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Comparative aspects of canine and human inflammatory breast cancer

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ABSTRACT

Inflammatory breast cancer (IBC) in humans is the most aggressive form of mammary gland cancer and shares clinical, pathologic, and molecular patterns of disease with canine inflammatory mammary carcinoma (CIMC). Despite the use of multimodal therapeutic approaches, including targeted therapies, the prognosis for IBC/CIMC remains poor. The aim of this review is to critically analyze IBC and CIMC in terms of biology and clinical features. While rodent cancer models have formed the basis of our understanding of cancer biology, the translation of this knowledge into improved outcomes has been limited. However, it is possible that a comparative “one health” approach to research, using a natural canine model of the disease, may help advance our knowledge on the biology of the disease. This will translate into better clinical outcomes for both species. We propose that CIMC has the potential to be a useful model for developing and testing novel therapies for IBC. Further, this strategy could significantly improve and accelerate the design and establishment of new clinical trials to identify novel and improved therapies for this devastating disease in a more predictable way.

1. Introduction

Dogs spontaneously develop cancers that share the biology and heterogeneity of cancers found in humans, including many clinical, molecular, and pathologic characteristics. Canine cancers are often relatively large tumors that develop spontaneously in large outbred mammals; are genetically complex and diverse; exist in the presence of an intact immune system, with complex interactions between the host immune system and tumor cells; have significant tumor heterogeneity both within patients and between patients; develop therapeutic resistance and metastasize to distant sites. The natural history and potential clinical use of cancers in companion dogs in general is out of the scope of this review and have been extensively reviewed elsewhere [1–4].

Inflammatory breast cancers in humans (IBC) and the corresponding canine disease, canine inflammatory mammary carcinoma (CIMC), are the most aggressive type of mammary cancer in both species with short survival times after diagnosis [4–6]. In humans, IBC was first described in 1814 by Charles Bell as a painful breast tumor with a poor prognosis, presenting purple discoloration of the overlying skin [7]. In 1924 the designation "inflammatory breast cancer" was applied by Lee and Tannenbaum, who provided a clinical description of the malignancy [8]. IBC is a rare and highly metastatic type of breast cancer comprising less than 3% of human breast cancer cases in the United States [9], with a higher incidence observed in Northern Africa where the incidence varies from approximately 7% in Tunisia [10] to 11% in Egypt [11]. The reasons for such a high incidence in this part of the world remain unknown. IBC is primarily a clinical adjunct to the histopathologic diagnosis of breast cancer. IBC presents unique histopathologic and clinical features for both humans and animals: edema, erythema, firmness, painful sensation, and warmth of the mammary glands coupled with histologic confirmation of tumor invasion of dermal lymphatic vessels [12,13]. Inflammatory

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mammary carcinoma in companion animals was initially described in dogs [14] and more recently in cats [15]. In a study at the Complutense University in Madrid, Spain, the reported prevalence of CIMC among dogs presenting for local consultation with mammary gland tumors and dysplasia was reported to be 7.6% [16]. Based on clinical and histologic similarities, the possibility of using CIMC as a model to study IBC has been proposed by several authors [16–19]. The comparative aspects between IBC and CIMC, including the etiology, molecular biology, diagnosis, treatment, and prognosis, supporting the rationale for using CIMC as a model for IBC are summarized and analyzed in Table 1 [6,14,20–52]. The effect of hormones on the etiology of CIMC and IBC is summarized in Table 2 [53–60].

2. Etiology

2.1. Endocrine etiology

The etiology of both IBC and CIMC is multifactorial, resulting from a combination of hormonal changes, accumulated genetic mutations [5], and environmental factors [61–63].

Several studies have been performed using canines to detect the expression of steroid hormones and their receptors that could be implicated in the genesis of the abnormal mammary epithelial proliferation observed in CIMC and in canine mammary tumors (CMT) overall [53–55]. Expression of estrogen receptor alpha (ERα), estrogen receptor beta (ERβ) and androgen receptor (AR) was evaluated by immunohistochemistry in a series of CIMC and non-CIMC tumors [54]. In all CIMC cases (N=14), ERα expression was absent and 13 of 14 cases (93%) were ERβ- and also AR-positive. Moreover, AR expression in CIMC was increased relative to non-CIMC and normal mammary gland [54]. A more recent study [56] using a quantitative scoring system generated by adding the percentage of positive cells and the intensity of immunolabelling (total score expressed as mean ± S.E.M.) showed significant increases in immunohistochemistry staining for aromatase ($P = .025$), an enzyme that converts androgens to estrogens in situ [64], and also ERβ ($P = .038$) and PR ($P = .0037$) in CIMC (n=21) versus non-CIMC (n=19). However, no differences were found for expression of AR between CIMC and non-CIMC [56]. This disparity in AR results studies [54,56] could be explained by the differences in scoring systems and tumor series used, as well as by an increase in the conversion of androgens to estrogens in CIMC through abundant aromatase expression and subsequent down-regulation of AR in the study by de Andres et al.

Hormone serum levels of dehydroepiandrosterone, androstenedione, testosterone, progesterone, and estrone sulfate were significantly higher in CIMC than in non-CIMC samples [53,54]. The abundance of steroid hormones might be an important contributing factor in the pathogenesis of CIMC by mechanisms of paracrine and/or autocrine action. Estrone sulfate in particular may be converted into estrone and estradiol by the enzyme steroid sulfatase [65] or can directly transactivate estrogen and ARs [66], therefore magnifying the effects of steroid hormonal regulation in CIMC.

In IBC, to the best of our knowledge, detailed imunoexpression of ERα and β, AR, and aromatase have not yet been reported in the literature. Of note, steroid hormones levels (including progesterone, androstenedione, testosterone), 17β-estradiol, and estrone sulfate levels have been shown to be higher in the conditioned media of the IBC cell line SUM149 than in the CIMC cell line IPC-366 by ELISA immunoassay [67]. This study demonstrated *in vitro* secretion of steroid hormones (progesterone, androstenedione, testosterone, 17β-estradiol, and estrone sulfate) [67], suggesting a role for hormonal regulation in IBC. However, studies with clinical samples, including tumor tissue and serum from patients with non-IBC and patients with IBC, would be required to confirm this hypothesis and overcome the inherent limitations associated with *in vitro* conditions.

2.2. Viral etiology

Regarding the role of infectious agents in the etiology of breast cancer, viral infections by high-risk human papillomavirus (HPV) have been identified in metaplastic mammary carcinomas [30], but a causal relationship has not been established. In patients with IBC, titers of human cytomegalovirus (HCMV) IgG antibodies were found to be higher than in non-IBC patients. The presence of HCMV has been suggested to be linked to the etiology and pathogenesis of IBC with HCMV playing an oncomodulatory role by infecting adjacent tissues, leading to overexpression and activation of NF-κB/p65 [29,68,69]. To support this hypothesis, a recent study that enrolled 91 patients with non-IBC and 44 with IBC reported DNA from HCMV and HPV-16 were the most detected viral DNAs in breast carcinoma tissues, although the frequency and prevalence of HCMV and human herpes virus type 8 (HHV-8) DNA were significantly higher in IBC than non-IBC tissue [70]. However, the high incidence found in this study could be because of cross-contamination during the handling, processing of tissue samples, and the isolation of viral DNA because the measures to prevent cross-contamination were not disclosed, therefore casting doubt on its results. The absence of papillomavirus DNA has been confirmed in the normal canine mammary gland (N=5) and CMTs (N=27). Whilst this suggests these viruses are not associated with canine mammary carcinogenesis, the small numbers of cases studied makes it impossible to rule out [71].

Mouse mammary tumor virus-like sequences (MMTV) have been associated with human breast cancer [72–74]. These sequences were also found in CMT at similar frequencies in normal, benign, and malignant CMTs, suggesting that MMTV is not causally associated with CMT [21]. Overall, the involvement of viruses in breast cancer, including IBC, remains unclear [75,76]. Given the influence of viruses in cancer [77], and in particular the oncogenic role of MMTV in murine mammary carcinogenesis [78–80], further research is warranted to determine the possible role of viruses in the malignant transformation of mammary gland cells of both dogs and humans.

3. Molecular biology of IBC

3.1. Inflammatory microenvironment

During carcinogenesis, it is often stated that malignant transformation is triggered by the accumulation of DNA mutations [81]. Some have suggested the high level of inflammation observed in IBC may serve to increase genetic instability and its associated DNA damage, promoting the malignant phenotype by increasing mutation rates [82,83].

Considering IBC or CIMC as types of cancer with flaring inflammation, the expression of diverse cytokines and inflammatory mediators has been evaluated to determine their role in the severity of the disease. In CIMC, a study analyzing the presence of several cytokines in the serum and tissue homogenates of CIMC (n=7), malignant non-CIMC (n=24), mammary-gland hyperplasia (n=7), and benign tumors (n=10) reported higher IL-10 and IL-8 *serum levels* in CIMC tumors than in the other groups, whereas in *tumor-tissue homogenates*, only IL-10 was significantly higher in CIMC than in the other groups, indicating a role for immunosuppression in the progression of CIMC [22]. One of the main