Large granular lymphocytic leukaemia complicated with histiocytic sarcoma in a dog

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ABSTRACT

A 10-year-old castrated male Golden retriever, weighing 36.3 kg was referred for evaluation owing to a decline in general condition. Findings from the complete blood count revealed a marked lymphocytosis (113 000/$\mu\ell$). Examination of Wright-Giemsa-stained films of peripheral blood revealed the presence of large granular lymphocytes (LGL). Seventy-two per cent (81 360/$\mu\ell$) of the lymphocytes were found to be 12–17 μm in diameter, containing nuclei with mature clumped chromatin and abundant lightly basophilic cytoplasm with a variable number of fine azurophilic granules. Based on these findings this case was diagnosed as LGL leukaemia. As a result of multiple-agent chemotherapy, the markedly elevated levels of lymphocytes gradually decreased to 7500/$\mu\ell$ on day 122 and the patient maintained a good quality of life for the following 3 months. However, on around day 237, a soft, raised, bosselated mass on the labial region was noted. The dog was diagnosed as having histiocytic sarcoma based on cytological and histological examination of the mass. Shortly after diagnosis, the dog developed sudden onset of central nervous system signs and died on day 270. A common outcome of canine LGL is the development of acute blast crisis or lymphoma. However, this case was notable for complication with histiocytic sarcoma from another origin.

Keywords: dog, histiocytic sarcoma, large granular lymphocytic leukaemia.

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INTRODUCTION

Canine large granular lymphocytic (LGL) leukaemia is a chronic lymphocytic leukaemia (CLL), characterised by a neoplastic lymphocyte population originating in NK or cytotoxic T cell proliferation clonally consists of large cells with abundant, lightly basophilic cytoplasm with azurophilic granules[6,7,12–14,16]. Primarily large-breed dogs, such as the Golden retriever, German shepherd and Siberian husky are affected and the disease tends to occur in older dogs of 8–13 years[7,13,16]. LGL leukaemia is usually a non-aggressive disease and thus may remain dormant for long periods during the illness[6,7,16].

Conversely, histiocytic sarcoma is an aggressive, commonly metastatic systemic neoplasm of atypical histiocytes originating in dendritic cells, affecting primarily the Bernese mountain dog, Rottweiler, Golden retriever and Flat-coated retriever, with multi-organ involvement possible[1–3,10]. Clinical findings commonly depend on the lesion site, respiratory abnormalities, neurological signs and anaemia. Untreated tumours have an aggressive clinical course which is invariably fatal[1–3,9–11].

In this clinical communication we present a canine case of LGL in which a good therapeutic response was achieved after immunosuppressive therapy but which subsequently became complicated with histiocytic sarcoma.

CASE HISTORY

A 10-year-old castrated male Golden retriever, weighing 36.3 kg, was referred to the Veterinary Teaching Hospital of Azabu University, Japan, for evaluation, owing to a decline in general condition that was accompanied by gradual weight loss, weakness and anorexia observed over a period of about 1 year. Although physical examination did not identify lymphadenopathy, abdominal radiographs revealed evidence of splenomegaly. The complete blood count (CBC) revealed marked leukocytosis (135 000/$\mu\ell$), including lymphocytosis (113 000/$\mu\ell$) (Fig. 1). An examination of Wright-Giemsa-stained films of peripheral blood revealed the presence of large granular lymphocytes (Fig. 2A); 72 % (81 360/$\mu\ell$) of lymphocytes were found to be 12–17 μm in diameter, compared with normal lymphocytes[5] which are 6–9 μm, and contained nuclei with mature clumped chromatin and abundant, lightly basophilic cytoplasm with a variable number of fine azurophilic granules. CBC further revealed mild anaemia but as reticulocytes were not increased, this observation was suggested to be a result of depression of haemopoiesis. Aspiration and core biopsy of bone marrow revealed mature lymphocytes containing cytoplasmic granules and clumped nuclear chromatin similar to those observed with light microscopy in the peripheral blood, accounting for about half of all nucleated cells (47.5 %). Overall, immature lymphoblasts were not found and myeloid cells and erythroid cells were observed at a low level of 30 % and 17 %, respectively. Ultrastructural examination revealed fine heterochromatin granules in the nuclear membrane, which were also present diffusely in the nuclei and seemed to be of mature shape. Elliptical granules 0.4–0.8 μm in diameter with an electron-dense core were present in the cytoplasm, a result similar to that observed by light microscopic investigation (Fig. 2B). LGL proliferative disorders of dogs can be either neoplastic or non-neoplastic[7,16]. Non-neoplastic LGL lymphocytosis can occur secondary to chronic *Ehrlichia canis* infection[4]. Although canine ehrlichiosis is not found in Japan, immunoglobulin IgG antibody titres for the agent of canine ehrlichiosis causing reactive LGL lymphocytosis were nevertheless investigated. As expected, the results were negative and ruled LGL out as a secondary disorder. This case was therefore diagnosed as LGL leukaemia classified as chronic lymphocytic leukaemia.

Despite the fact that the dog did not appear to be compromised, observed clinical signs included lethargy and weight loss. To reduce the tumour burden

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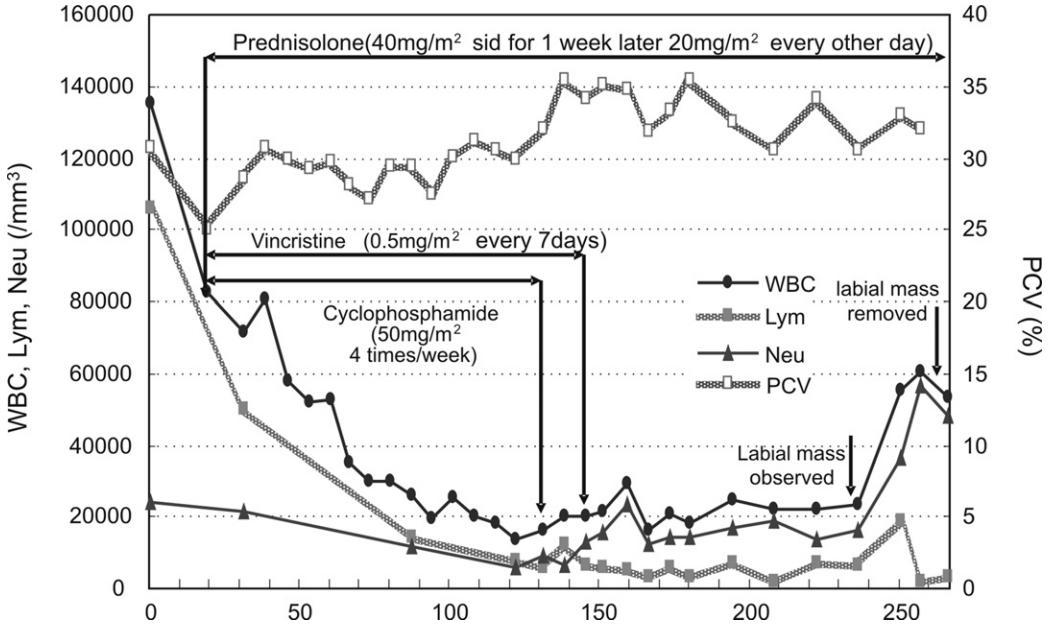

Fig. 1: **Clinical course of case. White blood cell, lymphocyte and neutrophil counts, packed cell volume and treatment employed. Lymphocytosis and anaemia gradually improved with the chemotherapy until day 122. Subsequently, a mass on the labial region was observed on around day 237 and removed on day 267.** WBC: white blood cell; Lym: lymphocytes; Neu: neutrophil; PVC: packed cell volume.

for as long as possible, multiple agent chemotherapy with cyclophosphamide (Endoxan®, Shionogi Co.) was administered at 50 mg/m^2 for 4 consecutive days followed by 3 consecutive days without treatment days for 14 weeks (Fig. 1). Vincristine (Oncovin®, Nippon Kayaku Co.) at 0.5 mg/m^2 once a week for 16 weeks and prednisolone (Prednisolone®, Sanwa Kagaku Kenkyusho Co.) at 20–40 mg/m^2 once a day to every other day were also administered. As a result of these treatments, the markedly elevated levels of lymphocytes gradually decreased to 7500/μl on day 122 and remained at this level after that; PCV values increased from day 20 to day 139 to 25 % and 36 %, respectively, and general condition remained good without tumour lysis syndrome from that point onwards.

The patient's physical condition had been good since around day 122 after discontinuing the cyclophosphamide and vincristine treatment and continuing prednisolone alone for 3 months. However, on around day 237 when PCV decreased, a soft, raised, bosselated mass on the labial region was noted. Because the mass rapidly enlarged at around 251 days, it was resected under general anaesthesia on day 267. The mass was examined cytologically and histologically. Impression smears stained with Wright-Giemsa and sections stained with haematoxylin and eosin (Fig. 3) revealed numerous histiocytes that appeared necrotic with mitotic figures, multinucleated tumour giant cells and erythrophagocytosis. Based on these findings, the dog was diagnosed as having histiocytic sarcoma. Immediately after the diagnosis was made, the dog developed sudden onset of central nervous system (CNS) signs and died on day 270. A necropsy was not performed.

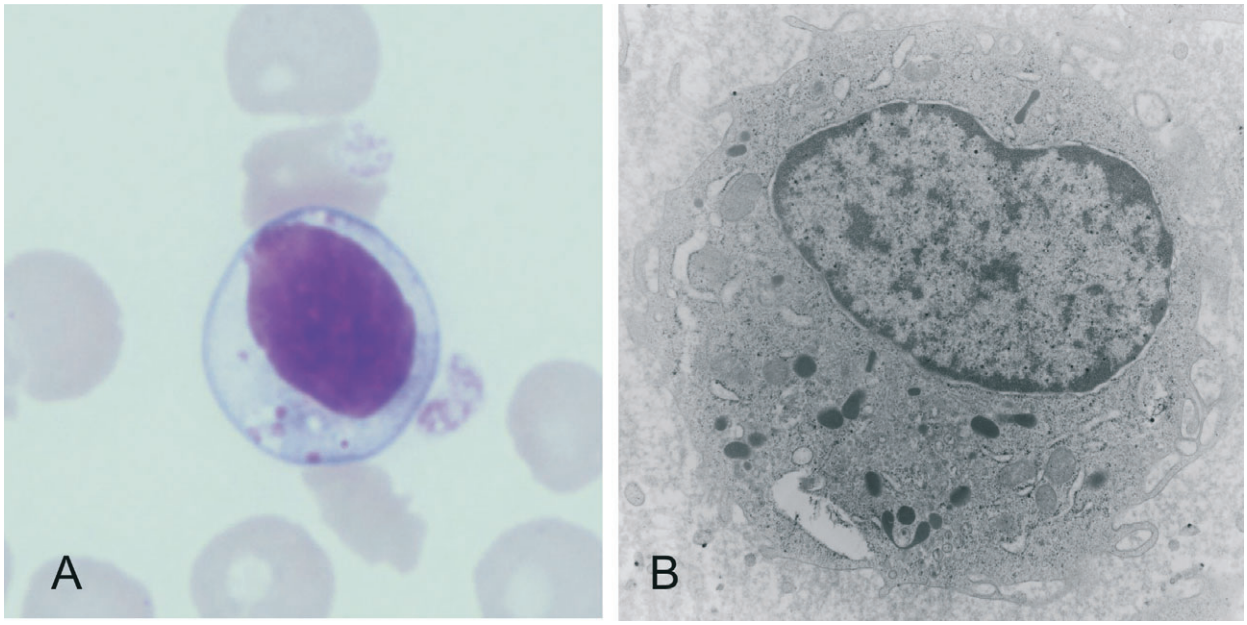

Fig. 2: **Large granular lymphocyte of peripheral blood.** A, **Photomicrograph; lymphocytes have nuclei with mature clumped chromatin and a pale cytoplasm that contains granules.** B, **Electron micrograph; fine heterochromatin granules are in the nuclear membrane and also diffusely in the nuclei, the cytoplasm has abundant volume, a rough-surfaced endoplasmic reticulum and some rounded granules with electron-dense cores.**

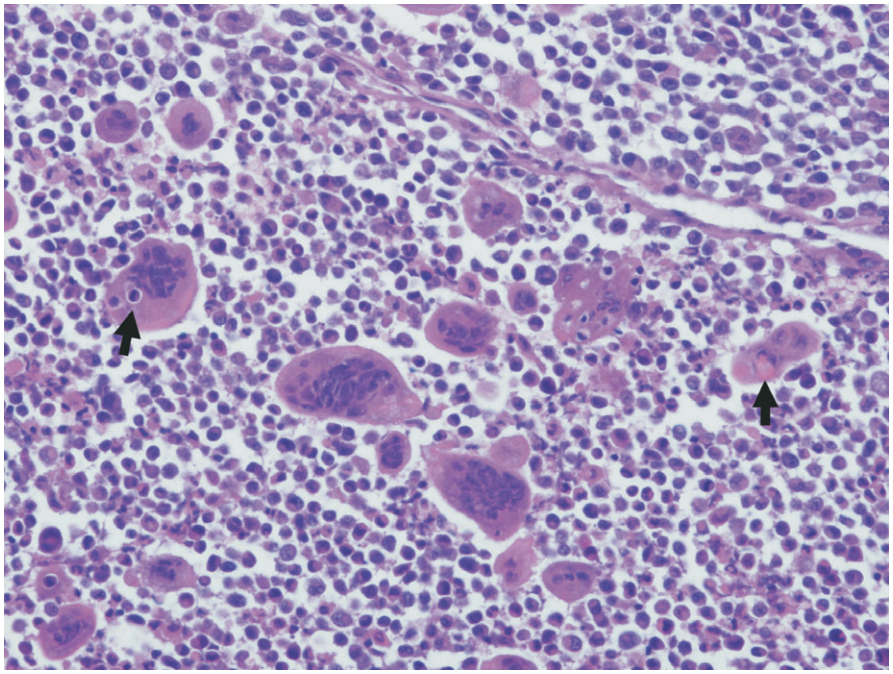

Fig. 3: **Histology of labial mass** (H&E stain)**. There are abundant multinucleated giant cells and numerous immature anisocytic histiocytes. Some giant cells contain intact red blood cells and mononuclear cells** (arrows)**. Some histocytes reveal karyomitosis.**

DISCUSSION

As immunophenotyping of peripheral lymphocytes was not carried out it was not possible to distinguish the subtype as T-LGL or NK-LGL. The case was therefore diagnosed as LGL leukaemia, classified as chronic lymphocytic leukaemia, based on the CBC, light microscopic and ultrastructural findings. Because LGL leukaemia is often indolent, treatment is not always required. As the general condition of this case gradually worsened, multi-immunosuppressive drugs were employed in a combination to which canine LGL is known to respond well. A common outcome of canine LGL is the development of acute blast crisis or lymphoma[8,15]. However, this case involved the sudden development of histiocytic sarcoma, with the possibility that the mass might have metastasised to the CNS. It was not possible to determine why 2 malignant diseases had occurred in 1 dog. This is the 1st reported case in a dog in which canine LGL leukaemia was complicated with histiocytic sarcoma from another origin.

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