A Case of Canine Lymphomatoid Granulomatosis with Cutaneous Lesions

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ABSTRACT. A 10-year-old, castrated, mixed-breed dog presented with a 1.5-month history of scattered, crateriform ulcers on the trunk and extremities. Some skin lesions appeared to regress spontaneously, but new lesions developed. Thoracic radiography revealed pulmonary consolidated lesions suggestive of tumor. A skin biopsy was performed for histopathological, immunohistochemical and clonality analyses. The presence of clonally expanded T-cells was revealed by the clonal rearrangement of T-cell receptor -chain gene.

NOTE Pathology

Canine lymphoma is one of most common malignancies and may affect the lymph nodes, bone marrow, liver, spleen, gastrointestinal tract, eye and skin. However, cutaneous lymphoma is relatively uncommon. Histopathologically, it can be divided into nonepitheliotropic and epitheliotropic forms. Epitheliotropic lymphoma is a subset of cutaneous T-cell lymphomas (CTCL) and is the most common form of cutaneous lymphoma. The nonepitheliotropic lymphoma is a heterogeneous group of T- and B-cell lymphomas, which have several morphologic subsets including lymphomatoid granulomatosis (LYG). LYG is a rare angiocentric lympho- cytic proliferative disorder in humans. This condition mainly involves the lung and occasionally the skin as multiple, recurrent, crateriform ulcers [5, 10]. However, skin lesions have been described in only 2 cases without minute evaluation in the literature [11].

A 10-year-old, castrated, mixed-breed dog presented with a 1.5-month history of skin lesions. The dog had been treated with several agents including antimicrobials in another veterinary clinic. The dog owner mentioned that new skin lesions had gradually developed despite the fact that other lesions had regressed spontaneously. Although the dog had regular appetite, mild diarrhea and vomiting were observed. On examination, there were scattered, crateriform, cutaneous ulcers with a diameter of about 1 cm on the trunk and extremities (Fig. 1). Clinical differential diagnoses included bacterial or fungal infection; neoplasia such as lymphoma, squamous cell carcinoma, basal cell tumor, histiocytic tumor, or vascular tumor; and miscellaneous disorders including vasculopathy, lupus erythematosus, pemphigus, drug eruption or panniculitis. Infectious disorders were carefully ruled out with standard diagnostic procedures. Complete blood counts and serum biochemical analysis were performed revealing mild leucocytosis (24.7 × 109 l−1, reference range 6.0–17.0 × 109 l−1) and neutrophilia (22.97 × 109 l−1, reference range 3.0–11.5 × 109 l−1). The dog was initially managed with symptomatic treatments including oral cephalaxine (Keflex, Shionogi, Osaka, Japan) 25 mg/kg q24h, tocopherol nicotinate (Juvela-N, Eisai, Tokyo, Japan) 1 capsule q24h, and lactobacillus (Biophelmine-R, Takeda Pharmaceutical, Osaka, Japan) 1 tablet q24h. Despite treatment, respiratory distress and anorexia were noted 1 week later. A second blood analysis revealed moderate leucocytosis (32.8 × 109 l−1) with slightly increased alkaline phosphatase, blood urea nitrogen, creatinine, phosphorus, and slightly decreased total protein, albumin and glucose. Thoracic radiography revealed approximately 10 consolidated densities with a diameter of about 7 mm on the caudal lobe of lungs suggestive of tumor. Other radiographic changes included a diffuse mixed lung pattern. There were no hilar adenopathy. Abdominal ultrasonography revealed slight hepatomegaly but cytology from fine-needle aspiration showed no marked abnormalities. A skin biopsy was performed with a 6-mm diameter punch instrument under local anesthesia using 2% lidocaine (Xylocaine injection 2%, AstraZeneca, Osaka, Japan). Tissues specimens were fixed in 10% neutral-buffered formalin, embedded in paraffin, and stained with hematoxylin and eosin (HE). On the same day, a subcutaneous injection with prednisolone (Prednisolone-KMK, Kawasaki-Mitaka, Kawasaki, Japan) 2 mg/kg, metoclopramide (Primperan, Astellas Pharma, Tokyo, Japan) 0.5 mg/kg, and ampicillin (Amipenix, Kawasaki-Mitaka, Kawasaki, Japan) 20 mg/kg were administered, but the dog died at home on the next day. Unfortunately, consent for necropsy was not given. Histopathological examination of the erethematous portion of the lesion revealed vasotropic and vasoinvasive infiltration of atypical lymphoid cells with some other cell populations around the blood vessels in the dermis (Figs. 2 and 3). Proliferating lymphoid cells showed polymorphism, round-oval nuclei with large nucleoli. Histopathological examination

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of the ulcerative portion of the lesion revealed extensive necrosis and haemorrhage with a significant infiltration of atypical lymphoid cells in the dermis. No apparent epitheliotropic infiltration was observed. Immunohistochemical staining was performed using rabbit anti-human CD3 anti-body (DAKO, Copenhagen, Denmark), rabbit anti-human CD20 antibody (Thermo Fisher Sci. Anatomic Pathology, Fremont, CA, U.S.A.) and monoclonal mouse anti-human HLA-DR antigen, Alpha-chain (Clone TAL.1B5, Dako) as primary antibodies. As secondary antibodies, peroxidase-conjugated anti-rabbit IgG (Histofine Simple Stain MAX-PO(R), Nichirei, Tokyo, Japan) for anti-CD3, anti-CD20 antibodies and peroxidase-conjugated anti-mouse IgG (Histofine Simple Stain MAX-PO(M), Nichirei) for anti-human HLA-DR antibody were used. Atypical lymphoid cells showed distinct membrane staining of CD3 (Fig. 4), and were negative for CD20 and HLA-DR. A few CD20-positive B lymphocytes and HLA-DR antigen-positive cells suspected of MHC II-positive cells were scattered in the cutaneous lesions. DNA samples extracted from formalin-fixed and paraffin-embedded skin biopsy tissues were subjected to polymerase chain reaction (PCR) to amplify antigen receptor genes as described by Burnett et al. [2] and Valli et al. [12]. A distinct DNA band of approximately 110 bp was generated by PCR using a pair of T-cell receptor γ-chain (TCR-γ) gene primers (Fig. 5), indicating the presence of a clonal T-cell population in the skin lesion.

In human LYG, there is a greater incidence in males than females, and patients present mainly with respiratory symptoms due to an infiltration of neoplastic cells in the lung. Skin lesions are seen in approximately 25–50% of cases, presenting as erythematous macules, papules and subcutaneous nodules. The average survival time is 14 months, and the survival rate is 38–85% [2, 11]. In dogs, 30 cases of LYG have been described in 7 reports. There were 19 different breeds accounted for, but no predilection was noted. Interestingly, 24 dogs (80%) were of a large size. The age of the onset ranged from 9 weeks to 14 years old, and the mean was 5.5 years old. Sex predilection was not found. Twenty-nine dogs (96.7%) had pulmonary lesions and there
Lymphomatoid granulomatosis (LYG) is a rare disease in both dogs and humans, characterized by the infiltration of atypical lymphocytes and angiocentric vasoinvasion. The present case described a dog with a skin lesion that was infiltrated by atypical lymphocytes, and based on these findings, the dog was diagnosed with LYG. The dog was presented with a progressive respiratory distress due to possible pulmonary neoplasia, and multi-organ involvement in 29 cases (96.7%). Extra-pulmonary lesions were noted in the lymph nodes in thoracic cavity in 12 cases (40.0%), liver in 7 cases (23.3%), spleen in 3 cases (10.0%), peripheral lymph nodes in 3 cases (10.0%), myocardium in 2 cases (6.6%), mesenteric fat in 2 cases (6.6%), skin in 2 cases (6.7%), kidney, pancreas, adrenal gland, colon, skeletal muscle, bone marrow, oral cavity, periocular areas, thyroid capsule, and synovial connective tissue in 1 case (3.3%). Skin lesions were reported as multiple crateriform ulcers in 2 cases, nodule in 1 case, alopecia in 1 case, and scaling on the face and elbows in 1 case. In our case, the lesion was composed of T-cells, similar to previous reported cases. Interestingly, human LYG shows clonal expansion of atypical B-cells with reactive T-cells (T-cell rich B-cell lymphoma). Epstein-Barr virus (EBV) is implicated as an etiological pathogen in patients with LYG. It is hypothesized that EBV infects B-cells in most healthy adult humans as an asymptomatic infection, but T-cell immunosuppression in the host results in the reactivation of EBV and subsequent EBV-induced B-cell proliferation. A dog with CD20- and CD79-positive B-cell-related LYG was recently reported [8], but there have been no reports investigating the relevance of this disease to viruses. Further analysis of LYG cases will be required to understand the phenotype of the population of neoplastic cells and its etiology in dogs.

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