ABSTRACTS

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Cytokines as immunological markers for systemic inflammation in dogs with pyometra

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OBJECTIVES AND METHODS: Pyometra is a disease that occurs in over 50% of adult intact dogs of certain breeds (1) and is caused by an opportunistic bacterial infection of the uterus (2). Pyometra progresses into a life-threatening condition, systemic inflammatory response syndrome (SIRS), i.e. sepsis, in nearly 6 of 10 cases (3). Clinical diagnostic criteria for SIRS evaluation include heart- and respiratory rates, body temperature, leucocyte concentrations and percentage band neutrophils (4). The lack of specific criteria for SIRS in dogs may pose a challenge when determining treatment for pyometra and may result in overuse of broad-spectrum antibiotics in false-positive cases. It is therefore of great importance to identify diagnostic criteria that will allow for early and specific diagnosis of both pyometra and SIRS.

A great variety of up-regulated cytokines and chemokines was previously found in uteri from dogs with pyometra (5). If detectable systemically, certain cytokines could act as biomarkers for diagnosing pyometra and possibly also SIRS in dogs. Moreover, because the inflammatory and coagulation changes that accompany severe infections in dogs are similar in humans (6), a pattern of SIRS-specific cytokines found in dogs could be of interest for human sepsis diagnosis.

We applied Luminex xMAP Technology (Milliplex MAP panel, Millipore) to measure nine different cytokines: IFN-γ, IL-4, IL-6, IL-7, IL-8, IL-10, IL-15, IL-18 and TNF-α, and a sandwich ELISA (Phase-range, Tridelta) to measure CRP in serum samples from 21 dogs with pyometra and 12 healthy control dogs. The study was approved by local ethical committee and in agreement with the owners of the dogs. Data were analyzed with Mann-Whitney nonparametric t-test and Spearman rank correlation, and p-value <0.05 was considered significant.

RESULTS: Five cytokines were detectable in more than 50% of all samples, i.e. IL-7, IL-8, IL-15, IL-18, and TNF-α. Although IL-10 was detected in only 27% of all samples, 100% of measurable values were detected in samples from dogs with pyometra. All samples had detectable amounts of TNF-α, but the concentration did not differ between the groups. Less than 4% of all samples had detectable levels of IL-4, IL-6 and IFN-γ.

In the pyometra group, 14 dogs fulfilled the criteria for SIRS. The amount of IL-7 in SIRS-positive pyometra dogs was significantly higher (p<0.05) compared to that in healthy controls, but did not differ between SIRS-positive and SIRS-negative pyometra cases. Higher concentrations of IL-8 were detected in SIRS-positive dogs with pyometra compared to the SIRS-negative group (p<0.05). Surprisingly, IL-8 concentrations were much lower in SIRS-negative pyometra dogs compared to the healthy controls (p<0.01). Although no difference between groups could be detected for IL-15 and IL-18, the levels of these cytokines demonstrated a strong positive correlation (p<0.0001) and they also significantly correlated to the levels of IL-7 (p<0.0001; p<0.0001). Moreover, IL-15 concentrations were correlated to levels of C-reactive protein (CRP) (p<0.05). Levels of CRP were increased in dogs with pyometra compared to healthy controls (p<0.0001) as has been described previously (3).

CONCLUSION: The results suggest that an increased level of IL-10 may be one of the immunological indications of pyometra. Significantly higher levels of IL-7 were distinguishing dogs with pyometra that were positive for SIRS. Because CRP concentration has earlier been shown to be associated with SIRS and prolonged hospitalization (3), the positive correlation between CRP, IL-7, IL-15 and IL-18 detected in this study might suggest a role for these cytokines in the development of a systemic disease in dogs with pyometra.