Fenway's Lazy Eye Gone Awry

Danica K. Wilson

Mississippi State University

College of Veterinary Medicine

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Advisor: Ryan Gibson, DVM, Neurology Resident

Introduction

Melanomas are the most common oral tumor in dogs, the third most common oral tumor in cats, and one of the most common tumor across all species.[6] The site of the tumor and the species of the patient is often more important in establishing the prognosis than the histologic and cytologic features.[8] Oral melanoma is considered an extremely malignant tumor with high probabilities of both aggressive local invasiveness and metastasis.[1] Melanoma is often under suspicion by its proliferative and pigmented appearance but it has a less common amelanotic presentation that can also occur. Due to the common presentation in the oral cavity, an associated inflammation and infection are common. Ocular melanomas have a varied prognosis depending on location. Melanomas located within the conjunctiva or on the third eyelid, they are often aggressive with local recurrence being common. In comparison, melanoma in the limbus is mostly benign in dogs and cats.[2] Animals with intraocular tumors can present with clinical signs such as glaucoma and uveitis, that can mask the underlying melanoma.[2] Histopathology is the definitive way to diagnose melanomas on any location of the body. Surgical resection is the initial treatment of choice. Melanomas are very radiation responsive and is often the treatment of choice for non-resectable lesions. Chemotherapy is often considered a last resort. Prognosis with oral melanoma is generally guarded in dogs as it often metastasizes to the lungs, which is the primary cause of death in these animals.[4]

History and Presentation

Fenway Blackwell is an approximately 11-year-old male neutered, 21 kg, mixed breed dog. He presented to the Mississippi State University Veterinary Specialty Center on August 5, 2020 to the Neurology department for a history of acute visual loss. On July 29, 2020, Fenway had been boarding at his primary veterinarian's office where it was noticed that he was stumbling

and would occasionally bump into things around the practice. An ophthalmic exam was performed at his primary care veterinarian's office and he was discovered to be completely blind in his left eye with a situational blindness in his right eye. Fenway was then referred to a local ophthalmologist for further diagnostics. The ophthalmologist found that Fenway was completely blind in his left eye and partially blind in his right eye. His left eye was described as "optic neuritis with concern for a dark optic nerve". It was at this point that Fenway was referred to the MSU-CVM Neurology Department.

On presentation to the MSU-CVM Veterinary Specialty Center, Fenway was bright and alert, but anxious. He had a normal body condition with a score of 6 out of 9. His body temperature was 101.4˚F, a pulse of 116 beats per minute, and a respiratory rate of 24 breaths per minute. His mucous membranes were pink and moist with a capillary refill time of fewer than 2 seconds. No crackles, wheezes, murmurs, or wheezes were appreciated on cardiothoracic auscultation. His right ear had minimal ceruminous debris and his nose was clear of discharge. Fenway had a clean coat with no evidence of infection, pruritis, or external parasites. No pain was elicited on abdominal palpation. A mass was found on the right ventral, caudal thorax (suspected lipoma). Fenway had symmetric muscle atrophy in his pelvic limbs.

Examination of his eyes revealed that they were both clear of discharge, with clear corneas, and dilated pupils. The pupillary light response (PLR) was absent in his left eye, but direct and consensual PLRs were present when his right eye was stimulated.

Neurologic examination revealed an absent menace bilaterally, absent tracking in the left eye, and diminished tracking in the right eye. It was confirmed that his left eye had an absent direct pupillary light reflex and that the right eye had an absent indirect (consensual) pupillary light reflex. All other cranial nerves were found to be intact, including palpebral reflexes.

Fenway also had an abnormal gait and was painful in his hips and throughout his spine. His pain was most significant along the thoracolumbar spine and the coxofemoral joints bilaterally. He favored his left pelvic limb when he moved. Proprioceptive placement and hopping were normal in all four limbs. Reflexes were intact and considered normal. The MSU-CVM Ophthalmology Department was contacted and agreed to help with Fenway's case. Their examination also confirmed our findings on physical examination, as well as complete blindness in his left eye and partial blindness in his right eye. Retinal imaging was performed, and the entire retina of the left eye was black in color.

Diagnostic Approach

After his physical examination, neurologic examination, and ophthalmologic examination were complete, a complete blood count (CBC) and neurochemistry panel were performed. Both the CBC and the neurochemistry panel had no significant findings. Thoracic radiographs were performed that revealed a normal thorax with no evidence of metastatic disease.

To better evaluate Fenway's hips and difficulty with hindlimb motor function, a thoracolumbar and hip CT were performed, and a moderate amount of soft tissue and mineral material was seen within the ventral and left aspects of the vertebral canal at T13-L1 causing narrowing of the spinal cord. A similar material was seen on the ventral aspects of the vertebral canal at T12-T13 and L1-L2 causing dorsal deviation of the spinal cord. Spondylosis deformans was seen on multiple thoracic and lumbar vertebrae. Many of the intervertebral disc spaces and sections of the dura had multifocal mineralization. Bilaterally, the coxofemoral joints had moderate to severe osteophyte formation circumferentially, and the femoral heads of the acetabula on either side had patchy sclerosis in the subchondral bone. Since these findings were

not his primary concern, and the disc protrusions were mild, it was elected to medically manage him for this condition.

An MRI was performed to further evaluate Fenway's neurological abnormalities. A mass was identified that was associated with the entirety of the left ophthalmic nerve, measuring 3.1 x. 1.0. 1.8 cm and caused dorsal and lateral deviation of the glove. The mass extended down appearing to involve the entirely of the optic chiasm and coursed ventrally along the right optic nerve for an additional 6.0 mm lateral to the optic chiasm. This mass was T1 hyperintense and T1/T2 FLAIR hypointense and strongly contrast-enhancing. There was multifocal round, smoothly marginated signal void within the mass on GRE with the largest region measuring 9.0 mm in diameter suggesting hemorrhage.

Based on our general, ophthalmological, and neurologic examination findings, in addition to the MRI, our top concern was for melanoma or other neoplasia, however, other differentials such as infectious or inflammatory conditions could not be fully excluded. A cerebrospinal fluid tap revealed no significant abnormalities and had 1 nucleated cell (< 5 is considered normal) and a protein of 21 mg/dl. Following MRI, an ocular ultrasound was performed, which confirmed the presence of the mass. Digital images of the eye were also taken, revealing a dark optic nerve. In addition to this, a fine needle aspirate was performed on the ocular mass with ultrasound guidance but was non-diagnostic with no atypical cells discovered.

Pathophysiology

Melanomas are the most common oral tumor in dogs and one of the most common tumor across all species. Melanomas are neoplasias of mesenchymal origin with abnormalities taking place within melanocytes.[6] The site of the tumor and the species of the patient is often more

important in establishing the prognosis than the histologic and cytologic features (5). Melanoma is often under suspicion by its proliferative and pigmented appearance but it has a less common amelanomtic presentation that can also occur.

On histopathology, melanomas appear as clusters of broad, proliferative, and pigmented melanocytes within the epidermis, and more specifically between the rete ridges. Because they can range from spindloid to epithelioid in appearance on histology, diagnosis can be challenging.[5] Though almost all melanomas reported in dogs occur in the oral cavity (most notably the cutaneous junction), they can also occur in the nailbed, on the skin, or in the eyes. Melanomas are highly metastatic and an associated inflammation or infection are common findings.

While not highly understood, there is high suspicion of melanoma having a genetic component due to the increased predilection in pure breed dogs such as Schnauzers and Doberman Pinschers. Current research is highly suspicious of the role of genes and proteins that regulate cell cycle control and apoptosis.[7] Most neoplasias occur due to a dysfunction somewhere within the cell cycle, in this case, within melanocytes. CDKs are involved in the cell cycle and are responsible for the temporary inactivation of growth suppressor proteins. CDK function does not have an intrinsic regulatory domain and instead, its activation relies on the binding of cyclin to regulate the mitogenic signal.[7]

There are several named functional proteins in the cell cycle that contribute to the malignancy and proliferation of melanomas. The p21/Waf-1 protein is responsible for CDK inhibition but can also result in apoptosis. Loss of function of p21/Waf-1 has been shown to be responsible for uncontrolled cellular growth. A study was performed examining the effects of p21 on the growth of the TLM1 canine melanoma cell line. In those cell lines that had prolonged

nuclear localization, growth arrest was seen in the TLM1 cell line. Once the p21 protein contact was lost, a loss of contact inhibition was seen, indicating that p21/Waf-1 may have an inhibitory function to the growth of canine melanocytic cells. There are many oncogenes and proteins that have been examined for their role in human melanoma but canine melanomas has not been explored to the same extent.[8]

Gross appearance is frequently highly suggestive but not diagnostic. Often melanomas are proliferative and irregular in appearance with a heavily pigmented color. Because of the highly metastatic capabilities of melanomas, a minimum database is required. Like all cancers, a 3-view radiographic study is recommended to evaluate for pulmonary metastasis. Many tumors can resemble melanomas cytologically, and thus histopathology is definitive. There are immunohistologic tests that can be used in addition to histopathology if needed, that select for MelanA (a protein recognized by T-cells with unknown functions) and tyrosinase-related proteins.[7]

Depending upon location of the tumor, computed tomography (CT) or magnetic resonance imaging (MRI) may be needed to assess local invasiveness of the tumor and the extent of the disease. A fine needle aspirates of local lymph nodes is helpful in staging level of metastasis. Staging of melanoma has been defined by the World Health Organization (WHO) and is based on size of the tumor. Stage I is any tumor < 2 cm, stage II, is a tumor 2-4 cm in diameter, stage III indicates a tumor > 4 cm in size, and stage IV indicates distant metastasis of the melanoma.[1]

Treatment and Management Options

Dermal melanomas tend to be benign and can often be cured with local excision. Oral, mucocutaneous, and uveal melanomas are aggressive and commonly metastasize to local tissue. These are poorly responsive to therapy and in general have a shorter survival time when diagnosed.[8] Malignant melanoma can be treatment with a combination of surgery, radiation, and vaccination. Overall, prognosis is based on the cell differentiation seen within the mass and how aggressively it behaves. However, ocular tumors often behave more aggressively than other tumor locations. Oral melanoma is very responsive to radiation. However, melanoma in general has a guarded prognosis due to the high likelihood of metastasis.[8] Surgery alone can extend the life of the patient by 5-10 months, and with the vaccine added on, can average a life expectancy of 13 months.

Currently, there is a melanoma tumor vaccine that has a conditional license and is licensed by the US Food and Drug Administration, but it is specifically labeled for use in stage 2-4 oral melanoma. The vaccine is administered in the left inguinal region every 14 days for 4 doses, and then repeated once every 6 months. Human tyrosinase genes are used in the vaccines and are used to stimulate an immune response against the tyrosinase present in canine melanoma cells and acts as an essential role in melanin synthesis. The human tyrosinase is able to work in dogs because the tyrosinase genes are similar in construct.[1,5] Current research suggests that the best application of the melanoma vaccine is in conjunction with surgery and/or radiation therapy, depending upon the size and location of the tumor. Several studies have looked at the efficacy of the melanoma vaccine for other locations, but efficacy has been highly debatable among studies. One study did find that adding on the vaccine to the treatment plan can extend survival times up to 389 days.[1]

Case Outcome

A referral appointment was scheduled through the MSU Oncology Department for staging and evaluation prior to surgical removal of the eye. Bilateral submandibular lymph node aspirates were taken and were found to be inconclusive with a generalized antigenic response. Abdominal radiographs and ultrasound were within normal limits. Given that no evidence of metastatic disease was identified, Fenway's owner elected to move forward with enucleation in order to obtain a definitive diagnosis.

Two weeks later, Fenway returned to MSU through the Ophthalmology Department for exenteration and biopsy of the mass. A complete blood count and neurochemistry panel were performed and both were within normal limits. The exenteration was performed and went smoothly. Fenway woke up from anesthesia without issue. Results of the biopsy were as follows: the corneal epithelium, iris, filtration angle, ciliary body, and choroid were largely unaffected by the mass. The retina was found to be atrophic and attenuated, including loss of the inner membrane, nerve fiber layer, ganglion cell layer, and the inner plexiform and nuclear layers. The definitive diagnosis was melanoma of the optic nerve.

The diagnosis was discussed with the owners, including concern over residual disease as well as tumor progression and metastasis. Due to the rare location of the melanoma, we weren't able to provide her with any definitive on aggressiveness of metastasis or overall prognosis. The options of radiation therapy and the melanoma vaccine were discussed. We also discussed with Mrs. Blackwell what further local invasion of the tumor could look like for Fenway due to location including possible cognitive and behavioral changes, further cranial nerve deficits, and potentially seizures depending on how the mass grew. Long-term NSAID use was advised for its potential anti-cancer effects.

Conclusion

Canine melanoma is one of the few neoplasias where location of the tumor plays a significant role in the prognosis for the patient. For the most part, doctors recognize the severe malignancy of oral melanomas and treat all melanomas as if they are highly malignant.7 If histopathology reveals necrosis, ulceration, a higher rate of proliferation, or if it is amelanotic, the prognosis worsens. While Fenway didn't have any of these, we are still at this time unable to provide his owners with any sort of information regarding prognosis or the effectiveness of treatment outside of what the standards are for oral melanoma. A search of optic nerve melanoma brings up a single scientific article done as a case study. in human medicine on one man who developed an optic nerve melanoma.[10]

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