FidoCure® Case Study: Lulu Rocha

Thyroid Carcinoma

Dr. Garrett Harvey, VMD
Veterinary Affairs, FidoCure®

Madison Luker, DVM Candidate 2024,
UC Davis School of Veterinary Medicine

After FidoCure® enabled therapy, Lulu remained free from additional metastases.

FidoCure®

Introduction

Thyroid carcinoma is a malignant tumor usually seen in middle-age to older dogs. The cause of this tumor development is still unknown and there are some breeds more affected than others such as Boxers, Beagles and Golden Retrievers.[1] Unfortunately, in many cases, thyroid tumors go unnoticed until they are extremely large in size. Although this tumor is typically not painful, the clinical signs are a consequence of the tumor size and the compression of the surrounding structures which cause discomfort for affected dogs. Hormone derangement (ie. hyperthyroidism) is rare.[2]

A fine needle aspiration (FNA) can be performed to identify malignant epithelial cells, but a definitive diagnosis of thyroid carcinoma requires a biopsy. A cervical (neck) ultrasound may be used to examine the regional lymph nodes for metastasis. Chest radiographs are always recommended to evaluate the lungs for possible metastasis due to the high metastatic rate of these tumors. The treatment options depend on the size, degree of invasion and the presence of distant metastasis at the time of diagnosis.[3] Surgery is a reasonable treatment option for unilateral noninvasive tumors, especially for freely moveable masses. For fixed tumors only treated with surgical excision, the prognosis is poor, with a median survival time of 10 months.[4] After the surgery with incomplete resection to reduce recurrence or for large unresectable tumors, radiation therapy may be recommended.[5] Chemotherapy can also be used as an adjuvant therapy in an attempt to control metastases, however use of this therapy has exhibited limited response in primary lesions.[6]

History, Initial Assessment, and Surgery

Lulu Rocha is a 12-year-old female, spayed Akita Inu who was originally diagnosed with left thyroid carcinoma following surgical excision in August 2017. Following this initial diagnosis, Lulu was monitored for disease recurrence at the Veterinary Cancer Group (VCG). In June 2019, Lulu was presented to VCG for another palpable left cervical mass.

Imaging revealed a 2.8cm left cervical mass adjacent to the previously excised left thyroid gland. Concurrently, the right medial parathyroid gland was noted to be mildly enlarged (3.5 cm), likely due to compensatory hyperplasia. Surgical removal was elected. The cervical mass and the right medial retropharyngeal lymph node were excised completely with narrow margins.

Post-Operative Evaluation and Treatment Plan

Histopathology of the left cervical mass revealed epithelial neoplasia of thyroid origin with moderate mitotic activity (10 mitoses per 10 HPF). The neoplastic cells had effaced approximately 95% of the left cervical lymph node. Evaluation of the retropharyngeal lymph node revealed a reactive draining node with small hyperplastic follicles around the periphery and congested subcapsular and medullary sinuses. Both lymph nodes had been completely excised. These results were found to be consistent with metastatic thyroid carcinoma.

There was no evidence of intrathoracic metastatic disease on radiographs, although a high potential for further metastasis was noted based on the pathology report. Lulu's family did not opt to pursue traditional chemotherapeutic treatment options and instead elected to enroll in the FidoCure® Precision Medicine Platform.

FidoCure® Analysis

Tumor tissue from the metastatic lesion was sent for genomic (DNA) and transcriptomic (RNA) analysis in July, 2019.

Genomic sequencing revealed potentially oncogenic mutations of the well documented tumor suppressor gene BRCA1,with several additional gene alterations classified as likely benign, germline single nucleotide polymorphisms (SNPs). BRCA1 (breast cancer susceptibility gene 1) is a tumor suppressor gene which normally functions in DNA repair and chromosome stability. Specifically, BRCA1 regulates key effectors that control cell cycle progression. Mutations in this gene, as well as BRCA2, have been described in human malignancies for contributions to cancer development and predisposition. The introduction of therapies such as PARP inhibitors have improved outcomes for some patients with BRCA mutant cancers.

Findings based on the RNA expression profile were consistent with overexpression of CDK4, EGFR, KDR, MEK1/2, and mTOR. CDK4 is the gene encoding cyclin dependent kinase 4. This family of proteins plays a critical role in cell cycle regulation and dysregulation of this pathway has been identified as a driver for increased cell proliferation.

EGFR is the gene encoding epidermal growth factor receptor,which is a receptor on the cell surface, and is involved with numerous intracellular signaling pathways. Over-expression of this gene may result in tumor cell growth and proliferation through pathways such as MAPK/ERK.

KDR is one of the subtypes of the family of vascular endothelial growth factor receptors (VEGFR). These receptors primarily bind vascular endothelial growth factor (VEGF) leading to an intracellular signal via pathways such as MAPK/ERK and/or PI3K/AKT. Overexpression of both VEGF and KDR can lead to increased cellular signaling resulting in proliferation, cell survival, and angiogenesis. Inhibition of KDR may reduce these potential tumorigenic effects.

MEK is a gene that codes for the protein MEK1. This is a downstream protein that belongs to the MAPK/ERK signaling pathway. Overexpression of this gene may result in tumor cell growth, proliferation, and survival. Inhibition of MEK1 may reduce effects that this genetic alteration has as a driver of canine cancer.

mTOR is a gene that encodes a serine–threonine kinase protein, a downstream component of the PI3K/AKT cellular signaling pathway. Overexpression of mTOR may result in increased cell cycle progression and survival. Targeted therapies that target mTOR, such as Rapamycin (sirolimus), have been investigated in numerous canine cancers and have shown some inhibitory effects.

Imatinib or toceranib as receptor tyrosine kinase inhibitors and rapamycin (sirolimus) as a mTOR inhibitor were proposed as potential initial therapies. These therapies were proposed based on the gene expression profile, available targeted therapies and literature on these treatment options.

FidoCure® Treatment

Genomic results from FidoCure® analysis indicated the potential benefit of targeted therapy use. Thus the following targeted therapies were prescribed by the patient's treating veterinary oncologist:

- Rapamycin (mTOR inhibitor)
  0.1 mg/kg/day PO
- Imatinib (RTK inhibitor)
  10 mg/kg/day PO

These FidoCure recommended medications were administered orally by the pet owners at home beginning in August, 2019. No additional cytotoxic chemotherapy treatment was elected. Following a month of taking these medications, Lulu experienced some inappetence, lethargy and diarrhea. A drug holiday significantly improved her symptoms; consequently, intermittent drug holidays (four day break every two weeks) were scheduled throughout Lulu's ongoing treatment. On April 24, 2021, thoracic imaging revealed no evidence of pulmonary metastatic disease or intrathoracic lymphadenopathy. Two years post diagnosis of metastatic thyroid carcinoma (approaching four years since her original diagnosis), Lulu "feels great at home" and continues therapy of rapamycin and imatinib with periodic treatment breaks. She continues to stage free of disease.

Conclusion

After FidoCure® enabled treatment, Lulu remained free from further metastases.

After more than 20 months of FidoCure® enabled therapy, Lulu has continued to thrive. There has been no evidence of disease recurrence or pulmonary metastasis. Lulu has maintained a positive quality of life while in treatment and achieved extended time with her pet owners.

What Lulu's Parent and Doctor Said

About two years ago during a routine checkup for Lulu's post thyroid carcinoma, we found out that the cancer had come back in a couple of her lymph nodes. This was 18 months after her initial diagnosis and surgery to remove a substantially sized tumor and her chemotherapy rounds.

A genetic analysis was recommended and through it two specific mutations were pinpointed. After another surgery Lulu began taking imatinib and sirolimus through FidoCure®.

She's been able to carry on with a great quality of life in her senior years. Aside from being a picky eater, no one would ever guess all that she's been through. She cruises through most days and still shares her playful side and unique personality, especially to family visitors.

— **Rolando Rocha**

With the addition of FidoCure® targeted therapy, we are able to maintain continuous pressure on Lulu's thyroid carcinoma long term with minimal disruptions to her quality of life - we are so proud of her progress!

— **Dr. Elizabeth Schuh, DVM**

Literature Cited

1. Harari J, Patterson JS, Rosenthal RC. Clinical and pathologic features of thyroid tumors in 26 dogs. J Am Vet Med Assoc. 1986 May 15;188(10):1160-4.
2. Barber LG. Thyroid tumors in dogs and cats. Vet Clin North Am Small Anim Pract. 2007 Jul;37(4):755-73, vii. doi: 10.1016/j.cvsm.2007.03.008.
3. Liptak JM. Canine thyroid carcinoma. Clin Tech Small Anim Pract. 2007 May;22(2):75-81. doi: 10.1053/j.ctsap.2007.03.007.
4. Carver JR, Kapatkin A, Patnaik AK. A comparison of medullary thyroid carcinoma and thyroid adenocarcinoma in dogs: a retrospective study of 38 cases. Vet Surg. 1995 Jul-Aug;24(4):315-9. doi: 10.1111/j.1532-950x.1995.tb01336.x.
5. Théon AP, Marks SL, Feldman ES, Griffey S. Prognostic factors and patterns of treatment failure in dogs with unresectable differentiated thyroid carcinomas treated with megavoltage irradiation. J Am Vet Med Assoc. 2000 Jun 1;216(11):1775-9. doi: 10.2460/javma.2000.216.1775.
6. Fineman LS, Hamilton TA, de Gortari A, Bonney P. Cisplatin chemotherapy for treatment of thyroid carcinoma in dogs: 13 cases. J Am Anim Hosp Assoc. 1998 Mar-Apr;34(2):109-12. doi: 10.5326/15473317-34-2-109.