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Source: Journal of Wildlife Diseases, 6(4) : 220-225

Published By: Wildlife Disease Association

URL: <https://doi.org/10.7589/0090-3558-6.4.220>

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Epizootiology of Tropical Canine Pancytopenia^{*}

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Abstract

Tropical canine pancytopenia (TCP) is a newly recognized infectious disease of dogs in diverse tropical and subtropical areas. The disease is characterized by hemorrhage, pancytopenia, severe emaciation and persistent infection. Dogs with TCP are often presented with epistaxis, which is the most dramatic sign of the disease; however, a large number of affected dogs develop severe pancytopenia and die without manifesting clinical signs of hemorrhage. The disease has been reported most frequently in the German Shepherd. Pathological findings consist of petechial and ecchymotic hemorrhages on serosal and mucosal surfaces of numerous organs. The most prominent histological finding is a perivascular plasma cell infiltrate in most organs. Disease, indistinguishable from the natural disease, has been produced in laboratory dogs inoculated with whole blood from affected dogs. *Ehrlichia canis* has been consistently recovered from all experimentally infected dogs. Attempts to transmit the disease to other laboratory animals and to propagate the agent in cell cultures and embryonating eggs have been unsuccessful. The tick is the probable vector of the disease.

In 1963 an unusual disease characterized by hemorrhage, severe emaciation, pancytopenia and high mortality occurred in British military dogs in Singapore.¹⁰ Between 1963 and 1968 this disease, known as tropical canine pancytopenia (TCP), was responsible for the death of numerous military and privately owned dogs in Singapore and Malaysia.^{9,11,16} From extensive studies in Singapore¹⁰ and Malaysia⁹ it became apparent that the disease was probably infectious; however, an etiologic agent was not recovered.

In the Republic of Vietnam TCP was first recognized in 1967 in several Labrador Retrievers which had previously been trained as tracker dogs in Malaysia.¹⁵ During the following year an epizootic of the disease occurred in Vietnam among German Shepherds which had originated in the United States.¹⁵ To date approximately 180 U.S. military dogs have died of the disease in Southeast Asia. TCP has also been reported in military and privately owned dogs in the Caribbean.⁸ The disease has been reported most frequently in the German Shep-

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herd which is the predominant breed used as military dogs; however, dogs of other breeds have also been affected.

Purebred and imported dogs seem to be affected more often than local, mixed or native breeds.

Clinical Findings

A sudden onset of epistaxis (Fig. 1) is often the first indication that a dog is affected with TCP.^{8,15} In some instances epistaxis is the only apparent clinical sign; however, it may be accompanied by one or more of the following signs: anemia; edema of limbs and scrotum; loss of weight; ecchymotic hemorrhages on the abdomen; petechial hemorrhages in the mucosa of the penis, buccal cavity and conjunctiva; anorexia; dyspnea; fever; corneal opacity; lethargy; lymphadenopathy; posterior weakness; and hyphema.^{8,9,15,16} Death often occurs within a few days following onset of hemorrhage. Some dogs survive the initial hemorrhagic episode; however, in many of these instances epistaxis reoccurs and the dog eventually succumbs to the disease. Some dogs become chronic bleeders and have intermittent episodes of mild epistaxis over a period of several months prior to death.¹⁵ Coagulation time and prothrombin time are normal; however, bleeding time is prolonged.^{8,15} Severe anemia, leucopenia and thrombocytopenia occur.^{8,9,15,16} The erythrocyte sedimentation rate is often elevated⁸ and uremia occurs in some affected dogs.¹⁵ A large number of dogs with TCP do not develop epistaxis. Hematologic signs in these dogs are similar to those observed in dogs with epistaxis but clinical signs of hemorrhage do not occur. These dogs often become severely debilitated prior to death.^{8,15}

Dogs with TCP usually have a history of a febrile episode occurring 2 or more months prior to the onset of epistaxis.¹⁵ In some dogs this febrile episode may be very mild and may go unrecognized; however, the fever may be accompanied by anorexia, decreased stamina, severe weight loss and edema of the limbs. A



FIGURE 1. German Shepherd with tropical canine pancytopenia. Epistaxis and corneal opacity are apparent.

lowering of the red and white blood cell counts occurs. In a few instances mild epistaxis may also be evident during the febrile episode. Following this the dog will usually regain a normal physical appearance; however, the anemia and leucopenia not only persist but often become more severe. Therefore, prior to the onset of epistaxis the only sign of disease may be an altered hemogram. In those dogs that die without clinical signs of hemorrhage, death may be attributable to extensive internal hemorrhage or secondary infections which are associated with severe anemia and leucopenia.

The tick is the probable vector of the disease. Outbreaks of TCP have often been associated with severe tick infestations, and the incidence of the disease has decreased or disappeared in some kennels after rigid tick control measures were enforced.⁹

Pathological Findings

Pathological findings have been similar in all forms of the disease. In most instances there is a generalized lymph-

adenopathy characterized by moderately enlarged lymph nodes which on cross section are often reddish-brown in color.

Petechial and ecchymotic hemorrhages are present on serosal and mucosal surfaces of major organs and in subcutaneous tissue (Fig. 2). Other changes include a brownish mottling of the lung and moderate enlargement of the spleen in some dogs.⁴

The most prominent microscopic lesion is a plasma cell infiltrate in numerous

organs, especially the meninges, lung, spleen, and kidney. The plasma cell infiltrate is often perivascular and becomes more severe as the disease progresses. In those instances where the disease is prolonged, centrilobular necrosis of the liver occurs. The bone marrow is hypoplastic.⁴

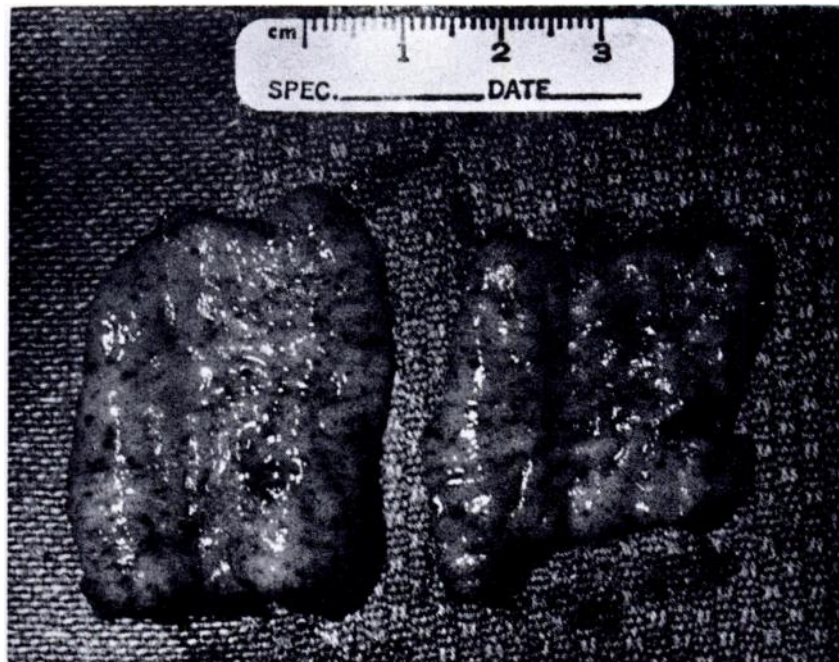


FIGURE 2. Small intestine of a dog infected with tropical canine pancytopenia. Petechial hemorrhages are evident in the mucosa.

Etiology and Experimental Disease

Experimental disease, indistinguishable from the natural disease, has been produced in laboratory dogs. German Shepherds and Beagles inoculated intravenously or intraperitoneally with fresh whole blood from an affected dog develop signs of disease within 10-15 days. The onset is characterized by fever, anorexia, depression, lowered red and white blood cell counts and elevation of the erythrocyte sedimentation rate. The length of the febrile period varies from a few days

to several months; however, in most instances it persists for 15-25 days. Many dogs develop anemia, leucopenia and thrombocytopenia and become severely debilitated with extreme loss of weight. Some dogs die during this period. Intracytoplasmic inclusions (Fig. 3) of *Ehrlichia canis*, a rickettsia, can be demonstrated in monocytes in capillary blood smears prepared during the febrile period and stained by any of the Romanovsky type stains.⁵ Although these inclusions



FIGURE 3. Impression smear prepared from lung tissue of a dog with tropical canine pancytopenia. Inclusions of *Ehrlichia canis* are evident in the cytoplasm of the monocyte. May-Grünwald Giemsa stain X 2000.

are most frequently found in monocytes, they may occur in lymphocytes and even neutrophils. These inclusions are more readily found in mononuclear cells in impression smears prepared from lung, spleen, liver and kidney tissue of an affected dog. The inclusions appear as compact, single or multiple, morula-like bodies in the cytoplasm. These morulae

are apparently aggregates or colonies of elementary bodies.

Many dogs survive the initial febrile period and often regain a normal physical appearance. Abnormal hematological signs may partially or completely disappear. Relapses, however, occur and are characterized by a reappearance of earlier signs. Epistaxis and other forms of hemorrhage, associated with thrombocytopenia, have occurred in experimentally infected German Shepherds as early as 10 days and up to 120 days post inoculation. Clinical signs of hemorrhage have not been observed in laboratory Beagles experimentally infected with the agent of TCP, and relapses are less common in Beagles. Following inoculation dogs have remained infected during an observation period of one year.

Pathological findings in experimentally infected dogs are compatible with those in the natural disease.⁷ Macroscopic changes include generalized lymphadenopathy and petechial hemorrhages on serosal and mucosal surfaces of major organs. The bone marrow is hypoplastic and perivascular cuffing with plasma cells is evident in most organs.

Ehrlichia canis has been recovered from 11 dogs with signs of tropical canine pancytopenia in Southeast Asia, Puerto Rico, the Virgin Islands and Florida (Table 1). It is apparent that some

TABLE 1. Summary of Isolates of *Ehrlichia* from Dogs with TCP

Location	Number of Isolates	Breed of Dog Providing Isolate	Epistaxis in Dog Providing Isolate	Concurrent Infection with <i>Babesia canis</i>
Southeast Asia	2	German Shepherd*	+	—
		German Shepherd*	—	+
Virgin Islands	3	German Shepherd	+	+
		Old English Sheepdog	+	—
		Mongrel	—	—
Puerto Rico	4	German Shepherd*	—	—
		German Shepherd*	—	—
		German Shepherd	+	—
		Labrador Retriever	—	—
Florida	2	German Shepherd	+	+
		German Shepherd	+	+

* Military dog

affected dogs had concurrent infections of *Ehrlichia canis* and *Babesia canis*. This is not unexpected since both organisms are transmitted by the same tick, *Rhipicephalus sanguineus*.³ However, the production of experimental TCP in laboratory dogs is not dependent on dual infections. Experimental disease, indistinguishable from the natural disease, is produced by *Ehrlichia* alone.

The conclusion that *Ehrlichia* is the etiologic agent of TCP is based on the consistent recovery of *Ehrlichia* from dogs affected with TCP from diverse geographical locations and the production of disease, indistinguishable from the

natural disease, in laboratory dogs experimentally infected with *Ehrlichia*.

Serologic tests for *Ehrlichia* are not available. The identification of *Ehrlichia canis* is based solely on its morphological characteristics in infected cells. The agent of tropical canine pancytopenia is indistinguishable from *Ehrlichia canis*, originally described by Donatien and Lestoquard.² Tropical canine pancytopenia may be a previously unrecognized manifestation of infection with *Ehrlichia canis*. However, the precise relationship of the agent of tropical canine pancytopenia with previously described strains of *Ehrlichia canis* has not been resolved.

Geographic Distribution

In addition to Southeast Asia, Puerto Rico, the Virgin Islands and Florida, TCP has also occurred in the Mideast¹¹ and is apparently the same disease observed in French military dogs in Tunisia as early as 1953 and referred to as hemorrhagic hepatonephritis.^{1,4} In 1938 Shirlaw¹³ described a disease known as Lahore canine fever which was responsible for the death of many dogs in India

and Pakistan. Shirlaw reported that *Babesia gibsoni* was the etiologic agent of this disease. However, the clinical findings of Lahore canine fever closely resemble those found in tropical canine pancytopenia. In fact Shirlaw reported that some dogs died with epistaxis or intestinal hemorrhage. Seneviratna¹² suggested that Lahore canine fever was probably caused by *Ehrlichia canis*.

Host Range

Laboratory mice, rats, guinea pigs and hamsters inoculated with the agent of tropical canine pancytopenia show no evidence of infection. Attempts to propagate the agent in embryonating eggs and many different cell cultures have been unsuccessful. There is no evidence of human infections.

The jackal,^{3,10} the coyote⁵ and even a monkey, *Macacus inuus*,³ have been successfully infected with *Ehrlichia canis*. Neitz and Thomas¹⁰ have suggested that in endemic areas wild dogs may serve as reservoirs for *Ehrlichia canis*. The host range of the organism requires additional study.

Diagnosis

Diagnosis of tropical canine pancytopenia is dependent on clinical signs, pathologic findings and demonstration of

the characteristic intracytoplasmic inclusions in infected cells.

Treatment

Effective means of treating all stages of the disease have not been developed. Preliminary studies have provided evidence that tetracycline may be effective during the early stages of the disease;

however, antibiotics, hemostatic drugs and massive blood transfusions have had little effect on the terminal stages of the disease.¹⁵

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