

## Idiopathic canine polyarteritis in control beagle dogs from toxicity studies

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**It is sometimes difficult to assess the relevance of polyarteritis with treatment-related lesions in dog toxicity studies, as number of dogs used in a toxicity study is small and the lesions are similar to those seen in spontaneous diseases. This report is intended to establish a general profile of idiopathic canine polyarteritis in beagle dogs. Data from a total of 40 dog studies including 4-, 13- or 52-weeks studies conducted between 1990 and 2003 at Huntingdon Life Sciences, UK, were collected and analysed. There was no death by this disease and also no prominent clinical signs related to this disease. Histologically, males tended to develop polyarteritis more frequently than in females and epididymis is the most probable tissues, followed by thymus and heart. Dogs in two studies showed higher incidences of these lesions, whereas animals in the other studies did not exhibit, suggesting that genetic predilection plays an important role in this disease.**

**Key words:** beagle, dog, pain, polyarteritis

### Introduction

There are some reports on spontaneously occurring polyarteritis in the dog, especially beagle dog, which were described as beagle pain syndrome [5], idiopathic canine polyarteritis [2,6], spontaneous disseminated panarteritis [8], or spontaneous extramural coronary arteritis [4]. The pathogenesis and incidence were reviewed by several authors [1,2,3,4,5,7,9,10,11]. Most of this disease is spontaneous and their occurrence in beagle dog is relatively common. As this disease often encounters in toxicity study, small vascular lesions are often mistaken as treatment-related changes which could be complicated if the treated compounds are expected to show vascular lesions. This report is intended to establish a general profile of idiopathic canine polyarteritis from large data pool with a plenty of studies per year, and sources of variabilities (source of

animal supply, laboratory methods, husbandry and feed) are strictly controlled and standardized, especially within the context of a single laboratory.

### Materials and Methods

#### Animals

Male and female beagle dogs were obtained from a variety of suppliers (Mostly from Interfauna UK, colony in HLS, Marshall Farm and few studies from five different sources). At the beginning of treatment, the estimated age of animals was approximately 24–30 weeks old and the body weights were in the range of 4 to 11 kg (average age was approximately 8 months old). Documentation provided by the Supplier included details of litter of origin, date of birth and confirmation of inoculation against distemper, hepatitis, leptospirosis and parvovirus. Dogs were acclimatized to conditions in the kennel units between 2 to 10 weeks and they were subjected to routine examination and acceptance procedures before treatment. During the acclimatisation period the dogs were inoculated against canine distemper virus, canine hepatitis virus (CAV2), canine parvovirus, *Leptospira*, *Leptospira icterohaemorrhagiae* and *Bordetella bronchiseptica*. They also received treatment with an anthelmintic drug. Prior to the start of dosing a review of animal health was undertaken by a veterinary officer. The dogs were housed in kennels which had a floor area of 4.5 square metres and accommodated up to two animals of same sex and dosage group. Animal room temperature was generally maintained at 15 to 24°C during the study. Artificial light was set to give 12 hours continuous light and 12 continuous dark per 24. Air was supplied into the animal room and extracted to provide approximately 12 air changes per hour. All dogs had free access to automatic tap water valve. Each animal received 400 of standard dry diet (Diet A; Special Diets Services, UK) each day. Drinking water and diet were routinely subjected to chemical analysis to monitor possible influence on study. Graded white sawdust was used as litter and changed daily.

#### Histopathology

On completion of treatment, animals were necropsied completely according to GLP requirements. All tissues were

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**Table 1.** Profiles of studies and incidences of polyarteritis in beagle dogs

Study duration	Numbers of studies	Numbers of animals		Numbers of animals with idiopathic canine polyarteritis	
		Male	Female	Male	Female
4-weeks	15	30	30	2 (6.6%)	1 (3.3%)
13-weeks	15	30	30	6 (20%)	0
52-weeks	10	20	20	2 (10%)	1 (5%)
Total	40	80	80	10 (12.5%)*	2 (2.5%)
		160		12 (7.5%)	

\*,  $p < 0.05$  statistically significant when compared with the incidence in females

preserved in 10% neutral buffered formaline. In addition, samples of any macroscopically abnormal tissues (all nodules and tissue masses), were routinely preserved, along with samples of adjacent tissues where appropriate. Tissues were cut and embedded in paraffin wax. Sections cut at 4-5  $\mu$ m were stained with haematoxylin and eosin. The initial examination was undertaken by the study pathologist, the results of which were then subjected to peer review by second pathologist. The diagnoses reported represent the consensus opinions of both pathologists.

### Study design

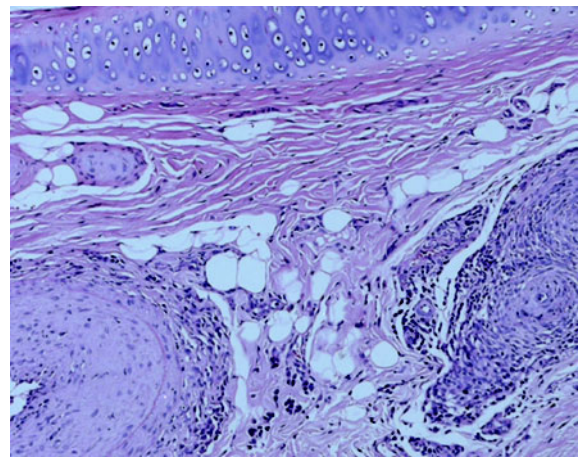
Retrospective survey was conducted for the idiopathic canine polyarteritis from control animals for 4-weeks, 13-weeks or 52-weeks toxicity studies previously performed at Huntingdon Life Sciences during the period of 1990-2003. Control animals from total 40 studies were designated for retrospective histopathological analysis and they consisted with a total 80 male and 80 female dogs. Animal number of each control group varied but at least 3 males and 3 females (Table 1).

### Statistical analysis

Comparison of the incidence of arteritis between the sexes was performed using the Fishers exact test. The data were analysed SAS 6.12.

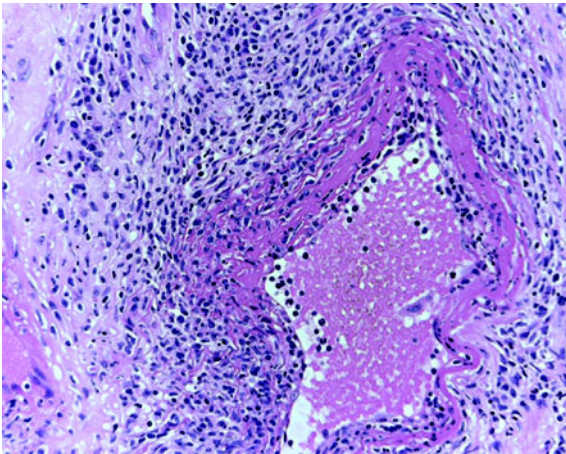
### Results

The profiles of studies and incidences of idiopathic canine polyarteritis of males and females are shown in Table 1. Although there were few sporadic deaths, there was no case that died from idiopathic canine polyarteritis. Also there was no case showing idiopathic canine polyarteritis indicating clinical signs or clinical pathology results in animals surveyed in this report. Histologically, idiopathic canine polyarteritis was characterised by intimal proliferation, medial necrosis with fibrin deposit, and marked mononuclear inflammatory cell infiltration with fibrosis, and occasionally thrombosis (Fig. 1, 2, 3). Generally any

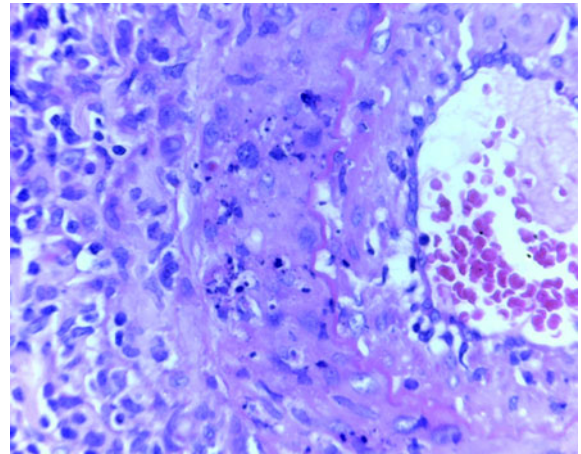


**Fig. 1.** Lung arteries from control male beagle dog from 13-weeks toxicity study. Marked intimal proliferation (left) and adventitial fibrosis (right) with inflammatory cell infiltration are seen.  $\times 100$ , H&E.

small to large muscular arteries were affected. In total, 12 (7.5%) dogs showed polyarteritis/periarteritis with a various tissue distribution, consisted of 10 (12.5%) males and 2 (2.5%) females. For 4-weeks of study, of these 2 (6.6%) males and a single female (3.3%) exhibited these lesions. For those numbers in 13-weeks and 52-weeks of study were 6 (20%) males and none in females, and 2 (10%) males and 1 (5%) female, respectively. Overall, males tended to show higher incidence of these lesions than those in females. Most of studies used in this survey did not show any case of polyarteritis but two 13-weeks studies had greater incidences of these findings. Male dogs including treated groups within these two 13-weeks studies showed that prominently higher incidence (10 out of 16 and, 5 out of 16 dogs identified polyarteritis). Data concerning the tissue distribution of idiopathic canine polyarteritis are presented in Tables 2. There was a trend toward that epididymis was the most probable tissue to have these findings, followed by thymus and heart.



**Fig. 2.** Affected artery in epididymis from the control male beagle dog from 52-weeks toxicity study. Note medial necrosis and mononuclear inflammatory cells around vessel.  $\times 200$ , H&E.



**Fig. 3.** Thymic artery from the control female beagle dog from 4-weeks toxicity study. See typical histological features of medial necrosis and fibrin deposits in idiopathic canine polyarteritis.  $\times 400$ , H&E.

## Discussion

Although this disease was called previously beagle pain syndrome, recently Kerns *et al.* [6] suggested it as idiopathic canine polyarteritis. This polyarteritis was mostly investigated by toxicologic pathologist and described mainly in laboratory beagle dogs [2]. Incidence of idiopathic canine polyarteritis varies with reports, from at the rate of about 3 % to these of one-third of the dogs [1,3,10,11]. Incidence rate in our survey was 7.5 %, which is similar to those other authors [1,3,10,11]. Possible sex predilection was discussed by several authors, although it was controversial among the studies. Many authors reported that there is no sex difference between both sexes [2,3,4,8], whereas Spencer A and Greaves [10] reported slightly higher incidence in males. In our study, we confirmed that males tended to develop more these lesions than in females. According to previous reports, there are specific clinical signs such as fever, weight loss, cervical neck pain and blood pictures including neutrophilic leukocytosis, hyperfibrinogenemia and hypoalbuminemia but we did not see any abnormalities during in-life phase, which are perhaps due to weak development or beginning

stage of this disease [1,2,3,9]. There was a higher incidence of these lesions in 13-weeks studies, however, it could be explained that incidentally included those two studies contributed higher rate to this figure rather than age specific difference of incidence. Detailed pathogenesis and etiology of this disease are not well known yet [8].

Ruben [8] speculated that parasitic infestation may have an important role in the pathogenesis as it alter immune system which lead to polyarteritis. As a probable cause of this disease, genetic predilection was also proposed by Stejskal *et al.* [11]. We confirmed that specific studies showed higher incidence of these lesions, whereas most of other studies did not exhibited any findings, which support that genetic background plays a some role in this disease. This idiopathic canine polyarteritis should be differentiated from treatment-induced vascular injury observed in dog pre-clinical studies. Clinical signs, distribution of lesions, characteristic features of histology provides important clues. For most types of vasodilator-induced vascular injury, the lesion is often restricted to coronary arteries, and associated with haemorrhage, whereas idiopathic canine polyarteritis

**Table 2.** Distribution of polyarteritis expressed by study duration and sex in beagle dogs

Study duration Tissue distribution	Male				Female				Total
	4 weeks	13 weeks	52 weeks	Total	4 weeks	13 weeks	52 weeks	Total	
Epididymis		5	1	6					6
Thymus	1	1	2	4	1			1	5
Heart	1		2	3			1	1	4
Cervical lymph node	1			1	1			1	2
Gall bladder				1					1
Spinal cords		1		1					1
Lung		1		1					1
Thyroid gland		1		1					1

often associated with fibrinoid necrotizing arteritis in many different arteries and also hemorrhage is not involved, which are differentiating this finding from other possible drug-induced vasculitis in dogs [2]. It would be necessary to characterize these lesions precisely from others, as some compounds could exacerbate these spontaneous lesions [2].

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