

Follicular dendritic cell sarcoma of the head and neck. Literature review and report of the tonsil occurrence in a Ugandan patient

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Key words

Palatine tonsil • Follicular dendritic cell sarcoma • Extranodal haematological malignancy • Immunohistochemistry

Summary

We report a case of follicular dendritic cell sarcoma (FDCS) in a 60-year-old Ugandan female who presented with a 6-year history of a progressive left sided tonsillary mass. General systemic examination was unrevealing and the patient underwent left tonsillectomy. She was subsequently lost to follow-up.

Grossly, the mass measured 6 cm in diameter and had a mottled appearance due to tissue microhaemorrhages. Markers specific for follicular dendritic cell differentiation (CD21, CD35 and CD23), p53 and EGFR were expressed on immunohistochemical analysis.

Review of all of the 49 published reports of tonsil FDCS showed that this entity tended to occur at younger age (mean: 44.5 yrs) in women than in men (mean: 49.4 yrs). Tumour size ranged from 0.8 to 5 cm in maximum dimension (mean 2.9 cm). Only 12.2% of the patients presented with metastatic disease at initial diagnosis, all localised in the cervical lymph nodes. Local or distant recurrences occurred after a mean period of 72.5 months.

In conclusion, although the pertinent literature suggests that FDCS should be considered at least of intermediate grade, our review indicates that FDCS of the tonsil region behaves as a low-grade sarcoma.

Introduction

Recently discovered follicular dendritic cell (FDC) precursors in the lymph node are sessile cells originating from the vascular wall stroma and expressing platelet-derived growth factor receptor beta¹. Follicular dendritic cells are nonphagocytic, antigen-presenting immune accessory cells, located in the germinal centres of primary and secondary follicles, which may undergo sarcomatous changes. Follicular dendritic cell sarcoma (FDCS) accounts for only 0.4% of soft tissue sarcomas, with only 400 cases reported in the English literature², but has significant recurrent and metastatic potential and is considered by most authors an intermediate grade malignancy³. The tumour usually occurs in the lymph nodes of the neck, mediastinum, and axilla. In approximately 30% of cases, the tumour develops in extranodal sites, preferentially in the head and neck area. In 1996, Nayler et al. reported the first case of FDCS of tonsil⁴.

The lack of awareness of this entity causes a high rate of misdiagnoses in extranodal cases^{5,6}, especially in the head and neck region. Head and neck FDCS have occurred in soft palate, retromolar trigone, nasopharynx and parapharyngeal space, parotid gland⁶. FDCS of tonsil is extremely rare and so far only a total of 49 cases (35 cases in the English literature and 12 in the Chinese literature) were reported (see Tab. I).

To date, no such cases occurring in Uganda are described in the literature. Therefore, we herein present our case, with a review of the pertinent literature.

Case report

A 60-year-old Ugandan female patient presented to Gulu Regional Referral Hospital (north Uganda) with a fungating, painless left tonsillar tumour of 6-year-duration. The mass had caused difficulty in swallowing for the

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Tab. I. Summary data of FCDS of the tonsil reported in the English literature. Data of cases reported in the Chinese literature were retrieved from the article by Lu et al.²⁶.

Ref	Pt's gender	Pt's age	Side	Max size (cm)	Metastases at diagnosis	PO treatment	Tobacco use	Follow-up (months)
16	F	76	L	3.5	/	RT	NA	NED (48)
8	F	48	L	3.5	1/44 cervical LN	Radical neck dissection	NA	NED (6)
8	M	48	R	3.5	/	None	NA	NED (8)
17	M	40	L	NA	/	None	NA	NED (12)
17	M	45	R	NA	/	None	NA	NED (12)
17	M	34	R	NA	/	None	NA	Recurrence (120)
18	M	44	L	1.5	/	None	NA	NED 36
37	F	18	R&L	2	/	CHT (CHOP)	NA	NA
Chen (26)	NA	NA	NA	NA	na	None	NA	NED (12)
Chen (26)	F	21	R	2.5	na	None	NA	na
9	F	27	R	4	1 cervical LN	Neck dissection + RT	Yes	NED (6)
19	M	48	L	1.5	Cervical LN	Neck dissection + RT	NA	NED (36)
5	M	41	L	3	/	None	NA	NED (9)
20	M	65	R	3	/	RT	NA	NED (24)
21	F	48	R	NA	/	CHT + RT	NA	REC (180) CHT
15	F	57	NA	NA	Cervical & axillary LN	None	NA	AWD (8)
22	F	36	L	3	/	None	NA	Cervical LN (6) CHT (CHOP) + RT AWD (15)
	F	59	L	4.5	/	None	NA	REC (17) DOD (24)
23	F	77	NA	NA	/	Pre-operative RT + radical neck dissection	NA	Lung and hilar LN metastases (96)
14	M	72	R	5	NA	CHT (only 1 dose)	NA	Dead (12)
24	F	30	L	2.2	/	None	NA	NED (6)
25	M	60	NA	5	/	RT	NA	NED (86)
	M	55	NA	2	/	RT	NA	REC (18) AWD (21)
Liu (26)	F	47	R	NA	/	None	NA	NED 10
26	M	59	R	4.6	/	RT	Yes	NED (44)
27	F	47	L	NA	NA	CHT at 3rd recurrence	NA	REC (132)
Ma (26)	F	19	NA	1	NA	None	NA	NA
	M	60	R	1	NA	None	NA	NA
	F	40	L	0.8	NA	None	NA	NA
28	F	59	R	4	/	RT	NA	NED (18)
6	M	27	L	2.8	/	RT	NA	NED (6)
4	F	18	R&L	4	NA	CHT (CHOP)	NA	Lost to FU
2	M	32	L	3.3	Cervical LN	Neck dissection CHT + RT	NA	Lung & liver metastases (48)
29	F	62	NA	NA	/	None	NA	NED (36)
30	M	80	L	1.9	/	Partial pharyngectomy	Yes	Died of cardiac arrest 1 wk PO
Shi (26)	M	37	R	1.5	/	CHT	NA	NED (36)

continues

Tab. I. *follows.*

Ref	Pt's gender	Pt's age	Side	Max size (cm)	Metastases at diagnosis	PO treatment	Tobacco use	Follow-up (months)
38	F	69	NA	na	/	Preoperative RT +radical neck dissection	NA	Lung and hilar LN metastases (96) AWD (108)
31	M	63	L	4.2		No treatment	NA	AWD (8)
32	F	52	R	2.5	/	CHT	NA	NED (12)
33	M	51	L	NA	/	RT	NA	NED (60)
34	M	50	L	2.5	/	None	Yes	NED (48)
35	F	54	L	3	Cervical LN	Radical neck dissection	Yes	NED (8)
36	M	24	L	2.5	/	CO2 laser tonsillectomy	NA	NED
Wang (26)	M	80	R	4.6	/	None	NA	NED (24)
Wu (26)	F	55	L	NA	/	None	NA	NED (4)
Yang (26)	F	49	R	5	/	CHT	NA	NED (22)
Yin (26)	M	35	R	5	/	None	NA	LN metastasis (12) bilateral neck dissection + RT NED (39)
Zhan (26)	M	36	R	NA	/	None	NA	NED (48)
Zhan (26)	F	43	R	3	NA	None	NA	NA

Abbreviations: NA: not available; M: male; F: female; CHT: chemotherapy; LN: lymph node; NED: no evidence of disease; DOD: died of disease; REC: recurrence; AWD: alive with disease

last three months. Intraoral examination revealed a red mass with an irregular surface over the left tonsil. Tonsil of the opposite side was normal and a neck examination revealed no enlarged lymph nodes. General systemic examination was unrevealing. The patient underwent tonsillectomy under general anaesthesia.

Grossly, the resected solid mass measured 6 cm in diameter and showed a bosselated outer surface. Cut section revealed a whitish firm tumour with numerous tiny areas of haemorrhage and smooth surface.

Microscopically, the tumour was situated underneath the squamous epithelial lining of the tonsil (Fig. 1a). It had a diffuse growth pattern and pushing borders. There were focal storiform areas arranged in centripetal whorls reminiscent of meningioma, and focal multinucleate giant cells. Individual cells tended to be ovoid, with central nuclei, slightly eosinophilic, fibrillary cytoplasm and indistinct cell borders. The nuclei had fine chromatin, small but distinct nucleoli and a delicate nuclear membrane. Small lymphocytes were scattered throughout the tumour and often clustered around blood vessels (Fig. 1b-c).

On immunohistochemistry, the tumour cells expressed strong membrane positivity for all the three markers specific for follicular dendritic cell differentiation e.g. CD21, CD35 and CD23 (Fig. 1a) and for EGFR (Fig. 2a). Nuclear positivity for p53 was also observed (Fig. 2b). It was negative for cytokeratins, CD45, S-100, CD68, TTF1 and EBV-latent membrane protein-1. The Ki-67 labeling index was about 25% (Fig. 2c).

Patient received no further treatment and was subsequently lost to follow-up.

Discussion

We reviewed all of the 49 published reports of tonsil FDCCS (Tab. I). Twenty-four cases occurred in women and 24 in men (gender not available in 1 instance). Patient's age at diagnosis ranged from 80 to 18 years (mean: 47.8 yrs). FDCCS in women tended to occur at younger age (mean: 44.5 yrs) than in men (mean: 49.4 yrs). The age difference between males and females is not statistically significant. A total of 20 tumours were located in the left tonsil, while 19 were located in the right tonsil; 2 were bilateral. The affected tonsil was not reported in eight cases. Tumour size ranged from 0.8 to 5 cm in maximum dimension (mean 2.9 cm). In approximately half of the instances (24 cases) tonsillectomy was the only treatment. Seven had additional radical neck dissection. Fourteen cases received pre- or postoperative radiotherapy, including five cases with concomitant neck dissection. Two cases received combined chemotherapy and radiotherapy and 7 chemotherapy alone. One patient received no treatment at all. Six patients (12.2%) presented with metastatic disease at initial diagnosis, all localised in the cervical lymph nodes.

Follow up information was present from 4 to 180 months with an average of 38.2 months. A minimum follow-up of 12 months was available for 28 patients. Of them, 25 cases were alive with no evidence of disease after this period of time, indicating a rate of approximately 50% disease-free survivals at 1-year.

According to Pang et al, oropharyngeal FDCCS are significantly more likely to present with regional metastases compared to non-oropharyngeal lesions, including FDCCS of the

Fig. 1 a. Histology shows tumour cells staining strongly for CD23 underneath the squamous epithelial lining of the tonsil (x100). **b.** Diffuse sheet of plump neoplastic cells with indistinct cellular outlines, often showing whorled or storiform patterns. Numerous lymphocytes and plasmacells are also visible (H&E, x200). **c.** Higher magnification of the sarcomatous follicular dendritic cells (H&E 400x).

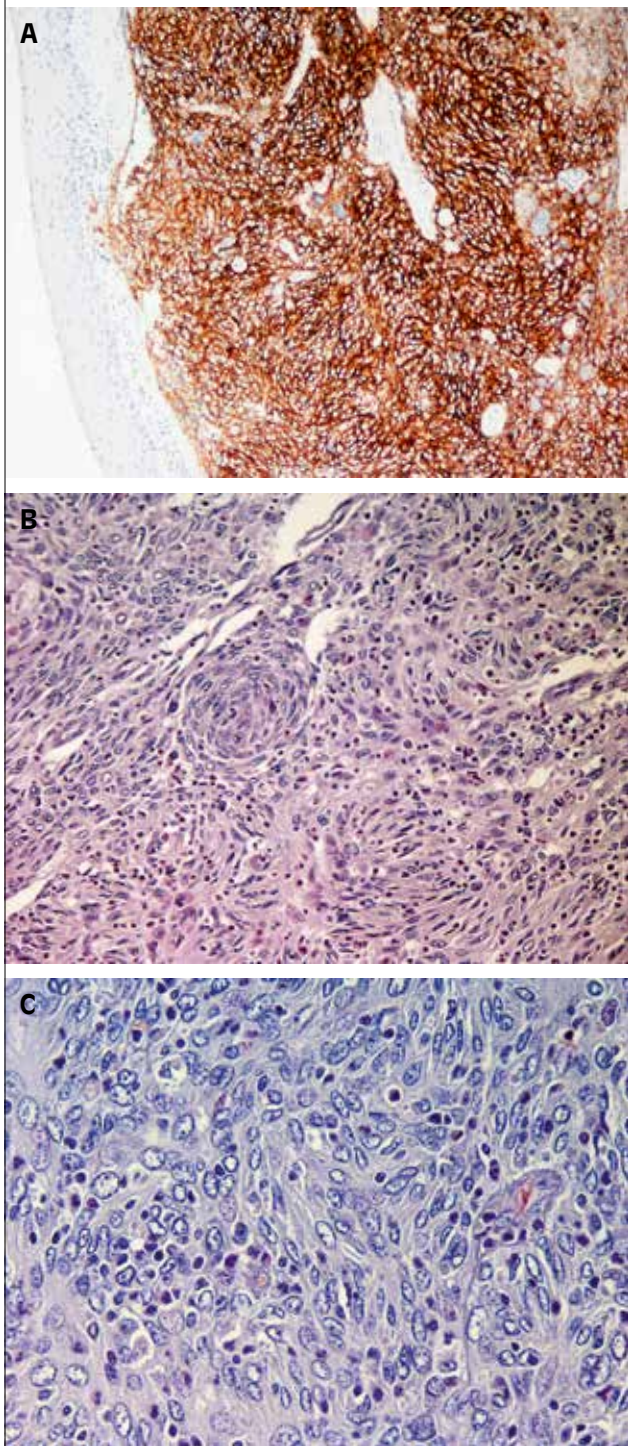
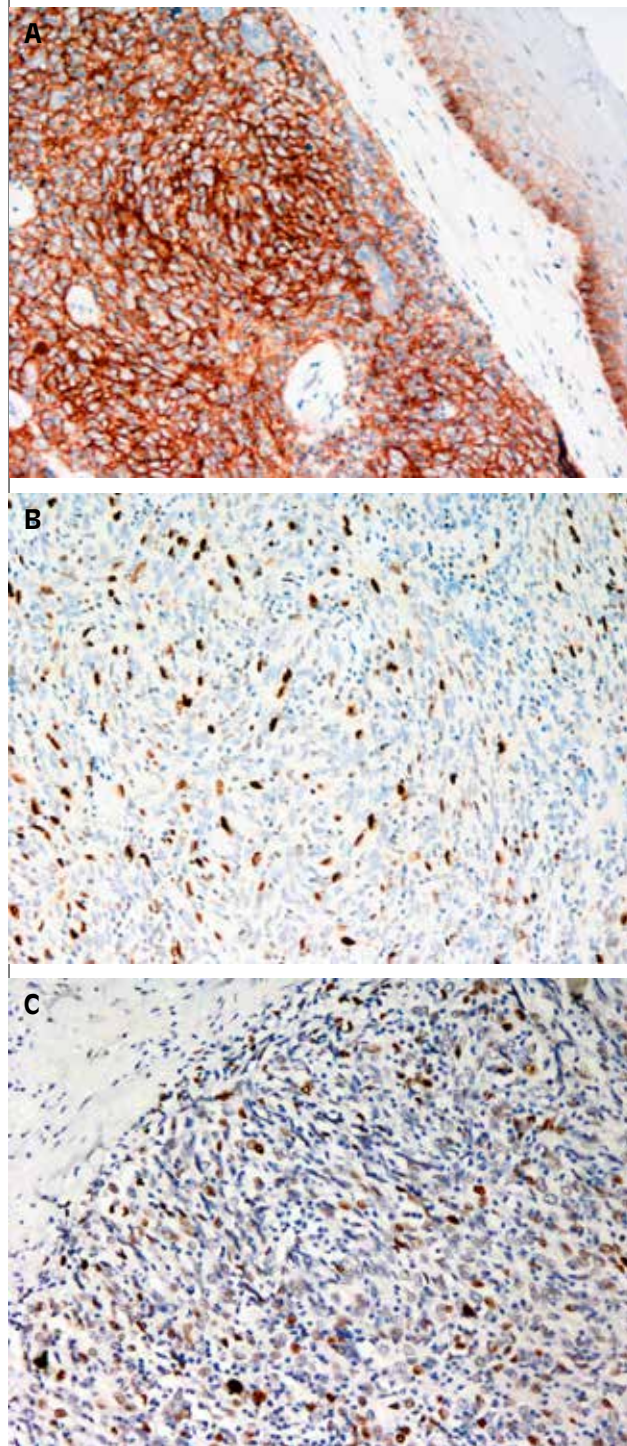


Fig. 2 a. Diffuse positivity of the FDCS for EGFR. Expression of EGFR in the normal appearing tonsillar squamous epithelium (right) is confined to the basal cell layer (x 100). **b.** Corresponding moderate to strong nuclear expression of p53 in scattered tumour cells (x 200). **c.** Immunoreactivity of the tumour cells for Ki67 antigen (x 100).



cervical lymph nodes. However, this does not hold true for the palatine tonsil, as only 6 of 49 cases (12.2%) showed local metastasis to lymph nodes at initial diagnosis. Presently, surgery with no adjuvant treatment is con-

sidered to be the standard for FDCS treatment ⁷. When metastasis to regional lymph nodes is suspected on imaging studies, a neck dissection is recommended. In the current case, dissection was not performed because no

findings suggestive of metastasis to the cervical lymph nodes were observed intraoperatively.

Adjuvant radiotherapy or chemotherapy can, however, be applied to cases with adverse pathologic features and in cases of advanced or incompletely resected lesions. Complete responses to CHOP are rare, and the benefits of this regimen may derive primarily from doxorubicin, one of the most broadly active agents against sarcoma in general. Although the pathogenesis of this neoplasm remains unknown, in 10% to 20% of cases it occurs in association with Castleman's disease of the hyaline-vascular type^{8,9}. Epidermal growth factor receptor (EGFR) expression has been investigated as another shared feature of both entities¹⁰. In addition, overexpression of the p53 protein is noted in FDCS. The present case showed diffuse hyperexpression of both EGFR and p53. Small molecule tyrosine kinase inhibitors and monoclonal antibodies are currently used to block EGFR activity and may prove of therapeutical interest in FDCS.

Reactive proliferations of FDCs are found in human immunodeficiency virus (HIV)-associated lymphadenopathy. Recent research studies have demonstrated that HIV infection may play a role in the formation of FDCS, via previous exposure to the Epstein Barr Virus (EBV)^{11,12}. The association with EBV infection is acknowledged in the setting of the inflammatory pseudo-tumour-like variant of FDCS. However, no cases of extranodal FDCS of the head and neck region have been associated with EBV. Heavy tobacco smoke habit was reported in some of the tonsillar (Tab. I) and extratonsillar cases.

According to the fourth edition of the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, most FDCS show low or intermediate-grade malignancy¹³. High-grade FDCS can be identified by large tumour size (greater than 6 cm), intraabdominal location, significant cytological atypia, extensive coagulative necrosis, and high proliferative index¹³. The present case was notable for the long duration of the disease (6 years) before the patient sought medical attention, as she lived in a poor rural area. Such a slow growth indicates a low-grade malignant potential of FDCS. Additionally, recurrences may be delayed for many years (Tab. I)¹⁴.

Owing to the short-term follow-up periods in the reported cases, the local recurrence and metastatic rates might be underestimated. 72.5 months was the mean period for local or distant recurrences in this reviewed series of tonsil FDCS, with the longest disease-free interval of 180 months.

FDCS are rare tumours that have been recognised only recently. The rarity of these tumours makes them difficult to accurately diagnose and treat, and they are often mistaken as non-Hodgkin lymphoma or other lymphoproliferative disorders. Immunohistochemistry may help in the diagnosis of FDCS (Tab. II). Of interest, despite coexpression of a leukocyte common antigen (CD45), and CD15, a monocyte common antigen in normal FDCs, in our experience and in all, but two reported cases of sarcomatous transformation, CD45 was negative. Revision of FDCS immunohistochemical literature data cannot confirm Grogg et al.¹⁵ impression that tu-

Tab. II. Summary data of immunohistochemical analyses in FDCS of the tonsil reported in the English literature. Data of cases reported in the Chinese literature were retrieved from the article by Lu et al.²⁶.

Ref	CD45	CD21	CD35	EMA	S100	EBV	other
16	NA	+	NA	NA	+/-	NA	CD68+/- Keratins-
8	-	+	+		-	-	Fascin +
8	NA	NA	NA	NA	NA	NA	na
17	-	+	+	-	+	NA	CD23+
17	-	+	-	-	-	NA	CD23+
17	NA	+	NA	NA	NA	NA	CD23+
18	+	+	+	na	-	-	CD10 MSA+ CD68-
37	NA	+	+	+	-	-	CD68-
9		+	+	-	+	-	NSE+ EGFR+ Keratins- CD68-
19	NA	+	+	-	-	NA	
5	-	+	+	+/-	-	-	CD23+/- CD68-
20	-	+	NA	NA	-	NA	Keratins- CD68-
21	NA	NA	NA	NA	NA	NA	na
15	NA	+	-	NA	-	NA	CD23+ CD68+ Fascin+
22	-	+	+	-	-	-	CD23+ CD68- CD23+ keratins+
23	-	+/-	+/-	+/-	+/-	-	CD68+ Desmin+
14	-	NA	NA	NA	-	NA	CD23+ Keratins-
24	NA	+	+	NA	+	NA	CD23+ Keratins-
25	- -	+ +	+ +	+ -	NA -	NA -	Keratins- Keratins- CD23+ CD68-
26	NA	+	-	NA	NA	NA	CD23+
27	NA	NA	NA	NA	NA	NA	CD68+ Fascin + CD23+
28	NA	+	+	NA	-	NA	CD23+ Keratins-
6	-	+	+	NA	NA	NA	CD23+ Cd1a- Desmin-
2	/	+	NA	NA	NA	NA	CD68+, fascin+, desmin- p16-, keratins-
30	NA	+	NA	NA	NA	NA	CD23+
38	NA	+	+	NA	+	-	Keratin -
32	NA	+	NA	NA	+	NA	
33	+/-	na	na	+/-	+/-	-	CD23+
34	-	+	+	NA	-	NA	CD23+ Keratins +/- CD68-
35	NA	+	NA	+	-		CD1a-, CD68-, keratins-
36	-	NA	NA	+/-	-	NA	CD23- Vimentin+ Ki-M4p+

Abbreviations: NA: not available; MSA: muscle specific actin; NSE: neuron specific enolase.

mours displaying more morphological and phenotypical (CD68+, S-100+) histiocytic differentiation may be associated with more aggressive behaviour, more akin to the behaviour of histiocytic sarcoma (Tab. II).

Conclusions

FDCS should be included in the differential diagnosis for any tonsillar mass, as an increasingly high number of cases are being added to the literature, thanks to increased awareness of this entity and more sensitive diagnostic tool. Our case shows that this tumour can also affect African patients. This should not come as a surprise in the light of a possible association of FDCS with viral infections, as the population of north Uganda is still plagued by AIDS and EBV infections.

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