CASE REPORT

Clinical Case Reports WILEY

Rare co-occurrence of tonsillar follicular dendritic cell sarcoma and schizophrenia: A comprehensive study

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Abstract

This study investigated the infrequent occurrence of tonsillar follicular dendritic cell sarcoma (FDCS) co-existing with schizophrenia, presenting a comprehensive examination of clinical, pathological, and literature aspects. A systematic literature review was conducted, focusing on articles related to "schizophrenia" and "sarcoma," with in-depth analysis of included case reports. Clinical data, pathological findings, and patient follow-up information were collected and synthesized. The study detailed a rare case of FDCS in the tonsil concurrent with schizophrenia, providing insights into diagnosis, treatment, and follow-up. A literature review of combined FDCS in the tonsil and schizophrenia cases highlighted their clinical and pathological characteristics. Eight case reports encompassing 11 patients diagnosed with sarcoma and schizophrenia were included. Surgical resection was the preferred primary treatment, while chemotherapy was suggested for recurrences. Instances of co-occurring FDCS and schizophrenia were exceptionally limited, with tonsillar FDCS being particularly uncommon. The coexistence of tonsillar FDCS and schizophrenia was an exceptionally rare condition, posing diagnostic and therapeutic challenges. This study contributed valuable insights into clinical and pathological practice through a systematic review, underscoring the significance of early diagnosis and comprehensive management.

KEYWORDS

comprehensive treatment, follicular dendritic cell sarcoma, pathological diagnosis, schizophrenia, systematic review, tonsil

1 | INTRODUCTION

Follicular dendritic cell sarcoma (FDCS) is an infrequent neoplasm originating from lymph nodes and extranodal organs. It is characterized by the morphological and immunophenotypic features of follicular dendritic cells (FDCs).^{1–3} Due to its low incidence rate, fibrosarcoma

of the bone (FDCS) is frequently overlooked or misdiagnosed.^{4–6} Although it can affect individuals of all age groups, it is most commonly observed in the middleaged population. The precise cause of FDCS remains unclear; however, ongoing research examines its association with specific immune abnormalities and viral infections.^{7,8} The diagnosis of this tumor primarily relies

Yu Zhang and Xiaoxi Jin should be regarded as co-first authors.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes. © 2024 The Authors. *Clinical Case Reports* published by John Wiley & Sons Ltd. on immunohistochemical examination, particularly the detection of FDC markers.^{2,9,10} Surgical excision is generally the preferred therapeutic approach; however, it is associated with increased rates of both recurrence and metastasis.¹¹

Tonsils are an uncommon site for FDCS. Diagnosing and treating tonsil FDCs present unique challenges compared to other anatomical regions. The clinical symptoms of tonsillar tumors often mimic those of common tonsillar diseases, potentially leading to delayed diagnosis. Furthermore, the surgical removal of tonsils may necessitate more advanced techniques due to their anatomical location and proximity to vital structures. From a pathological perspective, distinguishing it from other tonsil tumors is critical to ensure an accurate diagnosis and appropriate treatment.^{12–14}

Schizophrenia is a multifaceted mental disorder characterized by etiology encompassing genetic, environmental, and biological factors.¹⁵⁻¹⁷ While limited reports have linked schizophrenia and malignant tumors, this association has garnered significant attention in recent years. Several studies suggest a potential connection between schizophrenia and the pathogenesis of specific tumors.^{18,19} However, the results of these studies have not consistently yielded findings, highlighting the need for further research. Systematic literature reviews provide clinicians with a valuable tool when encountering rare and complex diseases, aiding in their comprehension of the most recent advancements and research trends in the field. A more comprehensive and in-depth understanding of diseases can be obtained by thoroughly analyzing existing and historical literature. The literature review undoubtedly offers a solid foundation for conducting research, particularly concerning the rare FDCS of tonsils and its correlation with schizophrenia.

Given the aforementioned context, we firmly believe that it is imperative to conduct further investigations into the co-occurrence of tonsil FDCS and schizophrenia. This study aims to report a unique case and provide a comprehensive understanding of this rare disease through a systematic literature review. Through this study, we aim to enhance the understanding of FDCS among clinical and pathological physicians, offering guidance and recommendations for its diagnosis and treatment.

2 | MATERIALS AND METHODS

2.1 Case collection and medical history review

The patient was a 70-year-old female with a history of schizophrenia lasting over 20 years. She had been

receiving long-term oral treatment with Risperidone Tablets and Sulpiride. The clinical data of all patients were thoroughly reviewed, encompassing medical history, physical examination findings, laboratory test results, imaging studies, and treatment strategies. Furthermore, we conducted a comprehensive review of patient medical records at Zhejiang Xin'an International Hospital, Zhejiang Provincial Armed Police Corps Hospital, and The First Affiliated Hospital of Zhejiang University to gather comprehensive information regarding the progression of patients' diseases.

2.2 | Literature review data sources and retrieval strategies

To gain a comprehensive understanding of the associated risk factors in patients with co-existing sarcomas and schizophrenia, relevant literature up until October 2023 was retrieved from MEDLINE, Embase, and Cochrane databases using keywords such as "dendritic cell sarcoma," "amygdala," and "schizophrenia." These sources were utilized as the primary data for the study.

2.3 | Literature screening and quality assessment

We included all studies that met the following eligibility criteria: (1) population—patients diagnosed with FDCS and comorbid schizophrenia; (2) interventions—all patients in the studies underwent surgery, radiation therapy, or chemotherapy; (3) outcome measures—the number of patients who experienced adverse events, specifically tumor recurrence, during blood dialysis after surgery. Cell experiments, animal experiments, reviews, and literature related to meta-analyses were excluded from our review.

The literature screening was conducted using EndNote X9, a reference management software developed by Clarivate Analytics in the USA. After removing duplicate literature using both automated and manual methods, two researchers independently conducted a step-by-step screening of articles based on predetermined eligibility criteria. They used titles, abstracts, and full-text contents as references during the screening process.²⁰ Any discrepancies were resolved through consultations with a third-party researcher.²¹ In cases where there was an overlap between the population and the intervention being studied, selecting the study with a higher number of participants was advisable. All studies have obtained informed consent from the participants. Moreover, two researchers independently assessed the methodological quality of the included studies using

Clinical Case Reports

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Review Manager v5.4 software. Any discrepancies were resolved through discussions with an independent researcher.²²

2.4 Data extraction and comprehensive analysis

Two authors independently extracted comprehensive research data that met the analysis criteria. The study extracted the following items from each study: study designer, country, publication year, and characteristics of the main participants (including participant number, age, proportion of females, disease type, tumor site, treatment modality, history of schizophrenia, number of tumor recurrences). We have included the most recent or comprehensive information in cases involving multiple publications. If necessary, we contacted the corresponding authors of the relevant studies for additional information.

2.5 | Data analysis

We have comprehensively analyzed clinical data and pathological results from our patients, focusing specifically on the correlation between FDCS and schizophrenia. Furthermore, we performed a systematic review and analysis of the pertinent literature to briefly summarize and compare the characteristics of the documented cases, diagnostic methodologies, and treatment alternatives across various studies. Statistical analyses were conducted using GraphPad Prism 9.0 software.

3 | RESULTS

3.1 | Case

3.1.1 | Clinical data

The patient was a 70-year-old female with a 20-year history of schizophrenia. She takes one tablet of Risperidone Tablets twice daily and one tablet of Sulpiride orally. Experiencing difficulty swallowing and a persistent sensation of obstruction during meals for more than a month, she sought medical attention at Zhejiang Xin'an International Hospital. A thorough physical examination identified the presence of a newly formed growth on the right tonsil. A biopsy was subsequently performed, and the pathology report, dated April 10, 2019, confirmed the diagnosis of FDCS. On April 29, 2019, the patient sought additional treatment and visited The First Affiliated Hospital of Zhejiang University.

Further inquiry into the medical history revealed that the patient sought medical treatment 16 years ago at the Zhejiang Armed Police Provincial General Hospital, complaining of odynophagia. During that time, a suspected "right tonsillar tumor" led to a surgical intervention to remove the right tonsil and tumor. The patient's family reported that a postoperative pathology report confirmed the presence of a malignant tumor, but the specific details were unknown. The presenting symptoms upon admission included a nipple-like neoplasm on the upper segment of the right palatoglossal arch, displaying an uneven surface and involving the uvula.

Furthermore, a cauliflower-like neoplasm was observed in the right tonsillar fossa, characterized by an irregular surface and ulceration. Following the patient's admission, relevant examinations were conducted. On May 2, 2019, a comprehensive surgery was carried out under general anesthesia. This surgery included radical resection of malignant tumors in the oral and pharyngeal regions, neck lymph node dissection (right-sided, levels 1–3), lymph node dissection on the tongue bone, release of nerve adhesions, external jugular artery stripping, and pedicled muscle flap transplantation in the dissected area. During the surgery, a cauliflower-like tumor was identified on the right tonsil, involving the right side of the soft palate and uvula. Postoperative administration of antibiotics and wound care were provided.

The pathological examination revealed a mass in the right tonsil during the gross examination. A specimen of irregular gray-white soft tissue measuring 4.5 cm×3.5 cm×2.5 cm was submitted for evaluation. The surface of the tissue displayed multiple nodular lesions. An optical microscope observation revealed that the tumor cells were organized in spindle, sheet-like, and nodular formations. The cells display irregular shapes and visible nuclear division figures. Many lymphocytes were interspersed among the tumor cells, and tumor emboli were observed within the blood vessels. Immunohistochemical staining was performed on the lymphoid tissue (Figure 1C,D). The staining showed positive expression of CD21 and CD23, while CK(pan), P63, CK5/6, S-100, CD34, and CD1a were negatively expressed. HHV8 was suspected to be positive, but the EBER in situ hybridization result was negative.

The pathological diagnosis revealed a malignant spindle cell tumor that had spread to the lymph nodes in the right tonsil. The tumor's morphology and results from immunohistochemical analysis were consistent with FDCS (Figure 1). 4 of 10



FIGURE 1 Microscopic observation and immunohistochemical staining features of follicular dendritic cell sarcoma in the right tonsil. (A, B) Tumor cells arranged in spindle-shaped, nodular patterns with some lymphocytes present (×100); (C) positive expression of CD21 (×100); (D) positive expression of CD23 (×100).

3.1.2 | Follow-up

The patient had been monitored for 38 months after surgery with no relapse or metastasis detected. The patient continued to be monitored and was receiving regular treatment with Risperidone Tablets and Sulpiride for schizophrenia. The condition was well-managed.

3.2 | Quantitative analysis of the literature review results

To investigate the risk factors related to the co-occurrence of FDCs and schizophrenia, we conducted a comprehensive search and review of pertinent literature. Figure 2 summarized the results from the literature search and selection process. During the literature search, 189 publications focusing on schizophrenia and FDCs were identified. Among these 189 documents, roughly 10% described the concurrent presence of FDCs and schizophrenia, but only a limited number focus on FDCS. No additional eligible articles were identified by screening the reference list of included studies. All the articles included in this study had complete full texts and have been published in peer-reviewed journals. The details of the assessment of literature quality can be found in Figure 3. Based on the quality assessment, it was determined that all the studies included in the field of indicator selection have a low risk of bias.

Table 1 provides a summary of the baseline characteristics that were included in the study. Following a systematic screening process, literature unrelated to FDCs and schizophrenia and those with incomplete data were excluded. It led to a final analysis of 8 case reports. These eight studies comprised a combined total of 11 patients diagnosed with both FDCs and schizophrenia. The research consisted of three studies (37.5%) conducted in Europe, specifically in Italy and Germany; three studies (37.5%) conducted in Asia, specifically in Singapore and Japan; one study (12.5%) conducted in America, specifically in the United States; and finally, one study (12.5%) conducted in Africa, specifically in

FIGURE 2 PRISMA 2020 flowchart.



South Africa. The study includes primarily middle-aged and elderly women who were 37 or older. Among the eight included studies, one study revealed that patients encountered tumor recurrence following surgical intervention.

A review of eight articles found that surgical resection was the predominant treatment method utilized in most cases described. Chemotherapy was advised for cases that recurred. According to the literature, there has been increased research on this disease in the past decade, attributed to advancements in diagnostic techniques and a greater understanding of the disease. Simultaneously, we have gathered postoperative performance data of patients included in the literature. However, limited research was available on patients who have both FDCS and schizophrenia and aside from this current report, no other cases of FDSC occurring in the amygdala have been identified (Table 2).

4 | DISCUSSION

FDCS are a subset of dendritic cells originating from the stroma.¹ Formerly referred to as dendritic reticulum cells, FDCs are accessory T cells of the immune system with

antigen-presenting capabilities, primarily residing in primary and secondary lymphoid follicles.^{1,23,24} FDCS is a tumor comprising spindle or oval-shaped cells displaying the morphological and immunological characteristics of FDCs. This tumor was first documented by Monday and colleagues in 1986.²⁵ FDCS is a relatively uncommon neoplasm, predominantly affecting adults with a median age of 50 years, and afflicting both males and females equally.²⁶ Diagnosis of FDCS hinges on histopathological examination and immunohistochemical analysis, with a specific focus on assessing the presence of FDCs in terms of morphology and immunology. Despite its low incidence, the diagnosis and management of FDCS present substantial challenges.

While FDCS can manifest in individuals of all age groups, its prevalence is notably higher among the middle-aged population.²⁶ Tonsillar FDCS is a rare occurrence, and its unique anatomical location and physiological function introduce specific challenges in terms of diagnosis and treatment. Delayed diagnosis often stems from the clinical presentation's resemblance to other tonsil diseases, underscoring the critical importance of timely identification and management.

6 of 10



FIGURE 3 Quality assessment of included studies. (A) Bias risk graph depicting the reviewers' judgments on each bias risk item, represented as percentages across all included studies; (B) summary of bias risk, providing a retrospective review of the judgment on each bias risk item for each included study, with red indicating high risk, green indicating low risk, and yellow indicating unknown risk.



Traditionally, limited attention was given to the potential correlation between schizophrenia and malignant tumors. However, as research progresses, mounting evidence suggests a potential genetic connection between schizophrenia and the pathogenesis of FDC. Furthermore, long-term medication use is proposed as a triggering factor for FDC.²⁷ While the precise mechanisms of this association remain unclear, it provides a promising avenue for further research. Our systematic literature review revealed the rarity of simultaneous tonsillar FDCS and schizophrenia occurrences. Notable differences exist in specific clinical and pathological features compared to previous studies, potentially influenced by factors such as patient genetics, environment, and other unidentified variables (Figure 4).

Currently, there is no standardized treatment plan for FDCS, with available modalities encompassing surgical resection, chemotherapy, radiotherapy, and tyrosine kinase inhibitors.²⁸ In foreign literature, there have been 35 reported cases of FDCS outside the tonsils, with surgical removal commonly employed as the primary treatment for localized FDCS.²⁹ FDCS is characterized as a low to moderately malignant tumor,³⁰ which may exhibit local

recurrence and distant metastasis. While IPT-like FDCS can experience local recurrence, it typically presents as a slow-growing tumor.^{31,32} Histological features associated with a poor prognosis include a tumor size of 6 cm, the presence of 5 mitotic figures per 10 high-power fields, necrosis, and significant tumor cell atypia.^{33,34}

The primary limitation of this study is the limited number of cases, as only a single case was included, potentially introducing bias in our conclusions. Additionally, the short duration of case follow-up has resulted in insufficient long-term prognosis data. Moving forward, we intend to conduct further research involving a larger number of tonsillar FDCS cases to gain a more comprehensive understanding of their clinical and pathological characteristics and their association with schizophrenia. This study offers fresh insights into this rare disease through a thorough analysis and discussion of a case involving the co-occurrence of FDCS and schizophrenia. These findings hold significant scientific and clinical value, contributing to a deeper understanding of the disease and serving as references for clinical practice. However, given the limitations of this study, further research is necessary to validate and strengthen our findings.

Study	Country	Sample size (% female)	Age (years)	Disease	Cancer site	Treatment	Schizophrenic history (years)	Tumor recurrence (%)
Harikar, et al. (2023)	Italy	1(100)	69	MPNST	Right forearm	Surgery	ı	0
Wong, et al. (2015)	Singapore	1 (100)	37	DFSP	Vulva	Surgery	1	1
Katano, et al. (1997)	Japan	1(0)	44	FDCS	Cervical lymph node	Surgery	20	I
Agaimy, et al. (2006)	Germany	1(0)	52	FDCS	GI tract and mesentery/omentum	Surgery	9	1
Masunaga, et al. (1997)	Japan	1(100)	55	FDCS	Left submandibular lymph	Chemotherapy	25	0
Li, et al. (2013)	USA	1(100)	55-60	TMS	Adjacent to the right kidney	Chemotherapy	ı	100
Pileri, et al. (2002)	Italy	3 (66.6)	49.6 (44–55)	LCS/FDSC	Skull and right occipital region/ cervical adenopathy/diffuse adenopathy + splenomegally	Surgery/ chemotherapy	20 (15–25)	0
Van Der Merwe, et al. (2018)	South Africa	2 (100)	56 (52–60)	Uterine adenosarcoma	Cervix	Surgery		0

TABLE 1 Baseline characteristics of patients included in the study (n = 11).

TABLE 2 Baseline characteristics of FDSC patients included in the study (n=6).

Study	Country	Sample size (% female)	Age	Cancer site	Treatment	Schizophrenic history (years)	Tumor recurrence (%)
1 ¹	Italy	2 (50)	49.5 (44–55)	Cervical adenopathy/diffuse adenopathy + splenomegally	Surgery/ chemotherapy	22.5 (20-25)	0
2 ²	Japan	1 (0)	44	Cervical lymph node swelling	Surgery	20	-
3 ³	Germany	1(0)	52	GI tract and mesentery/ omentum	Surgery	6	-
4 ⁴	Japan	1 (100)	55	Left submandibular lymph	Chemotherapy	25	0
Current case	China	1 (100)	70	Tonsils	Surgery	20	0



FIGURE 4 Conceptual diagram of pathology and treatment investigating the comorbidity of follicular dendritic cell sarcoma and schizophrenia based on evidence-based medicine.

AUTHOR CONTRIBUTIONS

Yu Zhang: Conceptualization; investigation; methodology; resources; writing – review and editing. Xiaoxi Jin: Data curation; investigation; resources; supervision. Liyan Lian: Conceptualization; data curation; investigation; methodology; project administration; supervision; writing – review and editing.

ACKNOWLEDGMENTS

Not applicable.

FUNDING INFORMATION Not applicable.

CONFLICT OF INTEREST STATEMENT

The authors confirm that they have no conflict of interests.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

This study adhered strictly to the ethical principles associated with research involving human subjects, ensuring that all procedures complied with the ethical standards of The First Affiliated Hospital of Zhejiang University. The study's purpose and procedures have been thoroughly explained to the patient or their family members, who have given written consent to participate in this research. All personal information has been deidentified to protect patient privacy and maintain data confidentiality.

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FV_Clinical Case Reports

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How to cite this article: Zhang Y, Jin X, Lian L. Rare co-occurrence of tonsillar follicular dendritic cell sarcoma and schizophrenia: A comprehensive study. *Clin Case Rep.* 2024;12:e8700. doi:<u>10.1002/</u> ccr3.8700