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Parasitic Infections and Inflammatory Diseases

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1. Introduction

The mammalian immune system is continuously exposed to infectious microorganisms as well as innocuous substances in the environment. Depending on the genetic makeup, the innate and adaptive immune responses develop and determine the frequency and the course of infectious diseases. The immune response to an infection is initiated by molecular recognition of damage-associated patterns (DAMPs) by receptors of the innate immunity, that, most of the time, occurs as an inflammatory reaction (Turvey & Broide, 2010).

The inflammation associated to parasite organisms is a complex reaction of the vascular tissues against infection, exposition to toxins or cellular injury involving extravascular accumulation of plasmatic proteins and leukocytes, as well as production of cytokines from the injured tissue. It is an essential component of multifactorial pathogenesis involved in different diseases (Scrivo et al., 2011). The acute inflammation is a common result of innate immune response; however local immune adaptative factors can also promote inflammation (Lukic et al., 2009). The morphologic transformations and functional characteristics of immunological responses and consequently, of the inflammatory processes intend to destroy, to dilute or to isolate the harmful agent. Virtually, all the acute or chronic diseases are lead or modulated by the inflammation. Although the inflammation serves to a protective function in the control of parasitic infections and promotion of tecidual repair, this can also cause injury and illness itself. Schistosomiasis is an exemple of parasitary disease caused predominantly by the host immune response to schistosome eggs (ova) and the granulomatous reaction they evoke (Burke et al., 2009). In some cases, the inflammation can even persist after the removal of the infectious agent, contributing to the chronic inflammation (Vodovotz et al., 2009).

Amongst the various infectious agents, helminth parasites are regarded as master manipulators of the host immune system, often inducing a long-lasting asymptomatic form of infection. Parasitic worms can establish and reproduce in mammalian hosts, switching off the inflammatory immune response and inducing a tolerant response to parasite antigens. The time of duration and the intensity of the inflammatory agent determine different degrees or phases of transformation in tissues (Zaccone et al., 2006).

Chronic infection with high burden of helminths can induce regulatory mechanisms to prevent excessive inflammation. Recent studies regarding immunological interactions between eosinophils and helminthic parasites have made important advances in understanding the innate role of eosinophils in controlling eosinophil-associated tissue inflammation involved in infection by tissue migratory helminthic parasites (Shin et al., 2009). These regulatory mechanisms may also affect the immune responses against other antigens, because it promotes a polarization of the response. The identification of regulatory mechanisms has already helped developing new models to understand helminth infections, which remain among the most prevalent chronic diseases in the world today. Several studies have verified that helminths can downregulate a range of immunopathological conditions, with the regulatory T cell being one of the most common mechanisms in play (Fallon & Mangan, 2007; Maizels & Yazdanbakhsh, 2008).

2. Helminth infection and inflammation

The inflammation involves a set of complex interactions between soluble factors and cells that can appear in any tissue during traumatic, infectious, after-ischemic, toxic or auto-immune injury (Nathan, 2002). It represents an adaptation of the loss of the cellular and tecidual homostasis, with important physiological functions, that include the defense of the organism host, remodelling and tecidual repairing, regulation of the metabolism, amongst others, controlled by transcription of genes (Medzhitov, 2008; Medzhitov & Horng, 2009).

The cellular profile of the acute inflammatory response is constituted basically by lymphocytes, neutrophils, monocytes, eosinophils and mast cells. The most defined subgroups of effective cells of CD4+ cellular ancestry are the Th1 and Th2 cells. These subgroups develop from CD4+ naïve (inactive) precursors and the differentiation pattern is initiated by stimulations at the beginning of the immunological response. INF-γ is the cytokine of signature of the Th1 cells; whereas IL- 4 and IL-5 are the cytokines that define Th2 cells. Th1 and Th2 Cells can also differentiate from the distinguishing expression of molecules of adhesion and receptors of chemokines and other cytokines. It is important to determine if the response to a pathogen will lead to protection of the host or to the evolution of the illness and this can be verified by the balance between Th1 and Th2 response (Jankovic et al., 2001; Yates et al., 2004). It has been also characterized the Th17 sub-group with pro-inflammatory activity, mainly in auto-immune illnesses, and the main cytokine involved is IL-17 (Weaver et al., 2006).

The Th2 cells are involved in the differentiation and proliferation of B lymphocytes, in the production of antibodies and activation of cells of the innate immune system. Therefore, the eosinophils found in subacute inflammations caused by helminthes, are very important cells in the inflammatory response mediated by Th2 cells. The neutrophils have high potential of diapedesis and fast migration speed, present fagocitic action, if deceased, can provoke tecidual necrosis due to the release of its lysosomal enzymes in the interstice. Basophils and mast cells are granular cells that have their number increased in chronic processes. The macrophages, originated from monocytes, are professional mononuclear fagocitc cells and antigen presenters that in the parasitic infection are activated by an alternative form, dependent on Th2 cytokines (Rothenberg & Hogan, 2006).

The vascular and esudative alterations that originate the inflammatory clinical signals (heat, redness, tumor, pain and loss of the function) culminate with the last inflammatory phase, the productive-reparative phase (Lukic et al., 2009).

The chronic response is a tecidual reaction characterized by the increase of the degrees of cells and other tissue elements next to the repairing area, ahead of the permanence of the aggressive agent. The chronic inflammation is always preceded by the acute inflammation. Clinically, in the chronic inflammation, the characteristic cardinal signals of the acute reactions are not observed (Cuzzocrea, 2005).

Although many physiological functions of the inflammatory response are unknown, the pathological aspects of diverse types of inflammation are well described and many are the organisms that serve as models for elucidating those concepts (Medzhitov, 2008).

Infection with helminth parasites induces immune effector responses that are characterized by IgE antibody production, tissue and peripheral blood eosinophilia, and participation of inflammatory mediator-rich tissue mast cells (Klion & Nutman, 2004). In parasitic infections, although these types of responses can certainly induce pathologic reactions, they have also been implicated in mediating protective immunity to the helminth parasites. Helminth infections are associated with a predominant induction of a Th2 type of immune response, that involves the interaction of signals from the T cells receptors, transcription factors like T-bet, STAT-6 and GATA-3 and cellular interactions mediated by cytokines (Jankovic et al., 2001; Yates et al., 2004). The Th2 response is polarized by interleukins: IL-4, IL-5, IL-9 and IL-13 (Fallon & Mangan, 2007). Activated mast cells, eosinophils and basophils infiltrate in the tissue as result of a Th2 exacerbated cellular type reaction that initiates the production of IgE and promote the tecidual eosinophilia and mast cells hyperplasia (Rothenberg & Hogan, 2006). The main points of the anti-helmintic response promoted by the Th2 profile are schematized in figure 1. Helminthes cause chronic stimulation of T cells, mostly without the strong immune natural reaction that is necessary for Th1 differentiation. Thus, Th2 cells can develop in response to the *A. vasorum* that possibly caused persistent or repeated stimulation of the T cells with little inflammation or activation of macrophages.

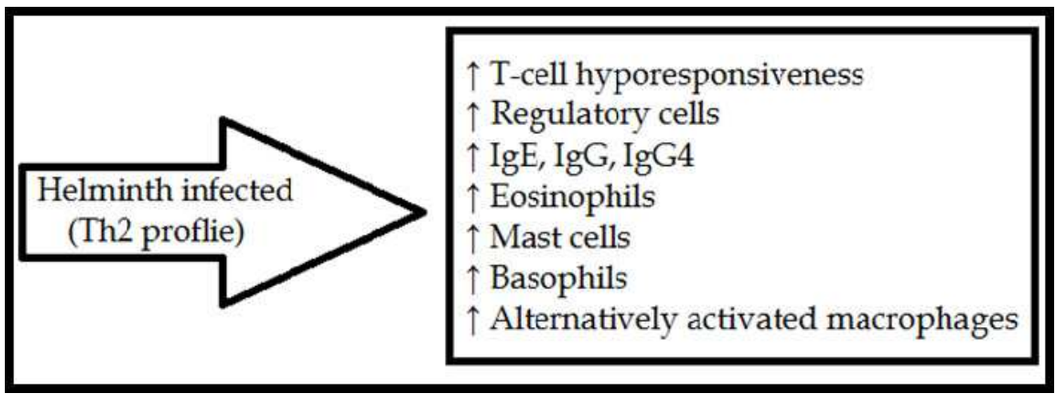

Fig. 1. Imunological alterations of the Th2 profile caused by helminth infections (Adapted from Fallon & Mangan, 2007).

The Th2 type response does not demand the activation of dendritic cells by microbial adjuvants, differently of the Th1 cells. It is reported that the initial production of IL-4 is not elicited by T cells (or at least not conventional T cells) in reaction to a constant infection that was not capable to induce an exacerbated initial inflammatory response by the production of INF-ɣ (Jankovic et al., 2001).

Helminth infections can modulate allergic processes due to association with the development of the Th2 response. They also stimulate regulatory mechanisms associated to animal suppression of the allergic response in human beings and animal models (Fallon & Mangan, 2007). Previous studies confirm this attractive potential of helminth infections to produce a suppressor reaction to different concomitant processes (Lukic et al., 2009).

3. The parasite model

Angiostrongylus vasorum is a nematode of the Metastrongyloidea superfamily which adult form is found in the right ventricle, pulmonary artery (and its branches) of domestic dogs and wild carnivores. The *A. vasorum* is widely spread in all continents. The infection is highly prevalent in dogs in the southeast of France, the United Kingdom, Ireland and Uganda (Guilhon & Cens 1973; Dodd 1973; Bwagamoi 1974) with several cases reported in the United States, Canada and Brazil (Lima et al. 1985; Lima et al. 1994; Edwards, 1995; Duarte et al., 2007).

Adult worms of *A. vasorum* live in the right ventricle of the heart and the pulmonary artery, where sexual reproduction and oviposture take place. The first-stage larvae (L1) hatch into the alveoli, migrate up the bronchial tree, are swallowed and eliminated to the environment with the host feces. The intermediate host, snails and slugs, either terrestrial or aquatic become infected through invasion or ingestion of L1. Larvae invade mollusks tissues where they undergo first and second molts, reaching the infective third-stage larvae (L3) (Guilhon & Afghahi, 1969; Rosen et al., 1970). Infection of the dog results from ingestion of free L3; ingestion of infective intermediate host or paratenic host (Barçante et al., 2003). Third-stage larvae (L3) invade mesenteric lymph nodes where they undergo third and fourth molt molts. Young adult nematodes migrate to the right side of the heart and pulmonary artery where they develop to sexual maturity.

A determinant factor in the pathology of canine angiostrongylosis seems to be related to the location of the parasite in the definitive host. The presence of the parasite inside the arteries and branches of the host promotes a mechanical and metabolic action on the vessels walls, which may alter its homeostasis, resulting in pneumonia, loss of racing performance, coughing and anemia (Jones et al., 1980). Severely infected dogs may develop cardiac insufficiency, pulmonary fibrosis followed by weight loss, hemorrhagic diatheses and death (Dood, K., 1973. *Angiostrongylus vasorum* (Baillet, 1866) infestation in a greyhound kennels.*Vet. Rec*. 92, p. 195.Dood, 1973; Lombard 1984; Cury & Lima, 1995; Costa & Tafuri, 1997; Oliveira-Jr et al., 2004).

In this context, *Angiostrongylus vasorum* has been used as a model for the study of pulmonary inflammatory diseases. In this series of experiments, we observed that the Bronchoalveolar lavage (BAL) is a valuable diagnostic technique that also provides additional diagnostic information for canine angiostrongylosis. In spite of the fact that the parasitological examination of the feces is considered the main standard for the diagnosis of angiostrongylosis in the patent period of the disease, the occurrence of animals with clinical symptomatology and without eliminating larvae with the feces is not rare (Barçante et al., 2008). The aims of this chapter is to present the results of BAL as a procedure to evaluate the acute and chronic phases of an *Angiostrongylus vasorum* infection for cytological and serological analyses of an pulmonary inflammatory disease caused by a parasitary infection.

3.1 Bronchoalveolar lavage (BAL) procedure

BAL is a procedure that retrieves cells and other elements from the lungs for evaluation, which helps in the diagnosis of many inflammatory and pulmonary diseases. The technique is considered to be a safe procedure performed in dogs to collect samples from the lungs (Clercx & Peeters, 2007, Basso et al., 2008, Hawkins et al., 2008).

BAL has been used to obtain specimens that could represent a development in distal lung, to diagnose viral, bacterial, protozoal and fungal infections, as well as neoplasia and other diseases (Hawkins, 1992). Cytologic and microbiologic evaluation of the fluid can be used to characterize pulmonary and inflammatory diseases in several mammalians species (Hawkins et al., 2008).

In the present work, the BAL procedure was performed through the use of an endotracheal tube on seven *A. vasorum* infected dogs and on five non-infected dogs lined as a control group.

3.2 Animals

Twelve one-year-old mongrel dogs (*C. familiaris*) free from any *A. vasorum* infections were used in this experiment. Following the manufacturer's directions, the dogs were treated 15, 30, 60 and 90 days after their birth with 7.5 mg of praziquantel; 7.5 mg of pyrantel and 37.5 mg of febantel per kg of body weight (Drontal®, Bayer-Saúde Animal, São Paulo, SP, Brazil) in order to eliminate any worm infections caused by other common canine parasites.

The experimentation protocols are in agreement with the Ethical Principles in Animal Experimentation, adopted by the Ethics Committee in Animal Experimentation (CETEA/UFMG), and were approved under number 060/03.

3.3 Parasitic infection

First-stage larvae of *A. vasorum* (L1) were isolated as described by Barçante et al. (2003). Third-stage larvae (L3) were recovered from snails, as described by Barçante (2004), and counted under a stereomicroscope (40×).

Seven dogs were orally inoculated with 100 L3 of *A. vasorum* per kilogram of body weight. Five non-infected animals were kept as control. From 20 days post-infection (dpi) to 330 dpi, fecal samples were collected daily from the cage of each animal of the infected group and submitted to a modified Baermann apparatus (Barçante et al., 2003) to recover the L1 to determine the pre-patent period (PPP).

BAL was performed on days 0, 30, 60, 90, 120, 180, 240 and 330 after the infection with *A. vasorum* L3 as described by Barçante et al. (2008).

3.4 Cellular evaluation of BAL

The viability of the cell population was estimated from 10 µL of total BALF diluted 1/10 in RPMI medium containing 0.4% Trypan Blue (Sigma). Membrane-damaged cells allowed the fast penetration of Trypan Blue, and these blue cells were immediately counted in a Neubauer's chamber and assumed as not viable. In order to quantify the recovered cells, the BALF was separated from the supernatant and cells through centrifugation at 200 × *g* for 10 min at 4 °C. The cell pellet was washed twice with a RPMI-1640 medium (Gibco, Grand Island, NY, USA) and resuspended in complete RPMI (10% fetal calf serum added). Total cell counts were determined by using a Neubauer's

chamber. For differential cell counts, aliquots were removed to make a final concentration of 1×10^5 cells/mL and the cytocentrifuge preparations (Cytospin 2, Southern Instruments, UK) were stained with May–Grünwald–Giemsa. The differential cell counts were performed based on the morphological appearance of the cells and on the frequency in which they appear. The total number of cells counted was 200 cells per preparation (Barçante et al., 2008).

The healthy immune system must keep the balance in order to react against infectious agents, to finish the immune response and to support the self-tolerance. The absence of adequate response submits the individual to deleterious effects of the invasion pathogen, since an overreaction can generate harmful inflammatory processes. The recent demonstration of different phenotype of cells, now called T regulatory cells, reintroduced the paradigm that the auto-reactivity and exacerbated responses are also regulated by particular subtypes of lymphocytes (Cruvinel et al., 2008). Characteristically, parasitic helminthes can infect their hosts for years or decades. To achieve such chronic infections, the host's immune system is tolerated to the presence of the parasite through the stimulation of selective immune suppression. Host immune responses limit, and in some instances eliminate nematode infections. There is considerable interest in enhancing these natural processes to achieve the control of infection or disease. Characteristically, parasitic helminths can infect their hosts for years or decades. To achieve such chronic infections, the host's immune system is tolerated to the presence of the parasite through the stimulation of selective immune suppression (Fallon & Mangan, 2007). Host immune responses limit, and in some instances eliminate nematode infections (Yazdanbakhsh et al., 2001). There is considerable interest in enhancing these natural processes to achieve the control of infection or disease.

This work reports that the *A. vasorum* infection resulted in an increase of relative neutrophils and eosinophils counts. In contrast, there was a significant decrease in the alveolar macrophage relative count in infected animals from 60 to 330 dpi. This study showed that the technique allowed retrieving cells and other elements that line the lung surface for cytological and serological evaluation, which provided information about inflammatory diseases, and the diagnosis and prognosis of pulmonary parasites such as *A. vasorum*.

There were no significant differences in the total average cell counts and the differential cell count data for non-infected animals among the seven procedures ($p > 0.05$) (Fig.2). On average, 69% or more of all nucleated cells in all the BALF of non-infected dogs were alveolar macrophages (Fig. 2A). Neutrophils accounted for 12% of the nucleated cells in the BALF from non-infected animals. On average, lymphocytes accounted for 14%, and eosinophils, for 4% of the nucleated cells. Epithelial cells were less than 1% of the total number of nucleated cells. This profile was unaltered during the 330 days of research (Fig. 2).

The differential cell count revealed significant differences between infected and non-infected dogs. Differently from what was observed in non-infected animals, dogs infected with *A. vasorum* showed notable variations in relative differential cell counts during the infection (Fig. 3). Absolute counts of infected animals revealed that alveolar macrophage showed a significant increase in number at 30 and 180 dpi. Relative counts showed that alveolar macrophage accounted for 73.1% of the cell population at day 0. Then there was a significant

decrease to an average of almost 25% of the cell population in infected animals from 60 to 330 dpi. Multinucleated giant cells were also identified (Fig. 4A).

Neutrophils were well preserved and were morphologically similar to those in peripheral blood. Cytoplasm was clear to slightly granular. Nuclear hypersegmentation (more than four distinct nuclear lobes) was seen occasionally. From 30 to 330 dpi, the relative number and absolute number of neutrophils was significantly elevated in the animals in the infected group ($p < 0.05$). Neutrophils comprised the vast majority of all cells seen from 90 to 330 dpi (Fig. 3, Fig. 4B).

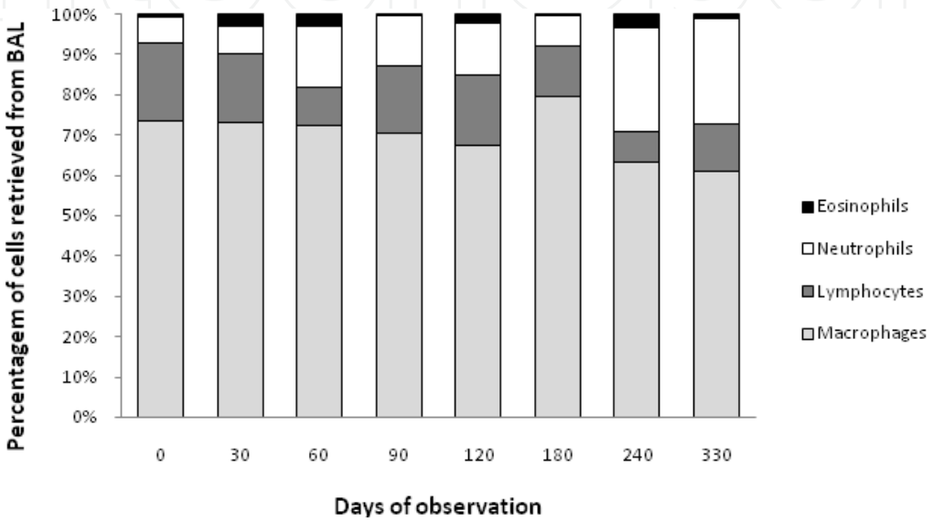

Fig. 2. Differential cell count (%) of the bronchoalveolar lavage fluid of the five non-infected dogs lined as a control group.

Eosinophils were clearly identified in the May–Grünwald–Giemsa stained specimens because of the presence of distinct eosinophlic cytoplasmic granules of various sizes. Nuclei of some eosinophils were lobed and the cells, therefore, resembled the circulating eosinophili of peripheral blood; however, in many eosinophils, the nucleus was spherical or ovoid rather than lobed, and was eccentrically located (Fig.4C). Absolute counts of infected animals revealed that eosinophils showed a significant increase in number from 30 to 330 dpi (Fig. 3). Relative counts showed that the eosinophils accounted for 2.8% of the cell population at day 0, and had a remarkable increase during the infection. Eosinophils predominated, accounting for 50.6% at 30 dpi and 37.1% at 60 dpi. From 30 to 330 dpi, the number of eosinophils in the BALF was significantly greater than in the non-infected animals or the normal values described in current literature.

The lymphocytes appeared as small round cells. The nuclei were round with dense chromatin patterns. Absolute counts of infected animals revealed that alveolar lymphocytes showed a significant increase in number at 30, 60 and 120 dpi. Relative counts showed that this type was increased in infected dogs from 30 to 120 dpi ($p < 0.05$) (Fig. 3). The lymphocytes accounted for 13.4% of the cell population at day zero and had a slight decrease during the infection with no statistical significance ($p > 0.05$).

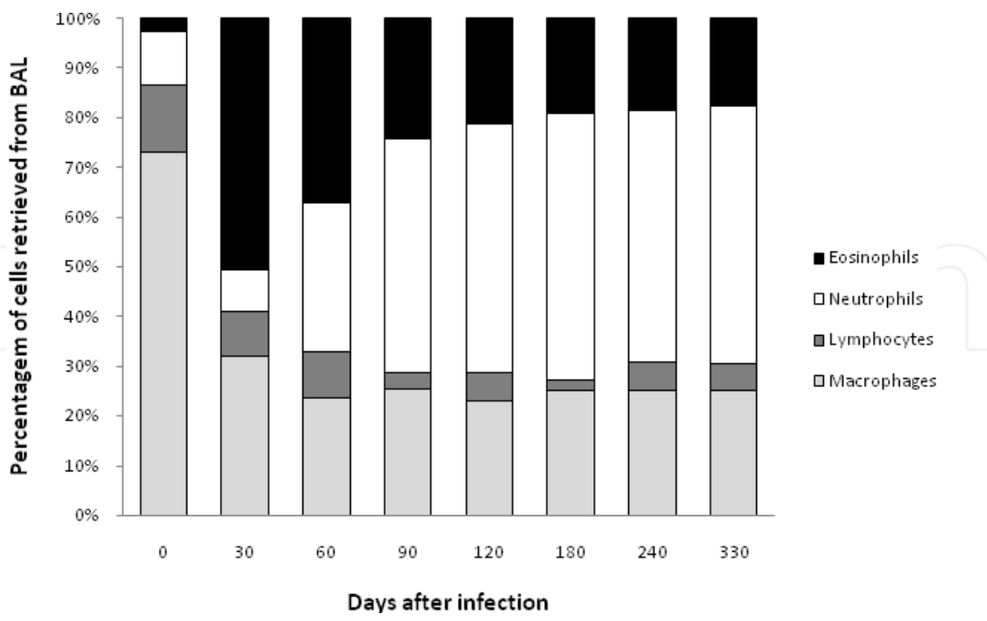

Fig. 3. Differential cell count (%) of the bronchoalveolar lavage fluid of the seven dogs infected with 100 third stage larva of Angiostrongylus vasorum/kg body weight.

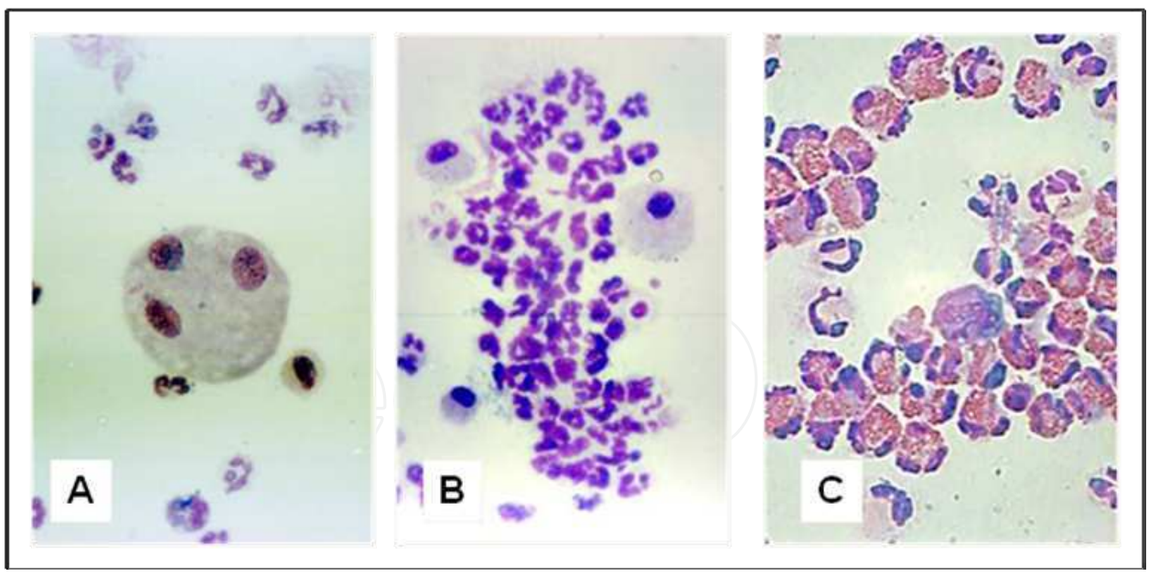

Fig. 4. Cytocentrifuged preparation of bronchoalveolar lavage fluid (BALF) from infected and non-infected dogs. May–Grünwald–Giemsa's stain. (A) BALF of a dog with chronical angiostrongylosis (120 dpi). The field contains a multinucleated giant cell (arrow) surrounded by neutrophils (40X objective). (B) BALF of a dog with chronical angiostrongylosis (120 dpi). The field contains a large amount of neutrophils. (C) BALF of a dog with acute angiostrongylosis (30 dpi). The predominant cells are eosinophils with presence of distinct eosinophlic cytoplasmic granules of various sizes.

4. Eosinophil response to parasitary infection

Profound blood and tissue eosinophilia are among the hallmark features of parasitic helminth infection, observed in response to activation of $CD4^+$ TH2 lymphocyte at specific stage of parasite life cycle (Rothenberg & Hogan, 2006). Despite of this, the kinetics of eosinophilia after infection with any parasitic infection have been difficult to define because the time of initial infection can be defined only rarely (Klion & Nutman, 2004). However, in the present study we described an experimental animal infection with the initiation of the eosinophilia and its natural regulation.

The eosinophils were proven to play a major role in the immune response to helminthic infections. Eosinophilia has been pointed out as a key factor in many helminthic infections, which demonstrated that eosinophils and neutrophils can be attracted and activated by host mediators or antigens excreted or secreted (E/S) by *Onchocerca volvulus*. Therefore, we can correlate the eosinophils and also the neutrophils influx in the lungs of infected dogs with the biology of the lifecycle of the parasite involved. Furthermore, larva growth and its products of secretion and excretion are known to induce an increase in pulmonary cellularity. In this context, transendothelial migration is essential for eosinophil recruitment from blood vessels into inflammatory tissues. The selective homing of Th2 cells in certain sites of inflammation is different from the Th1. The Th2 cells recruitment is dependent of particular chemokines that are highly expressed in places of helminthic infection, particularly in mucous tissues. At the inflammatory site, further interaction with invading parasites occurs via adherence with subsequent larval damage mediated by releases of eosinophil toxic granular effector molecules.

In this series of experiments, it was observed that the high pulmonary cellularity is inversely proportional to the larval output in dog feces. The larva migration from the vessels to the alveoli seems to be difficult because of the inflammatory process of the mucosal system, which consists of a mechanical and immunological barrier to larvae. The immune response that develops during this time often proceeds to cause pathologic changes that must be the primary cause of disease, since eosinophils exert a functional duality, participating in protective immune responses during parasitary infections as well as in the induction of cell and tissue damage. As results of the cell and tissue damage the larva spreads to different organs and tissues of the dog because of this mechanical barrier. The presence of larvae in sites different from those described in the natural route of the parasite lifecycle generally leads to animal death or lesions that can change the normal organ function. In this way, during chronic *A. vasorum* infection, the cellular infiltration typically observed is constituted predominantly of eosinophils and neutrophils. The eosinophils recruited into worm-infected tissues are further activated by various inflammatory stimuli, which may contribute to related eosinophil-mediated tissue inflammatory responses (Shin et al., 2009).

Despite major changes in the pulmonary cellularity following immunodulation that takes place during the chronic infection, the eosinophils may play an important role in the innate immune response of chronic infection. The activated eosinophils secrete the content of its granules, including main basic and cationic proteins, which are capable to destroy even the resistant tegument of helminthes, as it represents a relevant protective mechanism. These proteins perform various biological activities. Cytotoxic granules injure both the host tissue and the parasite (Brushi et al., 2008). It has been suggested that the immunoglobulins IgG and IgA are able to trigger eosinophils degranulation (Hogan et al., 2008). However, the presence of IgE receptors on eosinophils remains controversial. Recently, T cell has also been

shown to have a role in eosinophil degranulation. Knockout mice that lacked T and B cells were infected with *Nippostrongylus brasiliensis*, and IL-4- expressing eosinophils were recruited to pulmonary tissues but failed to degranulate. Reconstruction with CD-4$^+$ T cells promoted the accumulation of degranulated IL-4-expressing eosinophils, but only if the T cells were stimulated with a cognate antigen. These facts indicate that T-helper cells confer antigen specificity on eosinophils cytotoxicity but not on the cytokine responses (Brushi et al., 2008).

In the present work, we demonstrated that a peak eosinophil levels occurs 30-60 days after infection, which is consistent with the pre-patent period and initial larvae release. At the inflammatory site, it was observed larval damage mediated by releases of eosinophil toxic granular effector molecules. More interesting was a spontaneous decrease in eosinophil numbers in the absence of treatment, suggesting active downregulation of the eosinophlia. This active and spontaneous modulation of eosinophilia generally occurs when infections became patent (sexually mature adults began egg laying and larval release) (Klion & Nutman, 2004).

5. Mast cells – Eosinophils interaction

As one of the most highly cationic proteins synthesized by eosinophils, MBP (major basic protein) is a small protein that is expressed as two different homologs (MBP1 e MBP2). A substantial body of literature has emerged demonstrating that eosinophils have the capacity to regulate mast cell function (Rothenberg & Hogan, 2006). Several studies have shown that MBP induces mast cell activation. Interestingly, activation of eosinophils with the mast cell protease chymase promotes production of eosinophil-derived stem cell factor, a crictical mast cell growth factor (Rothenberg & Hogan, 2006). Eosinophils also produce nerve growth factor (NGF), a cytokine involved in survival, functional maintenance of sympathetic neurons and also in immune regulation. This cytokine is performed in eosinophil which promotes mast cell survival and activation and acts in an autocrine fashion by activating release of eosinophil peroxidase (EPO). EPO activates rat peritoneal muscles to release histamine, suggesting a role of eosinophil-derived NGF in mast cell-eosinophil interactions. Thus, eosinophil and mast cells communicate in a bidirectional fashion (Rothenberg & Hogan, 2006).

6. Antihelmintic therapy

In a recent article published by Morgan and Shaw (2010) it was reported that three antihelmintic drugs have been employed for the treatment of *A. vasorum* infection in dogs: Fenbendazole (off label use - Panacur, Intervet-Schering Plough Animal Health - 25-50 mg/kg orally once daily for 7-21 days); Milbemycin oxime (Milbemax, Novartis Animal Health 0.5 mg/kg orally once weekly for 4 weeks) and Moxidectin (Advocate, Bayer Animal Health Minimum 2.5 mg/kg topically – 0.1 ml/kg of 2.5% spot-on, single dose). Mebendazole (50-100 mg/kg orally two times daily over five to 10 days) was also considered effective elsewhere (Bolt et al., 1994).

Antihelmintic drugs are told to reduce adult worm burdens in experimental infected dogs (Milbemycin oxime) and also prevent establishment of adult parasites (Moxidectin) (Conboy, 2004; Schnyder et al., 2009). It is reported that antigens released during therapy (anaphylactic shock) and dead adult stages (emboli) can cause side effects (Staebler et al.,

2006).Corticosteroids can be used to prevent adverse reactions to killed worm antigen and to reduce fibrosis in recuperating lungs. The significance of these effects has not yet been recognized. Treatment is more likely to be successful with early antihelmintic therapy, which, given the low sensitivity of larval recognition, should not necessarily be delayed until an ultimate diagnosis is reached (Morgan & Shaw; 2010).

7. Conclusion

In this review, we emphasize two points. The first is that the BAL technique allowed the retrieval of cells and other elements that line the lung surface (airway) for cytological evaluation, providing information about inflammatory diseases and possible diagnosis and prognosis of pulmonary parasites like *A. vasorum*. The second is that in angiostrongyliasis, tissue-migratory phase has evolved to attenuate eosinophil-mediated tissue inflammatory responses for their survival in hosts.

We can conclude that BAL is an accurate technique for the diagnosis of canine angiostrongylosis, especially in situations when fecal exams are parasitologically negative and the clinical symptomatology matches the infection.

In this sense, the present chapter meant to point out that BAL is an important instrument for the differential diagnosis of occult infections and an auxiliary method for *A. vasorum* infection follow-up. In addition, an important model for the study of Th2 immune response and object of study to think of immune system modulation.

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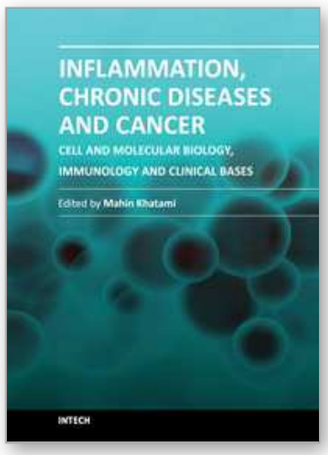

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This book is a collection of excellent reviews and perspectives contributed by experts in the multidisciplinary field of basic science, clinical studies and treatment options for a wide range of acute and chronic inflammatory diseases or cancer. The goal has been to demonstrate that persistent or chronic (unresolved or subclinical) inflammation is a common denominator in the genesis, progression and manifestation of many illnesses and/or cancers, particularly during the aging process. Understanding the fundamental basis of shared and interrelated immunological features of unresolved inflammation in initiation and progression of chronic diseases or cancer are expected to hold real promises when the designs of cost-effective strategies are considered for diagnosis, prevention or treatment of a number of age-associated illnesses such as autoimmune and neurodegenerative diseases as well as many cancers.

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