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

I. PECORELLA¹, T.R. OKELLO², G. CIARDI¹, E. OCHOLA³, M.D. OGWANG²

¹ Department of Radiological, Oncological and Anatomic Pathology Sciences University of Rome “Sapienza”, Rome (Italy);
² Department of Surgery of Gulu University Medical School, St. Mary’s Hospital Lacor, Gulu (Uganda);
³ HIV Research Department, St. Mary’s Hospital Lacor, Gulu (Uganda)

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 tonsillar 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 beta ¹. 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 literature ², but has significant recurrent and metastatic potential and is considered by most authors an intermediate grade malignancy ³. 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 tonsil ⁴.

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 gland ⁶. 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
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.

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

According to Pang et al, oropharyngeal FDCS are significantly more likely to present with regional metastases compared to non-oropharyngeal lesions, including FDCS of the
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 considered to be the standard for FDCS treatment. 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.

Epidermal growth factor receptor (EGFR) expression has been investigated as another shared feature of both entities. 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 FCDS.

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). 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 tonsillary (Tab. I) and extratonsillary cases.

According to the fourth edition of the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, most FDCS show low or intermediate-grade malignancy. 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 index. 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).

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. impression that tu-

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
Ref & CD45 & CD21 & CD35 & EMA & S100 & EBV \\
\hline
16 & NA & + & NA & NA & +/- & NA & CD68+/ Keratins- \\
8 & - & + & + & - & - & - & Fascin+ \\
8 & NA & NA & NA & NA & NA & NA & na \\
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+ \\
23 & - & +/- & +/- & +/- & +/- & - & CD68+ Desmin+ \\
14 & - & NA & NA & NA & - & NA & CD23+ Keratins- \\
24 & NA & + & + & NA & + & NA & CD23+ Keratins- \\
25 & - & + & + & NA & NA & Keratins- CD25+ CD68- \\
26 & NA & + & - & NA & NA & NA & CD25+ \\
27 & NA & NA & NA & NA & NA & CD68+ Fascin+ CD23+ \\
28 & NA & + & + & NA & NA & CD23+ Keratins- \\
6 & - & + & + & NA & NA & CD25+ Cd1a- Desmin- \\
2 & / & + & NA & NA & NA & NA & CD68+, fascin+, desmin-, p16-, keratins- \\
30 & NA & + & NA & NA & NA & NA & CD25+ \\
38 & NA & + & + & NA & + & - & Keratin- \\
32 & NA & + & NA & NA & + & NA & \\
33 & +/- & na & na & +/- & +/- & - & CD25+ \\
34 & - & + & + & NA & - & NA & CD25+ Keratins +/- CD68- \\
35 & NA & + & NA & + & - & CD1a-, CD68-, keratins- \\
36 & - & NA & NA & +/- & - & NA & CD23- Vimentin+ Ki-M4p+ \\
\hline
\end{tabular}
\caption{Summary data of immunohistochemical analyses in 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.}
\end{table}

\textbf{Abbreviations: NA: not available; MSA: muscle specific actin; NSE: neuron specific enolase.}
mors 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

FDACS 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 FDACS with viral infections, as the population of north Uganda is still plagued by AIDS and EBV infections.

References

15. Grogg KL, Lae ME, Kurtin PJ, et al. Clustein expression distinguishes follicular dendritic cell tumors from other dendritic cell neoplasms: report of a novel follicular dendritic cell marker and clinicopathologic data on 12 additional follicular dendritic cell tu-