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Original Article

Follicular dendritic cell sarcoma of the tonsil: case report and review of literature

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Abstract: Objective: To explore the clinicopathologic features, immunophenotype, differential diagnosis, and prognosis of tonsil follicular dendritic cell sarcoma (FDCS). Methods: In the Department of Pathology, the affiliated Yantai Yuhuangding Hospital of Qingdao University, in 2019, a case of tonsil FDCS was diagnosed and retrospectively analyzed to summarize its clinical and pathologic characteristics. Relevant literature was reviewed. Results: The patient was a 71-year-old man. The tumor occurred in the right tonsil with a maximum diameter of 3.5 cm. Microscopically, the tumor cells were spindle-shaped or oval-shaped, arranged in bundles or swirls, and some areas formed concentric circles around blood vessels. Small lymphocytes were distributed in the background. The nucleus was oval-shaped or round, with nuclear chromatin and small central nucleoli. Mitoses were up to 5/10 HPF at the highest. Immunohistochemistry showed positive expression of CD21, CD23, CD68, vimentin, and D2-40 in tumor cells, and Ki67 proliferation index was about 20%. CXCL13 was positive only in scattered background lymphocytes. In situ hybridization for EBER was negative. After surgical resection of the tumor, without radiotherapy or chemotherapy, the patient has been followed up for 4 months until now, without recurrence or metastasis. Conclusion: FDCS is a rare tumor, especially in extranodal sites. The pathogenesis, treatment and prognosis of FDCS still need further exploration.

Keywords: Tonsil, follicular dendritic cell sarcoma, FDCS, EBER, in situ hybridization

Introduction

In 1986, Monda et al. [1] first described follicular dendritic cell sarcoma (FDCS), a malignant tumor originating from follicular dendritic cells (FDC), and its morphological characteristics and immune phenotype. FDC are an important component of lymph node follicles, mainly distributed in primary and secondary lymph follicles, and play the role of antigen capture, presentation, and participation in immune response. In addition to lymph nodes, FDC are also present in the body's scattered lymphoid tissues, such as tonsils, liver, spleen, gastrointestinal tract, and mediastinum. Therefore, FDCS mainly occurs within lymph nodes, and a few can also occur in extranodal sites. Only dozens of cases in the tonsil have been reported in PubMed.

Case report

A 71-year-old male, who suffered from persistent dry throat for 7 months after a cold, went to the Department of Otorhinolaryngology of Yantai Yuhuangding Hospital on November 7, 2019, and was admitted as outpatient for "right tonsil hypertrophy". The patient had a history of smoking when he was young. He denied any symptoms of foreign body sensation in pharynx, blocking sensation, paroxysmal cough, blood in sputum or other symptoms. He had no breathlessness, dysphagia or dyspnea, with 2-kilogram loss of weight. Intraoral examination revealed that the right tonsil was enlarged and the surface was smooth without ulcerations, purulent substances, or secretions. No other masses or enlarged lymph nodes were found. Routine biochemical and hematologic investigations were within normal limits. The right tonsil was resected by surgery

without radiotherapy or chemotherapy, and the patient has been followed up for four months without recurrence or metastasis.

Materials and methods

Samples

Tissue specimen was from 1 patient, who was treated at the Affliated Yantai Yuhuangding Hospital of Qingdao University in 2019. It was collected and fixed in 10% buffered formalin, then dehydrated, embedded in paraffin and cut into 4-μm-thick sections for hematoxylin and eosin (H&E) staining, then observed under light microscopy.

Immunohistochemistry

Immunohistochemical reactions were performed on the paraffinized sections using the EnVision method. The antibodies included CD21, CD23, CD68, D2-40, Ki67, CK, CD10, P63, P40, CD20, CD3, LCA, HMB45, S-100, Desmin, SOX-10, PR, EMA, STAT-6, CgA, synaptophysin, and bcl-2 (purchased from Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.), vimentin, CK5/6, GFAP, SMA, and CD34 (purchased from Fuzhou Maixin Biotechnology Development Co., Ltd.).

In situ hybridization

In situ hybridization for EBV-encoded RNA (EBER) was performed and the probes were purchased from Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.

Pathology findings

The specimen received in formalin was a gray-red tissue, 3.5×2.5×1.5 cm, whose surface was smooth. Cut surface was gray-red, and the texture was medium. Histopathology showed that the tumor cells were spindle-shaped or oval-shaped, arranged in bundles or swirls, and some areas formed concentric circles around blood vessels. Small lymphocytes were distributed in the background (**Figure 1**). The nucleus was oval-shaped or round, with nuclear chromatin vacuoles and small central nucleoli. Mitoses were up to 5/10 HPF at the highest point (**Figure 1**).

Immunohistochemical findings

CD21, CD23, CD68, vimentin, D2-40 had positive expression; Ki67 proliferation index was about 20%; CXCL13 was only positive in scattered background lymphocytes (**Figure 2**). CK, CD10, CK5/6, P63, P40, CD20, CD3, LCA, HMB45, S-100, SMA, desmin, SOX-10, PR, EMA, GFAP, STAT-6, CgA, synaptophysin, CD34, and bcl-2 were negative.

In situ hybridization findings

In situ hybridization for EBER was negative.

Discussion

FDCS is a rare tumor, especially in extranodal sites. Its etiology and pathogenesis are unclear. Lin et al. believed that FDCS maypass through stages of development such as FDC hyperplasia-atypical hyperplasia-tumor [2].

We reviewed 33 cases of FDCS in the tonsil from 23 documents in the PubMed database from 2002 to 2020 (**Table 1**).

It was revealed that the patients' ages ranged from 16 to 76 years old [3-24], with an average age of 49 years and a median age of 51 years, which is consistent with other data. The male to female ratio is approximately 1.75:1. Literature shows no gender difference in the incidence of FDCS [25]. The left-to-right ratio is approximately 1.5:1. Most patients had dysphagia, some had dyspnea and throat pain, and a few had no symptoms. In a few cases, patients had a history of smoking. We think that FDCS that occurs in the tonsils may be related to smoking. The above-mentioned observation that there are more men than women who have FDCS in the tonsil may support this. In the next study we will collect more cases to explore the relationship between smoking and tonsil FDCS. Two patients had scleroderma. Studies have shown that [26] 10% to 20% of intranodal or extranodal FDCS can be associated with Castleman's disease, especially the hyaloid-vascular subtype. The pathogenesis of scleroderma and Castleman's disease is not clear, but both of them seem to be related to abnormal immune regulation and infection. We can conjecture that the incidence of FDCS is also related to these two factors.

The maximum diameter of the tumor was 2.5-6.0 cm. Most of the tumors had clear boundaries with smooth surfaces, and a few had ulcerations. FDCS in the head and neck is relatively small, ranging from 1 to 6 cm [27], and appears

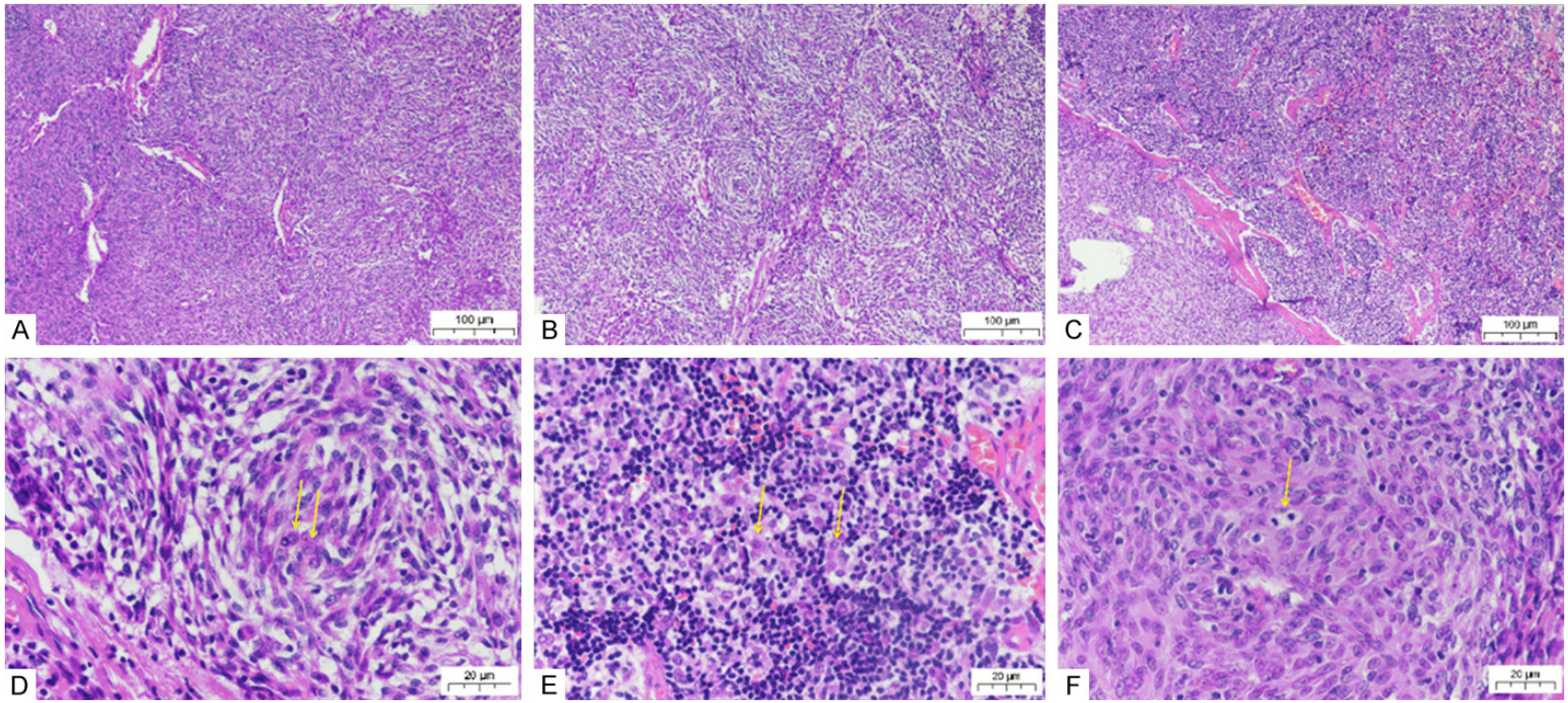

Figure 1. A. Tumor cells were spindle-shaped or oval-shaped, arranged in bundles or swirls, and some areas formed concentric circles around blood vessels (H&E 10× objective); B and C. Small lymphocytes were distributed in the background (H&E 10× objective); D and E. The nucleus was oval-shaped or round, with nuclear chromatin and small central nucleoli (H&E 40× objective); F. A mitosis can be seen in the center of the picture (H&E 40× objective).

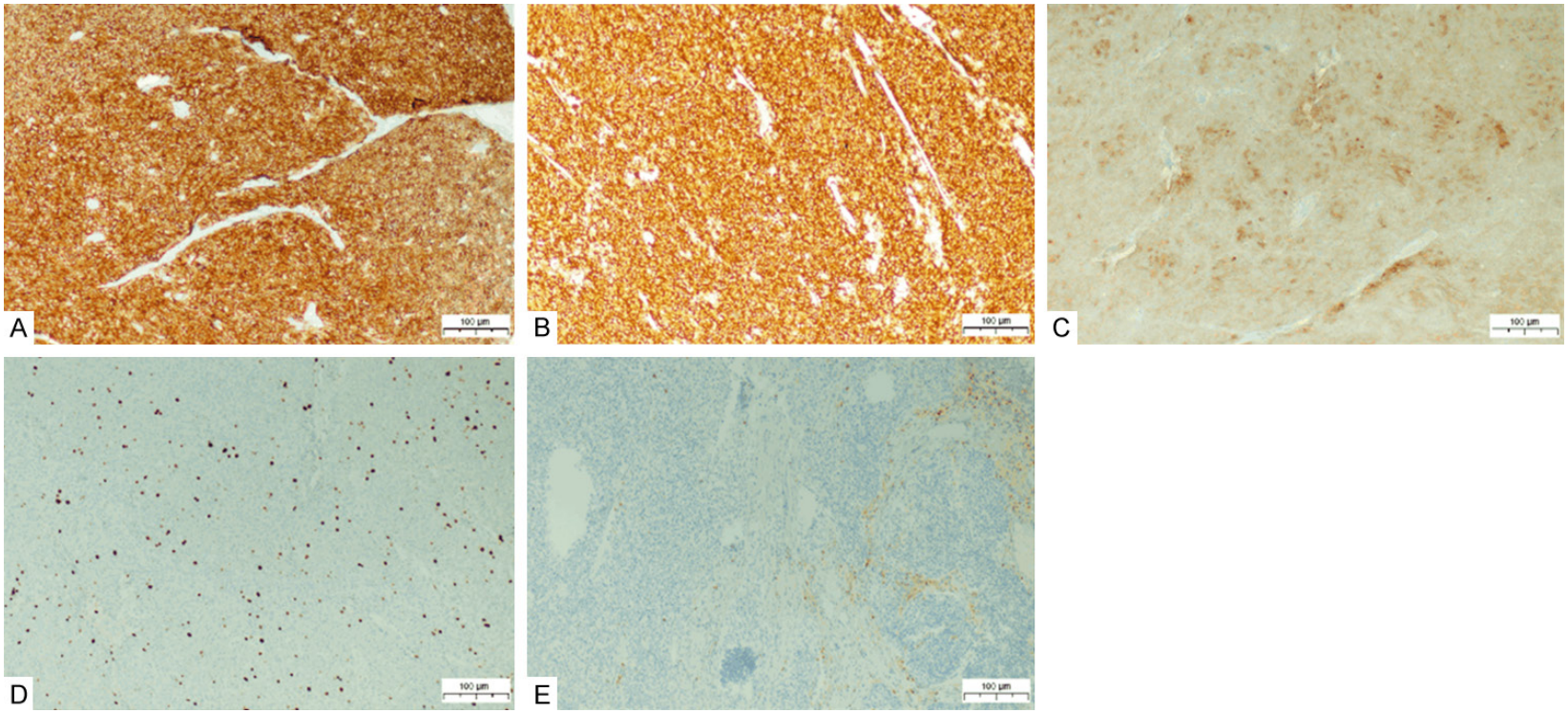

Figure 2. A-C. In tumor cells, positive expression of CD21, CD23, and D2-40 protein respectively (H&E 10× objective); D. Ki67 proliferation index was about 20%; E. CXCL13 was scattered in the background lymphocytes (H&E 10× objective).

Table 1. Datails of 33 cases

Case no.	Reference	Age (years)/ Gender	Left or Right	Maximum diameter (cm)	Clinical symptoms	Treatment	Prognosis	Follow-up (months)	EBER	Others
1	2019/Wu B et al. [3]	51/Male	Left	3.3	NA	Surg	NA	NA	Negative	
2	2017/Pecorella I et al. [4]	60/Female	Left	6	Dysphagia	Surg	NA	NA	NA	
3	2015/Horváth E et al. [8]	55/Male	Left	3.5	Dysphagia, hemoptysis	Surg+RT	NR, NM	36	NA	Smoking history
4	2015/Kulkarni MP et al. [6]	30/Female	Left	2.6	Dysphagia, throat pain	Surg	NA	NA	NA	
5	2015/Lu ZJ et al. [7]	59/Male	Right	4.6	Foreign body sensation	Surg+RT	NR, NM	44	NA	Smoking history
6	2015/Vorsprach M et al. [5]	24/Male	Left	2.5	Throat pain	Surg	NR, NM	NA	NA	
7	2014/Ribeiro L et al. [9]	52/Male	Left	3.3	No symptom	Surg	NA	NA	NA	Scleroderma
8	2013/Hu T et al. [11]	36/Female	Left	3	Dysphagia	Surg	R, NM	6	Negative	
9	2013/Hu T et al. [11]	59/Female	Left	4.5	Dysphagia, dyspnea	Surg, Surg+RT	R, DF	17	Negative	
10	2013/Kara T et al. [10]	72/Male	Right	5	Dysphagia, dyspnea	Surg+ChT	DU	NA	NA	
11	2012/Mondal SK et al. [12]	27/Male	Left	2.8	Dysphagia	Surg+RT	NR, NM	6	NA	
12	2010/Eun YG et al. [14]	65/Male	Right	3	Dysphagia	Surg+RT	NR, NM	24	NA	
13	2010/Suhail Z et al. [13]	52/Female	Right	2.5	Dysphagia, throat pain	Surg+ChT	NR, NM	12	NA	
14	2010/Duan GJ et al. [15]	41/Male	Left	3	NA	Surg	NR, NM	9	Negative	
15	2009/Vaideeswar P et al. [16]	50/Male	Left	2.5	Dysphagia	Surg	NR, NM	24	NA	Smoking history
16	2007/McDuffie C et al. [17]	59/Female	Right	4	Dyspnea	Surg+RT	NR, NM	18	NA	
17	2006/Aydin E et al. [19]	76/Female	Left	3.5	No symptom	Surg+RT	NR, NM	48	NA	
18	2006/Clement P et al. [18]	27/Female	Right	4	Dysphagia	Surg+RT	NR, NM	6	Negative	Smoking histeroy
19	2004/Domínguez-Malagón H et al. [20]	29/Female	Left	4.8	Dysphagia	Surg, Surg+RT	R, DF	120	NA	
20	2004/Domínguez-Malagón H et al. [20]	48/Male	Left	3.9	Dysphagia	Surg+RT	NR, NM	36	NA	
21	2003/Tisch M et al. [22]	51/Male	Left	NA	Dysphagia	Surg+RT	NR, NM	60	NA	
22	2003/Satoh K et al. [21]	16/Male	Right	3	Dysphagia, throat pain	Surg+RT+ChT	NR, NM	24	NA	
23	2002/Biddle DA et al. [23]	48/Male	Right	3.5	throat pain	Surg	NR, NM	18	NA	
24	2020/Baily H et al. [30]	39/Male	Right	2	Throat fullness	Surg	NA	NA	Negative	
25	2016/Amirtham U et al. [24]	63/Male	Left	<5	Dysphagia	Surg+RT	R	52	NA	
26	2016/Amirtham U et al. [24]	28/Male	Right	<5	Dysphagia, LNE	Surg, RT, ChT	NR, NM	NA	NA	
27	2016/Amirtham U et al. [24]	66/Male	Right	<5	Dysphagia, LNE	Surg, RT	R	31	NA	
28	2016/Amirtham U et al. [24]	68/Female	Left	<5	Throat pain	Surg	R	19	NA	
29	2016/Amirtham U et al. [24]	65/Female	Left	<5	Dysphagia	Surg, ChT	R	47	NA	
30	2016/Amirtham U et al. [24]	40/Male	Left	<5	Dysphagia	Surg, ChT	NR, NM	60	NA	
31	2016/Amirtham U et al. [24]	51/Female	Left	<5	Dysphagia	Surg, ChT	NR, NM	60	NA	
32	2016/Amirtham U et al. [24]	38/Male	Right	<5	Dysphagia, LNE	Surg, RT, ChT	R	45	NA	
33	Current case	72/Male	Right	3.5	Dry throat	Surg	NR, NM	12	Negative	Smoking histeroy

R: recurrence; NM: no metastasis; NR: no recurrence; DF: died of FDCS; DU: died of unknown cause; NA: not avallable; Surg: Surgery; RT: Radiotherapy; ChT: Chemotherapy; LNE: lymph node enlargement.

as a polyp-like or swollen growth, generally without bleeding and necrosis.

Microscopically, other cases were similar to the current case, consisting of spindle-shaped to oval cells and a large number of small lymphocytes. Tumor cells are arranged in sheets or bundles, and swirl-like or mat-like structures can be seen in some tumors. The cells have an unclear boundary, and a round or oval nucleus. Nuclear chromatin is translucent and vesicular. Sometimes pleomorphism is obvious, and giant tumor cells can be seen. Sometimes intranuclear pseudoinclusions can be seen. Due to these histopathologic features, FDCS of the tonsil requires differential diagnosis with several tumors: ectopic meningioma, nasopharyngeal carcinoma, malignant melanoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant lymphoma, and lymphoepithelioma-like carcinoma. The morphology of this case has misled our diagnosis at the outset. We considered almost all of the above diagnoses and later excluded them one by one due to negative expressions of EMA, PR, CK, HMB45, CD34, bcl-2, S-100 and LCA. Therefore, when we see bidirectional cell morphology of tumors in the tonsil, we must not neglect the diagnosis of FDCS.

CD21, CD23, and CD35 were positively expressed in all cases in the literature. These three are traditional markers of FDC. Their positive expression can confirm the diagnosis of FDCS. Our case also positively expressed D2-40. D2-40 has been used to label lymphatic endothelial cells, and is often used in the diagnosis of mesothelioma. In recent years, it has been found to be positively expressed in FDCS, making it another effective antibody to assist in the diagnosis of FDCS [28]. Research by Vermi et al. [29] showed that the expression of CXCL13 is physiologically restricted to FDCs in secondary lymphoid organs and is maintained in their dysplastic and neoplastic counterparts, respectively, in Castleman's disease and FDCS. In our case, CXCL13 was only scattered in background lymphocytes. Recent reports suggest that up to half of FDCSs show immunohistochemical positivity for p16 [30]. Additional immunostaining with follicular dendritic cell markers should be used to confirm or exclude the diagnosis in p16-positive oropharyngeal lesions showing subtle but characteristic histologic features of FDCS [30].

In situ hybridization for EBER was performed in 5 of the cases, and all were negative. Some long-standing literature suggested that FDCS in the liver was related to EBV infection [31], Cheuk et al. [32] proposed that EBV was displayed only in inflammatory pseudotumor-like FDCS, and its differences from conventional FDCS included: more common in women; selectively localized in the abdominal cavity, especially the liver and spleen; often presenting with systemic symptoms; exhibiting inert biologic behavior despite being located in the abdominal cavity; scattered distribution of tumor cells with obvious infiltration of lymphocytes; and close relation to EBV. However, the pathogenic mechanism of EBV in inflammatory pseudotumor-like FDC sarcomas is still unclear and needs further research. Therefore, FDCS of the tonsil is usually negative for EBER.

In terms of treatment and prognosis, all of the patients underwent surgical resection. Some of them underwent radiotherapy and chemotherapy after surgery. 8 cases of the patients relapsed, and 2 of them died [11, 20]. Although recurrence was followed by surgery and postoperative radiotherapy, the tumor still recurred multiple times until it could not be removed and eventually the patients died. The tumor's maximum diameter in the two dead patients exceeded 4 cm, and one of them had mitotic rate of about 10/10 HPF [20]. Some patients with enlarged lymph nodes have relapsed [24]. Another patient with a recurrence had a tumor with a maximum diameter of 3 cm, which was misdiagnosed as an inflammatory lesion at the time of the initial disease, without radical resection and enlarged resection [11]. In summary, we conclude that the prognosis of FDCS is related to the tumor size and may also be related to the number of mitoses. Li et al. [33] proposed a recurrence risk assessment model based on tumor size and histologic grade. Through this model, extranodal FDCS were divided into low, medium, and high risk groups with recurrence rates of 16%, 46%, and 73%, and mortality rates of 0, 4% and 45%. In this study, statistical analysis showed that compared with small tumors (longitudinal size <4 cm), large tumors (longitudinal size ≥ 4 cm) had a worse prognosis.

Treatment and prognosis are closely related. Due to the limited number of case reports and the lack of prospective studies on treatment

and prognosis, the best treatment options for FDCS are still being explored. Jian et al. [27] proposed that tumors with a larger size (> 6 cm), coagulative necrosis, obvious atypia, and mitotic rate > 5/10 HPF, should be vigilantly followed clinically. In addition to complete tumor resection, radiotherapy and chemotherapy are supplemented if necessary. However, we think that FDCS in a special site such as tonsil, if the primary tumor is small and has minimal atypia and necrosis, a lower level of postoperative chemoradiotherapy is needed.

Conclusion

FDCS is a rare tumor, especially in extranodal sites, and the latter is often easily misdiagnosed as malignant tumors of various mesenchymal or epithelial origins. The pathogenesis of FDCS is still unclear and the treatment is mainly surgery, supplemented by radiotherapy and chemotherapy if necessary. The standard line of postoperative radiotherapy and chemotherapy should be lower when the tumor occurs in the tonsil. The prognosis of tonsil FDCS may be mainly related to tumor size and the number of mitoses. The pathogenesis, treatment, and prognosis of FDCS still need further exploration and research. The correct pathologic diagnosis is the basis of all these.

Disclosure of conflict of interest

None.

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