosis illustrate the potential diagnostic difficulty and resultant morbidity. One patient was asymptomatic, but had diffuse lung lesions on chest radiograph with a persistently negative PPD and negative sputum acid-fast bacilli cultures. His tonsillectomy specimen revealed large, well-formed, and confluent granulomas with focal central caseating necrosis. Without special stains, and based on the histology alone, he was diagnosed with sarcoidosis. Approximately 1 year later, he was hospitalized with severe dyspnea and cough. Despite aggressive therapy he died of fulminant

pulmonary tuberculosis after 3 months of hospitalization. The histological specimens from the other two patients initially failed to reveal acid-fast bacilli. It was only after serial sections were stained with Ziehl-Neelsen that a few isolated organisms were identified, reinforcing the capricious nature of these studies. However, both patients were clinically diagnosed soon after the tonsillectomy, treated appropriately, and experienced no long-term sequelae.

Toxoplasma gondii typically affects the posterior cervical lymph nodes but has been described in the tonsils as well.[18,19] The characteristic histological pattern includes marked follicular hyperplasia and a granulomatous reaction within the germinal centers and at their immediate periphery. The granulomas are typically small and poorly delineated, but rarely may have areas of necrosis and giant cell formation.[20] Some have suggested that the occurrence of granulomas within germinal centers (Fig. 3) is nearly specific for toxoplasma lymphadenitis.[21] We were unable to support this conclusion based on our findings in tonsils. While our only confirmed toxoplasmosis case did indeed have granulomas within germinal centers, a similar localization was noted in four sarcoid, two tuberculosis, one Hodgkin's disease, and six idiopathic granulomatous cases. Therefore, we do not believe that the topographic localization can be used to yield a specific diagnosis. Furthermore, one cannot rely on serological confirmation of toxoplasmosis alone, because the antibodies may not develop early in the disease and there may be variations in immunoglobulin G and immunoglobulin M response. Therefore, one might question our seven "idiopathic" cases: perhaps they represent serologically silent toxoplasmosis. Nevertheless, none of those patients exhibited concomitant adenopathy, a finding present in other reported cases of tonsillar toxoplasmosis,[19] and all of the patients had tonsillar symptoms for many years, a finding not likely to be found in toxoplasmosis.

The association of granulomatous inflammation with neoplasia is well documented. As illustrated in our series, Hodgkin's disease can be accompanied by granulomatous inflammation, the pathophysiology of which is poorly understood. It likely represents a generalized immune response to the tumor, which can be manifest in organs uninvolved by Hodgkin's disease.[9,10] A localized granulomatous response to the keratin produced by squamous cell carcinomas may occur, particularly after irradiation.[12] A similar reaction is seen in ruptured epidermal inclusion cysts. Therefore, granulomas can be seen in both malignancy and acquired cystic lesions.

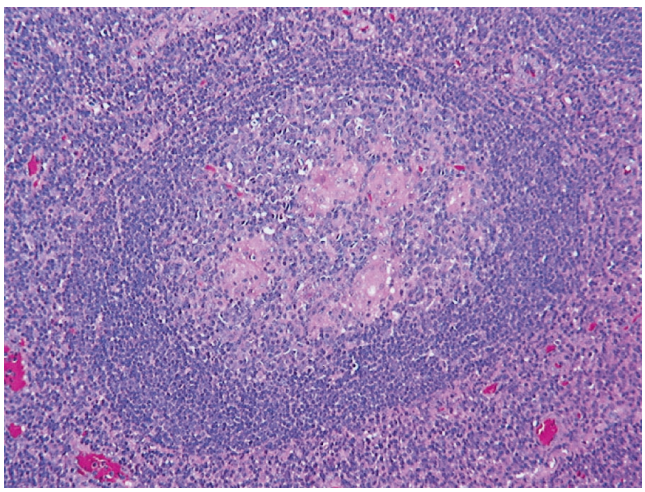

Fig. 3. Granulomas within germinal centers in a patient with idiopathic granulomatous inflammation of the tonsil. Original magnification × 200.

CONCLUSION

We described the histological and clinical features of 22 patients with granulomatous inflammation of the tonsils. While sarcoidosis was the most common diagnosable disease, we identified an equal company of patients who neither expressed concurrent nor developed subsequent systemic disease. Arguably, these cases may represent localized sarcoidosis of the tonsil, since sarcoidosis can be a mild and self-limited disorder, but in light of the clinical context, we believe these cases most likely represent an exaggerated immune response to the stimuli of chronic tonsillitis. We further brace the importance of the clinical presentation, especially for mycobacterial infections, particularly in the setting of negative special stains and cultures. Insight into the other etiologies of tonsillar granulomas, including toxoplasmosis, neoplasia, and Crohn's disease, will allow for an appropriate differential diagnosis in evaluating patients with similar presentations.

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