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Neoplastic disease

CD117 expression in canine ovarian tumours

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ABSTRACT

Canine ovarian cancer poses a significant diagnostic and therapeutic challenge. The heterogeneous nature of ovarian tumours makes accurate histological identification difficult, whilst treatment is limited to surgical excision. The tyrosine kinase receptor CD117 is neo-expressed in many tumours and represents a potential diagnostic and prognostic biomarker and therapeutic target. This study aimed to establish if CD117 is neoexpressed in canine ovarian tumours. Immunohistochemistry was employed to assess expression of CD117 in 29 canine ovarian tumour samples. CD117 labelling was assessed with a semi-quantitative immunoreactivity score, and the location of labelling was recorded as membranous, focal cytoplasmic or diffuse cytoplasmic. Histological morphology was assessed and used to assign subgroups based on growth pattern. Cytokeratin 7 labelling was used to indicate the tumour type as epithelial or sex-cord stromal in origin. Mitotic index, percentage of necrosis and vascular invasion were also assessed and evaluated for association with CD117 expression. Overall, 81% of ovarian tumours neoexpressed CD117 and normal ovarian tissue did not express CD117. Positive immunolabelling was seen in a subset of cells in both ovarian carcinomas (n = 20) and ovarian granulosa cell tumours (n = 3). There was no association between CD117 expression and patient age, histological subtype, mitotic index, percentage of necrosis or vascular invasion. This is the largest study to identify the expression of CD117 in canine ovarian tumours, but further research is needed to elucidate its prognostic and therapeutic value.

1. Introduction

Canine ovarian tumours are common and understudied. The disease occurs in up to 6.3% of unneutered dogs and can develop from ovarian remnants in neutered animals [1,2], with metastasis in 29% of cases [3]. Biopsy is contraindicated due to a high risk of seeding [4], and with non-specific clinical signs and the potential for quick metastasis, diagnosis is often made too late for ovariohysterectomy or chemotherapy to be curative [1]. Euthanasia on diagnosis is common as the prognosis can be poor [4] and the disease depletes quality of life, diminishes fertility [5] and can cause deleterious endocrinopathies [6]. In humans, severe pelvic and abdominal pain has been reported [7,8], which is probably also experienced by animals. There may be an increased risk of ovarian tumours in Boxers, German Shepherd Dogs, Yorkshire and Boston Terriers, Poodles [6] and Pointers [9], and it is most prevalent in dogs over 6 years of age [6].

The most prevalent canine ovarian tumours are carcinomas and granulosa cell tumours (GCTs) [10]. Ovarian carcinomas (OCs) arise from the ovarian surface epithelium and surface epithelial structures (SES) [10]. They are the most common and aggressive and have metastatic rates of up to 48% [3]. Histologically, OCs contain tubular, cystic and papillary growth patterns, characterized by large cuboidal or columnar cells with scant or moderate amounts of cytoplasm and basal nuclei [11,12]. GCTs derive from sex-cord stromal tissue and are unlikely to metastasize [1,3], but they have a greater variety of histological patterns, making accurate diagnosis difficult. Cytokeratin 7 (CK7) is a type II intermediate filament found in ovarian surface epithelium and thus can be used to differentiate epithelial from sex-cord derived tumours [13].

The tyrosine kinase receptor CD117 is encoded by the proto-oncogene *c-KIT* and belongs to the type III subfamily of receptor tyrosine kinases [14]. It is a transmembrane protein consisting of extracellular, transmembrane and juxtamembrane domains [15]. CD117 is expressed in normal tissue such as skin and mammary

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epithelium, mast cells, germ cells, epidermal melanocytes, cerebellar cells, Cajal cells of the gastrointestinal tract, spermatogonia, oocytes, primary follicles and stem cells [14]. Alongside its ligand stem cell factor (SCF), CD117 initiates pathways including the P13-kinase/AKT and RAS/MAPK pathways [13], with downstream effects on apoptosis, cell proliferation [16] and maturation [17], chemotaxis [18] and stem cell renewal [19]. In human epithelial OCs, neoexpression of CD117 is associated with an aggressive phenotype, recurrence and chemoresistance [20]. Targeted therapy with tyrosine kinase inhibitors (TKIs) can improve treatment in some human cancers that express CD117 [21]. CD117 neoexpression is also found in canine neoplasia, including mast cell tumours (MCTs) [22], gastrointestinal stromal tumours (GISTs) [23], seminomas [24], Merkel cell tumours [25] and renal [26], nasal [27], mammary [28] and prostatic carcinomas [29]. One study reported CD117 expression in three canine ovarian tumours, but each had differences in intensity and location of expression [30]. A larger characterization of CD117 expression in ovarian tumours is needed as CD117 may prove to be of prognostic or therapeutic use. The aim of this project was to determine if CD117 is neoexpressed in canine ovarian tumours.

2. Materials and methods

2.1. Tissue samples and histological examination

Ten primary ovarian tumour samples were retrieved from the Veterinary Pathology Group archives and nineteen samples were retrieved from the pathology archives at the Veterinary College, University of Lleida, Spain. All samples were surgical biopsies. Twenty samples contained areas of histologically normal ovary and two normal ovaries from routine canine ovariohysterectomies were also included in the study. Samples had been embedded in paraffin wax after fixation in 10% neutral buffered formalin for 24–48 h at room temperature. Samples were sectioned at 4 μm and stained with haematoxylin and eosin (HE). HE-stained tissue sections were histologically examined by two board-certified veterinary pathologists (A.S.B and S.L.P) for morphological assessment, necrosis, vascular invasion and mitotic count in 10 high-power fields in the most mitotically active area (2.37 mm^2).

2.2. Immunohistochemistry

Four-μm fresh-cut tissue sections from formalin-fixed, paraffin-embedded tissue blocks were labelled with monoclonal antibodies against CK7 (clone ab9021, 1:100; Abcam, www.abcam.com) and CD117 (clone T595, RTU; Leica Biosystems, www.leicabiosystems.com) on a BondMax Autostainer (Leica Biosystems).

Heat-induced antigen retrieval was performed using a pH 6 buffer (Bond ER1; Leica Biosystems) for 20 min (CK7) and pH 9 buffer (Bond ER2; Leica Biosystems) for 20 min (CD117) at 90°C. The Bond Polymer Refine Detection Kit (Leica Biosystems) was used for visualization with haematoxylin counterstain. A canine mast cell tumour (CD117) and a mammary gland adenocarcinoma (CK7) were used as positive controls. Negative controls were produced using Primary Antibody Diluent (Leica Biosystems) and omitting the primary antibody. When present in neoplastic tissue sections, histologically normal ovarian tissue was used as an internal control. Positive labelling was indicated by the presence of brown cytoplasmic and/or membranous labelling. Immunoreactivity and labelling intensity were assessed and any discrepancies discussed and agreed on with use of an Olympus BX43 double-headed microscope (Olympus, www.olympus.co.uk).

CK7 expression was positive if labelling was present in any neoplastic cells within the sample, and this identified tumours as carcinomas. Diagnosis of GCTs was based on lack of CK7 labelling and histopathological features.

CD117 expression was graded with a semiquantitative scoring system based on labelling intensity (LI) and percentage of positive cells (PC) as previously described [31–33]. An immunoreactivity score (IRS) was generated by multiplying LI by PC. LI was defined as: 0 (negative), 1 (weak), 2 (moderate), 3 (strong). PC was defined as: 0 (no positive cells), 1 (1–10% positive), 2 (11–40%), 3 (41–70%), 4 (>70%). PC was defined as the percentage of neoplastic cells rather than of the entire slide. The location of positive CD117 labelling was assessed as membranous or cytoplasmic (focal, multifocal or diffuse) and both staining patterns were used to generate the IRS. The slides were examined by two of the authors (A.S.B and H.E.M), and any differences in opinion were resolved with use of a double-headed microscope to reach an agreement.

2.3. Statistical analysis

Expression of CD117 was compared with histological subtype, mitotic count, vascular invasion, necrosis and inflammation. A chi-square test and a Fisher's exact test were used for studying categorical variables.

3. Results

3.1. Histopathology

Twenty-nine ovarian tumour samples were morphologically assessed as cystic (n = 2), solid/tubular (n = 4) or papillary (n = 23) based on the predominant pattern, as samples were often heterogeneous with more than one histological arrangement present. Samples represented 18 different dog breeds with the most common being crossbreed (n = 10) and Boxer (n = 2). Age ranged from 2 to 13 years, with a mean of 7.9 years. The signalment, histopathological and immunohistochemical features are summarized in Table 1.

3.2. CK7 immunolabelling

There were more OCs (n = 24) than GCTs (n = 5). Surface epithelium and SES were CK7 positive, whilst neoplastic cells displayed weak, moderate or strong cytoplasmic labelling. Expression was particularly strong apically in areas with papillary and tubular growth patterns. As neoplastic cells became histologically poorly differentiated, CK7 expression appeared reduced or was lost (Fig. 1A).

3.3. CD117 immunolabelling

There was no CD117 expression in normal canine ovarian tissue (Fig. 1B) but there was expression in a subset of ovarian neoplasms (n = 23, 79%). There were no statistically significant associations between CD117 labelling and any clinical or histological parameters (Supplementary Tables 1 and 2). CD117 labelling varied from multifocally weak to strong. A membranous and cytoplasmic labelling pattern was observed in all cases (Fig. 1C) in both OCs and GCTs. The labelling within the sections varied from focal to multifocal (Fig. 1C and D) or diffuse, and those cases with a diffuse expression normally had strong cytoplasmic labelling in poorly differentiated

Table 1
Signalment and histopathological and immunohistochemical features of canine ovarian cancer samples

Case	Breed	Age (years)	Growth pattern	% necrosis	Mitotic count	Lymphatic invasion	Tumour type	CD117 IRS
1	Bulldog	6	Cystic	–	2	–	OC	6
2	Crossbreed	10	Papillary	–	0	–	OC	6
3	Fox Terrier	11	Papillary	–	1	–	OC	3
4	Bernese Mountain Dog	4	Papillary	–	1	–	OC	2
5	Boxer	13	Papillary	–	3	–	OC	1
6	Crossbreed	4	Papillary	5	15	–	GCT	6
7	Crossbreed	13	Solid	1	4	–	OC	1
8	Crossbreed	12	Papillary	–	0	–	OC	1
9	Husky	11	Papillary	–	3	–	OC	2
10	Crossbreed	8	Solid	–	3	–	OC	0
11	Pug	8	Papillary	–	0	–	OC	2
12	Crossbreed	10	Papillary	–	6	–	OC	2
13	Rough Collie	10	Papillary	–	1	–	OC	4
14	Labrador Retriever	5	Solid	–	1	–	GCT	0
15	Bracco Italiano	4	Papillary	–	10	+	OC	1
16	Belgian Shepherd	10	Papillary	–	8	–	GCT	6
17	Crossbreed	Unknown	Papillary	–	2	–	GCT	1
18	Crossbreed	10	Papillary	–	1	–	OC	0
19	Crossbreed	8	Papillary	–	1	–	OC	3
20	Crossbreed	Unknown	Papillary	30	5	–	GCT	0
21	Boxer	11	Papillary	–	5	–	OC	0
22	Lurcher	8	Papillary	–	1	–	OC	0
23	Flat Coat Retriever	8	Papillary	30	12	–	OC	2
24	Rough Collie	2	Papillary	–	8	+	OC	4
25	Golden Retriever	10	Papillary	–	0	–	OC	6
26	Bichon Frise	7	Solid	–	18	+	OC	4
27	King Charles Spaniel	Unknown	Papillary	–	1	–	OC	3
28	Yorkshire Terrier	10	Solid	–	7	–	OC	9
29	Poodle	10	Cystic	–	0	–	OC	3

Mitotic count describes the number of mitoses in 10 high-power fields.
OC, ovarian carcinoma; GCT, granuloma cell tumour; IRS, immunoreactivity score.
+, present; –, none.

neoplastic cells (Fig. 1E and F). Rarely, interstitial cells and endothelial cells in capillaries were weakly positive (Fig. 1).

4. Discussion

This is the first comprehensive study and description of CD117 expression in a large sample of canine ovaries and tumours. Histopathological examination was used to characterize ovarian tumour samples and ascertain their morphological characteristics and histological subtype, mitotic count, extension of necrosis and vascular invasion. Further immunohistochemical assessment of CK7 was used to support the diagnosis of OC or GCT. An IRS was used to quantify the intensity and extent of CD117 expression.

Normal ovarian tissue did not express CD117 but positive CD117 immunolabelling was found in both GCTs and OCs and, although not statistically significant, OCs generally had more intense expression in comparison with GCTs.

There are a few mechanisms that may explain CD117 neoexpression. Mutations of *c-KIT* and *PDGF*, another member of the class III RTK family, perturb the interactions between domains of CD117, making it constitutively active [34]. SCF interacts with the RAS-Erk1/2, JAK/STAT and P13 kinase pathways and activates the Src family kinases, all contributing to cell survival and proliferation [15,35].

In human OCs, activating *c-KIT* mutations have not been found [36,37], but upregulation of CD117 may be caused by an increase in SCF triggered by TGF-β and the cAMP signalling pathway [38]. An autocrine feedback loop has been proposed as a mechanism of proliferation in human OCs which co-express CD117 and SCF [39]. CD117 may also contribute to tumourigenesis by promoting characteristics of cancer stem cells (CSCs). CD117 is a stem cell marker and has been proposed as a CSC marker and prognostic indicator in human epithelial ovarian carcinoma [40], and cancer cells expressing CD117 are described as having characteristics of 'stemness' [41].

In accordance with the present study where only one carcinoma had diffuse intense CD117 immunolabelling, a study of human ovarian carcinomas revealed low expression of CD117 in 10% of cases, while only 2% had intense expression [37]. The appearance of the positive labelling was also similar, and CD117 expression appeared to be associated with poor differentiation [37]. In the present study, poorly differentiated areas immunonegative for CK7 were often immunopositive for CD117. Neoplastic cells in which CD117 and CK7 were co-expressed may correspond to an earlier stage of tumourigenesis. Occasionally, interstitial cells were immunopositive for CD117. A similar finding has been reported in human epithelial OCs, whereby expression in fibroblast-like stromal cells was associated with advanced tumour stage and poor differentiation, suggesting that they may be a form of stem cell [42]. Positive CD117 labelling was intermittently seen in capillary endothelial cells, which may identify them as vascular endothelial stem cells [43].

Studies in canine MCTs have shown a strong correlation between cytoplasmic expression of CD117 and histological grade, mitotic index and necrosis [44]. Follow-up data on each of the present cases would be useful to examine if CD117 expression serves as a prognostic indicator, and further studies addressing this hypothesis are warranted. Many TKIs have shown good results in treating canine MCTs [45] and, based on the results of the

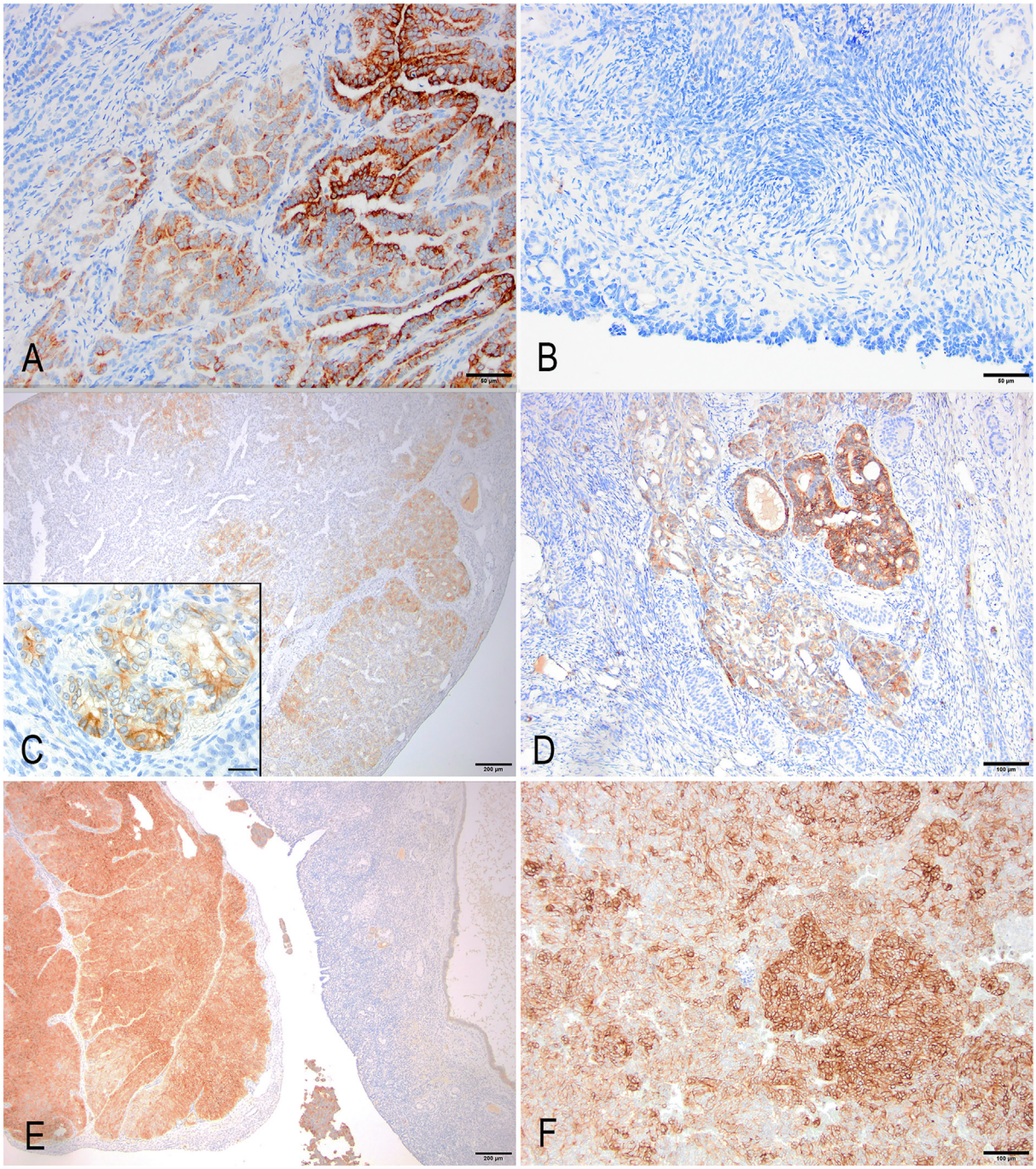

Fig. 1. Immunohistochemical evaluation of CK7 and CD117 in canine ovarian tissues. (**A**) CK7 variably expressed in ovarian carcinoma with intense to moderate labelling of neoplastic cells. Bar, 50 μm. (**B**) Normal canine ovary does not express CD117. Immunoreactive score (IRS) = 0. Bar, 50 μm. (**C**) Low-power magnification of an ovarian carcinoma with moderate multifocal CD117 expression. IRS = 6. Bar, 200 μm. Inset: high-power magnification of neoplastic cells with membranous and cytoplasmic CD117 immunolabelling. Bar, 40 μm. (**D**) Higher magnification of (**C**) showing moderate multifocal labelling of neoplastic cells. IRS = 6. Bar, 100 μm. (**E**) Low-power magnification of an ovarian carcinoma with moderate multifocal CD117 expression. IRS = 9. Bar, 200 μm. (**F**) Higher magnification of (**E**) showing strong diffuse CD117 expression. IRS = 9. Bar, 100 μm.

present study, they may have potential as a therapeutic option in canine OCs.

5. Conclusion

This study has demonstrated the neoexpression of CD117 in canine ovarian tumours. Further studies including a larger number of cases, focusing on possible associations between CD117 expression, clinicopathological characteristics and clinical staging, are warranted.

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Declaration of competing interests

The authors declared no conflicts of interest in relation to the research, authorship or publication of this article.

Appendix A. Supplementary data

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