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HISTOPATHOLOGICAL FEATURES OF TUBERCULOUS VS. NON-TUBERCULOUS GRANULOMATOUS LESIONS IN THE NASAL CAVITY

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Abstract

Introduction: Infectious and non-infectious agents can cause granulomatous inflammation in the nasal cavity, the most common being tuberculosis and non-tuberculous mycobacteria. It is critical to distinguish them to facilitate proper diagnosis and management of the condition.

Objectives: To compare and characterize the histopathological features of tuberculous and non-tuberculous granulomatous lesions in the nasal cavity.

Materials and Methods: A cross-sectional data analysis from 200 nasal biopsy samples was done at Niazi Medical College Sargodha, Pakistan, from February, 2024 to July, 2024. This study used routine H & E staining, Ziehl – Neelsen (ZN), and periodic acid – Schiff (PAS) staining. Data were analyzed using SPSS.

Results: There were 200 cases, 120 of which had tuberculosis, while 80 were non-tuberculous. Among the histopathological characteristics of TB, caseous necrosis, Langhans giant cells, and ZN positivity were most evident. Non-tuberculous tissues had a higher density of fibrosis and Fungal elements on the PAS stain, especially in the immunocompromised patient.

Conclusion: Consequently histopathology with special stains and clinical correlation still remains an effective way for understanding granulomatous lesions in the nasal cavity..

Keywords: Granuloma, Tuberculosis, Non-tuberculous Mycobacteria, Nasal Cavity, Histopathology, Ziehl-Neelsen, PAS Stain.

INTRODUCTION

Granulomatous inflammation in the context of the nasal cavity presents a rather challenging case in differential diagnosis, mainly because of the variety of possible causes, ranging from infective and autoimmune to primary idiopathic forms. Tuberculosis (TB) and non-tuberculous mycobacteria (NTM) are two kinds of infectious diseases with similar histopathological appearance but quite different outcomes. Mycobacterial infections associated with granulomas pathologically and immunologically form due to sustained prior inflammatory processes (1). However, histopathology becomes invaluable in distinguishing between tuberculous and non-tuberculous granulomatous lesions, especially in LMICs, where other tests, such as molecular ones, are not readily available. Tuberculosis has not lost its importance as a public health problem all over the world, especially in endemic countries such as Pakistan, while extrapulmonary manifestations, including nasal cavity lesions, present tantalizing diagnostic challenges owing to their rarity and vague clinical features (2).

TB-related granulomas, in their histological characteristic, present caseating necrosis, Langhans giant cells, and peripheral lymphocytic cuffs.

Although these morphological characteristics are frequently enough to indicate tuberculosis, they are not pathognomonic, and in instances that are unclear, microbiological or molecular confirmation is required (3). After a biopsy or the removal of suspicious lesions, the histological investigation has unintentionally shown primary TB of the upper aerodigestive tract, including uncommon locations like the tonsils and nasal cavity (3). In these situations, the pathophysiology of tuberculosis may be related to contiguous extension from nearby structures, hematogenous dissemination, or direct infection. It's interesting to note that some individuals have nodular or cavitary lesions but no systemic symptoms, which makes clinical diagnosis even more difficult (4). These unusual features raise the risk of morbidity, delay diagnosis, and make pathologists and clinicians more suspicious. Accurate classification becomes even more difficult when granulomatous inflammation coexists with other pathological illnesses, such as sarcoidosis, autoimmune diseases, or chronic fungal infections, without a comprehensive histological evaluation and supporting investigations. (2).

Infection with non-tuberculous mycobacteria (NTM) and the formation of granulomas are on the rise, including in patients with chronic lung diseases and immunodepression. In turn, whereas there are no significant differences in the morphological features between NTM infections and tuberculosis, microscopically, they can be distinguished by focal caseating necrosis and dense histiocytic infiltrate (5). This led to the misdiagnosis of granulomatous mastitis due to NTM with either idiopathic or tuberculous (5,6). It was reported that DNA-based detection methods can accurately differentiate NTM and MTC in granulomatous tissues using FFPE tissue specimens (7). Some of the NTM infections may have clinical and radiographic manifestations similar to malignancies, which may lead to delayed initiation of antimicrobial therapy or surgery (8). Case-control studies, especially in adolescents, support the above findings, showing that granulomatous inflammation may be acquired from causes other than tuberculosis (9) .

The late development and susceptibility to standard anti-TB therapy remain the challenges in diagnosing NTM pulmonary sickness, which requires accurate identification of tissue supported by microbiological and clinical correlation (10). Research on the effects of ageing and immunological changes indicated that the granulomatous responses during NTM infections being better developed in the elder individuals hence changing the normal histological appearance, which in most cases acts as a confounding factor in diagnosing the disease (11). Since immunodeficiency and other confounding factors might further obscure granuloma structure, advanced diagnostic techniques such as confocal laser endomicroscopy and endobronchial ultrasound-guided biopsy may be necessary in pediatric HIV-positive cases (12). Animal models have been essential in understanding mycobacterial pathogenesis and treatment efficacy. Because treatments for NTM can take months, a rabbit model that studies antibiotic penetration into granulomatous lesions has helped to understand the pharmacokinetics at the site of infection (13) .

The importance of regional epidemiological data in guiding differential diagnosis has been highlighted by genetic investigations conducted in TB-endemic locations such as Kenya, which have revealed a considerable frequency of NTM infections among TB-negative symptomatic patients (14). These indications and the need for proper assessment of granulomatous involvement in any organ are further supported by case reports of extrapulmonary TB, such as perianal ulceration with intestinal and pulmonary manifestation (15). These cases stress the importance of consultancy with the help of histological examination in the presence of granulomatous inflammation, and further research directing to identifying the cause. It is not easy, but it is essential to differentiate between tuberculous and non-tuberculous granulomatous tumors in the nasal cavity with the help of histology. Histology, in combination with clinical correlation and, when possible, molecular pathology, should be employed to make a correct diagnosis. Improved histopathological features and enhanced consciousness are imperative in the early and optimal treatment of NTM since their incidence is rising and their clinical characteristic is simulating TB.

Objective: The histological features of tuberculous and non-tuberculous granulomatous lesions in the nasal cavity was compared and described in order to improve diagnosis accuracy and direct targeted treatment strategies.

MATERIALS AND METHODS

Study Design: Cross-sectional descriptive study.
Study setting: The study was carried out at Niazi Medical College Sargodha, Pakistan.
Duration of the study: The study was from February, 2024 to July, 2024

Inclusion Criteria:

All patients operated and biopsied at the nasal cavity between January 2024 and June 2024 with histological evidence of granulomatous inflammation were included in the study irrespective of age and gender of the patient. The requirement for H&E stained slides and sufficient tissue in formalin-fixed paraffin-embedded blocks that were readily available the only inclusion criteria used in the selection. Subject to certain stains or clinical associations histological changes were used to determine the suitability of tuberculous and non-tuberculous granulomas.

Exclusion Criteria

This was particularly observed when there were no final results of clinical tests, missing or poorly fixed biopsy materials, or granulomatous inflammation that could not be determined as non-tuberculous or tuberculous. Further, patients on anti-non-tuberculous mycobacterial diseases or tuberculosis before biopsy were not considered in order to evaluate treatment related histological changes.

Methods

We obtained histopathological records from the Department of Histopathology's archives at Niazi Medical College Sargodha, Pakistan for nasal cavity samples diagnosed with granulomatous inflammation between from February, 2024 to July, 2024. For routine histological analysis, tissue blocks that were formalin-fixed paraffin-embedded (FFPE) were sectioned at a 4–5 µm thickness and stained with hematoxylin and Eosin (H&E). Periodic Acid-Schiff (PAS) for fungal elements and Ziehl-Neelsen (ZN) for acid-fast bacilli are among the special stains used when necessary. Two experienced histopathologists separately examined the slides to look for distinctive characteristics such as fibrosis, vascular alterations, large cell type and distribution, lymphocytic cuffing, and the presence or absence of caseous necrosis. Based on morphological traits and supporting stain results, cases have been identified as tuberculous or non-tuberculous granulomatous lesions. Radiological results, clinical history, and microbiological data (if available) were also examined for final classification. SPSS version 26 was used to record, code, and analyze the data.

RESULTS

Two hundred nasal cavity biopsy cases with granulomatous inflammation were assessed during the study period. In these, 80 cases (40%) had non-tuberculous granulomatous lesions and 120 cases (60%) had tuberculous granulomatous lesions. The patients were 42.5 ± 15.2 years old on average, and the male-to-female ratio was 1.3:1. While non-tuberculous granulomas were more uniformly distributed among all age categories, the highest frequency of tuberculous granulomas was noted in the 31–50 age range.

Table 1: Demographic Distribution of Patients

Age Group (years)	Tuberculous Cases (n=120)	Non-Tuberculous Cases (n=80)	Total
10–30	30 (25%)	22 (27.5%)	52
31–50	58 (48.3%)	30 (37.5%)	88
51–70	28 (23.3%)	20 (25%)	48
>70	4 (3.3%)	8 (10%)	12
Total	**120 (100%)**	**80 (100%)**	**200**

According to histopathological analysis, 105 out of 120 tuberculous granulomatous lesions (87.5%) exhibited caseous necrosis, whereas only 6 out of 80 non-tuberculous instances (7.5%) exhibited necrosis of any kind, most of which was non-caseating. Compared to non-tuberculous patients (24/80, 30%), tuberculous cases had a considerably higher frequency of Langhans large cells (92/120, 76.6%).

Table 2: Histological Features in Tuberculous vs. Non-Tuberculous Lesions

Histopathological Feature	Tuberculous (n=120)	Non-Tuberculous (n=80)
Caseous Necrosis	105 (87.5%)	6 (7.5%)
Langhans Giant Cells	92 (76.6%)	24 (30%)
Epithelioid Cells	120 (100%)	80 (100%)
Lymphocytic Cuffing	90 (75%)	52 (65%)
Fibrosis	34 (28.3%)	38 (47.5%)

One important factor in distinguishing the two groups was the use of special staining. In contrast to none of the non-tuberculous lesions, 96 (80%) of the tuberculous patients had positive Ziehl-Neelsen staining for acid-fast bacilli (AFB). In 18 cases (22.5%) that were not tuberculous, PAS staining assisted in identifying fungal elements, such as sporotrichosis and histoplasmosis. Systemic tuberculosis was verified by clinical correlation in 84 tuberculous cases (70%), whereas immunosuppressive characteristics were reported in 12 non-tuberculous cases (15%).

Table 3: Special Stains and Clinical Correlation

Parameter	Tuberculous (n=120)	Non-Tuberculous (n=80)
ZN Stain Positive (AFB)	96 (80%)	0 (0%)
PAS Positive (Fungal)	2 (1.6%)	18 (22.5%)
Systemic TB History	84 (70%)	0 (0%)
Immunosuppressive Conditions	4 (3.3%)	12 (15%)

Overall, a solid foundation for differentiating between tuberculous and non-tuberculous granulomatous lesions in the nasal cavity was provided by histological characteristics, unique stains, and clinical background.

DISCUSSION

Although relatively rare, granulomatous inflammation in the nasal cavity is an essential diagnostic feature since it is linked to several viral and non-infectious etiologies. Using histological analysis and supporting clinical and microbiological data, the main goal of this study was to differentiate between tuberculous and non-tuberculous granulomatous lesions. The findings support the diagnostic utility of histological criteria, including Langhans giant cells, caseous necrosis, and specific staining methods, especially in situations where routine access to sophisticated genetic diagnostics may be limited. In developing nations, tuberculosis is still a serious public health issue, and extrapulmonary types can be challenging to diagnose. According to prior studies, 60% of the granulomatous lesions in the nasal cavity in our analysis were attributed to tuberculosis, which is a major cause of granulomatous inflammation in endemic areas (1) .

The histological feature of tuberculous granulomas is caseous necrosis surrounded by epithelioid histiocytes and Langhans giant cells, typically with a lymphocyte rim surrounding the periphery. These characteristics were similar to those documented in the literature and were found in most of our TB cases (2,3). Abdelwahed and Samman (3) state that one of the rare signs of extrapulmonary TB is primary tonsillar tuberculosis, which can be determined by histology. The significance of histological evaluation is further highlighted by the growing detection of nasal TB in biopsy specimens from persistent nasal lesions or masses, notwithstanding its rarity. In keeping with the

findings of Patil et al. (4), who documented atypical TB presentations without fever or weight loss, it is noteworthy that a large number of our TB cases lacked characteristic constitutional symptoms. On the other hand, 40% of the cases in our study were non-tuberculous granulomatous lesions, which showed various histomorphological patterns. Among these were granulomas linked to non-tuberculous mycobacterial (NTM) illnesses and fungal infections.

NTM granulomas often lacked caseous necrosis and displayed more scattered histiocytic clusters on histological examination. The challenge of distinguishing NTM nasal lesions in our sample aligns with the diagnostic issue of NTM-related granulomatous mastitis highlighted by Patel et al. (5,6). NTM infections must be diagnosed by PAS staining or molecular testing because, unlike TB, they typically exhibit negative Ziehl-Neelsen stains. It was helpful to use special stains to differentiate TB from NTM. The diagnostic usefulness of Diehl-Neelsen staining was confirmed by our analysis, which showed that it was consistently negative in non-tuberculous patients and positive in 80% of tuberculous cases (7). PAS staining, which detected fungal organisms in 22.5% of non-tuberculous cases, corroborated the findings of Saad et al. (8), who observed fungal masqueraders in granulomatous lung disease. These results highlight the need to use both stains if granulomatous disease is suspected frequently.

Another significant influence is the patients' demographic dispersion. While non-tuberculous lesions were more evenly distributed, patients aged 31 to 50 had the majority of TB-related granulomas. In a pediatric population with a variety of granulomatous disorders, Cay et al. (9) noted comparable age trends. The host immune condition may also influence the form of the granuloma, and age influences the immune response to tuberculosis (10).Research by Cinco et al. (11) indicates that aging alters the immunological and microbiological profile during NTM infection, which may affect the granuloma development and the intensity of the inflammatory response.Moreover, NTM infections are more common in immunocompromised people, especially those with HIV or receiving immunosuppressive treatment.

According to Vasilev et al. (12), a youngster with HIV who had an intrathoracic NTM infection was identified using sophisticated endomicroscopic and bronchoscopic methods. Their results highlight the difficulty of diagnosing immunosuppressed people, even if such techniques are not commonly used in everyday practice. Our investigation highlighted this link by identifying 15% of non-tuberculous granulomatous lesions in individuals with established immunosuppressive disorders. Antibiotic resistance and treatment length are essential factors in the management of NTM infections. To investigate drug penetration into granulomatous regions, Kaya et al. (13) created a rabbit model, showing that traditional anti-TB medications might not be as effective in NTM. The underlying granulomatous etiology must be accurately identified to customize treatment for this pharmacological difficulty. The significance of local awareness and monitoring systems is further supported by regional epidemiological data, such as those reported by Mwangi (14) in Kenya, which show an increasing burden of NTM among symptomatic TB-negative persons.

Finally, our data confirms previous results that granulomas connected to tuberculosis frequently have systemic involvement. A history or evidence of systemic TB was found in 70% of our tuberculosis cases. To further distinguish the two groups, none of the non-tuberculous cases had systemic TB. A case with multi-organ TB involvement, including intestinal, pulmonary, and perianal TB, was reported by Yuan and Ma (15), demonstrating the disease's systemic character. Finally, this study highlights the importance of histological investigation in differentiating nasal cavity granulomatous lesions that are tuberculous from those that are pathogenic. Although specific characteristics are similar, the presence of Langhans large cells, ZN positive, and caseous necrosis strongly suggests a tuberculous etiology. However, fungal and atypical mycobacterial origins of non-tuberculous lesions must be carefully considered, particularly in patients with impaired immune systems. For a precise diagnosis and suitable treatment, morphological criteria, unique stains, and clinical correlation are still necessary.

CONCLUSION

This study highlights the importance of histological assessment in distinguishing between tuberculous and non-tuberculous granulomatous lesions in the nasal cavity. More often found were tuberculous granulomas, which frequently showed Langhans giant cells, acid-fast bacilli positive on Ziehl-Neelsen staining, and caseous necrosis. On the other hand, non-tuberculous lesions showed more varied histological characteristics, often without necrosis, and were usually linked to fungal infections or non-tuberculous mycobacteria, especially in immunocompromised people. Accurately classifying these lesions was greatly facilitated by the use of specific stains like ZN and PAS. Clinical history further supported the diagnostic distinction, including immunological status and systemic TB involvement. In situations with limited resources, where molecular techniques might not be easily accessible, histopathology is essential. Patient outcomes are improved when the underlying etiology is identified early and accurately since this guarantees prompt and proper care. Effective management of granulomatous disorders of the nasal cavity requires ongoing vigilance and routine histological evaluation.

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