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News & Comments

c-KIT and PDGFRA Mutational Analysis in Canine Gastrointestinal Stromal Tumours

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The most frequent mesenchymal tumours of the gastrointestinal (GI) tract wall in both humans and dogs, gastrointestinal stromal tumours (GISTs) are caused by the neoplastic transformation of interstitial cells of Cajal (ICC), which act as "pacemaker" cells between the myenteric and muscular tunic plexuses of the GI tract and regulate peristalsis. Human GISTs have been found to harbour mutations in the exons 11, 9, 13, and 17 of the c-KIT proto-oncogenes. Due to the frequent discovery of these mutations, they play a significant pathogenetic role in the constitutive dimerization and activation of the KIT receptor, which occurs regardless of the ligand-receptor contact.

The study was carried out on formalin-fixed paraffin-embedded histological samples of canine GISTs received at the Pathological Service for histological diagnosis over a period of 16 years at the Department of Veterinary Medical Sciences (DIMEVET) University of Bologna (Ozzano Emilia, Bologna, Italy). The classification was made using histological findings in accordance with the standards set forth by the WHO specifically for gastrointestinal tract tumours and the veterinary literature.

Gastrointestinal stromal tumours (GISTs) are a unique diagnostic neoplastic entity that, despite being very rare and incompletely characterized in dogs, has developed through time a distinct clinical and histological identity, and attracts a lot of attention for a variety of reasons. Indeed, canine GISTs are an ideal spontaneous comparison model since they closely resemble their human counterparts. The requirement for identifying these neoplasms as GISTs is CD117 positivity in more than 70% of neoplastic cells. In all our tumours, CD117 analysis indicated a strong and broad positivity to more than 90% of the cancerous cells. Most of the time, this positivity was of the finely granular variety, but in one instance, a paranuclear positivity manifested as tiny, spherical clusters with vibrant colours.

Human PDGFRA-mutated GISTs often manifest as epithelioid histology, are in the stomach, and are strongly immunopositively for PDGFR. It is noteworthy that instance #4 displays the same epithelioid histotype while being situated in the colon and having a moderate level of PDGFR immunopositivity. Imatinib mesylate (Gleevec), utilized for its capacity to inhibit protein kinases, causes a noticeable tumour response, and extends survival time, was studied on two dogs with known exon-11 c-KIT mutations. To comprehend their potential therapeutic efficacy, c-KIT and PDGRFA mutations in canine GISTs must be thoroughly explored.

In this study, c-KIT mutations were found in 50% of the cases, and it seems that their existence is

connected to malignancy. Canine GISTs had not yet been discovered to include an activating mutation of PDGFRA, which in humans is present in a sizable portion of GISTs. The study's findings support the hypothesis that c-KIT activating mutations contribute significantly to canine GISTs, are associated with a biological activity that is malignant, and have significant therapeutic implications. It will take more research with a larger sample size and follow-up information to show the prognostic and predictive value of KIT or PDGFRA mutations in canine GISTs.

Source: Veterinary Sciences

KEYWORDS

canine gastrointestinal stromal tumors; PDGFRA; c-KIT; GIST; PDGFRA mutation; c-KIT mutation