CASE REPORTS

Hypereosinophilic paraneoplastic syndrome in a cat with intestinal T cell lymphosarcoma

A 10-year-old, neutered female, domestic shorthair cat was presented with a recent history of weight loss, polydipsia, diarrhoea and vomiting. On physical examination, intestinal thickening and mesenteric lymph node enlargement were apparent. Clinical investigations revealed peripheral blood eosinophilia, eosinophilic abdominal effusion and eosinophilic mesenteric lymphadenitis. There was a temporary response to treatment with glucocorticoids but signs progressed and the cat was euthanased. On histology, there was eosinophilic infiltration and fibroplasia of intestine and mesenteric lymph nodes. Large aggregates of neoplastic round cells in the intestine and lymph nodes were identified as T lymphocytes using immunohistochemistry. A diagnosis of intestinal T cell lymphosarcoma was made. This case demonstrates that hypereosinophilic paraneoplastic syndrome may occur in cats with lymphosarcoma. Eosinophil chemotaxis may be a response to the production of interleukin-5 by neoplastic lymphocytes.

V. R. BARRS, J. A. BEATTY, I. A. MCCANDLISH* AND A. KIPAR†

Journal of Small Animal Practice (2002) **43**, 401–405

Feline Referral Centre, 496 Hornsey Road, London N19 4EF

*Idexx Laboratories, PO Box 4, Wetherby, West Yorkshire LS22 4ZR

†Institut für Veterinär-Pathologie, Justus-Liebig-Universität Giessen, Frankfurter Strasse 96, 35392 Giessen, Germany

J. A. Beatty's current address is Veterinary Specialist Centre, 14-20 Delhi Road, North Ryde, New South Wales 2113, Australia

V. R. Barrs's current address is North Shore Veterinary Specialist Centre, 64 Atchison Street, Crows Nest, New South Wales 2065, Australia

A. Kipar's current address is Department of Veterinary Pathology, Faculty of Veterinary Science, University of Liverpool, Crown Street, Liverpool L69 7ZJ

INTRODUCTION

Peripheral blood eosinophilia is a common finding in cats, occurring in association with immune-mediated disorders, endo- and ectoparasitism, infectious diseases, neoplasia and various other diseases (Table 1). Hypereosinophilic syndromes (HESs), in contrast, are uncommon in cats and are characterised by peripheral eosinophilia, tissue eosinophilia and associated organ dysfunction. Feline HESs can be classified as idiopathic (Hendrick 1981, McEwen and others1985), neoplastic (Hendrick 1981, Huibregtse and Turner 1994) or paraneoplastic (Bortnowski and Rosenthal 1992, Peaston and Griffey 1994, Howl and Petersen 1995). Idiopathic hypereosinophilic syndrome (IHES) has been described in detail (Hendrick 1981, McEwen and others 1985, Scott and others 1985, Saxon and others 1991, Muir and others 1993, Plotnick 1994, Wilson and others 1996). Paraneoplastic HES is considered to be a marker for systemic or intestinal mast cell neoplasia (Andrews 1987, Bortnowski and Rosenthal 1992, Peaston and Griffey 1994, Howl and Petersen 1995). However, while peripheral eosinophilia has been documented in cats with lymphosarcoma (Prasse and others 1987, Center and others 1990), paraneoplastic HES secondary to feline lymphosarcoma has not been reported.

This report documents hypereosinophilic paraneoplastic syndrome in a cat with intestinal T cell lymphosarcoma and illustrates that lymphosarcoma should be considered as an important differential diagnosis for HES. In humans, HES secondary to T cell lymphosarcoma is common and the mechanism of eosinophil recruitment is thought to be the elaboration of interleukin-5 (IL-5) from neoplastic lymphocytes (Samoszuk and others 1993).

CASE HISTORY

Clinical findings

A 10-year-old, neutered female, domestic shorthair cat presented with a two-month history of polydipsia and weight loss. Abnormal findings on physical examination were thickened intestines and enlarged mesenteric lymph nodes. On serum biochemistry and urinalysis a mild renal azotaemia was detected (urea 13·4 mmol/litre, reference range 5·7 to 12·8 mmol/litre; creatinine 185 µmol/litre, reference range 71 to 212 µmol/litre; urine specific gravity 1·030). On haematology, eosinophilia was detected($2{\cdot}38 \times 10^9$/litre, reference range 0·05 to $0{\cdot}7 \times 10^9$/litre) with eosinophils comprising 17 per cent of the total white cell count. Serological screening for feline leukaemia virus (FeLV) and feline immunodeficiency virus (FIV) was negative (Witness; Mérial).

Over the following three weeks the cat developed small bowel diarrhoea and vomiting and its bodyweight decreased from 3·2 to 2·9 kg. Diff Quik (Dade Behring, Switzerland) stained cytological preparations of percutaneous fine-needle aspirates from the enlarged mesenteric lymph nodes showed numerous mature eosinophils.

Table 1. Causes of peripheral blood eosinophilia in cats

Immune-mediated/allergic disorders
Flea-allergy dermatitis
Feline asthma
Eosinophilic granuloma complex
Feline atopy
Pemphigus foliaceus
Parasites
Intestinal endoparasitism
Lungworm
Dirofilariasis
Cuterebriasis
Ectoparasitism
Infections
Viral upper respiratory disease
Feline panleukopenia
Feline infectious peritonitis
Toxoplasmosis
Suppurative processes
Neoplasia
Systemic mast cell neoplasia
Intestinal mast cell neoplasia
Cutaneous mast cell neoplasia
Lymphosarcoma
Myeloproliferative disease
Solid tumours
Carcinomas (transitional cell, squamous cell)
Adenocarcinomas (salivary, sweat gland)
Non-haematopoietic sarcomas
Idiopathic and miscellaneous
Hypereosinophilic syndrome
Eosinophilic enteritis
Hyperthyroidism
Lower urinary tract disease
Cardiac disease
Renal failure
Pneumothorax
Soft tissue trauma

From Center and others (1990), Sellon and others (1992) and Fossum and others (1993)

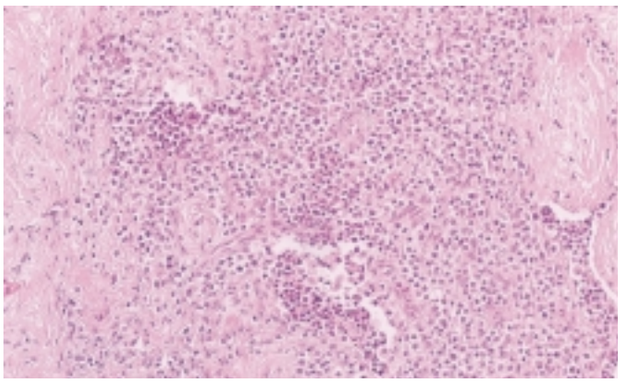

FIG 1. Mesenteric lymph node. There is a massive infiltrate of eosinophils and large round lymphoid cells. The cellular infiltrate is associated with severe reactive fibroplasia. Haematoxylin and eosin (H&E) ×40

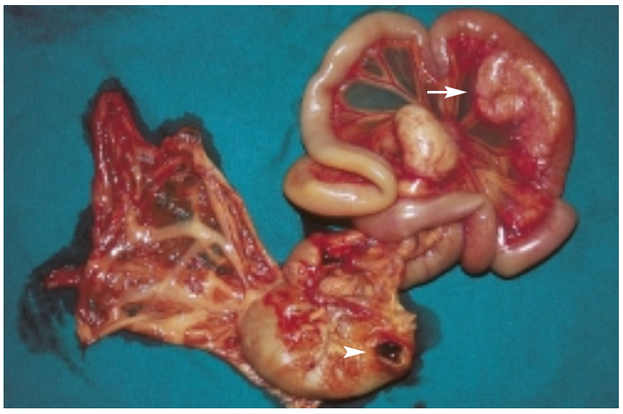

FIG 2. The alimentary tract at necropsy. There is mesenteric lymph node enlargement, thickening of the small intestine and a perforated gastric ulcer (arrowhead). A large plaque-like mass extends from the mesenteric border of the small intestine into the mesentery (arrow)

At exploratory laparotomy there was 280 ml of pale yellow fluid in the abdomen. The small intestinal wall was diffusely thickened and Peyer's patches were prominent. Several firm, pale, plaque-like masses, 2 to 4 cm long, were located in the mesentery adjacent to the intestinal wall. There were numerous similar, but smaller, plaques (3 to 5 mm diameter) in the omentum, liver serosa and parietal peritoneum. Mesenteric lymph nodes were enlarged (up to $5 \times 2 \times 1$ cm). The spleen and pancreas appeared normal. Abdominal fluid was collected for cytology and microbiology. Biopsies of mesenteric lymph nodes and omentum were submitted for histology. Intestinal biopsies were not taken because the risk of surgical dehiscence was considered high.

The abdominal effusion (protein 38 g/litre, specific gravity 1·026, nucleated cells $19{\cdot}7 \times 10^9$/litre) was sterile. Of the nucleated cells, 95 per cent were eosinophils and there were small numbers of macrophages and lymphocytes. Haematoxylin and eosin (H&E) stained sections of mesenteric lymph nodes showed severe eosinophilic lymphadenitis (Fig 1). The capsular zone was distorted by a massive infiltrate of eosinophils and large round cells. Mitoses were not seen. Toluidine blue staining revealed moderate numbers of disseminated mature mast cells but there was no metachromatic staining of the round cells. The lymph node parenchyma contained focal accumulations of eosinophils, small lymphocytes and large round cells similar to those in the capsular tissue. The cellular infiltrate in both sections was associated with severe, reactive fibroplasia. In the omentum and serosa, multifocal, perivascular aggregates of plasma cells, macrophages and lymphoid cells were seen. Immunohistochemistry for feline coronavirus antigen was negative (Kipar and others 1998).

Treatment with prednisolone (generic), at 2 mg/kg orally twice daily, was prescribed. The vomiting ceased and the cat's demeanour improved. However, three weeks after laparotomy the cat became anorectic and was euthanased. A partial postmortem examination was permitted.

Gross findings in the abdominal cavity at necropsy were similar to those at laparotomy except for a 1·5 cm diameter gastric perforation (Fig 2). Jejunal wall thickness ranged from 6 to 12 mm. In the thoracic cavity, the heart, lungs, mediastinum and lymph nodes appeared normal and no effusion was present. Tissues taken at necropsy included lungs, stomach, unaltered and altered small intestine, mesenteric lymph nodes, liver, spleen, pancreas, omentum and kidneys.

Histopathological and immunohistochemical methods

Biopsy and necropsy samples were fixed in 10 per cent neutral buffered formalin and embedded in paraffin wax. Sections (5 µm) were stained with H&E, toluidine blue or Giemsa. Chloracetate esterase activity was demonstrated in neutrophils and eosinophils (Osbaldiston and Sullivan 1978). Antisera recognising CD3 (rabbit anti-human CD3; Dako Diagnostica, Hamburg, Germany) and CD45R (rat anti-mouse CD45R [B220 Ly5], clone RA3-6B2; Cedar Lane Laboratories, Hornby, Canada) were used to identify T and B cells, respectively. Peroxidase-anti-peroxidase and avidin-biotin peroxidase complex methods were performed (Kipar and others 1998). Immunohistochemistry for FeLV gp70 and p27 antigen (Kovacevic and others 1997) was performed on sections of small intestine, lymph nodes and spleen.

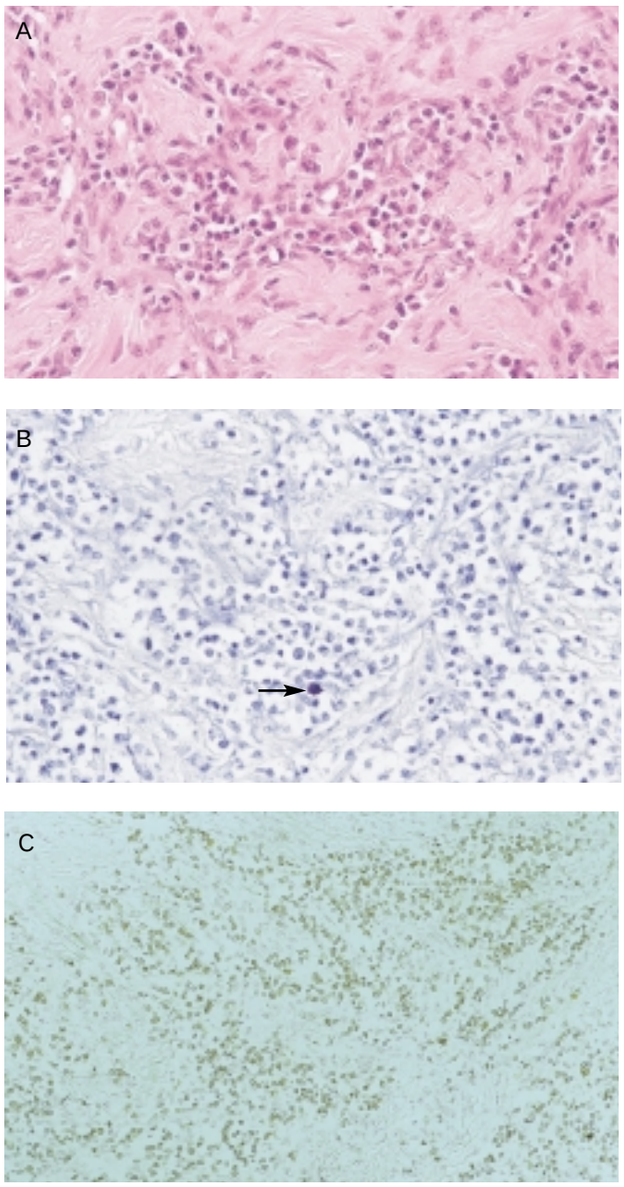

FIG 3. Intestinal plaque. (A) There is a mixed eosinophilic and neoplastic round cell infiltrate and extensive fibroplasia of the muscle wall. H&E ×40. (B) There is no metachromatic staining of neoplastic cells with toluidine blue. A mature mast cell can be seen among neoplastic round cells (arrow). Toluidine blue ×40. (C) The majority of neoplastic cells show a faint to moderate cytoplasmic or membrane staining for CD3. Streptavidin-biotin-horseradish peroxidase, haematoxylin counterstain ×20

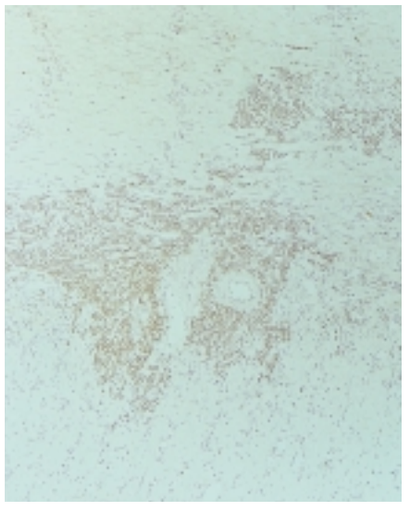

FIG 4. Intestinal wall. A perivascular, neoplastic (CD3+) T cell infiltrate is present between the circular and longitudinal layers of the muscularis. Streptavidin-biotin-horseradish peroxidase, haematoxylin counterstain ×10

Histopathological findings

The plaque associated with the mesenteric surface of the small intestine comprised extensive cellular infiltrates and reactive fibroplasia in the muscle wall and mesenteric attachment (Fig 3A). There were islands and cords of large round cells with scant, pale cytoplasm and round, ovoid or slightly indented nuclei with single, prominent nucleoli. Few mitoses were seen. Scattered eosinophils and smaller lymphoid cells were also present. The toluidine blue stain depicted individual, well-granulated, mature mast cells. No metachromatic granular staining was identified in the small lymphoid cells, the large round cells with prominent nucleoli or the mitotic cells (Fig 3B). There was an irregularly increased lymphoid infiltrate in the lamina propria, with associated villous stunting and crypt distortion.

Less severely thickened small intestine showed extensive lymphoid infiltration in the lamina propria and around vessels in the submucosa, muscle wall and serosa. Other areas of small intestine contained mild to moderate lymphoplasmacytic infiltration of the mucosa with occasional necrotic cells and detritis within crypt lumina. Focal infiltrates of large round cells were seen between smooth muscle layers and in the submucosa. Mesenteric lymph nodes showed reactive fibroplasia and massive focal infiltration with neoplastic round cells and eosinophils. In some areas, eosinophils formed the bulk of the infiltrate. In the stomach there was acute ulceration and perforation associated with focal infiltrates of neoplastic round cells. In other areas, lesions were restricted to gastric wall oedema, lymphatic vessel congestion and a mild, submucosal infiltrate of eosinophils and fibroblasts. The omentum showed perivascular, multifocal, mononuclear cell infiltration with occasional eosinophils. In the liver there was mild lymphoplasmacytic periportal and focal parenchymal infiltration. In the kidneys, tubular mineralisation, interstitial fibrosis, mononuclear interstitial infiltrates and glomerular hyalinosis were present. Lungs showed severe acute alveolar emphysema. The spleen and pancreas were unaltered.

The majority of neoplastic cells showed cytoplasmic or peripheral staining for CD3 (Figs 3C and 4). On the basis of this feature, together with the distribution of tumour infiltrates and the morphology of the neoplastic cells, a diagnosis of intestinal T cell lymphosarcoma was made (Harris and others 1994). In mesenteric lymph nodes, remnant B cell follicles were present and single B cells were found scattered among neoplastic cells. Eosinophils showed a strong reaction to chloracetate esterase and were present in large numbers, disseminated between neoplastic cells and forming focal accumulations. Immuno histochemistry for FeLV antigens was negative.

DISCUSSION

Prior to necropsy and immunohistochemistry, poorly differentiated mast cell neoplasia, eosinophilic enteritis or IHES were considered the most likely explanations for findings of peripheral blood eosinophilia, eosinophilic mesenteric lymphadenitis and eosinophilic abdominal effusion.

Intestinal mast cell neoplasia is the third most common intestinal tumour in the cat

after lymphosarcoma and adenocarcinoma (Graham 1997). Hypereosinophilic paraneoplastic syndrome secondary to intestinal mast cell neoplasia is uncommon. Affected cats can present with an abdominal mass resulting from eosinophilic infiltration of mesenteric lymph nodes, eosinophilic abdominal effusion and, rarely, peripheral eosinophilia (Bortnowski and Rosenthal 1992). Intestinal mast cell neoplasia can also mimic eosinophilic enteritis (Howl and Petersen 1995). The diagnosis of intestinal mast cell neoplasia can be otherwise complicated because intestinal mast cells, unlike mast cells at other sites, may be in a degranulated state and exhibit variable metachromatic staining with toluidine blue (Alroy and others 1975).

Systemic mast cell neoplasia, which usually arises in the spleen, mediastinum or lymph nodes, is frequently associated with peripheral blood eosinophilia and/or eosinophilic effusions in cats (Andrews 1987, Center and others 1990, Peaston and Griffey 1994). Affected cats may have the same triad of clinical features as this case: peripheral eosinophilia, peritoneal effusion and an abdominal mass (Peaston and Griffey 1994). However, splenomegaly is common in cats with systemic mast cell neoplasia and circulating neoplastic mast cells can sometimes be detected by cytological examination of buffy coat smears (Andrews 1987).

Reactive fibroplasia of lymph nodes, as seen in this case, is common in IHES (Hendrick 1981, McEwen and others 1985) and has been observed in cats with intestinal mast cell tumours (Alroy and others 1975, Howl and Petersen 1995) and with systemic mast cell neoplasia (Andrews 1987).

At necropsy a perforated gastric ulcer was found. Although prednisolone administration may have contributed to gastric ulceration, adjacent neoplastic lymphocytes may have been more important in the pathogenesis of the perforation. Intestinal perforation has been described in two cats with intestinal lymphosarcoma (Zwhalen and others 1998). Jejunal, gastric or colonic perforation is common in humans with intestinal T cell lymphosarcoma (Harris and others 1994). Gastrointestinal perforation has been reported in cats with IHES (Hendrick 1981, McEwen and others 1985) and in systemic mast cell neoplasia. In the latter, perforation is mediated by histamine release (Andrews 1987). In contrast, gastrointestinal ulceration does not occur where mast cell neoplasms are confined to the intestinal tract, perhaps due to an absence of histamine in neoplastic intestinal mast cells (Alroy and others 1975).

IHES is a rare condition in cats characterised by persistent, profound peripheral and tissue eosinophilia without an identifiable cause. The disease has been most commonly reported in FeLV-negative, middle aged, female domestic shorthaired cats (Hendrick 1981, McEwen and others 1985, Scott and others 1985, Saxon and others 1991, Muir and others 1993, Plotnick 1994, Wilson and others 1996). Presenting signs are often referable to severe eosinophilic enteritis and include weight loss, anorexia, vomiting, diarrhoea, haematochezia and intestinal thickening. Abdominal masses, due to eosinophilic infiltration of mesenteric lymph nodes, may also be present. Bone marrow cytology is characterised by hyperplasia of the eosinophil series with orderly eosinopoiesis, distinguishing the disease from eosinophilic leukaemia (Hendrick 1981). Cats with eosinophilic leukaemia also tend to have a higher myeloid:erythroid ratio, moderate to severe anaemia and a higher percentage of circulating immature eosinophils than those with IHES (Huibregtse and Turner 1994).

IHES is a diagnosis made after exclusion of known causes of eosinophilia. Eosinophil counts of up to 47×10^9/litre have been documented in cases of flea-allergy dermatitis, eosinophilic granuloma complex, feline asthma and endoparasitism (Center and others 1990). Eosinophilic enteritis may also be considered a hypereosinophilic syndrome, although many cases included in the original description of this disease had eosinophilic infiltration of other organs and could, thus, be classified as IHES (Hendrick 1981, Moore 1983). Proposed mechanisms for IHES in cats include immunoregulatory dysfunction or an intrinsic, probably preneoplastic, bone-marrow disorder (Hendrick 1981, McEwen and others 1985, Center and others 1990). Treatment of affected cats with prednisolone, at doses ranging from 2 to 4 mg/kg/day orally, has resulted in short-lived responses of weeks only and the overall prognosis is poor (Saxon and others 1991, Plotnick 1994, Wilson and others 1996). Combination therapy with prednisolone and hydroxyurea warrants further investigation, with long term responses reported in one cat (Muir and others 1993) and in a dog with IHES (Perkins and Watson 2001) of 28 months and 16 months, respectively.

Recently, some cases of IHES in humans have been attributed to underlying T cell lymphoproliferative disorders, characterised by clonal expansion of type-2 helper T cells. Overproduction of IL-5 by the expanded clone is thought to result in eosinophil chemotaxis and, ultimately, HES (Cogan and others 1994, Brugnoni and others 1996). Given the propensity of cats to develop lymphoproliferative diseases, a similar mechanism may be operating in a subset of feline IHES cases. Furthermore, similarities in eosinophil responses in cats and humans have been demonstrated. For instance, T cell-mediated IL-5 eosinophil chemotaxis in feline asthma is analogous to that in human asthma (Padrid 2000).

Although eosinophil counts of greater than $1{\cdot}5 \times 10^9$/litre in the cat are considered to be elevated (Center and others 1990), the magnitude of peripheral blood eosinophilia seen in this case ($2{\cdot}38 \times 10^9$/litre) was relatively mild. In a study of 312 cats with peripheral eosinophilia, six cats had lymphosarcoma and eosinophil counts ranging from $1{\cdot}9$ to $3{\cdot}2 \times 10^9$/litre (Center and others 1990). Markedly elevated eosinophil counts are most often associated with IHES (up to 107×10^9/litre, Saxon and others 1991) and eosinophilic leukaemia. However, eosinophil counts of $93{\cdot}6 \times 10^9$/litre, $45{\cdot}6$

$\times 10^9$/litre and greater than 60×10^9/litre have been recorded in cats with intestinal mast cell neoplasia, systemic mast cell neoplasia and lymphosarcoma, respectively (Bortnowski and Rosenthal 1992, Peaston and Griffey 1994, Prasse and others 1987).

Hypereosinophilic paraneoplastic syndromes are common in people with Hodgkin's lymphoma and non-Hodgkin's T cell lymphoma. In a subset of Hodgkin's disease patients, peripheral blood and tissue eosinophilia occurs in over 80 per cent of cases (Samoszuk 1997). In contrast, hypereosinophilia is rarely associated with lymphoma of B cell lineage (Navarro-Roman and others 1994). In lymphomas of both lineages the mechanism of eosinophil chemotaxis is thought to be due to the elaboration of IL-5 by neoplastic lymphocytes (Samoszuk 1997). Furthermore, neoplastic B cells in Hodgkin's lymphoma may produce the cytokines tumour necrosis factors alpha (TNF?) and IL-13, thereby inducing the production of eotaxin by fibroblasts (Poppema and van den Berg 2000). Eotaxin, an eosinophil chemotactic chemokine, is, like IL-5, a potent attractant of eosinophils. Hypereosinophilic paraneoplastic syndromes have also been reported in horses and ferrets with T cell lymphosarcoma (La Perle and others 1998, Blomme and others 1999).

Conclusions

This is the first report of HES secondary to lymphosarcoma in the cat. Relative cerebrospinal fluid eosinophilia has been documented in a cat with intravascular T cell lymphosarcoma (Lapointe and others 1997). These data support the assertion that neoplastic T cells can induce eosinophil chemotaxis and hypereosinophilic paraneoplastic syndromes in cats.

This case also illustrates the value of immunohistochemistry in distinguishing lymphosarcoma from poorly differentiated mast cell neoplasia and demonstrates that underlying lymphosarcoma should be considered in cats with peripheral and tissue eosinophilia.

Acknowledgements

The authors would like to thank Mr Ivan Walton for providing the postmortem photographs.

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