Hypercalcaemic multicentric lymphoma in a dog presenting as clitoromegaly

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Clitoromegaly is a clinical manifestation of various local and systemic conditions in all species. The external genitalia are a very rare site of primary or metastatic lymphoma in canines, with only one previously-reported case in a dog and only sparse reports in the medical literature. Lymphoma is also very rare in dogs less than four years of age. This account reports on a T-cell multicentric lymphoma in a 16-month-old Basset hound presented primarily for clitoromegaly. The patient survived for 68 days with cyclophosphamide-vincristine-prednisolone therapy. The causes of clitoromegaly in all species, including humans, are tabulated with references.

Introduction

Lymphoma is a common malignancy in dogs. The clinical manifestations of this disease are wide and varied, ranging from clinical signs relating to lymphadenomegaly, organomegaly, paraneoplastic syndromes and signs relating to obstruction of the airways by enlarged tonsils. Pleural and abdominal effusions have also been described, but the extranodal forms are considered less common than multicentric, mesenteric and mediastinal lymphomas (Vonderhaar & Morrison 2002). Furthermore, there is less veterinary information on the causes of clitoromegaly than is available in the medical literature. Discussion instigated by this novel patient (with primary clitoral lymphoma and an associated hypercalcaemia of malignancy) is of value in highlighting the possibilities for diagnosis of previously undiagnosed conditions in veterinary patients. In addition, no review of all reported causes of medical or veterinary causes of clitoromegaly could be found. To the authors' knowledge, this is only the second report of clitoral lymphoma in a dog (or any domestic animal species).

Case history and diagnostic evaluation

A 16-month-old, 22.7 kg (body surface area, 0.8 m^2), spayed female Basset hound was presented to the Onderstepoort Veterinary Academic Hospital (OVAH) with a history of a swollen vulva, lethargy and polydipsia. Clinical examination revealed generalised lymphadenomegaly with marked enlargement of the vulva and clitoris (Figure 1). Apart from a specific gravity of 1.008, urine analysis (dipstick, refractometry and sediment analysis) was unremarkable. Haematology was within normal limits (Table 1) and clinical chemistry revealed a moderate hyperalbuminaemia, mildly elevated serum urea nitrogen and hypercalcaemia (Table 2). Fine needle aspirates of lymph nodes were consistent with a diagnosis of centroblastic lymphoma. Cells showed anaplastic changes, bizarre shapes and a high mitotic index (Figure 2), which is characteristic of a T-cell lymphoma (Fournel-Fleury *et al*. 1997; Raskin & Nipper 1992; Teske & van Heerde 1996; Vonderhaar & Morrison 2002). Impression smears and fine needle aspirates of the clitoris revealed the same criteria of malignancy as the lymph nodes. Thoracic radiographs taken to investigate involvement of the intrathoracic organs (lungs, lymph nodes and thymus) were negative for metastasis. Abdominal ultrasound was performed as part of the staging procedure. A mass of mixed echogenicity and irregular shape measuring 30 mm x 10 mm was seen in the region of the medial iliac lymph node, consistent with regional metastasis to or from the clitoral mass. It was not aspirated due to its proximity to vascular structures.

The patient was placed on an intravenous saline infusion to lower the blood calcium by sodium-induced calciuresis and, once the patient was rehydrated, incisional biopsies of the submandibular and popliteal lymph nodes were taken and submitted for histopathology and immunophenotyping. The paracortical areas of both lymph nodes were infiltrated by large numbers of pleomorphic, neoplastic CD3+ CD79a– lymphocytes with a high mitotic rate (Figure 3 and Figure 4). On the basis of this, stage IIIb T-cell centroblastic lymphoma with hypercalcaemia of malignancy was diagnosed.

Note: The corresponding author, Anthony Zambelli, is currently affiliated with Inanda Veterinary Hospital and Specialist Referrals, Waterfall, KwaZuluNatal, South Africa.

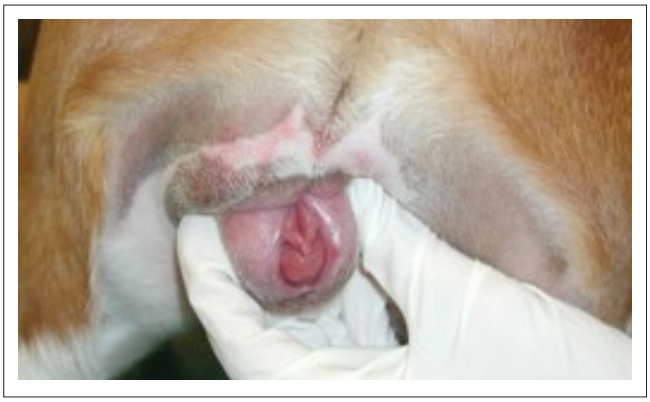
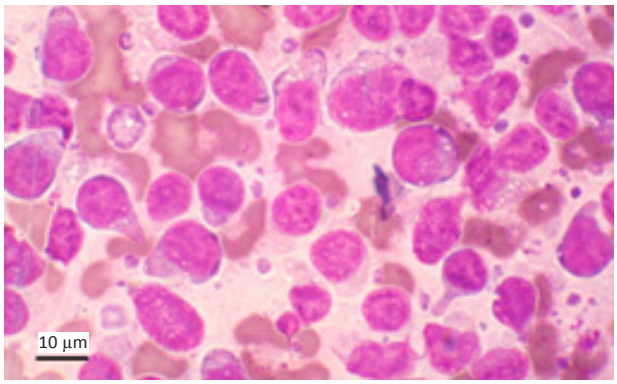


FIGURE 1: Photograph showing spherical clitoral mass.

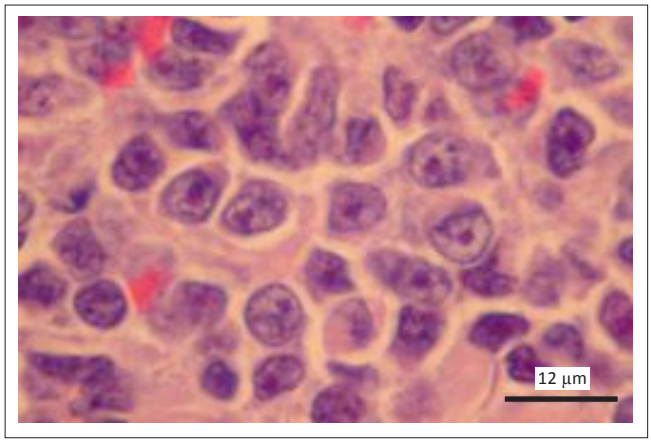


Note: The presence of large, bizarrely-shaped cells with multiple nucleoli is indicative of centroblastic morphology.

FIGURE 2: Fine needle aspirate cytology of the clitoral mass (shown in Figure 1).

The patient was then placed on a standard protocol of weekly vincristine (ABIC-Vincristine, Pharmachemie, Irene, South Africa) at 0.5 mg/m^2 IV q7d, cyclophosphamide (Endoxan, Sanofi-Aventis, Midrand, South Africa) at 50 mg/m^2 PO every other day and prednisolone (Prednisolone tabs, Centaur, Isando, South Africa) at 40 mg/m^2 PO q24h.

Where necessary, nausea induced by treatment was controlled with oral metoclopramide syrup (Clopamon Syrup, Sanofi-Aventis, Midrand, South Africa) at 0.5 mg/kg PO, for three



Note: Malignant lymphocytes possess vesicular nuclei the approximate size of 1.5 red cells in diameter. Nuclei irregularly indented and nuclear membranes, though distinct, are unevenly thickened. The chromatin pattern is diffuse to finely granular and juxtamembranous and peri-nucleolar stippling is prominent. Cells are distinctly nucleolated. The large, commonly single magenta nucleoli are typically central or paracentral in location. The pale basophilic to amphophilic cytoplasm is scant and cell boundaries usually poorly defined. H&E.

FIGURE 3: Vulva: Canine, diffuse small cell lymphoma (Tissue section).

TABLE 1: Haematology values.

Parameter	Day 1	Day 37	Day 52	Day 59	Day 66	Reference range
Haemoglobin (Hb)	196	162	160	157	163	120–180 (g/L)
Red cell count (RCC)	7.87	6.58	6.21	6.32	6.42	5.5–8.5 x 10^{12}/L
Haematocrit (Ht)	0.553	0.463	0.444	0.454	0.461	0.37–0.55 (L/L)
Mean cell volume (MCV)	70.3	70.4	71.5	71.8	71.8	60–77 (fL)
Mean cell haemoglobin concentration (MCHC)	35.5	35.0	36.0	34.7	35.5	32–36 (g/dL)
Total white cell count (WCC)	6.4	4.8	5.9	5.6	5.4	6.0–15.0 x 10^9/L
Segmented neutrophils	4.81	2.77	4.78	3.49	3.62	3.0–11.5 x 10^9/L
Band neutrophils	0	0	0	0	0	0–0.5 x 10^9/L
Monocytes	0.49	0.73	0.24	0.45	0.45	0.15–1.35 x 10^9/L
Lymphocytes	0.69	1.18	0.59	1.36	0.84	1.0–4.8 x 10^9/L
Lymphoblasts	0	0	0	2+	0	-
Eosinophils	0.42	0.12	0.30	0	0.49	0.1–1.25 x 10^9/L
Basophils	0	0	0	0	0	0–0.1 x 10^9/L
Thrombocytes	274	344	295	221	295	200–500 x 10^{12}/L
Anisocytosis	1+	1+	1+	2+	3+	-
Rouleaux	Y	Y	N	N	N	-

TABLE 2: Clinical chemistry values.

Parameter	Day 1	Day 3	Day 12	Day 37	Day 52	Day 59	Day 66	Reference range
Total serum proteins	69.5	-	-	-	-	-	-	53–75 (g/L)
Albumin	43.1	-	-	-	-	-	-	27–35 (g/L)
Globulins	26.4	-	-	-	-	-	-	20–37 (g/L)
Albumin/Globulin ratio	1.63	-	-	-	-	-	-	0.6:1–1.2:1
Alanine aminotransferase (ALT)	19	-	-	-	-	-	-	5–40 (U/L)
Urea	9.4	-	-	9.1	6.9	-	-	3.6–8.9 (mmol/L)
Creatinine	97	-	-	-	-	-	-	40–133 (µmol/L)
Na+	150	-	-	-	-	-	-	140–155 (mmol/L)
K+	4.37	-	-	-	-	-	-	3.6–5.1 (mmol/L)
Na:K ratio	34.3:1	-	-	-	-	-	-	> 27:1
Total calcium	3.99	3.14	2.85	2.87	3.37	3.12	3.40	2.2–2.9 (mmol/L)

days after each treatment. The clitoral mass (as well as the enlarged lymph node) showed a marked reduction in size within a week of initiation of treatment (Figure 5).

At week 3 of treatment (day 37), vincristine dosage was lowered by 25% because of gastrointestinal side effects. This alteration in dosage and metoclopramide treatment prevented further nausea. The patient was still normocalcaemic at this time, but all subsequent evaluations showed hypercalcaemia (Table 2). On day 37, the patient was severely neutropaenic (Table 1) and vincristine and cyclophosphamide treatment was delayed.

On day 66, the patient exhibited diarrhoea of two days' duration. On clinical evaluation the vulvar mucosa was reddened. The dog was euthanased on day 68 when clinical signs of nausea and vomition became more severe and the clitoral mass and lymphadenomegaly returned.

The duration of the first remission (66 days) was defined as the time between the start of treatment and the first relapse (recurrence of lymphadenomegaly, hypercalcaemia or clitoral mass as assessed by cytological examination). Overall survival time (OST), 68 days, was defined as the time between the start of treatment and the death of the dog.

Post-mortem findings

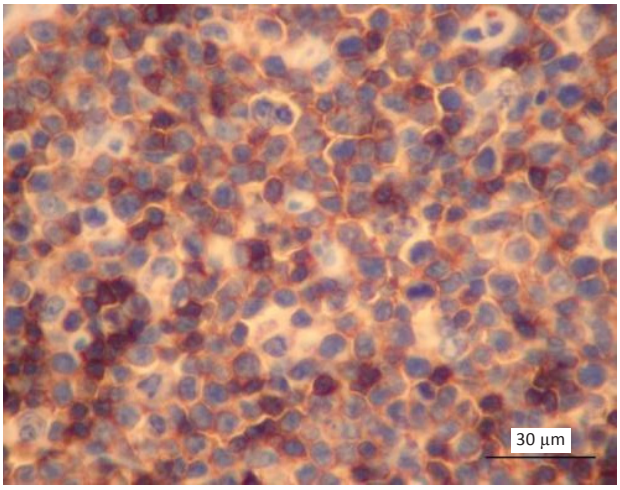
A *post-mortem* examination was performed and additional samples taken for histopathology. On gross pathology, there was diffuse lymphomatous infiltration of the bilaterally- and symmetrically-enlarged prescapular, popliteal, inguinal and sublumbar lymph nodes, as well as the severely-enlarged vulva and clitoris. On the cut surface, the infiltrated organs were diffusely whitish grey and uniformly rubbery in texture.

Histopathology

Pieces of enlarged lymph node, clitoris and vulva were trimmed into tissue cassettes after 48 hours in 10% neutral buffered formalin and then dehydrated in graded ethanol, cleared in xylene and embedded in paraffin wax. Duplicate paraffin sections of 3 mm were prepared, one series being stained with haematoxylin and eosin (H&E), whilst the second series was utilised for immunohistochemical (IHC) staining.

Histology of the lymph nodes revealed the presence of multiple small clusters of neoplastic lymphocytes within the thinned capsule, the extracapsular connective tissue and the intact peripheral sinus. The cortex was residual, featuring only a few germinal centres. In all sections there was a solidly cellular interfollicular proliferation of neoplastic lymphocytes admixed with normal small, cleaved lymphocytes. The same admixture of cells caused the marked expansion of medullary trabeculae and filled the medullary sinuses. Postcapillary venules in the deep cortex appeared moderately hyperplastic in the sections examined.

The histology of the vulva and clitoris revealed diffuse sheets and cords and nodular perivascular accumulations of fairly monomorphic neoplastic lymphocytes in the subepithelial stroma, with diffuse invasion of the stratified squamous epithelium at both sites (see Figure 6). At 1000x magnification,



Note: Immunohistochemical staining for CD3 detection demonstrating weakly- to moderately-positive malignant lymphocytes (predominantly cytoplasmic membrane staining) intermingled with several strongly-positive normal small, cleaved lymphocytes and a few malignant cells that failed to express CD3. A modified streptavidin-peroxidase-biotin complex procedure was applied, using cross-reacting rabbit anti-human CD3 primary antibody (1:100, DAKO) and diaminobenzidine (DAB) as the chromogen, with a haematoxylin counterstain.

FIGURE 4: Vulva: Canine, diffuse small T-cell lymphoma (Tissue section).

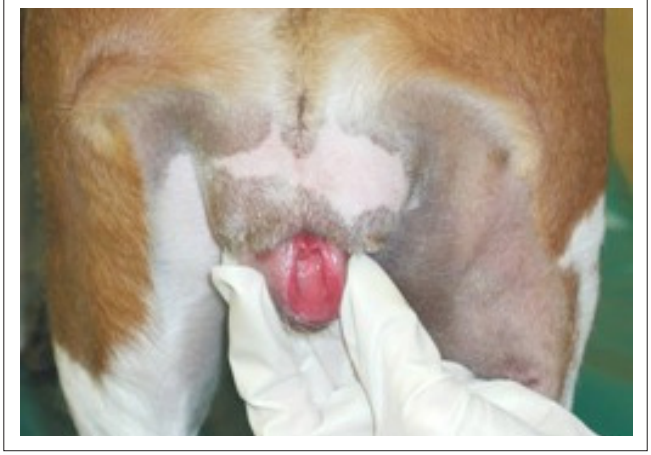
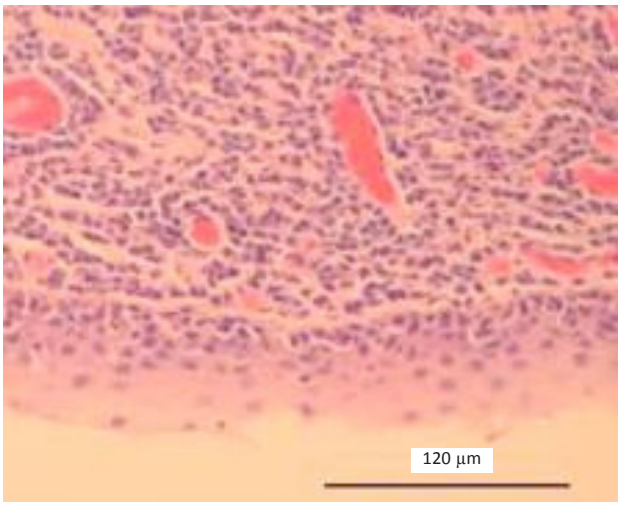


FIGURE 5: Photograph showing remission of clitoral lymphoma.



Note: Diffuse sheets and rows of comparatively monomorphic neoplastic lymphocytes were observed in the hyalinised stroma. The same cells had also infiltrated the basal and deep spinosal layers of the nonkeratinised squamous mucosa. H&E.

FIGURE 6: Clitoris: Canine, diffuse small cell lymphoma (Tissue section).

quite significant nuclear pleomorphism was observed in the neoplastic cells. Nuclear shape was particularly varied; there were round, cleaved, reniform, angular, irregular and horseshoe-shaped nuclei. The nuclei were generally vesicular and measured approximately 1.5 red cells in diameter. The chromatin was commonly diffuse to quite finely granular with irregular juxtamembranous and peri-nucleolar stippling. The nuclear membranes were sharply delimited and unevenly thickened, usually with multiple irregular indentations (Figure 3). The prominent magenta nucleoli were typically quite large, single and centrally or paracentrally located (Figure 3). On average, there was one mitotic figure per field at 1000x magnification. The neoplastic cells had scant, irregularly-distributed, weakly -basophilic to -amphophilic cytoplasm and cellular boundaries were usually indistinct. A few normal small, cleaved lymphocytes and fewer plasma cells, eosinophils and neutrophils were scattered between the neoplastic lymphocytes.

Immunohistochemistry

For immunophenotyping, the 3 µm-thick tissue sections were mounted on Superfrost Plus glass slides and dried overnight in an oven at 58 °C to enhance tissue adhesion. Routine dewaxing and rehydration were performed in xylene and graded ethanol and the sections were washed in distilled water. Antigen unmasking was performed by immersing the sections to be stained with the pan-T cell anti-CD3 polyclonal antibody in a plastic container with 0.01 M citrate buffer (pH 6). The sections to be stained with the pan-B cell anti-CD79a monoclonal antibody were immersed in a separate container with 0.01 M Tris buffer and 0.001 M EDTA (pH 9). Both containers were microwaved at high power for 15 min. After cooling for 15 min at room temperature, the buffer was decanted and the sections were washed in distilled water and then for 5 min in phosphate-buffered saline (PBS) containing 0.1% bovine serum albumin (BSA) (pH 7.6).

The tissue sections were further treated according to a streptavidin-immunoperoxidase staining system (specifically the LSAB+ Kit, HRP from Dako, K0690). As the first stage in the LSAB+ Kit, endogenous peroxidase activity was quenched by incubating the tissue sections with 3% hydrogen peroxide (provided in the kit) for 5 min, followed by rinsing in PBS-BSA buffer (pH 7.6) for 5 min. Thereafter, selected slides were incubated with a monoclonal mouse anti-human CD79a antibody (Dako, M7051) for 1 h at a dilution of 1:75. Slides for CD3 staining were incubated with the polyclonal rabbit anti-human CD3 antibody from Dako, A0452 (dilution 1:100) for 30 min. Both of these antibodies have been shown to be cross-reactive to canine B- and T-lymphocytes respectively (Jacobs, Messick & Valli 2002; Milner *et al.* 1996). The incubation of slides with the primary antibody was followed by sequential incubations with biotinylated link antibody and peroxidase-labelled streptavidin according to specific kit directions. Staining was completed after incubation of the sections at room temperature with the 3,3′-diaminobenzidine substrate-chromogen solution provided. Sections were then rinsed in distilled water, counterstained with Mayer's haematoxylin, washed in PBS-BSA buffer (pH 7.6) for 5 min, then dehydrated and mounted. Positive immunohistochemical controls for the CD3 and CD79a antibodies included normal canine lymph node. Negative controls were done on duplicate sections of canine lymph node that were treated identically to the other sections, except that the primary antibody was replaced with PBS-BSA buffer (pH 7.6) in each case. Samples were subsequently reviewed by a pathologist.

Cells were considered to be CD3 or CD79a positive if there was clear perinuclear, cytoplasmic and/or cell membrane staining (Day 1995; Jacobs *et al*. 2002). In this particular case, 80% – 100% of the neoplastic cells in the sections of lymph node, clitoris and vulva were consistently CD3+ (pale to moderate cytoplasmic and cytoplasmic membrane staining) and CD79a–. They were therefore considered to be of the T-cell phenotype (Figure 4). The normal small, cleaved lymphocytes that were intermingled with the neoplastic T-lymphocytes in the sections of lymph node, vulva and clitoris were consistently strongly CD3+ (Figure 4). The observation that some of the neoplastic cells were not positive for the CD3 molecule can, in all probability, be ascribed to a loss of expression of the CD3 surface molecule in these cells (Day 1995). It is unlikely that tissue treatment and antigen retrieval methods played a part in the variable staining of the tumour cells in this case, since the positive control sections of normal canine lymph node revealed strong CD3 and CD79a expression and the normal T-lymphocytes in all of the sections of tumour were strongly CD3-positive. In addition, the lymphatic nodules within the residual cortex of several neoplastic lymph nodes in this case contained numerous strongly CD79a-positive B-lymphocytes.

Discussion

Clitoral neoplasia is very rare, with one source reporting that only eight cases (the last in 1987) had been described in the medical literature up to the time of the literature search in 2004 (Alvarez & Varner 1987), although an extensive literature search revealed more case reports (Table 3) but no reviews of all reported cases. In the veterinary literature, only one report exists of a clitoral lymphoma and this seems unlikely to have been primary (Ladds, Strafuss & Clifford 1969).

Extranodal lymphoma is less common than other forms of this disease in dogs and, depending on its specific manifestation, carries a worse prognosis than certain other forms. Extranodal lymphoma is defined as any such neoplasm arising or manifesting outside the lymph nodes, mesentery or intestinal submucosa, thymus or mediastinum. The previously-reported veterinary patient was young (a one-year-old German Shepherd dog), but had far more advanced disease than the patient described in this report and treatment was not attempted (Ladds *et al*. 1969). The authors reported involvement of the clitoris, presumably as a site of metastasis via the sublumbar lymph nodes or, alternatively, to the rest of the lymphatic system. Lymphatic drainage of

TABLE 3: Reported causes of clitoromegaly in the veterinary and medical literature.

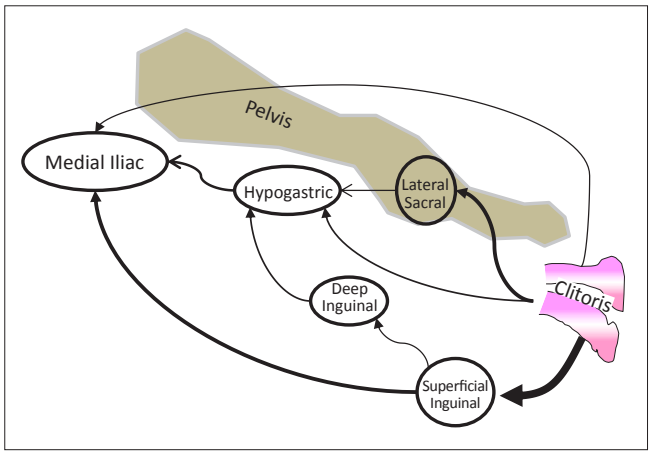
Cause	Condition	Species	References
Chromosomal and developmental abnormalities	Epispadias	H, C	Soderberg 1986; Tammer *et al.* 1998
	Freemartinism	B, O, G, P, E	Bruere *et al.* 1968; Dennis 1979; Hunter & Greve 1996; Ilbery & Williams 1968; Jankowski & Ildstad 1997; Kästli & Hall 1978; Padula 2005; Parkinson *et al.* 2001; Smith *et al.* 2000; Wilkes *et al.* 1978
	Freemartinism with *atresia ani* and *recti*	B	Ghanem *et al.* 2005
	Intersexuality including Mixed Gonadal Dysgenesis (true and pseudohermaphroditism)	H, P, C, E, O, B, F, G, L	Bannasch *et al.* 2007; Bredal *et al.* 1997; Brown & Warne 2005; Christensen & Juul 1999; Cohen, Berezin & Goldman 1985; Constant *et al.* 1994; Houk & Lee 2005; Hunter & Greve 1996; Hyun & Kolon 2004; Jaubert *et al.* 1999; Lara-Torre & Kives 2003; Li *et al.* 2004; Linck & Hayes 2002; Matthews *et al.* 1983; Meyers-Wallen *et al.* 1987; Milliken *et al.* 1995; Moreno-Millan *et al.* 1989; Nowacka *et al.* 2005; Oyama *et al.* 2004; Padula 2005; Papazoglou *et al.* 2004; Raspa *et al.* 1985; Roberts 1986; Sommer & Meyers-Wallen 1991; Tammer *et al.* 1998; Van Camp 1986; Warne *et al.* 2005; Whitfield 2004; Wilker *et al.* 1994; Williams *et al.* 1997; Wylie 2004
Acquired virilisation syndromes	α-Adrenergic antagonists	H	DiGiorgi *et al.* 2004
	Androgen therapy (iatrogenic virilisation)	H, C, B	Groot *et al.* 1989; Horejsí 1997; Medina 2002; Soderberg 1986
	Blood dyscrasias	H	DiGiorgi *et al.* 2004
	Selective serotonin reuptake inhibitors (SSRSs) e.g. trazodone causing clitoral priapism	H	DiGiorgi *et al.* 2004; Medina 2002
Endocrinopathies causing virilisation	Adrenocortical steroidogenic tumour	H	Horejsí 1997; Linck & Hayes 2002; Sabbaga *et al.* 1993
	Androgenic tumour of mother	H	Elterman & Hagen 1983; Lara-Torre & Kives 2003
	Congenital adrenal hyperplasia	H	Lara-Torre & Kives 2003; Oyama *et al.* 2004; Schmidt *et al.* 1999
	Granulosa cell tumour	E, C	Bertazzolo *et al.* 2004; Schulin-Zeuthen *et al.* 2003; Soderberg 1986
	Hyperadrenocorticism	C	Dow *et al.* 1988
	Malignant paraganglioma	H	Kitahara *et al.* 1993
	Mixed gonadal dysgenesis	H	Lara-Torre & Kives 2003; Oyama *et al.* 2004
	Os clitoridis development	C	Grandage & Robertson 1971
	Ovarian steroidogenic tumour (testosterone, 17β-OH progesterone)	H	Horejsí 1997; Snyder & LaFranchi 1999
	Polycystic ovarian syndrome	H	Guelinckx & Sinsel 2002; Linck & Hayes 2002
	Sertoli-Leydig ovarian tumour	H	Hansen & Sorensen 1993
	Stromal hyperthecosis	H	Linck & Hayes 2002
Primary neoplasia and benign growths	Angiokeratoma	H, E	McNeely 1992; Moreno-Millan *et al.* 1989
	Congenital haemangiopericytoma	H	Brock, J.W., 3rd *et al.*, 1995
	Corpus cavernosum-like tumour	H	Björses *et al.* 1997
	Dermoid cyst	H	Abudaia *et al.* 1999
	Epidermal cyst	H	Schmidt *et al.* 1999
	Glomus tumour	H	Jagadha, Srinivasan & Panchacharam 1985; Stange 1951
	Gonadoblastoma	H, C	Bertazzolo *et al.* 2004; Iliev *et al.* 2002
	Granular (Abrikossoff) tumour	H	Ortiz-Hidalgo *et al.* 1997
	Keratoacanthoma	H	Nascimento *et al.* 2005
	Lymphoma	H, C	DiGiorgi *et al.* 2004; Ferrando-Marco *et al.* 1992; Kosari *et al.* 2005; Ladds *et al.* 1969
	Malignant melanoma	H	Landthaler *et al.* 1985; Rzempoluch *et al.* 1992
	Malignant rhabdoid tumour	H	Haidopoulos *et al.* 2002
	Mucinous cystadenoma	H	Alvarez & Varner 1987
	Neurofibromatosis	H	Horejsí 1997; Kantarci *et al.* 2005
	Neuroma	H	Sonnendecker *et al.* 1993
	Nevus lipomatosus cutaneous superficialis	H	Hattori *et al.* 2003
	Pagetoid breast adenocarcinoma of the vulva-clitoris	H	Ohira *et al.* 2004
	Primary granular cell tumour in pregnancy (clitoral)	H	Degefu *et al.* 1984
	Squamous cell carcinoma of the clitoris	H	Chan *et al.* 2004; Jones & Matthews 1999; Semczuk *et al.* 2005
	Pesudoangiosarcomatous carcinoma	H	Pitt *et al.* 1995
	Pseudolymphoma	H	Minderhoud-Bassie *et al.* 1992
	Schwannoma	H	Llaneza, Fresno & Ferrer 2002; Thomas *et al.* 1989
	Sebaceous or epidermoid cyst	H	Guelinckx & Sinsel 2002; Linck & Hayes 2002
	Transitional cell carcinoma	H	DiGiorgi *et al.* 2004
Growths metastasising to the clitoris	Carcinosarcoma of bladder	H	Hanna *et al.* 2004; Langenstroer *et al.* 2003
	Cervical and vulvar cancers extending to the clitoris (many types)	H	DiGiorgi *et al.* 2004
	Squamous cell carcinoma of the bladder	H	DiGiorgi *et al.* 2004
	Transitional cell carcinoma of the bladder metastasising to clitoris	H	DiGiorgi *et al.* 2004; Powell & Jones 1983
Idiopathic or miscellaneous conditions causing clitoromegaly	Abscessation, clitoris (including granular or lymphoid nodular)	H, C	Chinnock 2003; Lein 1986; Sur 1983
	Clitoral priapism	H	DiGiorgi *et al.* 2004
	Clitorism as presentation of acute non-lymphocytic leukaemia	H	Williams *et al.* 1997
	Isolated clitoral hypertrophy	H	Lara-Torre & Kives 2003; Shiraishi *et al.* 1999
	Pseudohypertrophy	H	Horejsí 1997

B, bovine, C, canine; E, equine; F, feline; G, caprine; H, human; L, llama; O, ovine; P, porcine

the clitoris and vulva is complex (Figure 7), but the majority of lymph flow is toward the superficial inguinal lymph node, with afferents to the medial iliac and deep inguinal nodes and from the latter to the hypogastric lymph node. Drainage also proceeds directly via the lateral sacral, hypogastric and medial iliac lymph nodes (Evans & Christensen 1979).

Although treatment was initiated in the patient described in this report, OST was relatively short (68 days vs 153 days) by the standards of other T-cell lymphomas (Vonderhaar & Morrison 2002). There are insufficient cases described to enable any predictions about outcomes of clitoral lymphoma. Nonetheless, this case was remarkable for its poor response to treatment despite an initial remission, a characteristic shared by many multicentric T-cell lymphomas. Also, unusually, the cytological and immunohistochemistry were not in complete agreement, although both predicted a high-grade lymphoma (Fournel-Fleury *et al.* 1997; Milner *et al.* 1996; Raskin & Nipper 1992). In humans, there are only a few reports of clitoral involvement in non-Hodgkin's lymphoma (Ferrando-Marco *et al.* 1992; Kosari *et al.* 2005; Ludwig, Heinrich & Brandeis 1987; Minderhoud-Bassie, Chadha-Ajwani & Huikeshoven 1992). One report described an adult patient with primary, isolated vulvar pseudolymphoma, a condition difficult to distinguish from lymphoma and of uncertain aetiopathogenesis. It represents a reactive, non-neoplastic accumulation of lymphocytes in the skin (usually the nipples or face), containing an admixture of B- and T-cell types. Other names for pseudolymphoma are Spiegler-Fendt sarcoid, lymphocytoma cutis or cutaneous lymphoid hyperplasia (Minderhoud-Bassie *et al*. 1992). To the authors' knowledge, these entities have not been reported in dogs. The report by Ludwig and coworkers described a two-year-old girl admitted for clitoromegaly, who was subsequently found to have renal, mediastinal, central nervous and multicentric involvement. After treatment with chemoradiation, the patient was still in full remission six years later (Ludwig *et al*. 1987).

A review of 186 cases of lymphoma of the human female genital tract described only one primary lymphoplasmacytic lymphoma, which occurred on the clitoris (Kosari *et al.* 2005). Nonetheless, Table 3 illustrates the wide array of benign and malignant neoplastic and non-neoplastic growths that may occur in this organ or even metastasise or extend into it. The importance of fine needle aspiration cytology, incisional biopsy and proper evaluation of the draining lymphatics and adnexa become obvious when the malignant nature of some of the neoplasms listed is considered (Fournel-Fleury *et al.* 1997; Raskin & Nipper 1992; Teske & Van Heerde 1996).



Source: Adapted from Evans, H. & Christensen, G.C. (eds.), 1979, *Miller's anatomy of the dog*, WB Saunders Company, Philadelphia
Note: Arrow thickness denotes relative significance of efferent flow from the clitoris.

FIGURE 7: Schematic illustration of lymphatic drainage of the canine clitoris.

A trait of around 20% of canine lymphomas is hypercalcaemia of malignancy (Vonderhaar & Morrison 2002). This normally results from production of parathyroid hormone-related peptides (PTHrP) by the lymphomatous cells, although local factors related to the paracrine effects of TNF-α, IL-1 and other cytokines secreted by marrow lymphoma cells may also be involved. Unfortunately, a bone marrow aspirate or biopsy that might have detected myelophthisis was not performed on the patient in this report. Nevertheless, the patient did not have a leukaemic presentation and the hypercalcaemia responded to saline diuresis, although recalcitrant hypercalcaemias of malignancy may require additional treatment with one or more of the following drugs: prednisolone, furosemide, mithramycin, salmon calcitonin or pamidronate (Vonderhaar & Morrison 2002). Although the patient was hypercalcaemic and hyperalbuminaemic at initial presentation, there is evidence that correction of calcium levels for alterations in albumin status is superfluous (Schenck & Chew 2005). In any event, both ionised and total calcium were markedly raised, both initially and in the terminal stages of therapy (Table 2).

Conclusion

Clitoromegaly as a presentation of lymphoma is extremely unusual, although it should be included on differential lists for this presenting complaint, together with endocrinopathies and non-endocrine causes (Table 3). It could conceivably be primary (which would require demonstration of any other sites of involvement) or secondary (most likely and suspected in this patient) in which case it may represent a form of non-epitheliotropic lymphoma. Patients presenting with clitoromegaly, with or without obvious concurrent lymphadenomegaly, should be examined thoroughly. The minimum database should include fine needle aspiration cytology for most masses where overt evidence of simultaneous endocrinopathy does not exist or where the history does not indicate conditions such as androgen administration or intersexuality (Table 3). In all cases, abdominal ultrasound examination should be performed, paying particular attention to the superficial inguinal, medial iliac and hypogastric lymph nodes, adrenal glands, ovaries and internal genitalia. In selected cases, ACTH-stimulation tests with measurement of cortisol, 17-hydroxyprogesterone and androstenedione, positive contrast retrograde vaginourethrocystography or intravenous pyelography, exploratory laparotomy, karyotyping and human chorionic

gonadotrophin stimulation tests in apparently sterilised animals, should be performed to elucidate the chromosomal, hormonal and anatomical sexual status of the patient.

In humans, primary neoplastic clitoromegaly can be managed by surgery, including cosmetic reconstruction techniques, radiotherapy, or combinations thereof (Björses *et al.* 1997; Brown & Warne 2005; Chan *et al.* 2004; Houk & Lee 2005; Hyun & Kolon 2004; Jones & Matthews 1999; McNeely 1992; Oyama *et al.* 2004; Sur 1983; Warne, Grover & Zajac 2005). In this patient, adequate medium-term control was obtained by the use of chemotherapy alone, although surgical clitorectomy is reported in the veterinary literature (Soderberg 1986). It is possible that chemoradiation of the clitoris and draining lymphatics could play a role in future cases of isolated or regional clitoral lymphoma (and other animal neoplasms in this area), although it is difficult to advise this with any degree of certitude. The presence of a paraneoplastic syndrome with this lymphoma complicated management and contributed to the patient's demise. Nonetheless, both the neoplasm and paraneoplastic syndrome responded well to initial management.

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Competing interests

The authors declare that they have no financial or personal relationship(s) which may have inappropriately influenced them in writing this article.

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