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Follicular dendritic cell sarcoma of the head and neck: Case report, literature review, and pooled analysis of 97 cases

John Pang, MD¹, Wojciech K. Mydlarz, MD¹, Zhen Gooi, MBBS¹, Kevin M. Waters, MD, PhD³, Justin Bishop, MD³, James J. Sciubba, MD, PhD², Young J. Kim, MD, PhD¹, and Carole Fakhry, MD^{1,2,*}

¹Department of Otolaryngology and Head and Neck Surgery, Johns Hopkins University School of Medicine, The Johns Hopkins Hospital, Baltimore, Maryland ²Milton J. Dance Jr. Head and Neck Cancer Center, Johns Hopkins Head and Neck Surgery, Baltimore, Maryland ³Department of Pathology, Johns Hopkins University School of Medicine, The Johns Hopkins Hospital, Baltimore, Maryland

Abstract

Background—Follicular dendritic cell sarcoma (FDCS) is a rare lymphoid neoplasm presenting in the head and neck. There are no pooled analyses of head and neck FDCS cases in the English language literature.

Methods—A MEDLINE and PubMed review of cases from 1978 to February 2014 was performed. Demographics, clinicopathologic data, and outcomes were summarized.

Results—We presented 2 patients and analyzed 97 cases. The mean age was 42.7 years (SD = 16.3 years). Outcomes were available for 76 patients. Tumors ≥ 4 cm had better disease-free survival (63% vs 28% at 5 years; $p = .0282$). Locoregional recurrence was significantly less likely with surgery and radiation compared to surgery alone (15% vs 45%; $p = .019$) and in patients receiving a neck dissection (10% vs 43%; $p = .046$).

Conclusion—This pooled analysis provides the largest sample size of FDCS of the head and neck to date and suggests that radiation and neck dissection may be beneficial to locoregional oncologic control.

Keywords

follicular dendritic cell sarcoma (FDCS); head and neck; dendritic cell; sarcoma

INTRODUCTION

Follicular dendritic cell sarcoma (FDCS) is a rare neoplasm arising within lymphoid tissue, with only 400 cases reported in the English literature.^{1–3} Follicular dendritic cells are nonmyeloid, nonphagocytic, innate immune cells found primarily in germinal centers of

*Corresponding author: C. Fakhry, Department of Otolaryngology and Head and Neck Surgery, Johns Hopkins University School of Medicine, The Johns Hopkins Hospital, 601 N. Caroline Street, 6th Floor, Baltimore, MD 21287-0910. cfakhry@jhmi.edu.

secondary lymphoid organs and characterized by CD21, CD35, R4/23, and KiM4 surface expression.⁴ One of their main functions is to present antigens and immune complexes to B and T lymphocytes. Since its discovery in 1986, FDCS has continued to be a poorly understood clinical entity. The majority of FDCS literature, especially pertaining to the head and neck, consists of case reports and case series.

FDCS is characterized as intranodal or extranodal. Extra-nodal sites include the oropharynx, parapharyngeal space, neck soft tissues, thyroid, liver, kidney, and axial skeleton.^{5–13} Overall, cervical lymph node groups are the most commonly involved sites.¹³ Diagnosis of FDCS is challenging as approximately 50% of cases are misdiagnosed as undifferentiated carcinomas.^{1,14} Histopathologically, these malignancies are characterized by ovoid, polygonal, and spindle-shaped cells arranged in a whorling-type storiform pattern with admixed lymphocytes.^{1,15} Further complicating the issue, biopsies and fine-needle aspirates often contain necrotic or reactive lymphoid tissue, making the definitive diagnosis of FDCS challenging.

FDCS is assumed to be a low-grade neoplasm with the majority of patients surviving up to 10 years and beyond in most published reports.^{1,2,5,16} Prognostic factors for FDCS have not been systematically evaluated to date. Although surgical resection has been the mainstay of treatment for local disease, chemotherapy and radiation are often used as adjunctive treatments with limited evidence to guide these decisions. Indeed, the rarity of FDCS has precluded the type of clinical studies necessary to drive evidence-based adjuvant treatment of FDCS.

In the absence of such data, pooling outcomes from the available literature may serve to clarify clinicodemographic and prognostic trends. In this study, we present 2 new FDCS cases and objectively review treatment and prognosis of FDCS of the head and neck. Case 1 is the first FDCS arising in the mandible, whereas case 2 describes tonsillar FDCS with positive nodal disease.

Case 1

A 45-year-old white man with a previous right mandibular lesion diagnosed as an odontogenic keratocyst presented with 4 months of right mandibular numbness and pain, as well as an unintentional 10-pound weight loss. Physical examination revealed scarring in the right retro-molar trigone without cervical lymphadenopathy. An MRI showed an enhancing, expansile, lobulated 2.5- × 1.3- × 4.0-cm lesion in the body of the mandible extending to the right mandibular angle abutting the posterior molar dentition and partially extending through the buccal cortex (Figure 1). For diagnostic purposes, the patient underwent dental extraction of tooth 30, wide local excision, and curettage of the cyst epithelium. The lesion had eroded through the lateral wall of the ramus. Pathology was notable for a cystic lesion of dense aggregates of rounded cells in a fascicular and whorled pattern mixed with lymphocytes, typical of that described for FDCS.¹⁷ Immunohistochemical stains were positive for clusterin and CD21, partially positive for CD35 and CXCL13, and negative for p63, CK5, S100, MART-1, Melan-A, LCA, kappa, lambda, CD3, CD30, CD138, CD163, Alk-1, OSCAR, MUM-1, PAX5, CD4, CD2, and CD43, which are also consistent with

FDCS. No suggested markers of poor prognosis (absence of lymphoplasmacytic response, tumor size >6 cm, atypia, or high mitotic count) were identified.

Staging positron emission tomography/CT identified intense uptake (standardized uptake value = 15.83) in the right mandibular ramus near the third molar as well as mild uptake (standardized uptake value = 2.97) in a right submandibular node. The patient underwent a right composite hemimandibulectomy with a right selective neck dissection of levels I through IV (Figure 2). Final pathology revealed negative resection margins. The lesion was morphologically identical to the biopsy material, with similarly spindled to ovoid cells arranged in a storiform pattern with scattered lymphocytes (Figure 3A; hematoxylin-eosin stain, original magnification $\times 100$). On high power, the tumor cells had nuclei with mild atypia, prominent nucleoli, few mitoses, and a moderate amount of eosinophilic cytoplasm with indistinct cell borders (Figure 3B; hematoxylin-eosin stain, original magnification $\times 400$). Immunohistochemical stains for CD21 and CD23 showed strong membranous reactivity in the tumor cells, confirming a follicular dendritic cell origin (Figure 3C and 3D, respectively, hematoxylin-eosin stain, original magnification $\times 400$). All 48 lymph nodes were negative for tumor.

The patient was evaluated by radiation oncology and the multidisciplinary consensus was to not treat further with adjuvant therapy. At 1-year follow-up, the patient has had no evidence of recurrent disease.

Case 2

A 32-year-old Hispanic man presented with a 10-week history of painless left-sided neck swelling. He denied dysphagia, hoarseness, and otalgia. Examination was significant for a firm, nonfixed 5 cm left neck mass, extending from level II to III and induration of the left tonsil. There was no evidence of other lesions in the nasopharynx, oropharynx, or larynx on nasopharyngolaryngoscopy. CT revealed a 3.0- $\times$ 3.0-cm left level II anterior neck mass compressing the internal jugular vein, as well as a 1.8- $\times$ 2.3-cm submucosal left tonsillar mass with central hypodensity consistent with fluid or necrosis. Fine-needle aspiration of the neck mass was consistent with a malignant neoplasm in a background of necrosis, possibly a poorly differentiated carcinoma. Biopsy of the left tonsil was negative for carcinoma. The patient underwent bilateral palatine tonsillectomy for diagnostic purposes. A 3.3-cm tumor containing malignant lymphoid cells consistent with FDCS was noted in the left tonsil. Immunohistochemical staining demonstrated expression of CD21, CD68, and fascin, but not desmin, keratins AE1/3, CAM 5.2, CK 5/6, or P16.

A staging positron emission tomography/CT was performed but did not reveal any distant metastases, indicating T2N2aM0 disease according to American Joint Committee on Cancer staging criteria for head and neck pharyngeal cancer.¹⁸ He subsequently underwent a left lateral pharyngotomy, radical tonsillectomy, left selective neck dissection of levels II through V, and anterolateral free flap reconstruction. Final pathology revealed that additional tumor tissue was found in the left oropharynx infiltrating skeletal muscle, and 2 of 71 lymph nodes were positive for malignancy (largest measuring 7.0 cm). Postoperatively, he received chemoradiation. The radiation regimen was 66 Gy split into 33 fractions of 2 Gy to the left oropharynx and bilateral necks. He was initiated on a chemotherapy regimen of

cyclophosphamide (350 mg/m²) and topotecan (0.75 mg/m² on days 1–5). However, he developed radiation recall. He subsequently received gemcitabine (675 mg/m² on days 1 and 8) and docetaxel (75 mg/m² on day 8). Unfortunately, the patient developed lung and liver metastases 2 years later and was ultimately transitioned to palliative care.

METHODS

A MEDLINE and PubMed review of cases of FDCS of the head and neck from 1978 to February 2014 was conducted. Ninety-five previous cases of head and neck FDCS were identified in the English language literature, constituting a total of 97 cases including our own (Table 1).^{1,2,4,6–9,11,12,15–17,19–60} Information on patient demographics, location, tumor size, adjuvant therapies, recurrence, and mortality was recorded for analysis. Associations between clinicopathologic features, treatment methods, and outcomes were analyzed using chi-square testing. Analysis of variance, multiple analysis of variance, and *t* tests were conducted on quantitative data. Kaplan–Meier analysis was performed and Wilcoxon log-rank testing was used to evaluate disease-free survival (DFS) and overall survival (OS). Statistical analyses were performed with STATA SE and Graphpad Prism software.

RESULTS

Clinical features

Demographic and clinicopathologic features of FDCS in the English language literature are summarized in Table 1. The mean age at the time of presentation was 42.7 years (range, 9–76 years). Fifty-three percent of the patients were men. The mean tumor dimension was 4.5 cm.

The most common primary tumor sites were the cervical lymph nodes (40%; 39 of 97), oropharynx (24%; 23 of 97), and neck soft tissue (10%; 10 of 97). Interestingly, tumors located in the soft tissue of the neck presented at the youngest age (30.1 ± 16.5 years; mean $\pm$ SD) and those located in the thyroid presented at the most advanced age (61.5 ± 17.0 years; $p = .0276$). Tumors in the soft tissue of the neck presented with the largest tumors (7.0 ± 4.6 cm) and tumors in the thyroid presented with the smallest (1.8 ± 0.4 cm).

In total, 7 patients (7%) presented with regional metastases to the cervical lymph nodes and 2 patients (2%) presented with distant lung metastases. Of note, oropharyngeal lesions were significantly more likely to present with regional metastases compared to nonoropharyngeal lesions (including FDCS of the cervical lymph nodes, 17% vs 4%; $p = .031$).

Treatment

Various treatment approaches exist for FDCS (Table 2). The majority of patients with available treatment data (91 of 97 patients) received surgery alone (57%; 52 of 91). Thirteen of 91 patients (14%) underwent a neck dissection along with primary resection. Twenty-three percent of the patients (21 of 91) received surgery with adjuvant radiation (mean and median doses were 5345 and 5625 cGy, respectively; reported in 13 cases). The remaining patients were treated with surgery and adjuvant chemotherapy (7%; 6 of 91), surgery and chemoradiation (5%; 5 of 91), chemoradiation (4%; 4 of 91), and chemotherapy only (3%; 3

of 91). Two of the 4 patients receiving chemoradiation had tumors >8 cm,^{39,53} and 1 of the 4 presented with a metastatic lesion in the lung.²³ Common therapeutic agents included gemcitabine,⁵³ cisplatin and docetaxel,² ifosfamide, carboplatin, and etoposide,^{2,4} and cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP).^{9,21,39}

Clinical outcomes

There was a wide range in length of follow-up among the reported case series. The mean follow-up was 3.0 years (SD = 2.9 years) and follow-up data were unavailable for 22% of patients (21 of 97; Table 2). Therefore, analysis of clinical outcomes was limited to 76 of 97 patients (78%).

Among studies with available survival and recurrence data, 65% of patients had no evidence of disease, 21% were alive with disease, and 14% had died of their disease. Kaplan–Meier survival curves for all cases are shown in Figure 4A. OS was 91% at 2 years and 81% at 5 years. The incidence of local, regional, locoregional, and distant recurrence was 31%, 5%, 38%, and 7%, respectively. The mean time to recurrence of any type was 2.7 years (SD = 3.4 years). DFS was 64% at 2 years and 34% at 5 years. There was no association between tumor site, tumor size, or presence of regional metastases and the decision to treat with radiation or chemotherapy. The locoregional recurrence rate was significantly lower in patients receiving a neck dissection and in those receiving adjuvant radiotherapy after resection of the primary tumor, as discussed below.

Clinicopathologic characteristics and outcomes

There was no significant relationship among age, sex, or metastases at presentation on the locoregional recurrence rate ($p = .688$, $p = .217$, and $p = .453$, respectively). Lesions in the oropharynx were significantly more likely to present with regional metastases (17% vs 4%; $p = .031$), yet, they were not more likely to have either locoregional or distal recurrence (20% vs 43%; $p = .158$). However, patients with oropharyngeal lesions had significantly better DFS than patients with tumors at other sites (61% vs 26% at 5 years; $p = .0445$; Figure 4B). There was also a relation between tumor size and DFS. Patients with tumor sizes ≤ 4 cm had significantly better DFS compared with patients with tumor sizes >4 cm (63% vs 28% at 5 years; $p = .0282$; Figure 4C).

Adjuvant therapies and clinical outcomes

There is currently no consensus on the specific role of chemotherapy and radiation in FDCS management. Therefore, we evaluated relationships between therapeutic modalities and clinical outcomes. Patients were categorized into groups as follows: (1) surgery only; (2) surgery + chemoradiotherapy; (3) surgery + chemotherapy; (4) surgery + chemoradiotherapy; (5) chemoradiotherapy; and (6) chemotherapy only. Specific outcome data for each treatment group are shown in Table 2.

Only the first 2 categories (surgery alone and surgery plus chemoradiotherapy) had enough patients for meaningful statistical comparisons. When comparing surgery alone ($n = 52$) versus surgery plus chemoradiotherapy ($n = 21$), tumors were significantly less likely to recur locoregionally in the surgery plus chemoradiotherapy group (15% vs 45%; $p = .019$;

Table 2). The surgery alone group and the surgery plus chemoradiotherapy group were not different at baseline with regard to sex distribution ($p = .854$), age ($p = .675$), initial site ($p = .190$), presence of regional metastasis ($p = .386$), percentage of tumors >4 cm ($p = .508$), and tumor size ($p = .931$). However, there was no difference between these 2 treatment groups in the time to the first recurrence ($p = .7956$), death rate ($p = .366$), DFS ($p = .3070$), or OS ($p = .7117$; Table 2).

Chemotherapy was not associated with improved locoregional recurrence (50% vs 37%; $p = .379$). However, neck dissection did confer a statistically significant advantage in locoregional recurrence rate. Specifically, 10% of the patients (1 of 10) receiving neck dissection developed locoregional recurrence compared to 43% of the patients (28 of 65) who did not receive a neck dissection ($p = .046$). However, neck dissection was not associated with better DFS ($p = .7364$) or OS ($p = .8964$).

DISCUSSION

FDCS is a rare malignancy of lymphoid tissue that is thought to behave similarly to a low-grade sarcoma rather than a lymphoma.¹³ Because of its clinical obscurity, a paucity of evidence is available to guide clinical decision-making in the management of head and neck FDCS. Currently, there exist neither multicenter prospective studies nor pooled analyses focusing on FDCS cases of the head and neck in the English literature. In an attempt to more fully and objectively characterize this clinical entity, we conducted a MEDLINE and PubMed search of the available English literature. Including the 2 cases from our institution, we identified 97 cases meeting criteria for analysis.

Our analysis revealed that, in accordance with previous literature, the mean age was 42.7 years and the sex distribution was essentially 1:1. We found that the mean tumor size was 4.5 cm. This is consistent with another report that examined extranodal FDCS tumors, which reviewed 46 cases at 10 different sites.⁶¹ As expected, the most common site was the cervical lymph nodes, although FDCS presented with notable frequency in the nasopharynx, oropharynx, oral cavity, and thyroid gland. Literature-reported local recurrence rates range from 23% to 43%, metastases rates average approximately 21%, and mortality rates range from 3% to 7%.^{5,9,61} We found the locoregional recurrence rate and mortality rate to be 38% and 14%, respectively. Two and 5-year DFS rates were 64% and 34%, respectively, and the 2-year and 5-year OS rates were 91% and 81%, respectively. These outcome data suggest that FDCS indeed has a prognosis akin to a low-grade sarcoma, as suggested by previous literature.^{2,4}

Clinical and histologic diagnosis of FDCS is challenging. Although the tumor morphologies in cases 1 and 2 were consistent with prior descriptions of FDCS,¹⁷ correct diagnosis is difficult because of the infrequency with which FDCS is encountered in the head and neck. In addition, many other neoplasms, including sarcomatoid (spindle cell) carcinomas, melanomas, lymphomas, and mesenchymal tumors, can have a whorling pattern with intermixed lymphocytes. In fact, 2 of 3 cases in a series of FDCS in the head and neck region by Biddle et al⁸ were initially misdiagnosed. Given the mandibular location of case 1, it should be noted that the morphology of FDCS is not similar to that typically seen in

odontogenic lesions. Immunohistochemical stains can be helpful in distinguishing FDSC from other spindle-cell neoplasms. Specifically, CD21 and CD23 are markers of follicular dendritic cells that have been shown to be positive in the majority of FDSC specimens.^{8,62} Additionally, clusterin has been found to be a sensitive and specific stain for FDSC.^{63,64} A study of 14 FDSC cases and 188 cases of 15 different types of spindle-cell tumors found clusterin positivity to have a sensitivity of 100% and a specificity of 93%.⁶⁴ Studies have also shown that FDSC is not immunoreactive for cytokeratins and CD45,^{8,65} which would argue against alternative diagnoses of a sarcoma-toid (spindle cell) carcinoma or lymphoma, respectively. Negative S100 staining has been reported in the majority of cases,^{8,64,65} which helps rule out a diagnosis of melanoma.

Previous literature has concluded that patients with localized disease have significantly better OS compared with patients with distant disease.² Young age, absence of lymphoplasmacytic response, tumor size >6 cm, and high mitotic count (>5 per field) have been significantly associated with a poor prognosis in the literature.² We investigated whether demographic and clinicopathologic factors had prognostic implications. One interesting finding was that FDSC tumors located in the oropharynx were significantly more likely to present with regional metastases than tumors located outside of the oropharynx (17% vs 4%; $p = .031$). A potential explanation for this finding is that lymphatic spread from the oropharynx is more easily accomplished because of the rich and extensive lymphatic network draining this region. Interestingly, oropharyngeal location was associated with significantly improved DFS ($p = .0445$), despite this higher rate of regional metastases at presentation. Additionally, we found that tumors >4 cm in size seemed to be more aggressive than those ≤4 cm, with DFS being 28% versus 63% at 5 years ($p = .0282$). Of note, tumor size is a prognostic factor in soft tissue sarcoma as well, with tumor size >5 cm placing patients in a T2 versus T1 classification according to American Joint Committee on Cancer criteria.¹⁸ Therefore, patients with large FDSC tumors should be considered for more aggressive treatment.

Surgical resection has been the mainstay of treatment for all FDSC sites. However, there seems to be no consensus regarding indication for neck dissection. In our analysis, at least 46 patients were candidates for neck dissection (39 with primary tumors in the neck plus 7 with regional metastases at presentation); yet only 13 neck dissections were performed. Of the 10 patients who underwent neck dissection who were followed longitudinally, only 1 (10%) developed locoregional recurrence compared to 43% (28 of 65) in patients who did not receive a neck dissection ($p = .046$). This suggests that patients with primaries in the neck and patients with regional metastasis should be considered for neck dissection.

Adjuvant chemotherapy and radiotherapy are often used for large tumors or those with high-grade features, such as cytologic atypia.⁶⁶ However, previous literature has not demonstrated outcome benefits from adjuvant therapies.^{1,16} Indeed, a recent pooled analysis by Saygin et al² found no benefit of surgery with adjuvant radiotherapy compared to surgery alone, although this analysis included tumors outside of the head and neck.

Because there is no consensus on the role of adjuvant radiation for FDSC management, one of our primary interests was to compare outcomes in patients receiving surgery alone to

patients receiving surgery plus radiation. Although the majority of patients in our analyses received surgical resection only (57%), 23% received surgery plus radiotherapy. Interestingly, we noted that patients receiving surgery plus radiation had a significantly lower locoregional recurrence rate than patients receiving surgery alone (15% vs 45%; $p = .019$). The 2 groups were not significantly different at baseline with regard to age, sex distribution, presence of regional metastasis, or tumor size. Therefore, it seems that chemoradiotherapy should be considered for patients with FDSCS. Although it is difficult to make strong recommendations about high-risk groups in which chemoradiotherapy may be particularly advantageous, patients with tumors >4 cm were found in our analysis to have worse DFS than patients with smaller tumors, and, as such, should receive consideration for adjuvant chemoradiotherapy. Radiation may also be considered in patients with close resection margins (<1 cm), which is a recommendation based on National Comprehensive Cancer Network clinical practice guidelines for soft tissue sarcoma.⁶⁷

Unfortunately, our attempt to identify subgroups of patients with FDSCS who may be better served with adjuvant chemoradiotherapy was precluded by our sample size. Larger multicenter prospective studies would more effectively evaluate adjuvant therapies, yet are difficult to perform for a tumor as rare as FDSCS. A more practical solution may be expansion of the American Society of Clinical Oncology's CancerLinQ health information technology program, which collects electronic medical record data in real-time for large-scale clinical studies.⁶⁸ Although this program is currently in a prototype stage focused on breast cancer, expansion into additional oncologic fields may prove especially helpful in guiding the management of rare tumors, such as FDSCS.

Currently, chemotherapy is included in the treatment of most cases of metastatic FDSCS, although there is no consensus on the most effective regimen. CHOP and ifosfamide, carboplatin, and etoposide protocols are the most commonly chosen chemotherapeutic regimens,³⁰ which might be due to their success in treating nodal malignancies, such as intermediate grade lymphomas.² However, recent studies have elucidated that follicular dendritic cells have a vascular stromal rather than a hematopoietic origin, a finding that is consistent with their clinical behavior and prognosis being similar to low-intermediate grade soft tissue sarcomas.^{69,70} Therefore, treatment with agents better suited to mesenchymal stromal tumors rather than hematopoietic malignancies may be more appropriate. Indeed, Conry⁶⁹ reported 2 cases of FDSCS metastatic to the liver that exhibited durable objective responses to gemcitabine and docetaxel. Khalid and Folman⁷¹ also reported a partial response of hepatic FDSCS to gemcitabine after failure of the CHOP protocol. Addition of imatinib, a tyrosine kinase inhibitor, to gemcitabine and cisplatin for a case of metastatic FDSCS resulted in complete pathological remission.⁷²

Our study had several limitations. Complete follow-up data was unavailable for 22% of patients. We only identified 18 patients who received chemotherapy, which precluded statistical analyses on the impact of chemotherapy on survival. In addition, histologic features were inconsistently reported. Thus, we were unable to assess for correlation of immunophenotypic markers and histologic features with clinical outcome.

CONCLUSION

FDCS is a low-grade malignancy of lymphoid tissue that presents in the head and neck. In addition to presenting the first known case of FDCS in a mandible, we conducted a MEDLINE and PubMed review and identified 95 additional cases of head and neck FDCS in the English literature. Statistical analyses revealed that oropharyngeal tumors were more likely to present with regional metastases. Tumors >4 cm in size had significantly worse DFS. Patients who received surgery plus radiation compared to surgery alone, and patients who had a neck dissection, were significantly less likely to recur locoregionally, although DFS and OS were not significantly improved.

Our findings may inform clinicians treating and counseling patients with this rare entity. Radiotherapy should be considered in patients with FDCS, specifically those with tumor sizes >4 cm. Neck dissection should be considered in patients with locoregional metastases. Unfortunately, the limitations of our study design preclude us from making stronger recommendations. Future health information technologies may better aggregate and analyze cancer data, building on meta-analyses and preclinical laboratory studies to more fully understand the biology, behavior, and treatment responses in head and neck FDCS.

References

1. Hu T, Wang X, Yu C, et al. Follicular dendritic cell sarcoma of the pharyngeal region. *Oncol Lett*. 2013; 5:1467–1476. [PubMed: 23761812]
2. Saygin C, Uzunaslan D, Ozguroglu M, Senocak M, Tuzuner N. Dendritic cell sarcoma: a pooled analysis including 462 cases with presentation of our case series. *Crit Rev Oncol Hematol*. 2013; 88:253–271. [PubMed: 23755890]
3. Fonseca R, Yamakawa M, Nakamura S, et al. Follicular dendritic cell sarcoma and interdigitating reticulum cell sarcoma: a review. *Am J Hematol*. 1998; 59:161–167. [PubMed: 9766802]
4. Chan JK, Fletcher CD, Nayler SJ, Cooper K. Follicular dendritic cell sarcoma. Clinicopathologic analysis of 17 cases suggesting a malignant potential higher than currently recognized. *Cancer*. 1997; 79:294–313. [PubMed: 9010103]
5. Perkins SM, Shinohara ET. Interdigitating and follicular dendritic cell sarcomas: a SEER analysis. *Am J Clin Oncol*. 2013; 36:395–398. [PubMed: 22772431]
6. Araujo VC, Martins MT, Salmen FS, Araújo NS. Extranodal follicular dendritic cell sarcoma of the palate. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1999; 87:209–214. [PubMed: 10052377]
7. Beham-Schmid C, Beham A, Jakse R, Aubock L, Hofler G. Extranodal follicular dendritic cell tumour of the nasopharynx. *Virchows Arch*. 1998; 432:293–298. [PubMed: 9532010]
8. Biddle DA, Ro JY, Yoon GS, et al. Extranodal follicular dendritic cell sarcoma of the head and neck region: three new cases, with a review of the literature. *Mod Pathol*. 2002; 15:50–58. [PubMed: 11796841]
9. Chan AC, Chan KW, Chan JK, Au WY, Ho WK, Ng WM. Development of follicular dendritic cell sarcoma in hyaline-vascular Castleman's disease of the nasopharynx: tracing its evolution by sequential biopsies. *Histopathology*. 2001; 38:510–518. [PubMed: 11422494]
10. Choi PC, To KF, Lai FM, Lee TW, Yim AP, Chan JK. Follicular dendritic cell sarcoma of the neck: report of two cases complicated by pulmonary metastases. *Cancer*. 2000; 89:664–672. [PubMed: 10931467]
11. Desai S, Deshpande RB, Jambhekar N. Follicular dendritic cell tumor of the parapharyngeal region. *Head Neck*. 1999; 21:164–167. [PubMed: 10091986]
12. Galati LT, Barnes EL, Myers EN. Dendritic cell sarcoma of the thyroid. *Head Neck*. 1999; 21:273–275. [PubMed: 10208672]

13. Swerdlow, SH.; Campo, E.; Harris, NL., et al. WHO classification of tumors of haematopoietic and lymphoid tissues. 4. Lyon, France: International Agency for Research on Cancer; 2008.
14. Al-Hussain T, Saleem M, Velagapudi SB, Dababo MA. Follicular dendritic cell sarcoma of parapharyngeal space: a case report and review of the literature. *Head Neck Pathol.* 2015; 9:135–139. [PubMed: 24668593]
15. Perez-Ordoñez B, Rosai J. Follicular dendritic cell tumor: review of the entity. *Semin Diagn Pathol.* 1998; 15:144–154. [PubMed: 9606805]
16. Satoh K, Hibi G, Yamamoto Y, Urano M, Kuroda M, Nakamura S. Follicular dendritic cell tumor in the oro-pharyngeal region: report of a case and a review of the literature. *Oral Oncol.* 2003; 39:415–419. [PubMed: 12676264]
17. Monda L, Warnke R, Rosai J. A primary lymph node malignancy with features suggestive of dendritic reticulum cell differentiation. A report of 4 cases. *Am J Pathol.* 1986; 122:562–572. [PubMed: 2420185]
18. Greene, FL.; Page, DL.; Fleming, ID., et al. American Joint Committee on Cancer: AJCC Cancer Staging Manual. 6. New York: Springer; 2002. p. 20
19. Duan GJ, Wu F, Zhu J, et al. Extranodal follicular dendritic cell sarcoma of the pharyngeal region: a potential diagnostic pitfall, with literature review. *Am J Clin Pathol.* 2010; 133:49–58. [PubMed: 20023258]
20. Encabo RS, McHugh J, Carrau RL, Kassam A, Heron D. Follicular dendritic cell sarcoma of the nasopharynx. *Am J Otolaryngol.* 2008; 29:262–264. [PubMed: 18598838]
21. Fan YS, Ng WK, Chan A, et al. Fine needle aspiration cytology in follicular dendritic cell sarcoma: a report of two cases. *Acta Cytol.* 2007; 51:642–647. [PubMed: 17718144]
22. Karabulut B, Orhan KS, Guldiken Y, Dogan O. Follicular dendritic cell sarcoma of the nasopharynx. *Int J Oral Maxillofac Surg.* 2012; 41:218–220. [PubMed: 21835593]
23. Soriano AO, Thompson MA, Admirand JH, et al. Follicular dendritic cell sarcoma: a report of 14 cases and a review of the literature. *Am J Hematol.* 2007; 82:725–728. [PubMed: 17373675]
24. Chan JK, Tsang WY, Ng CS, Tang SK, Yu HC, Lee AW. Follicular dendritic cell tumors of the oral cavity. *Am J Surg Pathol.* 1994; 18:148–157. [PubMed: 8291653]
25. Kara T, Serinsoz E, Arpacı RB, Vayisoglu Y. Follicular dendritic cell sarcoma of the tonsil. *BMJ Case Rep.* 2013; 2013
26. McDuffie C, Lian TS, Thibodeaux J. Follicular dendritic cell sarcoma of the tonsil: a case report and literature review. *Ear Nose Throat J.* 2007; 86:234–235. [PubMed: 17500398]
27. Mondal SK, Bera H, Bhattacharya B, Dewan K. Follicular dendritic cell sarcoma of the tonsil. *Natl J Maxillofac Surg.* 2012; 3:62–64. [PubMed: 23251062]
28. Nayler SJ, Taylor L, Cooper K. HHV-8 is not associated with follicular dendritic cell tumours. *Mol Pathol.* 1998; 51:168–170. [PubMed: 9850342]
29. Sahadevan K, Banerjee A, Wight R. Follicular dendritic cell sarcoma of a cervical lymph node: case report and review of the literature. *Ear Nose Throat J.* 2004; 83:848–849. [PubMed: 15724745]
30. Tisch M, Hengstermann F, Kraft K, von Hinuber G, Maier H. Follicular dendritic cell sarcoma of the tonsil: report of a rare case. *Ear Nose Throat J.* 2003; 82:507–509. [PubMed: 12955835]
31. Vaideeswar P, George SM, Kane SV, Chaturvedi RA, Pandit SP. Extranodal follicular dendritic cell sarcoma of the tonsil – case report of an epithelioid cell variant with osteoclastic giant cells. *Pathol Res Pract.* 2009; 205:149–153. [PubMed: 18774654]
32. Clement P, Saint-Blancard P, Minvielle F, Le Page P, Kossowski M. Follicular dendritic cell sarcoma of the tonsil: a case report. *Am J Otolaryngol.* 2006; 27:207–210. [PubMed: 16647987]
33. Domínguez-Malagón H, Cano-Valdez AM, Mosqueda-Taylor A, Hes O. Follicular dendritic cell sarcoma of the pharyngeal region: histologic, cytologic, immunohistochemical, and ultrastructural study of three cases. *Ann Diagn Pathol.* 2004; 8:325–332. [PubMed: 15614735]
34. Georgalas C, Kanagalingam J, Gallimore A, O'Flynn P. Follicular dendritic cell sarcoma arising from the hypopharynx. *J Laryngol Otol.* 2004; 118:317–318. [PubMed: 15117477]
35. Hangai K, Nonaka S, Iwakiri H, et al. Follicular dendritic cell tumor of the cervical lymph node. *ORL J Otorhinolaryngol Relat Spec.* 2002; 64:229–232. [PubMed: 12037393]

36. Alexander AA, Zapanta PE, Khan A. Diagnosis and recurrence of follicular dendritic cell sarcoma. *Otolaryngol Head Neck Surg.* 2007; 137:832–834. [PubMed: 17967656]
37. Amiri-Kordestani L, Priebat D, Chia SH. Follicular dendritic cell sarcoma of the neck: case report and review of current diagnostic and management strategies. *Ear Nose Throat J.* 2010; 89:E14–E17. [PubMed: 20628972]
38. Chera BS, Orlando C, Villaret DB, Mendenhall WM. Follicular dendritic cell sarcoma of the head and neck: case report and literature review. *Laryngoscope.* 2008; 118:1607–1612. [PubMed: 18596475]
39. Cyriac S, Praveenkumar D, Majhi U, Sagar TG. Follicular dendritic cell sarcoma of the neck with an aggressive and fatal course. *J Cancer Res Ther.* 2010; 6:114–116. [PubMed: 20479564]
40. Hynes B, Lock M, Lubynski R, Hynes B. Follicular dendritic cell sarcoma: case report and review of current management principles. *J Otolaryngol.* 2005; 34:434–436. [PubMed: 16343408]
41. Jabbour MN, Fedda FA, Tawil AN, Shabb NS, Boulos FI. Follicular dendritic cell sarcoma of the head and neck expressing thyroid transcription factor-1: a case report with clinicopathologic and immunohistochemical literature review. *Appl Immunohistochem Mol Morphol.* 2012; 22:705–712. [PubMed: 21836499]
42. Karligkiotis A, Contis D, Bella M, et al. Pediatric follicular dendritic cell sarcoma of the head and neck: a case report and review of the literature. *Int J Pediatr Otorhinolaryngol.* 2013; 77:1059–1064. [PubMed: 23684177]
43. Katano H, Kaneko K, Shimizu S, Saito T, Irié T, Mori S. Follicular dendritic cell sarcoma complicated by hyaline-vascular type Castleman's disease in a schizophrenic patient. *Pathol Int.* 1997; 47:703–706. [PubMed: 9361105]
44. Kure K, Khader SN, Suhrlund MJ, Ratech H, Grossberg R, Oktay MH. Fine needle aspiration of follicular dendritic cell sarcoma in an HIV-positive man: a case report. *Acta Cytol.* 2010; 54:707–711. [PubMed: 20968160]
45. Ono Y, Terashima K, Liu A, et al. Follicular dendritic cell sarcoma with microtubuloreticular structure and virus-like particle production in vitro. *Pathol Int.* 2009; 59:332–344. [PubMed: 19432677]
46. Pisani F, Marino M, Sentinelli S, Petti MC. Follicular dendritic cell sarcoma of the neck: report of a case treated by surgical excision and COP plus (PEG)-liposomal doxorubicin. *J Exp Clin Cancer Res.* 2008; 27:33. [PubMed: 18761751]
47. Pizzi M, Ludwig K, Palazzolo G, Busatto G, Rettore C, Altavilla G. Cervical follicular dendritic cell sarcoma: a case report and review of the literature. *Int J Immunopathol Pharmacol.* 2011; 24:539–544. [PubMed: 21658332]
48. Romero-Guadarrama MB, Reyes-Posada O, Hernández-González MM, Durán-Padilla MA. Follicular dendritic cell sarcoma/tumor: 2 cases of a rare tumor of difficult clinical and pathological diagnosis. *Ann Diagn Pathol.* 2009; 13:257–262. [PubMed: 19608084]
49. Singer AD, Weinberger PM, Seybt MW, Jackson LL, Teague DJ, Figueroa RE. Imaging characterization of follicular dendritic cell sarcoma of the neck. *Ear Nose Throat J.* 2010; 89:296–297. [PubMed: 20628983]
50. Tokyol C, Yilmaz MD, Ekici O, Aktepe F. Follicular dendritic cell sarcoma: a case report. *Acta Cytol.* 2008; 52:235–239. [PubMed: 18500003]
51. Vicandi B, Jiménez-Heffernan JA, López-Ferrer P, Viguer JM. Fine needle aspiration cytology of follicular dendritic cell sarcoma. A case report. *Acta Cytol.* 2000; 44:1106–1110. [PubMed: 11127744]
52. Weeks DM, O'Leary M, Gattuso P, Petruzzelli GJ. Pathology quiz case 1. Follicular dendritic cell sarcoma (FDS). *Arch Otolaryngol Head Neck Surg.* 2012; 138:687–688. [PubMed: 22801898]
53. Voigt LP, Hmidi A, Pastores SM, et al. Management dilemmas due to a paratracheal follicular dendritic cell tumor. *Ann Thorac Surg.* 2006; 82:1898–1900. [PubMed: 17062273]
54. Silver AL, Faquin WC, Caruso PA, Deschler DG. Follicular dendritic cell sarcoma presenting in the submandibular region in an 11 year-old. *Laryngoscope.* 2010; 120(Suppl 4):S183. [PubMed: 21225781]

55. Wang XI, Zhang S, Thomas JO, Adegboyega PA. Cytomorphology, ultra-structural, and cytogenetic findings in follicular dendritic cell sarcoma: a case report. *Acta Cytol.* 2010; 54(5 Suppl):759–763. [PubMed: 21053535]
56. Bradshaw EJ, Wood KM, Hodgkinson P, Lucraft H, Windebank KP. Follicular dendritic cell tumour in a 9-year-old child. *Pediatr Blood Cancer.* 2005; 45:725–727. [PubMed: 15926163]
57. Karaman E, Saritzali G, Kilic E, Korkut N, Enver O. Follicular dendritic cell sarcoma of the parotid gland recurring 6 times within 12 years. *J Craniofac Surg.* 2009; 20:2171–2172. [PubMed: 19884836]
58. Yu L, Yang SJ. Primary follicular dendritic cell sarcoma of the thyroid gland coexisting with Hashimoto's thyroiditis. *Int J Surg Pathol.* 2011; 19:502–505. [PubMed: 19448067]
59. Perez-Ordóñez B, Erlandson RA, Rosai J. Follicular dendritic cell tumor: report of 13 additional cases of a distinctive entity. *Am J Surg Pathol.* 1996; 20:944–955. [PubMed: 8712294]
60. Aydin E, Ozluoglu LN, Demirhan B, Arikan U. Follicular dendritic cell sarcoma of the tonsil: case report. *Eur Arch Otorhinolaryngol.* 2006; 263:1155–1157. [PubMed: 16896752]
61. Shia J, Chen W, Tang LH, et al. Extranodal follicular dendritic cell sarcoma: clinical, pathologic, and histogenetic characteristics of an under-recognized disease entity. *Virchows Arch.* 2006; 449:148–158. [PubMed: 16758173]
62. Sun X, Chang KC, Abruzzo LV, Lai R, Younes A, Jones D. Epidermal growth factor receptor expression in follicular dendritic cells: a shared feature of follicular dendritic cell sarcoma and Castleman's disease. *Hum Pathol.* 2003; 34:835–840. [PubMed: 14562277]
63. Grogg KL, Lae ME, Kurtin PJ, Macon WR. Clusterin 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 tumors and 6 additional interdigitating dendritic cell tumors. *Am J Surg Pathol.* 2004; 28:988–998. [PubMed: 15252304]
64. Grogg KL, Macon WR, Kurtin PJ, Nascimento AG. A survey of clusterin and fascin expression in sarcomas and spindle cell neoplasms: strong clusterin immunostaining is highly specific for follicular dendritic cell tumor. *Mod Pathol.* 2005; 18:260–266. [PubMed: 15467709]
65. Andriko JW, Kaldjian EP, Tsokos M, Abbondanzo SL, Jaffe ES. Reticulum cell neoplasms of lymph nodes: a clinicopathologic study of 11 cases with recognition of a new subtype derived from fibroblastic reticular cells. *Am J Surg Pathol.* 1998; 22:1048–1058. [PubMed: 9737236]
66. Starr JS, Attia S, Joseph RW, Menke D, Casler J, Smallridge RC. Follicular dendritic cell sarcoma presenting as a thyroid mass. *J Clin Oncol.* 2014 Epub ahead of print.
67. Demetri GD, Antonia S, Benjamin RS, et al. Soft tissue sarcoma. *J Natl Compr Canc Netw.* 2010; 8:630–674. [PubMed: 20581298]
68. Schilsky RL, Michels DL, Kearbey AH, Yu PP, Hudis CA. Building a rapid learning health care system for oncology: the regulatory framework of CancerLinQ. *J Clin Oncol.* 2014; 32:2373–2379. [PubMed: 24912897]
69. Conry RM. Response of follicular dendritic cell sarcoma to gemcitabine and docetaxel: report of two cases and literature review. *Clin Sarcoma Res.* 2014; 4:6. [PubMed: 25009738]
70. Aguzzi A, Kranich J, Krautler NJ. Follicular dendritic cells: origin, phenotype, and function in health and disease. *Trends Immunol.* 2014; 35:105–113. [PubMed: 24315719]
71. Khalid T, Folman R. Symptoms in cancer patients and an unusual tumor: case 3. Follicular dendritic cell sarcoma. *J Clin Oncol.* 2005; 23:9425–9426. [PubMed: 16361643]
72. Azim HA, Elsedewy E, Azim HA Jr. Imatinib in the treatment of follicular dendritic sarcoma: a case report and review of literature. *Onkologie.* 2007; 30:381–384. [PubMed: 17596748]

FIGURE 1.

MRI evaluation from case 1. (A) Demonstrates the right mandibular lesion from an axial view (white arrow; T1-weighted postcontrast). The tumor was enhancing, expansile, lobulated, and $2.5 \times 1.3 \times 4.0$ cm in size. It was located in the body of the mandible extending to the right mandibular angle abutting the posterior molar dentition and partially extending through the buccal cortex. (B) Demonstrates the lesion with T2-weighting (white arrow).

FIGURE 2.

Resected specimen from case 1. (A) Demonstrates a lateral view of the resected specimen from the right segmental mandibulectomy. (B) Demonstrates the surgical specimen from a medial view.

FIGURE 3.

Histology from case 1. (A) On low magnification, the tumor contained spindled to ovoid cells arranged in a storiform pattern with scattered lymphocytes (hematoxylin-eosin stain; original magnification $\times 100$). (B) On high power, the tumor cells had nuclei with mild atypia, prominent nucleoli, few mitoses, and a moderate amount of eosinophilic cytoplasm with indistinct cell borders (hematoxylin-eosin stain; original magnification $\times 400$). Immunohistochemical stains for (C) CD21 and (D) CD23 showed strong membranous reactivity in the tumor cells, confirming a follicular dendritic cell origin (hematoxylin-eosin stain; original magnification $\times 400$). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

FIGURE 4.

Clinical outcomes depicted as survival curves. On Kaplan–Meier analysis, 2-year and 5-year disease-free survival (DFS) was 64% and 34%, respectively (A). Two-year and 5-year overall survival (OS) was 91% and 81%, respectively (A). Tumors with a primary location (Loc) in the oropharynx had statistically significantly better DFS than tumors with a primary location outside of the oropharynx ($p = .0445$) (B). OS was 75% versus 61% at 2 years and DFS was 61% versus 26% at 5 years (B). Tumors ≤ 4 cm in size had statistically significantly better DFS than tumors > 4 cm in size ($p = .0282$) (C). OS was 72% versus 37% at 2 years and DFS was 63% versus 28% at 5 years (C).

TABLE 1

Demographic data and clinicopathologic features.

	No. of cases	Mean age, y, mean $\pm$ SD	Regional metastases on presentation	Distant metastases on presentation	Longest tumor dimension, mean $\pm$ SD, cm	Longest tumor dimension range, cm	Tumor ≥ 4 cm
All head and neck	97	42.7 $\pm$ 16.3	7% (7/97)	2% (2/97)	4.5 $\pm$ 3.2	1–20	24/66 (36%)
Nasopharynx ^{7,9,19–23}	9	42.6 $\pm$ 9.5	0%	0%	2.4 $\pm$ 0.8	1–3	0%
Oral cavity, case 1 ^{4,6}	3	40.7 $\pm$ 11.8	0%	0%	2.3 $\pm$ 0.8	1.5–3	0%
Oropharynx, case 2 ^{1,4,8,15,19,21,25–34,60}	23	46.2 $\pm$ 15.5	17% (4/23)	4% (1/23)	3.4 $\pm$ 1.2	1.5–4.5	2/18 (11%)
Parapharyngeal region ^{1,8,11,16,33}	7	38.1 $\pm$ 8.6	14% (1/7)	0%	4.6 $\pm$ 1.5	3–6	3/5 (60%)
Cervical lymph node ^{2,4,8,15,17,28,35–53}	39	44.3 $\pm$ 15.8	0%	3% (1/39)	5.4 $\pm$ 4.0	1–20	14/25 (56%)
Neck soft tissue ^{2,8,28,54,55}	10	30.1 $\pm$ 16.5	0%	0%	7.0 $\pm$ 4.6	3–14	3/5 (60%)
Parotid ^{2,4,56,57}	4	31.5 $\pm$ 7.3	25% (1/4)	0%	6.0 $\pm$ 1.4	5–7	2/2 (100%)
Thyroid ^{12,58}	2	61.5 $\pm$ 17.0	50% (1/2)	0%	1.8 $\pm$ 0.4	1.5–2	0%

A total of 97 cases were identified in the English language literature. The mean age at presentation was 42.7 $\pm$ 16.3 years (range, 9–76). Seven patients presented with regional metastases and two with distant metastases. The mean length of the tumor's longest dimension was 4.5 $\pm$ 3.2 cm. Thirty-six percent of tumors were ≥ 4 cm in size.

TABLE 2

Clinical outcomes by intervention and anatomic location.

	No. of cases	Regional metastases on presentation	Locoregional recurrence	Distant recurrence	Mortality	2-y OS, %	2-y DFS, %	5-y OS, %	5-y DFS, %
By treatment	97	7% (7/97)	38% (29/76)	7% (6/76)	14% (10/71)	91	64	81	34
Surgery only	57% (52/91)	8% (4/52)	45% (20/44)	5% (2/44)	14% (6/42)	93	55	84	31
Surgery + chemoradiotherapy	23% (21/91)	14% (3/21)	15% (3/20)*	15% (3/20)	6% (1/17)	92	74	92	44
Surgery + chemotherapy	7% (6/91)	0%	25% (1/4)	0%	25% (1/4)	75	100	75	0
Surgery + chemoradiotherapy	5% (5/91)	0%	80% (4/5)	0%	20% (1/5)	100	80	75	25
Chemoradiotherapy	4% (4/91)	0%	50% (1/2)	0%	50% (1/2)	50	0	50	0
Chemotherapy only	3% (3/91)	0%	—	—	—	—	—	—	—
By location of primary									
Nasopharynx	9	0%	38% (3/8)	0% (0/8)	13% (1/8)	86	75	86	0
Oral cavity	3	0%	0%	0%	0%	100	100	100	100
Oropharynx	23	17% (4/23)	25% (5/20)	5% (1/20)	15% (3/20)	85	75	77	61
Parapharyngeal region	7	14% (1/7)	29% (2/7)	29% (2/7)	14% (1/7)	100	60	100	0
Cervical lymph node	39	0%	42% (16/38)	3% (1/38)	17% (5/29)	93	52	75	10
Neck soft tissue	10	0%	40% (2/5)	40% (2/5)	0%	100	40	100	40
Parotid	4	25% (1/4)	50% (1/2)	0%	0%	100	100	0	0
Thyroid	2	50% (1/2)	0%	0%	0%	100	100	0	0

Abbreviations: OS, overall survival; DFS, disease-free survival.

Local recurrence was 31% (27/76), regional recurrence was 5% (4/76), and mortality rate was 14% (10/71). Two-year and 5-year OS was 91% and 81%, respectively. Two-year and 5-year DFS was 64% and 34%, respectively. Surgery alone was the most common intervention, followed by surgery plus adjuvant radiation. There was a statistically significant benefit to surgery plus radiation in local recurrence rate (15% vs 45%; $p = .019$).

* Indicates $p = .019$ in local recurrence between surgery alone and surgery + radiotherapy. Hyphen (—) indicates no follow-up data reported.