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Successful management of feline CD4⁺ CD8⁺ T-cell mediastinal lymphoma with pericardial effusion

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Abstract: A 2-year-old, castrated, male Russian blue cat presented with acute dyspnoea, cyanosis, and lethargy. A thoracic radiography revealed a large cranial mediastinal mass; the computed tomography revealed caudal lobe atelectasis of the right lung with pericardial and pleural effusions. The cytodiagnostic tests revealed high-grade CD4⁺ CD8⁺ T-cell mediastinal lymphoma as clinical stage Vb; L-asparaginase-cyclophosphamide-doxorubicin-vincristine-prednisolone (L-CHOP)-based chemotherapy was initiated, following which the mass shrunk rapidly; 1 week after the initiation of chemotherapy, the appetite-related and respiratory symptoms improved dramatically, and the pleural and pericardial effusion resolved. The patient remains in complete remission three years after the initiation of the L-CHOP chemotherapy. Therefore, the accurate diagnosis and instantaneous initiation of chemotherapy may resolve life-threatening pleural and pericardial effusions in cats with high-grade aberrant T-cell mediastinal lymphoma.

Keywords: cat; flow cytometry; L-CHOP; multi-agent chemotherapy; pleural effusion

Lymphoma is one of the most common feline haematopoietic neoplasias, and the mediastinum is the third most common site of lymphoma in cats (Simon et al. 2008; Sato et al. 2014). A definitive diagnosis of lymphoma is made based on a histopathological examination of the affected lymph nodes or organs (Sapierzynski 2010). However, unlike canine lymphoma, which shows a predominance of multicentric forms, feline lymphoma shows the predominant involvement of extra-nodal regions and mediastinum (Twomey and Alleman 2005). Furthermore, owing to the generally poor condition of patients, a biopsy under anesthaesia can be difficult to perform (Sapierzynski 2010). Therefore, diagnosis and phenotyping are achieved using relatively less invasive cytodiagnostic methods, such as cytology, immunocytochemistry (ICC), and flow cytometry (Sapierzynski 2010; Aniolek et al. 2014).

Common clinical signs of feline mediastinal lymphoma are dyspnoea, anorexia, regurgitation, a cough, and fever; pleural effusion is also observed in 51% of cats with mediastinal lymphoma (Fabrizio et al. 2014). Furthermore, lymphoma, without cardiac involvement, rarely causes pericardial effusion in cats (Hall et al. 2007). Moreover, to date, no case of pericardial and pleural effusions occurring with-

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out heart failure has been reported in cats with high-grade aberrant T-cell mediastinal lymphoma. To the best of our knowledge, this is the first report describing the presentation, cytodiagnostic results, clinical course, treatment, and successful outcome of life-threatening pleural and pericardial effusions in a feline patient with a high-grade aberrant $CD4^+$ $CD8^+$ double-positive T-cell mediastinal lymphoma.

Case description

A 2-year-old, castrated, male Russian blue cat, weighing 3.3 kg, presented with acute dyspnoea, cyanosis, and lethargy. At presentation, the cat showed open-mouth breathing and was severely depressed. The physical examination revealed hyperthermia (39.5 °C), tachypnoea (90 breaths/min), and tachycardia (215 bpm) without detection of a cardiac murmur. Enlarged submandibular lymph nodes were detected. The findings of the initial laboratory tests were as follows: increased aspartate aminotransferase activity (1.48 μkat/l; reference range: 0–0.8 μkat/l), increased lactate dehydrogenase activity (31.96 μkat/l; reference range: 0–13.3 μkat/l), and mild hyperlactataemia (0.42 mmol/l; reference range: 0.07–0.28 mmol/l). The feline coronavirus antibody (Ab) test was positive with an in-house kit (Antigen Rapid FCoV Ab test kit; Bionote, Gyeonggi-do, Republic of Korea); however, the feline leukaemia virus (FeLV) antigen test (indirect fluorescent Ab assay) and feline immunodeficiency virus and FeLV Ab tests (enzyme linked immunosorbent assays) were all negative (IDEXX Laboratories Inc., Westbrook, ME, USA). The thoracic radiography revealed a large, opaque soft-tissue mass in the cranial mediastinum, which led to the collapse of all the lobes of both lungs and elevation of the trachea (Figure 1).

On the computed tomography, the mass was assumed to be a tumour derived from the cranial mediastinal lymph node. The cranial lobes of both lungs and the middle lobe of the right lung showed atelectasis with pericardial and pleural effusions, which resulted in the displacement of the heart to the right (Figure 2A,B). Furthermore, several enlarged mesenteric lymph nodes were observed in the abdominal cavity (Figure 2C), and a mass enclosing the aorta was identified between the kidneys at the level of the T13–L3 vertebrae. The dorsal margin of the mass was in contact with the hypaxial muscle, which led to the suspicion of invasion (Figure 2D). An echocardiography revealed normal cardiac function and pericardial effusion.

The pleural effusion revealed the following characteristics: it had a serosanguinous appearance with a total nucleated cell count of 238 780 cells/ml and a total protein content of 46 g/l. The results of aerobic and anaerobic bacterial culture tests were negative. Furthermore, a negative test result was obtained for the feline infectious peritonitis virus via a real-time polymerase chain reaction (PCR). The cytologic evaluation of the pleural effusion revealed medium- to large-sized lymphoid cells with a highly basophilic cytoplasm and nuclei with diameters 1.5–3 times those of the red blood cells. The cytology also showed mitotic figures,

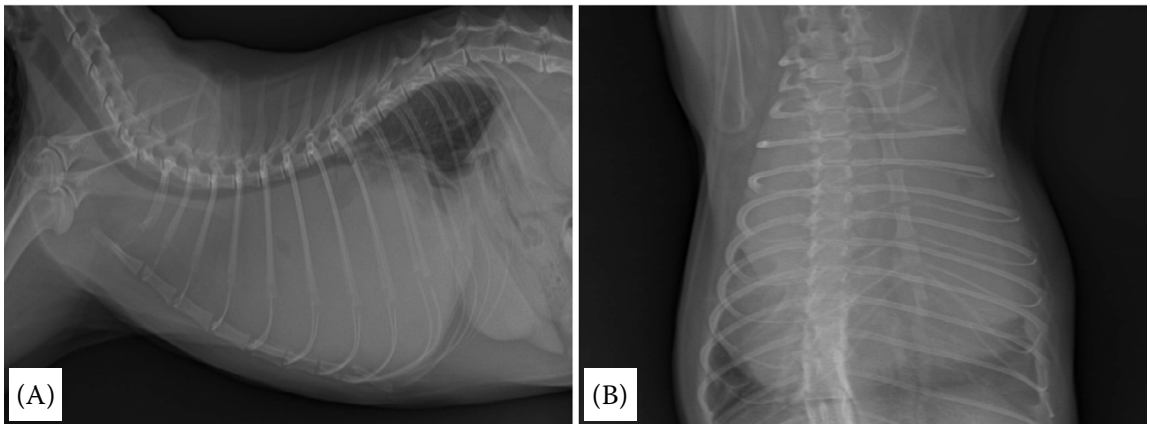

Figure 1. Thoracic radiograph of a cat with a mediastinal mass

Right lateral view (A): The entire thoracic trachea is displaced dorsally, and a huge soft tissue mass is occupying the cranial portion of the thorax. Overall, atelectasis of the lung lobes can be observed (A). Dorsoventral view (B): The cardiac silhouette is shifted to the right side, and the soft tissue mass effect occupies the right cranial and left lung field

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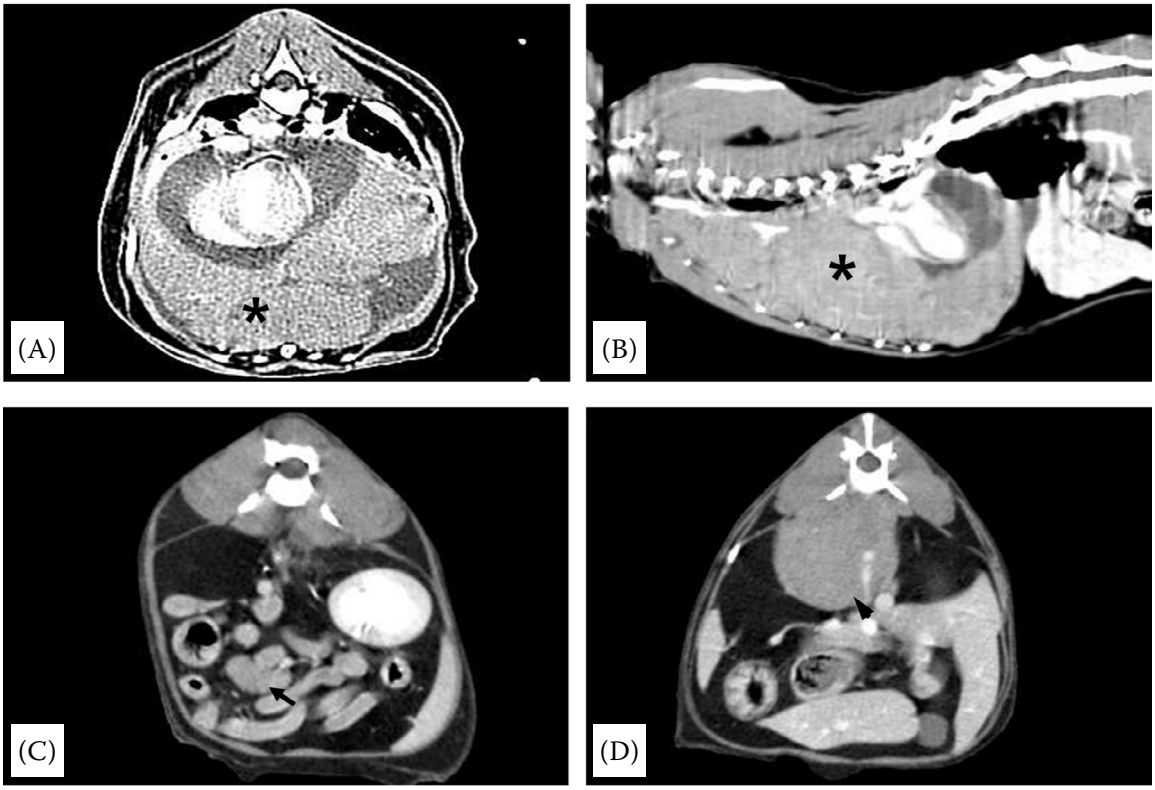

Figure 2. Computed tomography images of the cranial mediastinal and abdominal masses in a cat
Intra-thoracic mass (*) is suspected to have originated from the cranial mediastinal lymph node (A). Pericardial and pleural effusions are observed within the thoracic cavity (A). The mass can be observed to occupy a major portion of the thoracic cavity, which resulted in the collapse of all the lobes of the lungs and the dorsocaudal displacement of the heart and bilateral caudal lung lobes (B). The mesenteric lymph nodes (arrow) are enlarged (C), and a mass (arrowhead), presumed to be intra-abdominal lymph nodes, encloses the aorta (D)

consistent with malignancy (Figure 3A). Although there was no lymphocytosis in the peripheral blood, medium- to large-sized lymphocytes were observed in the peripheral blood smear (Figure 3B). A further diagnostic examination was recommended to confirm that the lymphocytes were indeed infiltrating neoplastic cells. However, the owner declined further examinations due to financial constraints.

Ultrasound-guided fine-needle aspiration biopsy (FNAB) samples of the mediastinal mass were sent to Colorado State University for cytology, ICC, and flow cytometry. Cytologically, these neoplastic cells were large lymphoid cells with a minimal amount of a deeply basophilic cytoplasm and a single round nucleus with condensed or granular chromatin. These results were similar to the cytological characteristics of the pleural effusion (Figure 3C). In addition, on the immunocytochemical testing, PAX5 and MUM1, which are usually stained in B-cells, were negative, and CD3, which is expressed in T-cells, was strongly positive (Figure 3D). Furthermore, the flow cytometry results conducted at the clinical immunology laboratory of Colorado State University revealed that most cells in the FNAB samples of the mediastinal mass were large lymphocytes that co-expressed CD4 and CD8 (Figure 4). Although this immunophenotype is usually associated with a thymoma, these cells were significantly larger and more uniform than those usually found in a thymoma.

Based on these results, the patient was diagnosed with a high-grade aberrant $CD4^+$ $CD8^+$ T-cell lymphoma of clinical-stage V (substage b), and the prognosis was considered poor. To improve the patient's quality of life, we initiated chemotherapy by following the University of Wisconsin-Madison's 25-week L-CHOP protocol (L-asparaginase-cyclophosphamide-doxorubicin-vincristine-prednisolone) for malignant lymphoma. According to the L-CHOP protocol, L-asparaginase (Leunase Injection; Nipro Pharma Corporation, Akita, Japan) [400 IU/kg, once subcutaneously (s.c.)] and pred-

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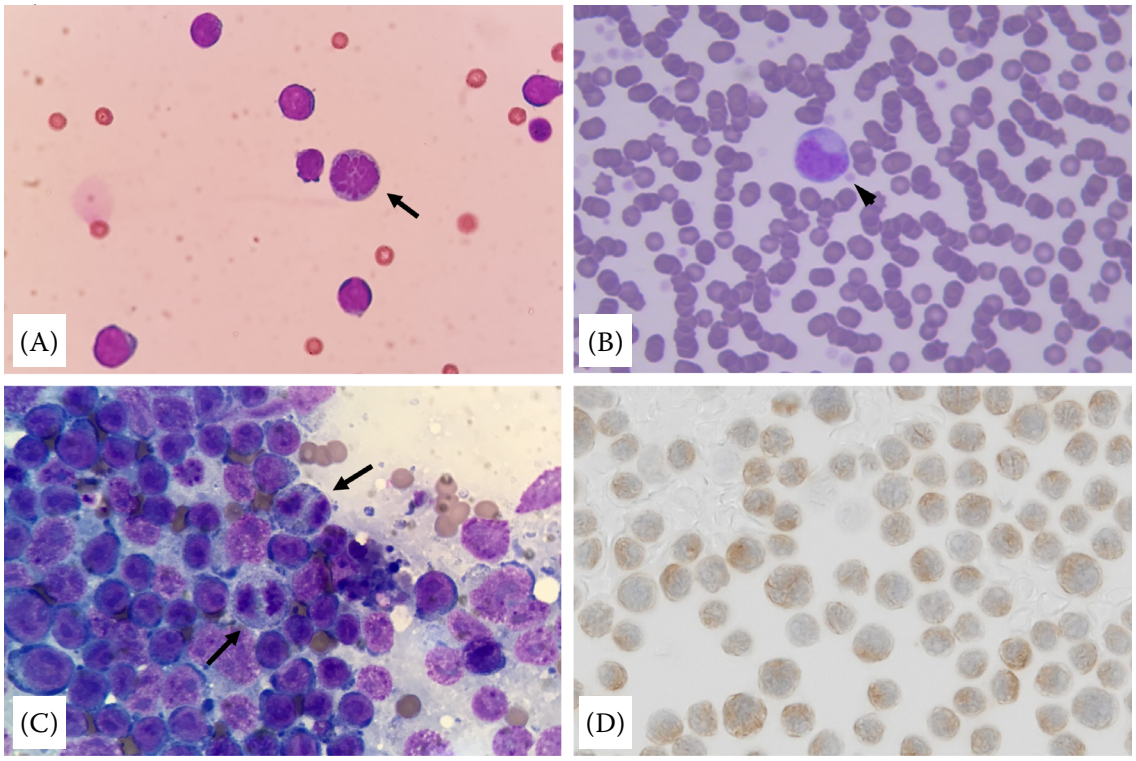

Figure 3. Cytologic images of a pleural effusion, peripheral blood smear, and fine-needle aspiration biopsy (FNAB) samples collected from the mediastinal mass (magnification, × 60)

Diff-Quik staining (A–C) and immunocytochemical staining (D) were performed. In the pleural effusion, small- to large-sized lymphocytes that have one or more nucleoli and a small quantity of cytoplasm and malignant characteristics, such as mitotic figures (arrow), can be observed (A). Medium- to large-sized lymphocytes (arrowhead) can also be observed in the peripheral blood smear (B). Large neoplastic lymphocytes with a diameter 2–3 times that of a red blood cell and predominant nucleoli can be observed in the FNAB samples of the mediastinal mass (C). There are several mitotic figures (arrow) similar to those in the pleural effusion (C). Immunocytochemical staining of the FNAB samples of the mediastinal mass is strongly positive for CD3, which is stained in T-cells (D)

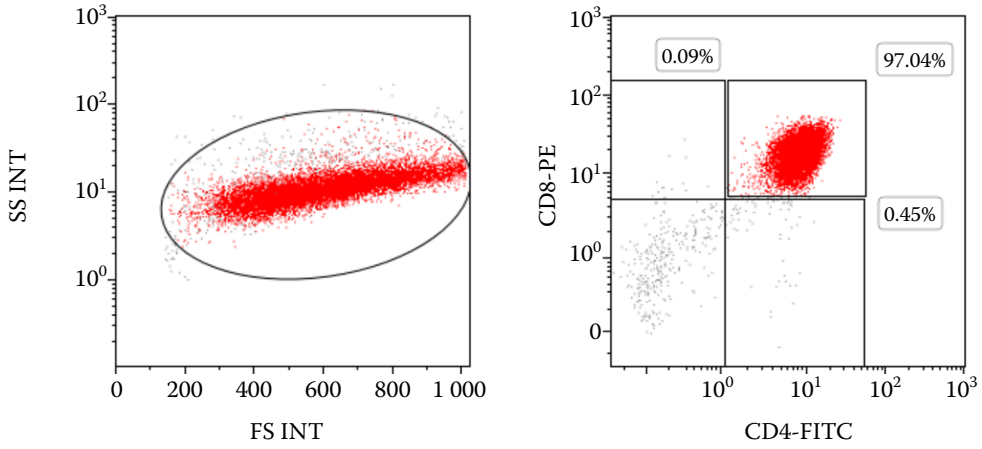

Figure 4. Flow cytometry of the mediastinal mass

The cells in the left panel show the size (FS INT) and granularity (SS INT) after gating out the dead cells using staining with propidium iodide and gating on the leukocytes using anti-CD18. The mediastinal mass from the patient demonstrates a uniform population of large cells. The cells in the right panel are stained with anti-feline CD4-fluorescein isothiocyanate and anti-feline CD8-phycoerythrin and gated on the lymphocyte cells based on the scatter properties. These scattergrams reveal $CD4^+$ $CD8^+$ lymphocytosis

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nisolone (PDS) (Solondo Tab.; Yuhan Corporation, Seoul, Republic of Korea) [2 mg/kg per os (p.o.), once daily (s.i.d.)] were administered on the first day of hospitalisation. Oxygen treatment was also initiated for the severe dyspnoea. Approximately 9 h after the administration of L-asparaginase, the respiration gradually improved; however, side effects, such as gastrointestinal signs with severe retching, were observed. Therefore, ondansetron (Zofran Injection; Aspen Bad Oldesloe GmbH, Bad Oldesloe, Germany) [0.4 mg/kg intravenous (i.v.) injection every 6 h] and maropitant (Cerenia®; Fareva Amboise, Poce Sur Cisse, France) (1 mg/kg s.c. injection s.i.d.) were added to the treatment. On the second day, a vincristine (Pfizer Vincristine Sulfate Injection; Hospira Australia Pte Ltd., Melbourne, Australia) (0.7 mg/m^2) i.v. injection was administered along with oral PDS. After symptomatic treatment using the anti-emetics, the gastrointestinal adverse effects of the chemotherapy were gradually alleviated. Moreover, the patient's overall condition and appetite improved.

Two days after the initiation of chemotherapy, the thoracic radiography revealed significant shrinkage of the mediastinal mass (Figure 5A–D), and no vomiting was observed. The patient's general condition improved dramatically, and was discharged on the fourth day of hospitalisation.

At visit for the second cycle of chemotherapy, the patient showed normal breathing. Oral cyclophosphamide (Alkyloxan Tab.; Ildong Pharmaceutical Co. Ltd., Anseong, Republic of Korea) (250 mg/m^2) and PDS (1.5 mg/kg p.o. s.i.d.) were administered. The patient tolerated the chemotherapy well with no significant toxicity; complete clinical remission was noted on the thoracic radiography seven weeks after the initiation of the chemotherapy (Figure 5E,F).

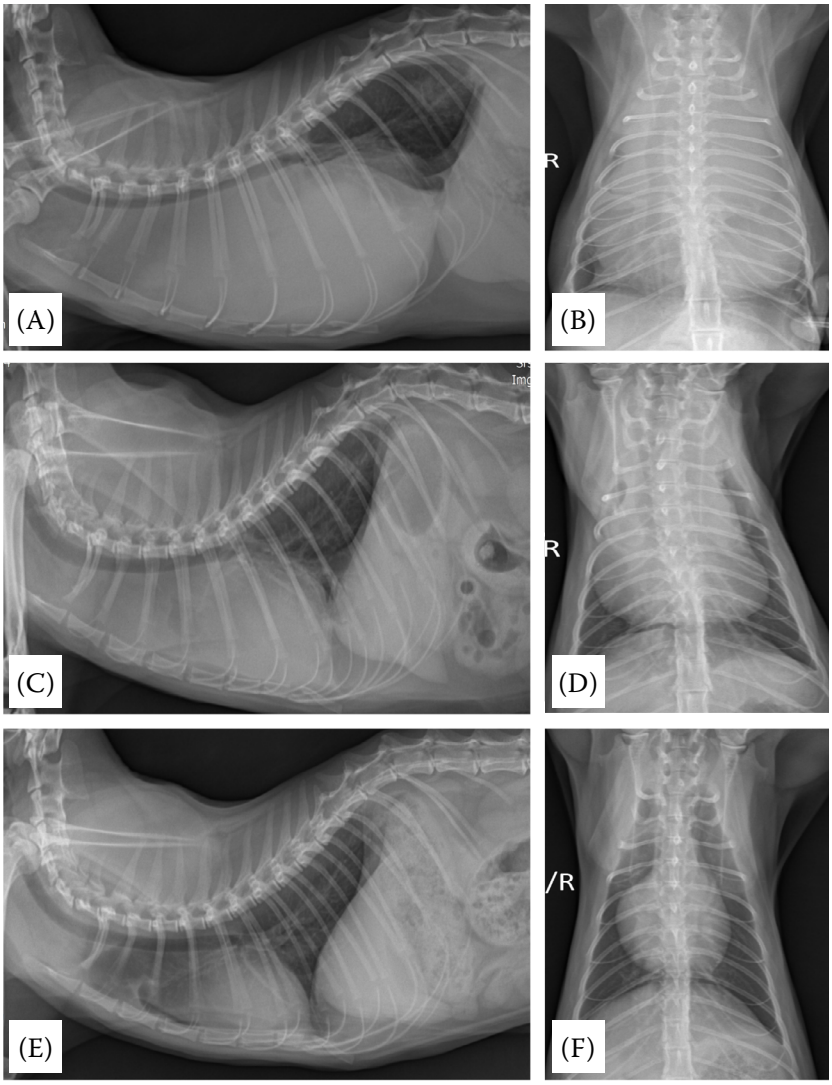

Figure 5. Thoracic radiographic outcomes after chemotherapy of the mediastinal lymphoma in a cat

Thoracic radiographs of the mediastinal lymphoma in a cat before (A, B) and after (C, D, E, F) L-asparaginase-cyclophosphamide-doxorubicin-vincristine-prednisolone (L-CHOP) chemotherapy. Images show a decrease in the huge intra-thoracic mass effect and improvement in the collapsed lungs two days after the initiation of chemotherapy (C, D). The carina can be identified in a more normal position one week after the initiation of the treatment than at the previous examinations. Improvement in the large soft-tissue opacity in the cranioventral thorax and the collapse of the lung lobes compared with previous images can be observed (E, F)

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The stabilised patient was transferred to a local animal hospital owing to the owner's financial constraints; however, chemotherapy was continued until completion. Almost three years later, through a follow-up call, we confirmed that the patient had a good quality of life with complete remission and no recurrence.

DISCUSSION AND CONCLUSIONS

Lymphoma is a neoplasm of lymphocytic origin that can occur in lymphoid or non-lymphoid tissues (Shih et al. 2014). Feline lymphoma can be classified depending on the anatomical location and the histological, cytological, and immunophenotypic criteria (Gabor et al. 1998; Gabor et al. 1999). It can occur at various anatomical locations and is classified according to the distribution (Gabor et al. 1998). The most common form of feline lymphoma shows alimentary involvement, followed by mixed, mediastinal, multicentric, and atypical involvement (Gabor et al. 1998). According to a study that focused on the anatomic features of feline lymphosarcoma, 29 of 118 cats with lymphosarcoma (25%) showed mediastinal involvement (Gabor et al. 1998). Nine of them had tumours in the mediastinum alone, while the other 20 had tumours in the mediastinum as well as other tissues (Gabor et al. 1998). Multicentric, alimentary, and extra-nodal forms of lymphoma are associated with a relatively high average age (≥ 8 years at diagnosis), whereas mediastinal lymphoma occurs very frequently in young cats, aged < 2 years, especially pure-breed Siamese cats (Court et al. 1997). Unlike alimentary lymphoma, which causes gastrointestinal signs, such as vomiting, mediastinal lymphoma is usually accompanied by respiratory distress and depression (Court et al. 1997). In the case of mediastinal lymphoma, the patient may die due to secondary hypoxia, which is caused by the compression of the lung by the tumour mass, rather than due to the tumour itself. Dyspnoea is exacerbated by the accompanying pleural effusion (Shih et al. 2014). In the present case, pleural and pericardial effusions occurred in the mediastinum along with abdominal lymphoma, although the cardiac function was normal. In addition, the compression of the lung from the mass caused severe respiratory distress, which could have led to death. Therefore, it was a life-threatening condition.

A definitive diagnosis of lymphoma can be made based on the findings of the histopathologic and immunohistochemical examinations (Twomey and Alleman 2005). A cytologic examination of the affected tissue is a highly effective and less invasive method for diagnosis, especially in canine patients with multicentric lymphomas. However, a cytologic examination alone is not highly sensitive and specific (Aniolek et al. 2014). Therefore, a combination of this method and additional methods, including ICC, immunophenotyping by flow cytometry, and clonality assessment by PCR for antigen receptor rearrangements, is used for diagnosing lymphoma and to provide prognostic information (Twomey and Alleman 2005; Aniolek et al. 2014). Furthermore, it is crucial to distinguish the thymic involvement caused by mediastinal lymphoma from genuine thymoma (Twomey and Alleman 2005). Flow cytometry is a very useful technique for distinguishing between thymoma and lymphoma (Lana et al. 2006). The flow cytometry results of a normal feline thymus show thymocytes that express both CD4 and CD8, or CD4 only, or CD8 only (Tompkins et al. 1990). In addition, in one case report related to feline thymoma, the flow cytometry results demonstrated that the majority of the cells were co-expressing CD4 and CD8, and that additional cells were only CD4 or CD8 positive, consistent with normal T-cell development within a neoplastic thymus (Lara-Garcia et al. 2008). In the case of dogs, if the flow cytometry is performed on a mediastinal mass and if the contribution of $CD4^+$ $CD8^+$ double-positive T-cells is more than 10%, it is highly suggestive of thymoma (Lana et al. 2006). However, in one study that analysed the immunophenotypes of feline mediastinal masses using flow cytometry, eight of the 12 lymphoma cases (67%) examined were of $CD4^+$ and $CD8^+$ T-cell phenotype (Bernardi et al. 2020). Moreover, all the double-positive cases showed a dominant population of small- to medium-sized lymphoid cells (Bernardi et al. 2020). Furthermore, in a feline patient with a mediastinal mass, FNAB samples showed small- to medium-sized double-positive lymphocytosis; conversely, in a canine patient, a definitive diagnosis was made by several diagnostic methods, including flow cytometry and PCR for Antigen Receptor Rearrangements (PARR) (Bernardi et al. 2020). However, when the mediastinal mass is composed of large-sized $CD4^+$ CD8 lymphocytes, mediastinal lymphoma can be con-

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firmed through flow cytometry, such as in dogs (Bernardi et al. 2020). In the present case, most cells in the FNAB samples from the mediastinal mass were large lymphocytes that co-expressed CD4 and CD8, which was different from the result reported in Bernardi et al. (2020). Although the composition of these cells is very unusual, the cat was diagnosed with a high-grade aberrant $CD4^+$ and $CD8^+$ T-cell lymphoma through the cytology, ICC, PARR, and flow cytometry. Moreover, it revealed a very aggressive form of lymphoma in which multiple masses were observed, not only in the thoracic cavity, but also in the abdominal cavity.

Several chemotherapeutic strategies are used for the treatment of feline lymphoma. Multi- or single-agent chemotherapy are considered the most useful treatments for lymphoma (Kristal et al. 2001; Collette et al. 2016). In general, single-agent chemotherapy protocols involving doxorubicin or chlorambucil, or multi-drug chemotherapy protocols, such as L-CHOP and COP (cyclophosphamide-vincristine-prednisolone), are used (Kristal et al. 2001; Stein et al. 2010; Waite et al. 2013). Multi-agent chemotherapy is especially very effective, and the treatment response rate is high (Fabrizio et al. 2014). In a mediastinal lymphoma, the overall response rate of the COP protocol is 95.5% and that of the Wisconsin-Madison (MW) protocol is 91.7% (Fabrizio et al. 2014). Furthermore, the complete response rate of COP is 61.5% and that of MW protocol is 66.7% (Fabrizio et al. 2014). However, previous studies showed that high-grade or T-cell lymphomas led to shorter survival times than low-grade or B-cell lymphomas (Gabor et al. 1999; Sato et al. 2014). Interestingly, one study found that when chemotherapy was used to treat feline lymphomas, young cats with T-cell lymphoma tended to survive significantly longer than those with B-cell lymphoma (Malik et al. 2001). In addition, for the multi-drug chemotherapy protocol of L-CHOP, the average period from the onset of chemotherapy to the confirmation of remission was reported to be approximately eight days (range: 1–113 days), which indicated a relatively rapid response (Limmer et al. 2016). Moreover, another case report showed that a patient with an extra-nodal lymphoma responded to treatment three days after the initiation of the L-CHOP chemotherapy and eventually achieved complete remission (Zoia et al. 2004).

To conclude, the present report described the case of a cat with an aberrant $CD4^+$ $CD8^+$ double-positive T-cell mediastinal lymphoma in which a multi-drug chemotherapy protocol led to the rapid reduction in the tumour size without any surgical intervention and, consequently, a marked improvement in the clinical signs. This outcome shows that the use of chemotherapy, especially multi-agent chemotherapy, may improve the treatment of a mediastinal lymphoma as well as the quality of life of the patient. The cat, in this case, was alive with a very good quality of life three years after the initiation of chemotherapy. Additionally, we suggest that a large-scale study is needed in the future to identify the relationship between the initial responsiveness to chemotherapy and the mean survival time.

Conflict of interest

The authors declare no conflict of interest.

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