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Mini Review

Canine rangeliosis due to *Rangelia vitalii*: From first report in Brazil in 1910 to current day – A review

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ABSTRACT

Canine rangeliosis (popular names: "nambi-uvú", i.e. "bleeding ears"; "peste de sangue", i.e. "bleeding plague"; and "febre amarela dos cães", i.e. "yellow fever of dogs") is a tick-borne haemolytic and haemorrhagic disease caused by the protozoan parasite *Rangelia vitalii* which infects erythrocytes, leukocytes, and endothelial cells of blood capillaries. *Rangelia vitalii* was first reported as a novel piroplasm of dogs in 1910 in Brazil, a discovery that was met with skepticism at that time. Canine rangeliosis has been diagnosed in domestic dogs not only in Brazil but also in other South American countries (Argentina and Uruguay). *Rangelia vitalii* infection has also been found incidentally in Brazil in wild dogs (*Cerdocyon thous*, the crab-eating fox). Despite the fact that researchers in the early 1900s suggested that *R. vitalii* was a hitherto unidentified piroplasm that would be transmitted by the tick *Amblyomma aureolatum*, it was not until 2012 that these hypotheses were actually confirmed by PCR and transmission studies. Molecular studies have shown that *R. vitalii* is related to the *Babesia* sensu strictu clade, but genetically different from other morphologically similar species of *Babesia* that infect dogs. Another difference between *Babesia* spp. and *R. vitalii* is the ability of *R. vitalii* to invade endothelial cells, erythrocytes, and leukocytes. Experimental infection in dogs has successfully reproduced the clinical picture and pathology of the natural disease. In this article, epidemiology, clinical signs, laboratory findings, pathogenetic mechanisms including oxidative stress and immune response, necropsy findings, microscopic lesions, diagnosis, and treatment of canine rangeliosis are reviewed. What is currently known about this protozoal disease since its first report over a century ago is presented herein.

Contents

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Introduction

Rangeliosis is a haemorrhagic and haemolytic tick-borne disease of dogs in South America caused by the piroplasm *Rangelia vitalii*. This disease is also known as "bleeding ears" ("nambi-uvú" in the indigenous language Tupi-Guarani), "bleeding plague" ("peste de sangue" in Brazilian Portuguese), and "yellow fever of dogs" ("febre amarela dos cães" in Portuguese) (Carini, 1908, 1948; Pestana, 1910a,b; Carini and Maciel, 1914a; Braga, 1935; Rezende, 1976). This article provides an overview about what is currently known about this protozoal disease and its causative agent since its first report approximately a century ago.

History

A paper published in 1908 by Antonio Carini about infectious and parasitic diseases of domestic animals diagnosed in Brazil is the earliest reference to canine rangeliosis in the literature. Carini states in his article that "nambi-uvú" of dogs (canine rangeliosis) is similar to "malignant jaundice" of dogs (canine babesiosis) (Carini, 1908). A few years later, Bruno Rangel Pestana published a more thorough research article about "nambi-uvú" and claimed that this disease was possibly caused by a previously undescribed piroplasm which he named *Piroplasma vitalii* (Pestana, 1910b) in honor of the Brazilian scientist Vital Brazil. In 1914, another manuscript about "nambi-uvú" was published this time by Antonio Carini and Jesuno Maciel (Carini and Maciel, 1914a). They suggested that the scientific name of this new piroplasm should be changed to *Rangelia vitalii* as a tribute to Rangel Pestana who first described the organism. Their paper corroborated the theory first proposed by Pestana that *R. vitalii* was a novel canine piroplasm and that this organism should be placed in the entirely new genus *Rangelia*. They also mentioned that, by the time that their paper about "nambi-uvú" in dogs was published in 1914, no cases of "malignant jaundice" had been diagnosed in dogs in Brazil. At the time when these first papers about canine rangeliosis came out, there was widespread disbelief among scientists about the statement that *R. vitalii* was a novel piroplasm. Skeptical researchers rejected Pestana's hypothesis that *R. vitalii* was a new protozoan parasite claiming that the organism that he had found in the blood of the affected animals was not *R. vitalii* but actually *Babesia*, and that the organism found in tissues was in fact *Toxoplasma* (Paraense and Vianna, 1948). From 1985 until 1993, a number of cases of canine rangeliosis were misdiagnosed as canine visceral leishmaniasis in southern Brazil and published as a retrospective study about kala-azar by *Leishmania* sp. in dogs (Pocai et al., 1998). These misdiagnoses added another chapter to the already confusing story of *R. vitalii* (Krauspenhar et al., 2003; Loretti and Barros, 2005). Nothing new about canine rangeliosis was published over decades as researchers were uninterested in pursuing the subject (Fighera, 2007; Loretti, 2012). Over the years, veterinarians presented with dogs showing severe ear margin bleeding, epistaxis, anemia, jaundice, and a history of tick exposure did not consider *R. vitalii* in their differential diagnosis as most of them were unfamiliar with this pathogen since no information about it was published for decades. Early papers on canine rangeliosis were written in Brazilian Portuguese which is a language that most researchers do not read. Besides, most of these publications are not readily available in libraries or online. Therefore, until recently, the majority of scientists were unaware of the existence of *R. vitalii*. In 2003, a retrospective study about canine rangeliosis – which included those cases that were previously misdiagnosed as visceral leishmaniasis (Pocai et al., 1998) – was published (Krauspenhar et al., 2003). This publication sparked interest in the subject, and instigated new research. Since then, many articles about *R. vitalii* have been published (Krauspenhar et al., 2003; Loretti and Barros, 2004, 2005; Fighera, 2007; Fighera et al., 2010; França et al., 2010, 2012, 2013; Da Silva et al., 2011, 2012, 2013a,b,c; Puntel et al., 2011; Soares et al., 2011, 2014; Costa et al., 2012; Lemos et al., 2012; Loretti, 2012; Paim et al., 2012a,b; Paim et al., 2013a,b). Recently, this piroplasm has received some attention in a multi-authored book about infectious diseases of dogs and cats published in the US as there is a short section about rangeliosis in a chapter about protozoal diseases (Sykes, 2013).

Taxonomy, life cycle, morphology, and molecular phylogeny

Rangelia vitalii is a protozoan parasite of the phylum Apicomplexa, class Aconoidasida, order Piroplasmida, family Babesiidae (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=1401992&lvl=3&lin=f&keep=1&srchmode=1&unlock). To date, there is no detailed information available about the life cycle of *R. vitalii* in its invertebrate hosts (ticks) or vertebrate hosts (canids). In domestic dogs, *R. vitalii* is found in the blood inside erythrocytes, leukocytes, and free in the plasma (Fig. 1A–D) while in tissues it parasitizes endothelial cells of blood capillaries (Fig. 2). The hard tick *Amblyomma aureolatum* (Ixodidae) (Fig. 3), the proven vector of this piroplasm, transstadially transmits *R. vitalii* from nymph to adult (Soares et al., 2012). Inside erythrocytes, *R. vitalii* is a round, oval, or teardrop-shaped organism that can occur singly or in pairs and can be arranged at different angles with their narrow ends abutting. In blood smears stained with Giemsa, intraerythrocytic merozoites of this piroplasm have an abundant, pale red cytoplasm and an eccentric dark blue small nucleus. Inside red blood cells, this piroplasm is 3.34 ± 0.54 μm long and 2.09 ± 0.34 μm wide, and its nucleus is 1.07 ± 0.20 μm long and 0.87 ± 0.15 μm wide. Inside leukocytes (monocytes and neutrophils), there can be many zoites which look similar to the ones found inside erythrocytes. Inside white blood cells, this protozoan parasite measures 2.97 ± 0.68 μm in length and 1.94 ± 0.26 μm in width, and its nucleus is 1.17 ± 0.34 μm long and 0.85 ± 0.23 μm wide. *Rangelia vitalii* zoites that are found free in the plasma have morphological and tinctorial features that are similar to the ones of those that are present in red blood cells and white blood cells. They measure 3.94 ± 0.67 μm in length and 2.23 ± 0.42 μm in width, and their nucleus is 0.97 ± 0.17 μm long and 0.84 ± 0.11 μm wide (Da Silva et al., 2011). Histologically, *R. vitalii* zoites are seen inside the cytoplasm of endothelial cells of blood capillaries as round, homogeneous, and basophilic organisms in slides stained with hematoxylin and eosin (HE). The cytoplasm of this protozoan parasite on HE-stained sections is abundant and faintly eosinophilic, and the nucleus small but prominent, basophilic, and eccentric. Individual organisms measure 2.0–2.5 μm; 20–30 organisms can be seen within the cytoplasm of each endothelial cell (Pestana, 1910a,b; Carini and Maciel, 1914a; Loretti and Barros, 2005; Fighera et al., 2010). Transmission electron microscopy studies show that *R. vitalii* is found in endothelial cells of blood capillaries from a variety of organs and is located inside intracytoplasmic membrane-bound parasitophorous vacuoles. *Rangelia vitalii* has ultrastructural features of a protozoan parasite from the phylum Apicomplexa including a polar ring, the presence of rhoptries in