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A case of chronic lymphocytic leukemia (CLL) in a Maltese dog

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Abstract : An 11-year-old, 3.3 kg, male Maltese dog was referred to Veterinary Teaching Hospital of Konkuk University because of diarrhea and severe anemia. Abnormal physical examination findings included left submandibular lymph node enlargement, pale mucous membrane, cataract, and bloody diarrhea. Results of hematologic examination revealed a marked lymphocytosis resulting in leukocytosis and the markedly increased numbers of small, well-differentiated lymphocytes in the peripheral blood. Serum biochemical abnormalities consisted of elevated AST and ALP, hyperphosphatemia, hypoglycemia, and hypoalbuminemia. Radiographic examination showed cardiomegaly and hepatosplenomegaly. Results of urinalysis included bilirubinuria and proteinuria. Based on results of examination described above, chronic lymphocytic leukemia was diagnosed. Chemotherapy was initiated with cyclophosphamide (300 mg/m^2, IV once every 2 weeks), vincristine (0.75 mg/m^2, IV once every 2 weeks, alternating weeks with the cyclophosphamide), and plus prednisolone (50 mg/m^2, PO, SID for a week, then 20 mg/m^2, PO every other day). The response to chemotherapy was partially present. This study first demonstrates clinicopathological findings and chemotherapeutic response of chronic lymphocytic leukemia in Korea.

Key words : chronic lymphocytic leukemia, chemotherapy, dog

Introduction

Chronic lymphocytic leukemia (CLL) is a form of leukemia characterized by abnormal proliferation of small lymphocytes in bone marrow. Although morphologically normal, these lymphocytes have functional abnormalities [10]. The clinical presentations are nonspecific and can include peripheral lymphadenopathy, hepatosplenomegaly, lymphocytosis, anemia, thrombocytopenia, and increased lymphocyte proliferation in bone marrow [6].

However, some dogs and cats are asymptomatic and a diagnosis is found incidentally following routine blood work. The markedly elevated numbers of small, well differentiated lymphocytes in the blood formed the basis for the diagnosis of lymphocytic leukemia. Hematologically, a normocytic, normochromic, nonregenerative anemia usually accompanies a marked mature peripheral lymphocytosis, which may range from 100,000 to 300,000/ml or more [5].

According to a previous report [8], the use of several different drugs in combination has greatly improved remission and survival times in dogs with CLL.

The objective of this case report is to describe the clinicopathological findings, diagnosis, and the effectiveness of a combination chemotherapy in a dog with CLL.

Case Report

An 11-year-old, 3.3 kg, male Maltese dog was referred to the Veterinary Teaching Hospital of Konkuk University due to bloody and watery diarrhea, severe anemia, lethargy, and poor appetite.

Left submandibular lymph node enlargement, pale mucous membrane, and senile cataract were observed on physical examination. Profiles of an initial hematological examination revealed nonregenerative anemia ($2.99\times10^6/\mu l$; reference range, 5.5 to $8.5\times10^6/\mu l$) and marked lymphocytosis ($47.77\times10^3/\mu l$; reference range, 1.0 to $4.8\times10^3/\mu l$) resulting in leukocytosis ($72.08\times10^3/\mu l$; reference range, 6.0 to $17.0\times10^3/\mu l$). On differential counting of blood film marked lymphocytosis (98 per cent) was evident. Most of the cells in the peripheral blood were small to medium-sized

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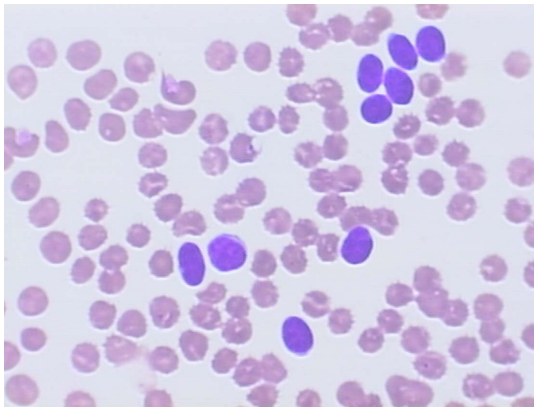

Fig. 1. Peripheral blood smear (Wright's-Giemsa stain, 1000x) of a dog with chronic lymphocytic leukemia (CLL). Morphologically mature lymphocytes characteristic of CLL are predominant and lymphocytes with normal condensed nuclear chromatin are observed.

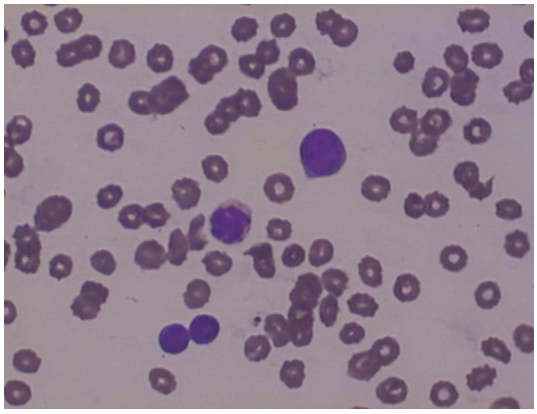

Fig. 2. Peripheral blood smear (Wright's-Giemsa stain, 1000x) of a dog with chronic lymphocytic leukemia (CLL). Number of mature lymphocytes characteristic of CLL is decreased and segmented neutrophils are observed after chemotherapy.

lymphocytes with normal morphology (Fig. 1). Serum chemistry profiles showed increased hepatic enzymes, hyperphosphatemia, and hypoalbuminemia. Results of serum protein electrophoresis exhibited hyperglobulinemia (4.9 g/d*l*), resulting from alpha-2 fraction. Radiographic examinations revealed cardiomegaly on thoracic radiographs and hepatosplenomegaly was noted on abdominal radiographs. On ultrasonographic findings, dilated hepatic vein and mild ascites were noted. Abnormalities in urinalysis included bilirubinuria and proteinuria.

Presumptive diagnosis was made as a CLL based on physical examination, clinical signs, hematological and serum chemical profiles, radiographic and ultrasonographic findings.

Chemotherapy was applied with COP (Cyclophosphamide, vincristine, prednisone) protocol; administration of cyclophosphamide (300 mg/m^2, IV once every 2 week), vincristine (0.75 mg/m^2, IV once every 2 weeks, alternating weeks with the cyclophosphamide) and plus prednisone (50 mg/m^2, PO sid for a week, then 20 mg/m^2, PO every other day).

After first chemotherapy, the number of white blood cells was decreased to normal limit ($17.40\times10^3/\mu l$; reference range, 6.0 to $17.0\times10^3/\mu l$) (Fig. 2). The patient survived 24 more days with chemotherapy. Blood transfusion (DEA 1 negative donor) was performed for the correction of severe anemia in this case as a supportive care.

Although bone marrow biopsy was essential for definitive diagnosis of CLL, it was denied from the owner of the patient. This is the limitation of this case report.

The response to chemotherapy was partially present and this case was survived more than 24 days. This study first demonstrates clinicopathological findings and chemotherapeutic response of chronic lymphocytic leukemia in South Korea.

Discussion

Lymphomas are solid tumors of neoplastic lymphocytes that develop outside the bone marrow. However, leukemia is defined as a neoplastic proliferation of hematopoietic cells originating within the bone marrow.

In the dog, as in man, CLL is disease of middle- and old-age. This patient was an old-aged dog which is consistent with a previous report [8]. Generally in CLL, on routine hematology, nonregenerative anemia is observed. In addition, lymphocytosis and bone marrow infiltration by small and mature lymphocytes confirm the diagnosis in CLL. The patient evaluated in this study showed the same hematological profiles described previously. Anemia in dog with CLL might be a poor prognostic sign, necessitating more supportive care with transfusions. In addition, anemia and thrombocytopenia, often life-threatening, can be counteracted with fresh blood transfusions. Supportive care during induction therapy in dogs with lymphocytic leukemia is essential.

In this case, fresh whole blood (DEA 1 negative donor) were administered to correct severe anemia. Five days following blood transfusion, the hemogram was changed into mild leukocytosis and elevation of packed cell volume.

Mild peripheral lymphadenopathy and hepato-splenomegaly were detected on physical examination in dogs. This is contrast to the massive peripheral lymphadenopathy commonly observed in dogs with multicentric lymphosarcoma.

Clinical findings of CLL are generally more insidious and chronic than those characteristic of acute lymphoblastic leukemia (ALL) and lymphoma, and generally less aggressive therapy and supportive measures are required. Usually ALL is poorly differentiated on the peripheral blood vessels, showing immature lymphoblast cells. In addition, lymphomas also have immature lymphocytes in peripheral blood smears. Basically, these are contrast to CLL.

Clinical signs of CLL which may include anemia, depression and hepatosplenomegaly, develop suddenly and progress rapidly. In general, the paraneoplastic syndromes of monoclonal gammopathy, monoclonal light-chain proteinuria and hyperviscosity syndrome do not appear to influence the survival time or response to therapy in dogs with CLL [3]. About 50 per cent of patients have monoclonal gammopathies. Results of serum protein electrophoresis in this patient showed elevation of alpha-2 fraction and this was similar with those described previously.

Unlike ALL, CLL can have a protracted clinical course and is usually initially responsive to chemotherapy.

Treatment is not instituted unless significant clinical signs, organomegaly or peripheral cytopenias (anemia, neutropenia and thrombocytopenia) that impact or threaten the animal's quality of life [5].

If therapy is indicated, cyclophosphamide (200-300 mg/m^2, IV once every 2 week) and vincristine (0.5-0.75 mg/m^2, IV once every 2 weeks, alternating weeks with the cyclophosphamide) are combined with prednisone (50 mg/m^2, PO sid for a week, then 20 mg/m^2, orally) [9]. Corticosteroid therapy is specific to anti-inhibiting lymphocytes and symptomatic to CLL. Corticosteroids have the advantage of being lympholytic and nontoxic to the bone marrow.

Clinical signs of patient in this study were partially responsive to chemotherapy with combination of cyclophosphamide, vincristine and prednisone. However, administration dosage of this chemotherapy should be tunned up according to the severity of the patient's hemogram.

This case indicates that CLL can be diagnosed in routine hematological examination and should be suspected one of differential diagnosises if severe lymphocytosis is noted in peripheral blood without any antigen stimulus.

Unfortunatelly, this case was severe critical status when presented to our veterinary clinic. In addition, patient's owner was declined to invasive and/or further diagnostic test due to long-term management and other tests related to this disorder in local animal hospital. Thus, further tests including flow cytometric and lymph node aspiration examination were not performed.

In conclusion, more clinical studies are needed to determine the optimal chemotherapeutic protocol and to further identify factors that may be of prognostic or therapeutic importance in CLL.

In addition, if more information related to chemotherapy protocol of CLL in dogs is available, this case can be manageable with long-term survival.

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