CASE REPORT

Generalised lymphadenomegaly associated with methimazole treatment in a hyperthyroid cat

A nine-year-old, domestic shorthair cat was diagnosed with hyperthyroidism and treated with methimazole, which resulted in lethargy, inappetence and marked generalised lymphadenomegaly within two weeks of initiation of therapy. Cytology, histopathology and immunohistochemistry were suggestive of atypical lymphoid hyperplasia. Cessation of treatment resulted in resolution of all clinical signs and physical abnormalities within two days. Subsequent treatment with radioactive iodine cured this cat of its hyperthyroidism. The lymphadenomegaly did not return at any stage and the cat is currently asymptomatic. Although methimazole administration for feline hyperthyroidism has been associated with many side effects, lymphadenomegaly has, to the authors' knowledge, not been previously reported.

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INTRODUCTION

Thioureylene antithyroid drugs are used for preoperative and chronic medical management of feline hyperthyroidism. Propylthiouracil has a high incidence of adverse reactions and is no longer recommended (Mooney and Peterson 2004). Methimazole (Felimazole; Arnolds) is widely used in the USA, the UK and many other countries. Carbimazole (Neo-Mercazole; Roche) is the pro-drug of methimazole. Methimazole interferes with the synthesis of thyroid hormones by inhibiting thyroperoxidase-catalysed reactions, the iodination of tyrosyl residues in thyroglobulin and the coupling of mono-iodotyrosines or di-iodotyrosines to form triiodothyronine (T3) and thyroxine (T4). It has no effect on iodide (I^-)-uptake, release of preformed hormone and does not inhibit peripheral de-iodination of T4 to T3.

As a veterinary licensed product, methimazole has replaced carbimazole as UK's first-line treatment of feline hyperthyroidism (Mooney and Peterson 2004, Tennant 2005). Side effects are relatively common following treatment with methimazole (Peterson and others 1988) and most often occur within the first three months of treatment (Mooney and Peterson 2004). Many of these reactions are gastrointestinal in nature, tend to be transient and do not require drug withdrawal.

However, more serious reactions do occur, including blood dyscrasias, serious hepatopathies and cutaneous drug reactions. In these instances, withdrawal of the drug is mandatory. Although anecdotal reports exist, to the authors' knowledge, generalised lymphadenomegaly has not been previously reported as a prominent methimazole side effect in hyperthyroid cats.

CASE HISTORY

A nine-year-old male, neutered, domestic shorthair cat, weighing 4·45 kg, was presented to Oakwood Veterinary Surgery for routine vaccination. It was, however, also established that the cat had a three-month history of intermittent vomiting and diarrhoea, possible polydipsia, polyphagia and concurrent weight loss. On physical examination, the presence of a small thyroid nodule was detected. Hyperthyroidism was suspected and complete haematology, biochemistry, total T4 concentration (TT4) and free T4 measured via equilibrium dialysis (fT4d) confirmed the diagnosis (TT4: 60·7 nmol/l, reference range 15 to 40 nmol/l, 40 to 60 nmol/l suspicious for hyperthyroidism; fT4d>141 pmol/l, reference range 10 to 40 nmol/l). On receipt of these results, methimazole was started at a dose of 5 mg every 12 hours.

The cat showed initial improvement, with normalisation of appetite and decreased gastrointestinal signs. However, within two weeks, the cat became lethargic, inappetent, showed occasional vomiting and bilateral epiphora. On physical examination, marked generalised peripheral lymphadenomegaly was found (both prescapular and both popliteal lymph nodes were walnut sized). Biochemistry and haematology were unremarkable. Subnormal TT4 (10·1 nmol/l, reference range 15 to 40 nmol/l) was detected, consistent with effective therapy or significant concurrent

non-thyroidal disease; feline leukaemia virus (FeLV) and feline immunodeficiency virus (FIV) serology proved negative.

Fine-needle aspirates were obtained from the right prescapular and both popliteal lymph nodes. Cytology revealed moderate numbers of lymphoid cells consisting of approximately 75 per cent small and 25 per cent medium to large cells. Some preparations showed higher percentages of larger cells (approaching 50 per cent). The nucleus to cytoplasm ratio was moderately high and the nuclei were typically round and eccentrically placed. Some of these cells appeared to have prominent single and multiple nucleoli. One mitotic figure and low numbers of plasma cells were seen. No bacteria, foreign material or organisms were identified. On the basis of the mixed nature of the lymphoid cell population, the lymphadenomegaly was suspected to be reactive. However, concern was present over the relative lack of plasma cells and the number of medium to large lymphoid cells. Therefore, a heterogeneous lymphoma could not be excluded.

In light of this, the left prescapular and right popliteal lymph nodes were surgically removed. Histopathology (Figs 1 and 2) showed the normal lymph node architecture to be completely obscured and replaced by diffuse sheets of cells, which were extending out through the capsule into the pericapsular tissue. The capsule showed fibrous thickening. The cells were a mixture of small and medium lymphoid cells with frequent plasma cells. Histiocytoid cells and larger round cells with prominent single central nucleoli were also seen. There were two to three mitotic figures per high-power field. This was therefore thought to be consistent with atypical hyperplasia. However, an unusual form of lymphoma, such as Hodgkin's-like lymphoma could not be excluded. Immunohistochemistry was therefore requested. The case was discussed with the drug's fabricant, who were not aware of reported cases of methimazole-induced lymphadenopathy.

Pending histopathology and immunohistochemistry results, treatment with methimazole was ceased. On re-examination two days after discontinuation, the owner reported the cat to be brighter, showing improved appetite but still vomiting occasionally. Physical examination was unremarkable with all peripheral lymph nodes having regressed to a normal size. A bland diet was prescribed in light of the continued sporadic vomiting.

For the immunohistochemistry, sections of lymph node were labelled with the pan T-lymphocyte marker CD3 and the B-lymphocyte receptor antigen CD79a. Although there were areas of predominantly CD3-positive lymphocytic expansion within the lymph node tissue, there were also some discrete CD79a-positive follicular aggregates distinct from the T-cell areas (Fig 3). No predominance of one lymphocyte phenotype was found, that was more consistent with atypical lymphoid hyperplasia than lymphoma.

Twenty-three days after cessation of methimazole treatment, the owner reported the cat to have been showing good appetite, no vomiting and normal behaviour. No peripheral lymphadenopathy was noted. Its weight was unchanged from previously. T4 levels were elevated once again (TT4: 80·7 nmol/l) and results of biochemistry were unremarkable.

The cat was referred to the Queen Mother Hospital, Royal Veterinary College for radioactive iodine therapy. This was successfully carried out without side effects and, apart from occasional vomiting, the cat remained well over the following three months.

DISCUSSION

In a study of 262 hyperthyroid cats receiving methimazole, clinical side effects developed in 48 cats and included anorexia, vomiting, lethargy, self-induced excoriation of face and neck, bleeding diathesis, and icterus caused by hepatopathy (Peterson and others 1988, Mooney and Peterson 2004). Mild haematological abnormalities developed in 43 cats, which included eosinophilia, lymphocytosis and slight leucopenia, however, without clinical effect. In 10 cats, more serious haematological reactions developed including agranulocytosis, immune-mediated haemolytic anaemia and thrombocytopenia (associated with bleeding). These haematological abnormalities resolved within one week after cessation of treatment. The study by Peterson and others (1988) reported immunological abnormalities associated with methimazole treatment, which included the development

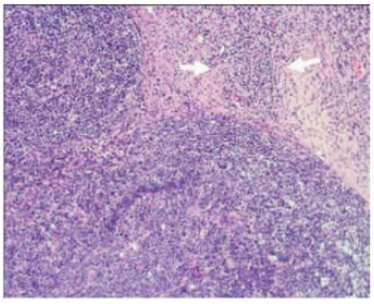

FIG 1. Histopathology of one of the lymph nodes showing diffuse sheets of cells extending out through the capsule (arrows). H&E. ×100

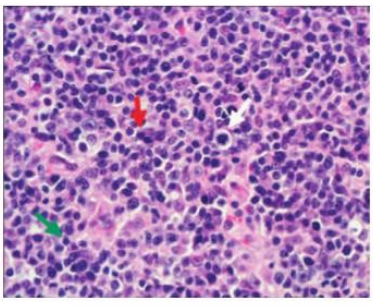

FIG 2. Histopathology of one of the lymph nodes showing the mixed cell population. The white arrow indicates a mitotic figure, the red arrow a plasma cell and the green arrow a small lymphocyte. H&E. ×400

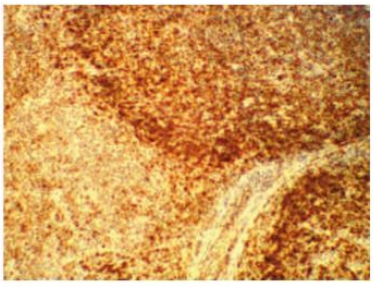

FIG 3. Immunostaining with CD79a revealed B-cell follicular aggregates (brown areas) distinct from adjacent areas of lymph node. ×100

of antinuclear antibodies (ANA) in 52 of 238 cats tested and red cell autoantibodies in three of 160 cats tested. A further study reported primarily gastrointestinal tract upset and facial pruritus (Trepanier and others 2003). Rarely methimazole treatment induces prolongation of protein-induced vitamin K antagonism clotting time, which may explain bleeding tendencies which are not associated with thrombocytopenia (Randolph and others 2000). Another reported side effect, although rare, is acquired myasthenia gravis (Mooney 2001).

The present case report demonstrates that the administration of methimazole can also lead to dramatic lymphadenomegaly. This could easily be mistaken for lymphadenomegaly due to other processes (infection, inflammation or neoplasia), lymphoma being the most likely cause (although multicentric lymphadenomegaly is not a common presentation of this disease in cats). The fact that the cat currently is still alive without having received any cytotoxic treatment argues against the lymphadenomegaly having been caused by a progressive neoplastic process such as lymphoma. No evidence of infectious agents were found on basic blood work, blood smear examination or histopathology, and no antibiotics were given to treat any infection, making a bacterial cause less likely; FIV and FeLV were excluded via serology.

The onset and disappearance of clinical signs with the start and cessation, respectively, of methimazole, in the absence of any other therapy or environmental change, were highly suggestive of involvement of this drug in the aetiology of lymphadenomegaly. Ideally, one would want to re-challenge the cat with methimazole to confirm this suspicion. However, this was not believed to be ethical as it would be potentially hazardous for the cat. Also, lymphadenomegaly has been previously described to occur in cats with the thiourylene antithyroid drug propylthiouracil, which has many chemical structural similarities to methimazole. An immune-mediated disease was induced in nine out of 17 normal healthy cats by daily administration of this drug; this was characterised by lethargy, weight loss, lymphadenopathy (in seven of 17), haemolytic anaemia, a positive direct antiglobulin test and development of ANA. On cessation of propylthiouracil, clinical signs resolved in all cats within two weeks (Aucoin and others 1985).

In human medicine, carbimazole, methimazole and propylthiouracil are known to cause lymphadenomegaly, which is thought to be an immunological reaction (Laurence and others 1997, Grahame-Smith and Aronson 2002). These reactions, also called drug allergies or hypersensitivity reactions, show no relationship with the usual pharmacological effects of the drug; often a delay is seen between the first exposure to the drug and the occurrence of the adverse reaction; there is no formal dose–response curve; the reaction disappears on discontinuation of the drug and the illness is often recognisable as a form of immunological reaction, for example a rash, asthma, urticaria or lymphadenomegaly (Grahame-Smith and Aronson 2002). Also, a human patient with Graves' disease has been reported to develop a methimazole-induced lupus-like syndrome characterised by generalised lymphadenopathy, migrating polyarthritis and myalgia, and results of tests for ANA, anti-DNA antibody and lupus erythematous were positive (Takuwa and others 1981). All abnormalities disappeared after cessation of treatment.

This case also highlights the difficulty of definitively excluding lymphoma even following histopathology; although in this case, immunohistochemistry helped to differentiate between hyperplasia and neoplasia. The histopathology was similar to that described by Mooney and others (1987) in which six young cats were described that were initially diagnosed with lymphoma but subsequently determined to have lymphoid hyperplasia.

The lethargy and inappetence seen in this case following initiation of treatment could have represented gastrointestinal side effects, previously described to occur with methimazole (Peterson and others 1988). The sporadic vomiting, which persisted even after successful radioactive iodine treatment, might have been due to underlying intrinsic gastrointestinal disease or food intolerance.

When severe idiosyncratic reactions occur after initiation of methimazole, permanent drug withdrawal and symptomatic treatment are advisable. Changing from methimazole to carbimazole is not indicated since carbimazole is metabolised into methimazole by the body. In those cases, alternative treatment options should be explored. Permanent solutions, such as surgical thyroidectomy or radioactive iodine treatment, are considered superior to temporary solutions such as stable iodine (Foster and Thoday 1999), beta adrenoreceptor blocking agents (Mooney and Peterson 2004) or cholecystographic agents (Murray and Peterson 1997). Radioactive iodine treatment cured the hyperthyroidism of the cat in this report.

In summary, an adverse reaction to methimazole should be considered as a potential cause of lymphadenomegaly in cats, and cessation of therapy is advised in these cases to assess the subsequent response before embarking on further investigations. A rapid clinical resolution of signs may make procedures such as lymph node biopsies, with the attendant risk of anaesthesia, unnecessary.

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