CASE REPORT

Paraneoplastic T cell lymphocytosis associated with a thymoma in a dog

A four-year-old male neutered Australian shepherd dog was diagnosed with a thymoma and concurrent mature T cell lymphocytosis. The lymphocytosis consisted of a mixed population of T cells expressing either CD4 or CD8 or neither marker, and the result of polymerase chain reaction for antigen receptor rearrangement was negative. The peripheral lymphocytosis resolved within 24 hours following thoracotomy and thymectomy. Similar cases have been reported in man, but the aetiology of the increased circulating lymphocytes remains unclear. Although peripheral lymphocytosis is an uncommon paraneoplastic syndrome associated with thymomas, thymoma should be considered as a differential when the increased lymphocytes consist of a mixed population of T cells.

INTRODUCTION

In humans, peripheral T cell lymphocytosis is a rare non-neoplastic condition associated with thymomas. Thymoma-associated lymphocytosis has not been well described in dogs, and myasthenia gravis, megaesophagus and polymyositis are more commonly reported paraneoplastic syndromes (Aronsohn 1985). An increase in T cell lymphocyte count in peripheral blood should raise the index of suspicion for either lymphoproliferative disease (T cell lymphocytic leukaemia) or paraneoplastic thymic disease resulting in an increased production of T cells and subsequent release into the systemic circulation (Atwater and others 1994). A case of an invasive thymoma in a dog with persistent T cell lymphocytosis that resolved following thymectomy is described here.

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evaluation showed a decreased myeloid:erythroid ratio at 0·6:1. Mild erythroid hyperplasia was deemed more likely than a myeloid hypoplasia, as the erythroid series was complete with orderly maturation, mild left-shifting and a normal amount of polychromasia. There was also an increase in the lymphoid component at 20%, comprising small, well-differentiated lymphocytes, further indicating the presence of a mild erythroid hyperplasia. The erythroid hyperplasia was considered incident, whereas the high normal proportion of lymphocytes was attributed to possible chronic lymphocytic leukaemia or a lymphoid nodule.

Thoracic radiographs were performed as preoperative staging and to rule out thoracic disease before lipoma removal. A large cranial mediastinal mass was identified, and ultrasound-guided tissue aspiration of the mass was performed. A highly cellular, mixed lymphoid population composed predominantly of small, well-differentiated lymphocytes with occasional intermediate and large lymphocytes was seen. Occasional thymic epithelial cells exhibiting mild anisocytosis and anisokaryosis were identified individually and in moderately cellular sheets (Fig 1). Computed tomography was performed which showed the mass encircling the heart and extending along the right and left hemithorax, further caudally on the left than on the right. Atelectasis of the compressed left lung was also noted (Fig 2). A median sternotomy was performed to enable thymectomy and samples sent for histopathological analysis (Figs 3 and 4, respectively).

Peripheral blood and excised thymic tissue were resubmitted 24 hours after surgery for flow cytometry. Evaluation of blood showed a mild elevation in CD8+ cells at 1348 cells per µl with normal overall distribution of the remaining T cell phenotypes. Flow cytometry of thymic tissue showed 50% of the population of cells co-expressing CD4+ and CD8+ consistent with a thymoma confirming the histopathological diagnosis (Aronsohn 1985, Lana and others 2006). Plots comparing the flow cytometry of the abnormal, circulating lymphoid population at presentation and the thymoma lymphoid populations were constructed for phenotypic comparison (Fig 5).

Total lymphocyte counts obtained at two weeks and one day before surgery were increased at 6190 cells per µl and 7580 cells per µl, respectively, but were within reference range 24 hours postoperatively at 3240 cells per µl. Lymphocyte count had decreased to 1900 cells per µl six weeks after surgical removal of the thymoma. There was no evidence of a mediastinal mass or pleural effusion on repeat tho-

**FIG 1.** Photomicrograph of an ultrasound-guided fine needle aspirate taken from the mediastinal mass. A highly cellular, mixed lymphoid population composed predominantly of small, well-differentiated lymphocytes with occasional intermediate and large lymphocytes is seen. Occasional thymic epithelial cells exhibiting mild anisocytosis and anisokaryosis are identified individually and in moderately cellular sheets (Wright-Giemsa x50)

**FIG 2.** Dorsal computed tomogram of the thorax illustrating a very large soft tissue mass occupying the cranial and mid-right hemithorax and the majority of the left to the level of the diaphragm. The mass surrounds the heart cranially and laterally, and atelectasis of the left caudal and caudal subsegments of the left cranial lung lobe is evident
canine thymoma with paraneoplastic lymphocytosis

Racic radiographs at the six-week recheck appointment, and plans were made to remove the lipoma after two weeks.

**DISCUSSION**

Peripheral T cell lymphocytosis is rarely seen with thymomas in either human beings or dogs. Of 23 dogs with thymoma in one retrospective study, concurrent conditions described included non-thymic neoplasms, myasthenia gravis, hypercalcemia and third-degree atrioventricular block, but lymphocytosis was not reported (Atwater and others 1994). Bellah and others (1983) described 22 dogs with similar clinical findings including additional cases with myositis and cranial vena cava syndrome but no lymphocytosis. Increased lymphocyte counts have been reported in one cat and in two of nine canine thymoma cases, but the composition of the circulating lymphocytes was not described (Avery and Avery 2007).

Increased peripheral T cell numbers are seen in human patients with T cell chronic lymphocytic leukaemia, Sézary syndrome, idiopathic benign lymphocytosis, T cell mediastinal lymphoma and rarely in conjunction with malignant thymoma (Scha-chor and others 1988). Although a few cases have been reported with lymphoblastic monoclonal populations of cells associated with locally invasive thymomas, most thymoma-related cases in human beings are mature, well-differentiated polyclonal T cell populations with peripheral counts declining following removal of the neoplasm (De Jong and others 1997). Our patient showed the same clinical progression, with the lymphocytosis resolving immediately post thymectomy, with no signs of relapse at follow-up.

In most cases of lymphocytosis associated with thymomas, there is an expansion of both CD4 and CD8 T cells (Barton 1997). One patient was reported in the human literature to have a population of cells similar to those described here – T cells expressing the pan T cell markers CD3 and CD5 but not the differentiation markers CD4 or CD8 (Lishner and others 1994). The presence of lymphocytes with predominantly CD3+ and CD5+ universal T cell markers in our patient’s peripheral blood before...
thymectomy suggests that the lymphocytes were released before expression of the CD4/CD8 receptor as seen in the human being by Lishner and others (1994). Alternatively, these cells may have been mature γδ T cells, which might be predicted to have a similar phenotype, although these cells have not been well described in the dog. Since this case was presented, the Clinical Immunology Service at Colorado State University has received two additional cases of canine thymoma. Each dog had a mild increase in circulating lymphocytes with a similar distribution as in this index case: CD4+ T cells (2406 and 4157 cells/μl), CD8+ T cells (601 and 1802 cells/μl) and CD5+/CD4−/CD8− T cells (1203 and 1237 cells/μl).

The origin of the increased T cells in the peripheral blood is unknown and several theories have been proposed. Lymphocytosis may result from “spillover” of the increased thymic lymphocyte population into the periphery produced by the hyperactive thymic epithelium. These lymphocyte populations are most often CD4+ or CD8+ single-positive T cells, but in one human patient, double-positive T cells, immature cortical cells that are usually inactive and indicate abnormal lymphocyte maturation and release, were reported (Tamaoki and others 1997). As rare recurrences of lymphocytosis have been seen in some patients following removal of the neoplasm, Barton (1997) disagreed with this spillover theory and offered a combination of bone marrow dysfunction and disturbances in the endothelium–lymphocyte interaction during lymphocyte migration. Abnormal function of thymic hormones leading to abnormal thymic cell release has also been proposed, but it is difficult to attribute this as the sole mechanism. A higher incidence of lymphocytosis would be expected with thymomas and the increased cell counts would be expected during the lifespan of the tumour, whereas in many cases, the elevations are seen sporadically (Smith and others 1994).

Debate over a malignant versus benign origin of the peripheral population of T cells leads most authors to agree with the latter due to lack of bone marrow involvement in most cases and resolution of the increased levels of T cells with a normal phenotypic distribution following removal of the neoplasm (Doll and others 1991). Although this case was initially diagnosed as a possible lymphoproliferative disease due to the aberrant phenotype of a subset of circulating T cells, the polyclonal nature and immediate resolution post thymectomy makes a benign explanation more likely.

Persistent lymphocytosis in adult dogs is commonly a result of a clonal lymphoproliferative disease such as chronic lymphocytic leukaemia. Less commonly, polyclonal lymphocyte expansions due to tick-borne diseases such as Ehrlichia canis or Addison’s disease are reported (Avery and Avery 2007). Although an increased peripheral lymphocyte count is not a common finding among patients with thymomas, it should be considered differential when a peripheral lymphocytosis is identified. Increased levels of hormones such as thymosin α1 have been detected in the thymic epithelial cells of malignant thymomas in human beings (Medeiros and others 1993). Future studies might aim to determine the role of these hormones in our canine patients, to determine whether paraneoplastic lymphocytosis affects prognosis or to determine the origin of the cells, which may predict response to therapy and help monitor disease progression.

Documenting the frequency of occurrence of this sporadic paraneoplastic phenomenon may also be helpful.

**Conflict of interest**
None of the authors of this article has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

**References**


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**FIG 5. Dot plots of peripheral blood taken on the day of surgery (left) and the mediastinal mass (right), stained with anti-CD8–flourescein isothiocyanate and anti-CD4–phycoerythrin and gated on the lymphocyte population based on size and scatter properties. Quadrants were set using isotype controls. Dead cells were excluded using propidium iodide staining.**