Epitheliotropic T-cell Lymphoma in the Canine Patient

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Introduction

Dermatologic conditions are one of the most common reasons for a canine patient to present to a veterinary hospital. When considering differentials, neoplasia is usually low on the list with ectoparasites and immune mediated diseases higher depending on presentation.[19] However, epitheliotropic T-cell lymphoma must be considered especially in older patients that do not have a history of atopy or in patients that have depigmentation of the mucous membranes and footpads.[16] Epitheliotropic T-cell lymphoma is a rare, but fatal neoplasm of the epidermis and adnexal structures.[8] While it can affect dogs of any age, it has a mean age range of 9-12 year.[5] There have also been studies that suggest a breed predisposition for the English Cocker Spaniel, Boxer, and Bichon Frisé.[19] There are 3 subforms derived from human medicine including mycosis fungoides (MF), pagetoid reticulosis (PR), and Sézary syndrome.[16] These subforms describe the clinical presentation of the patient. However, to definitively distinguish pagetoid reticulosis and mycosis fundoides, histopathology must be utilized. Mycosis fungoides tends to be a more generalized condition with erythema, scaling, nodules, and plaques; pruritus is also common. The mucocutaneous junctions can be ulcerated and depigmented. Pagetoid reticulosis is similar to mycosis fungoides. Pagetoid reticulosis is a more superficial condition where neoplastic cells only affect the epidermis and adnexa while neoplastic cells with mycosis fungoides affect the underlying dermis. The last subform, Sézary syndrome is an advanced and rare form of mycosis fungoides where the neoplastic lymphocytes are in the peripheral blood. These cells are identified by their cerebriform or convoluted nuclei. In general, epitheliotropic T-cell lymphoma can be difficult to diagnose, but a thorough history and complete physical exam are essential. The overall prognosis is poor, and the median survival time is 6 months.[16]

History and Presentation

Kelsey was an approximately 10-year-old, male neutered, black Labrador retriever who first presented to Mississippi State University College of Veterinary Medicine in July 2018 for severe and progressive dermatologic lesions. His owners first noticed a change in Kelsey's previously shiny and full coat in January 2018. They noticed his muzzle began turning white which they believed was an ageing change. However, his condition worsened progressively from January to July. He had severe scaling of the truncal skin that had developed into pruritic erosions. There was depigmentation from his ventral muzzle to the nasal planum. Previous therapies included antibiotics, shampoos, antifungals (ketoconazole), supplements (essential fatty acids), and Apoquel. None of the therapies resulted in improvement of Kelsey's condition. His lesions continued to worsen and upon presentation, he was lethargic and inappetent.

A physical exam was performed to adequately asses Kelsey's condition. Kelsey was severely pruritic, scratching at his face and neck during the exam. The physical exam revealed depigmentation of the rostral muzzle and the mucocutaneous junction of the lips. There were multifocal crusts and raised lesion on the lower palpebra. There was peripheral lymphadenopathy marked by enlargement of the prescapular lymph nodes and mild enlargement of the popliteal lymph nodes. Cardiothoracic auscultation revealed normal bronchovesicular sounds bilaterally and a grade IV/VI left sided heart murmur and a grade II/VI right sided heart murmur. The abdomen had diffuse scaling, along with crusts and erosions. Erythema and multifocal erosions were apparent on the inguinal skin. There were depigmentation and hyperkeratosis of the paw pads. The remainder of the physical exam was within normal limits. Although unrelated to Kelsey's presentation, the heart murmur was concerning, and an echocardiogram was performed; he was diagnosed with chronic valvular disease.

Diagnostic Approach/Considerations

Due to the clinical presentation of epitheliotropic T-cell lymphoma, dermatologic conditions must be ruled out by diagnostics. Skin surface cytology is recommended if ulcerated plaques and nodules are present. While this does not always yield a definitive diagnosis for epitheliotropic T-cell lymphoma, it can reveal a secondary skin infection, a common sequela to this disease. Nevertheless, to definitively diagnose epitheliotropic T-cell lymphoma, dermatohistopathology is essential. This allows for visualization of T-cells showing tropism for the epidermal and mucosal epithelium as well as adnexa.[16]

Kelsey's clinical presentation and history provided a strong basis of suspicion for epitheliotropic T-cell lymphoma or pemphigus foliaceous. Several diagnostics were used to differentiate between the two as well as rule-out all other possibilities. Deep skin scrapings were performed, and no mites were seen. Samples were taken from lesions on the extremities and shoulders for skin cytology; they were within normal limits. A dermatophyte culture was also submitted, and it revealed that no dermatophyte was isolated at 4 weeks. Bloodwork including a CBC, serum chemistry, and urinalysis were completed to evaluate for systemic disease. The only significant finding was a mildly increased ALP at 165 U/L. A bacterial culture was submitted from various sites of skin lesions. There was moderate growth of two types of Staphylococcus sp. (Staphylococcus hyicus and Staphylococcus intermedius). Five punch biopsies were then taken from Kelsey's left truncal region and one punch biopsy was taken from the rostral aspect of his muzzle. The punch biopsies revealed that the cause of Kelsey's clinical signs was epitheliotropic T-cell lymphoma. His bacterial pyoderma was treated with Rifampin (imitated on August 3, 2018) and he was transferred to the Mississippi State University College of Veterinary Medicine Oncology service.

Pathophysiology

Epitheliotropic T-cell lymphoma is an uncommon neoplasm in the canine patient. In fact, lymphoma (non-epitheliotropic and epitheliotropic) is the cause of only 1% of all canine skin tumors.[8] The etiology is not fully understood. There are several hypotheses especially in human medicine. One of these proposes that chronic inflammation, more specifically, chronic dermatitis predisposes a patient to epitheliotropic T-cell lymphoma. Lymphocytes can be activated by environmental allergens or Langerhans cell dysfunction and this clonal expansion progresses into T-cell lymphoma. However, other studies found that epitheliotropic T-cell lymphoma develops spontaneously.[8]

The epidermis and adnexal structures are affected in epitheliotropic T-cell lymphoma. The malignant T-cells are able to infiltrate into the skin because they release skin-homing receptors (cutaneous lymphocyte antigen or CC-chemokine receptor 4). Once in the skin, they bind to epidermal keratinocytes and Langerhans cells. They express β1 integrin intercellular adhesion molecule (ICAM) at high levels which explains the disease's tropism for the epidermis and adnexal structures.[8]

When a skin biopsy is performed, the aforementioned epitheliotropism is observed. Neoplastic lymphocytes can be seen uniformly, or in clusters known as Pautrier's microabscesses or microaggregates. These microabscesses are normally seen in the upper layers of the epidermis. The lymphocytes progress in size in different stages of the disease. Patches and plaques contain small or medium lymphocytes while larger lymphocytes are found within tumors. While biopsy is the only definitive method of diagnosis for epitheliotropic T-cell lymphoma, the early stages of disease may yield a misleading result. The neoplastic cells may resemble a dermatitis and future skin biopsies may be indicated.[16]

A noteworthy difference between human and canine epitheliotropic T-cell lymphoma is the marker and subtype. The majority of canine epitheliotropic T-cell lymphoma has the CD8 marker and gamma/delta T-cell receptor. CD8 T-cells are of the cytotoxic subtype. This difference explains why the canine patient has such a poor prognosis with this aggressive neoplasm.[16]

Treatment and Management

Once a diagnosis of epitheliotropic T-cell lymphoma is made, it is essential to start therapy as soon as possible. Currently, there is not a cure, but there are treatment options that allow a better quality of life for the patient. Treatment options include CCNU, CHOP, safflower oil, oral retinoids, pegylated doxorubicin, rabacfosadine, and total skin electron beam therapy.[16]

CCNU or lomustine is an alkylating agent that can be administered orally. It can be effective against refractory lymphoma and cutaneous mast cell tumors. One retrospective study evaluated 36 dogs with epitheliotropic T cell lymphoma and their response to CCNU. There was a 78% response rate with 6 dogs attaining a complete response, and the most common side effect was increased liver enzyme activity. The study concluded that CCNU was a reasonable treatment option for epitheliotropic lymphoma.[19] Another retrospective study evaluating 46 dogs found similar results and it had an overall response rate of 83% with 15 dogs achieving complete remission. Neutropenia was the most common side effect in this study. Overall, CCNU was well tolerated and provided a high response rate. However, duration of response was short with a median of 94 days.[15] These studies help provide support that CCNU is a worthy treatment option for epitheliotropic T cell lymphoma.

The CHOP protocol includes cyclophosphamide, doxorubicin, vincristine, and prednisolone. While commonly used to treat various types of high-grade lymphoma, it has only been mildly successful for managing epitheliotropic T-cell lymphoma. The survival times with this therapy range from 2-6 months. However, it has been found to be a viable option after a patient has failed CCNU therapy.[19]

There has been some success with increased median survival times in patients where safflower oil and oral retinoids have been used. Safflower oil has linoleic acid, a polyunsaturated fatty acid.[2] Linoleic acid has been shown to be cytotoxic, and it can cause apoptosis as well as necrosis of lymphocytes.[3] Retinoids activate retinoid receptors. Neoplastic cells in epitheliotropic T-cell lymphoma have both types of retinoid receptors, RAR and RXR. These receptors can affect cell proliferation, differentiation, and immunoregulation. It has also been suggested that they can cause DNA fragmentation and apoptosis of some T-cell lines. In epitheliotropic T-cell lymphoma, they affect the epithelial cells as well as the mononuclear cell infiltrate (neoplastic lymphocytes). This has the potential to improve future therapies.[16, 20] At this time, further research is indicated.

Pegylated doxorubicin or a liposomal encapsulated form of doxorubicin has been evaluated in the treatment of various neoplasms including epitheliotropic T-cell lymphoma. It was chosen to be evaluated due to its decreased risk of cardiotoxicity. Nine patients with cutaneous lymphoma were evaluated and three had a complete response. These results speak to the benefit of future efficacy studies.[16]

Rabacfosadine, an anticancer nucleotide prodrug, has been conditionally approved by the FDA in the United States for the treatment of lymphoma.[16] A clinical trial that evaluated its use in epitheliotropic T-cell lymphoma found a 64% biologic response rate with 1 out of 11 patients

achieving a complete response and 4 others achieving partial responses. This trial proved that rabacfosadine has some activity against epitheliotropic T-cell lymphoma and it could provide a viable treatment option.[12]

Another therapy with some success is total skin electron beam therapy. It can be used palliatively or in patients with more localized disease. At this time, it is not feasible in most cases due to the extensive time commitment and necessity for anesthesia.[14]

After diagnosis with epitheliotropic T-cell lymphoma, Kelsey presented to Mississippi State University College of Veterinary Medicine Oncology service on August 6, 2018. A CBC and small animal liver panel were completed. They revealed similar findings to when he presented. CCNU/prednisone therapy was initiated due to its success in cases of epitheliotropic T-cell lymphoma. Denamarin and alpha-lipoic acid were added to the therapeutic regimen for liver protection and to reduce oxidative stress.[7] Kelsey returned on August 28, 2018 with a decreased appetite of 3 days duration. Due to his presentation and history a complete blood count, serum chemistry, and bile acids test were complete. Severely elevated liver enzymes (ALT 841 U/L and ALP 6196 U/L) resulted. The bile acids test was also abnormal. These findings lead to CCNU being discontinued. Rifampin, previously prescribed for the bacterial pyoderma, had been discontinued 2 days prior. Kelsey next presented on September 5, 2018. He had been doing well at home and his liver values had improved. A modified CHOP chemotherapy protocol was initiated since it could not be determined if the CCNU or Rifampin caused the increased liver enzymes. A modified CHOP protocol where mitoxantrone replaced doxorubicin was used due to Kelsey's historic endocardiosis. Kelsey continued to do well on this protocol and prednisone was discontinued on September 19, 2018. However, when Kelsey returned on September 26, 2018, he had increased, open skin lesions. Prednisone was re-initiated

at an immunosuppressive dose (2 mg/kg). Approximately one week (October 3, 2018) after mitoxantrone administration, Kelsey presented for lethargy and inappetence. He was diagnosed with grade 3 symptomatic neutropenia, and he was hospitalized with intravenous antibiotic support. The modified CHOP (CMOP) chemotherapy protocol was discontinued. Due to the previous success of the CCNU therapy, it was re-started on October 16, 2018. Kelsey did not present again until November 1, 2018. During his time at home, he had two episodes where he was unwilling to rise. His owners administered ibuprofen without consulting a veterinary professional. He also was noticed to have an increased respiratory rate at rest. Thoracic radiographs were taken to ensure that there was no progression of his heart disease. There were no signs of advancement or congestive heart failure. A CBC and chemistry were also performed to evaluate if he was still on course to receive his second dose of CCNU. His CBC remained unremarkable, but his liver enzymes remained slightly elevated. Gabapentin was prescribed for analgesia and omeprazole was prescribed as a gastroprotectant. On November 8, 2018, Kelsey was able to receive his second dose of CCNU. His condition had been static at home except for one episode of diarrhea and one new skin lesion on the right side. Kelsey did not return to Mississippi State University College of Veterinary Medicine after this visit.

Case Outcome

Due to the lack of response to the final CCNU treatment, Kelsey's deteriorating condition, and his declining quality of life, he was humanely euthanized on December 6, 2018. As previously mentioned, the overall prognosis for epitheliotropic T-cell lymphoma is poor. If the condition remains localized such as with the subform pagetoid reticulosis, the median survival time may increase up to 2 years. Cases such as Kelsey's with a more diffuse condition face shorter survival times and euthanasia is often elected because of the severity of the disease, lack of response to

treatment, and poor quality of life of the patient. When natural death does occur, it results from generalized lymphoma, Sézary syndrome, or a secondary septicemia.[8]

*This paper was written in loving memory of Kelsey. He brought joy to the hospital every time he visited.

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