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REVIEW

Balantidium coli INFECTION, IMMUNE STATUS AND COMORBIDITIES: LITERATURE REVIEW

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ABSTRACT

Balantidiasis, a disease caused by the ciliated protozoan *Balantidium coli*, mainly infects the large intestine and may present intestinal spread. The purpose of this literature review was to study the infection by *B. coli* and comorbidities to identify the factors that can contribute to the establishment of the disease. In this review, we attempt to explore and describe the various comorbidities associated with *B. coli* infection. We reviewed the literature based on comorbidities with a focus on the association with *B. coli* infection. The primary platforms targeted were PubMed, LILACS, SciELO and Google Scholar. Studies published between 1990 and 2020 in Portuguese, English, and Spanish were considered. The comorbidities reported in the papers were diverse, associating infection by *B. coli* with the immunosuppression that they generate. The intestinal microbiota may also play an important role, because when dysbiosis is present, its composition and structure are affected, which may enable the invasion of the mucosa. The review shows that the presence of the parasite and establishment of balantidiasis can influence in the clinical stage of chronic and autoimmune diseases, considering the modulation of the immune response in presence of *B. coli.*

KEY WORDS: *Balantidium coli*; autoimmunity; balantidiosis; comorbidities; immunodepression.

INTRODUCTION

Balantidium coli is a ciliated protozoan, capable of infecting a variety of mammals (Zaman, 1964; Nakauchi,1999; Gerald & Bailey, 2002; Fletcher et al., 2012; Ahmed et al., 2019; Bianchi et al., 2019; Zhao et al., 2020). However, pigs are considered the main hosts (Hernández et al., 1993; Pomajbıkova et al., 2013). The protozoan can also infect, causing balantidiasis (Solaymani-mohammadi et al., 2005).

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The infectious form, dispersed in the environment, is a spherical or slightly ovoid cyst presenting a thick protective wall, and measuring approximately 40 µm to 70 µm in diameter (Fletcher et al., 2012; Ponce-Gordo et al., 2011; Ponce-Gordo & Jirků-Pomajbíková, 2017). The trophozoites measuring approximately 30 µm to 200 µm in length are ovoid shaped and covered by somatic cilia, allowing a rotating movement and facilitating locomotion (Fletcher et al., 2012; Farthing & Kelly, 2005; Schuster & Ramirez-Avila, 2008). In the anterior portion, there is an oral apparatus characterized by a depression where the cytostome covered by oral lashes can be seen. In an opening in the posterior region is the cytopigium (excretory structure) (Ponce-Gordo et al., 2011; Ponce-Gordo & Jirků-Pomajbíková, 2017; Nilles-bije & Rivera, 2010).

Human infections by *B. coli* generally occur in rural and agrarian areas where individuals have direct contact with pigs, however, the lack of personal and environmental hygiene in some places predisposes human infection (Schuster & Ramirez-Avila, 2008). Cysts can contaminate water and food, and when ingested they reach the large intestine, where excision occurs. The trophozoites then develop and remain active in the intestinal lumen by feeding or, in some cases, promoting ulcerations in the intestinal mucosa by releasing the enzyme hyaluronidase, which degrades the important hyaluronic acid in the epithelium. The trophozoites that remain in the lumen encyst and are excreted along with feces (Schuster & Visvesvara, 2004; Hechenbleikner & Mcquade, 2015).

In general, balantidiasis is asymptomatic, but when it presents clinical manifestations, these are characterized by dysentery, similar to that of the amoebiasis caused by *Entamoeba histolytica*, including diarrhea that can be mucous-bloody, abdominal cramps, fever, nausea, and vomiting (Parija & Giri, 2012; Kumar et al., 2016). More serious disease complications often affect individuals with weakened immune systems (Schuster & Ramirez-Avila, 2008). The presence of ulcers in the intestinal mucosa allows the invasion of trophozoites, in addition to the production of the enzyme hyaluronidase by the protozoan, which aggravates the ulceration, and may spread to other organs such as lungs, liver, vermiform appendix, and bladder (Dodd, 1991; Anargyrou et al., 2003; Karuna & Khadanga, 2014; Kapur et al., 2016). In these cases, the individual's immunological condition is crucial, as reports indicate that balantidiasis, especially extra-intestinal, occurs in immunologically weakened people affected by other comorbidities, and in cases related to malnutrition or alcoholism (Schuster & Ramirez-Avila, 2008; Schuster & Visvesvara, 2004; Vasilakopoulou et al., 2003).

Although there are published studies on *B. coli* infection in humans, research concerning pathogenesis and mechanisms of infection in immunologically compromised individuals are scarce. Based on this information, the purpose of this literature review was to carry out a bibliographic study of

human infection by *B. coli* and the relationship between the immunological conditions of an infected individual and comorbidities present to identify the host factors that may be associated with the establishment of the disease.

MATERIAL AND METHODS

A bibliographic review was carried out, using the electronic platforms PubMed, Latin American and Caribbean Literature in Health Sciences (LILACS), Scientific Electronic Library Online (SciELO), and Google Scholar for data collection (Figure).

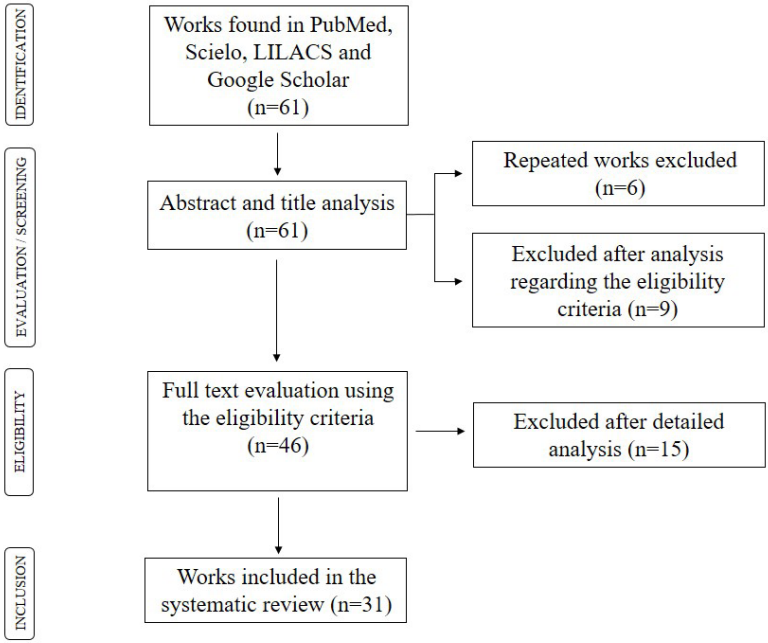

Figure. Flowchart of the selection of works published from 1990 to 2020 relating *Balantidium coli* infection to comorbidities

In the research, the descriptors DeCS/MeSH "*Balantidium coli* infection" and "Balantidiasis" were associated with the Boolean operator "AND" followed by the descriptors for comorbidities and infection site "Crohn Disease", "Diabetes mellitus", "Cancer", "Immunosuppression", "Systemic Lupus Erythematosus", "HIV", "Psoriasis", "Lung", "Liver", "Urinary Tract", and "Intestines". The research was conducted in English, Portuguese, and Spanish.

For inclusion criteria, the following were considered: case reports, cross-sectional, observational studies, and other scientific papers, published in Portuguese, English or Spanish from 1990 to 2020, that considered *B. coli* infection associated with comorbidities.

For exclusion criteria, the following were dismissed: papers that did not address infection by the parasite, that did not present the involvement of comorbidities and that were published in other languages or before 1990.

Initially, paper selection was performed by reading the titles and abstracts, later by reading the complete report and, finally, by discarding those that did not fit the inclusion criteria. In addition, we searched for reference lists of studies, which provided other studies in order to include the largest number of articles on the topic.

RESULTS

The purpose of this review was clarify the relationship between individuals who acquire *B. coli* infection and their comorbidities, in order to understand the immunological factors involved in this interaction. The literature on the subject is limited and there are no other reports addressing this interaction.

Regarding the frequency of events indicating a relationship between *B. coli* infection and comorbidities, the presence of the Human Immunodeficiency Virus (HIV) was mentioned in 10 studies (32.3%), followed by cancer (5 studies - 16.1%), diabetes mellitus (DM) (5 studies - 16.1%), alcoholism (4 studies - 12.9%), renal failure (2 studies - 6.5%), chronic obstructive pulmonary disease (COPD) (2 studies - 6.5%), pemphigus vulgaris (1 study - 3.2%), psoriasis (1 study - 3.2%), and systemic lupus erythematosus (SLE) (1 study - 3.2%) (Table).

Regarding the infection site, the most prevalent was intestinal balantidiasis (16 studies - 51.6%), followed by urinary (seven studies - 22.6%) and pulmonary (five studies - 16.1%) balantidiasis. Other infection sites were reported, such as liver (1 study - 3.2%), peritoneum (1 study - 3.2%), and spine (1 study - 3.2%) (Table).

India presented the highest number of published papers on the topic involving *B. coli* with seven (22.6%) studies, followed by Brazil and Nigeria with three (9.7%) publications each, and Greece and Venezuela, each with two articles (6.4%) (Table).

Table. Data from studies published and selected from 1990 to 2020, addressing the infection by *Balantidium coli* and association with comorbidities.

Authors	Year	Country	Study type	Infection site	Associated comorbidity
Pinheiro MC, et al [71]	1991	Brazil	Case report	Intestine	COPD
Clyti E, et al [16]	1998	French Guiana	Case report	Intestine	HIV
Anargyrou K, et al [3]	2003	Greece	Case report	Lung	Chronic lymphocytic leukemia
Carmeño JR, et al [12]	2003	Venezuela	Case report	Intestine	HIV
Sharma S, et al [85]	2003	Canada	Case report	Lung	Diabetes mellitus
Vasilakopoulou A, et al [98]	2003	Greece	Case report	Lung	Anal cancer
Arcoverde C, et al [4]	2004	Brazil	Observational	Intestine	HIV
Ferry T, et al [29]	2004	France	Case report	Peritoneum	Alcoholism
Yazar S, et al [102]	2004	Turkey	Case report	Intestine	Non-Hodgkin's lymphoma
Cristescu B, et al [17]	2007	Bangladesh	Case report	Intestine	Diabetes mellitus
Udeh EO, et al [96]	2008	Nigeria	Observational	Intestine	HIV
Maino A, et al [58]	2010	Italy	Case report	Urinary tract	Non-Hodgkin's lymphoma
Liyanage P, et al [56]	2011	Sri Lanka	Case report	Intestine	Pemphigus vulgaris
Figueiredo SM, et al [30]	2012	Brazil	Case report	Intestine	HIV
Basavaraj, et al [7]	2012	India	Observational	Intestine	HIV
Dhawan S, et al [22]	2013	India	Case report	Spine	Alcoholism
Pamo O, et al [68]	2013	Peru	Case report	Intestine	Gastric and rectal cancer

Karuna T, et al [50]	2014	India	Case report	Urinary tract	Chronic kidney failure
Khanduri A, et al [52]	2014	India	Case report	Urinary tract	Acute renal failure
Trejo M, et al [95]	2014	Argentina	Case report	Lung	Diabetes mellitus
Oteng-Seifah EE [67]	2015	Ghana	Dissertation	Intestine	HIV
Eriso F [26]	2015	Ethiopia	Observational	Intestine	HIV
Soleimanpour S, et al [88]	2015	Iran	Case report	Urinary tract	Diabetes mellitus
Ikpeama OJ, et al [43]	2016	Nigeria	Observational	Intestine	HIV
Kapur P, et al [48]	2016	India	Case report	Liver	Alcoholism
Kaur S, et al [51]	2016	India	Case report	Urinary tract	COPD
Kumar M, et al [53]	2016	India	Case report	Intestine	Alcoholism
Bratta D, et al [10]	2018	Venezuela	Case report	Lung	Diabetes mellitus
Tanja PZ, et al [91]	2018	Slovenia	Case report	Urinary tract	Psoriasis
Udeh EO, et al [97]	2019	Nigeria	Observational	Intestine	HIV
Martviset P, et al [60]	2020	Thailand	Case report	Urinary tract	SLE

DISCUSSION

Human Immunodeficiency Virus (HIV)

Three of the 10 (30%) studies regarding HIV positive patients are case reports. The report by Clyti et al. (1998) was the first case described in the literature regarding an HIV patient in French Guiana, who developed balantidian dysentery, and the study by Carmeño et al. (2003) was the first case of a patient with HIV described in Venezuela. According to these authors, the infection was aggravated mainly, by the immunosuppressive characteristic of the disease.

Infection by the HIV virus directly influences CD4+ T cell functions, modulates CD4+ and CD8+ T responses, damages specific antigen responses and compromises the production of cytokines by natural killer cells (NK), necessary functions in the response to infections (Janssen et al., 2015; Cerveja et al., 2017).

The combination of different antiviral agents for antiretroviral therapy (ART) was determined to decrease the viral load and thus improve the patient's immune system due to an increase in the CD4+ T count, reducing morbidity and mortality (Pau, 2014; Souza et al., 2019). However, adverse effects of short or long-term gastrointestinal infections, such as diarrhea, nausea, and abdominal pain, can arise at the same time as infections by opportunistic enteric pathogens (Montessori et al., 2004).

Figueiredo et al. (2012) describe the first case in Brazil of an HIV-positive patient on combined antiretroviral therapy with intestinal balantidiosis. The clinical manifestations of balantidiosis in this patient coincided with the presence of side effects caused by ART, a fact that deserves attention by health professionals who treat this type of patient.

Research addressing HIV balantidiosis consisted of observational studies, with a view to investigate the prevalence of intestinal parasites in HIV-positive patients treated in hospitals. Four papers found a higher prevalence of infection by *B. coli*, as follows. The report by Basavaraj et al. (2012) investigated parasitic infections in eight children admitted to a hospital in the city of Hubli, in India, where *B. coli* was the most prevalent intestinal parasite (13.3%), with 5 (62.5%) children with severe immunodeficiency and 1 (12.5%) with mild immunodeficiency. The study by Udeh et al. (2019), in Makurdi, Nigeria, with *B. coli* prevalence in 10 (3.8%) HIV-positive patients undergoing treatment (ART), of which six (60%) presented a CD4 + T lymphocyte count <350 cells/uL and four (40%) presented <500 cells/uL.

The CD4+T lymphocyte count indicating a state of severe immunosuppression and involvement by opportunistic infections is generally below 200 cells/uL. However, counts below 350 cells/uL, in some studies, already indicate an increased risk of infections by opportunistic microorganisms (Udeh et al., 2019).

In a study carried out in Nigeria, Ikpeama et al. (2016) investigated the prevalence of intestinal parasites in HIV-positive individuals and identified infection by *B. coli* in 10 (3.4%) patients in hospitals in Sokoto. Checking the prevalence of opportunistic intestinal parasites, Eriso (2015) found 19 (2.68%) HIV-positive patients infected with *B. coli* in Ethiopian hospitals. The rest of the selected studies identified only one patient infected by *B. coli* in the search for intestinal parasitic infections (Udeh et al., 2019; Arcoverde et al., 2004; Udeh, et al., 2008; Kurts, et al., 2013; Oteng-Seifah, 2015).

All selected reports that include HIV-positive patients infected with *B. coli* show clinical manifestations of intestinal balantidiosis. As is known, HIV patients present a greater chance of opportunistic intestinal parasitic infections, caused by protozoa (extra and intracellular) and helminths. The severe diarrhea caused in these individuals negatively influences the defense mechanisms of the gastrointestinal mucosa, such as the production of IgA antibodies and local immune cells, making them more susceptible to opportunistic infections (Adamu et al., 2013). Among the protozoa, the most reported in the studies include *Cryptosporidium* spp., *Blastocystis* spp., *Isospora belli, Giardia lamblia* and *Entamoeba histolytica / E. dispar* (Adamu et al., 2013; Bachur, et al., 2008; Nissapatorn & Sawangjaroen, 2011; Taye et al., 2014). However, the number of articles reporting a correlation between *B. coli* infections and HIV-patients is significant, meaning that it is also a protozoan to be considered in intestinal infections in this population.

Cancer

Two of the reports relating balantidiosis and the presence of cancer or an infection with pulmonary involvement occurred in Greece. Anargyrou et al. (2003) report *B. coli* infection in a patient with chronic lymphocytic leukemia (CLL-B). CLL is a neoplasm characterized by the abnormal accumulation, in the case of the patient in question, of type B lymphocytes in the peripheral blood, bone marrow, and lymphoid organs (Gonçalves et al., 2009; Marrero, 2019). The patient was in the Rai 0 stage, which indicates an early stage of the disease, but presented cervical, axial and inguinal lymphodenopathy, which is an increase in lymph nodes, and was, therefore, immunocompromised, due also to long-term use of corticosteroids and chemotherapic treatment, impairing lymphocyte function (Anargyrou et al., 2003).

Vasilakopoulou et al. (2003) portray the fatal case of a patient with anal cancer, in addition to other associated comorbidities, such as diabetes mellitus and arterial hypertension, presenting impairment of the immune system due to chemotherapy and radiotherapy sessions, which was probably the cause of the exacerbation of pulmonary balantidiasis and consequent death. The study of Pamo et al. (2013) reports four cases of patients infected with intestinal *B. coli* seen in hospitals in Lima, Peru. Among these, one patient had gastric cancer, and another was diagnosed with rectal carcinoma.

Chemotherapy and radiotherapy treatments can cause a series of clinical complications to the patient, immunosuppression being the most recurrent and interfering with effective immune response mechanisms, such as T and B lymphocytes, NK cells, dendritic cells and macrophages. In addition, it causes suppression of the bone marrow, which recomposes blood cells, including components of the immune system, which can impair the fight against infections, mainly by opportunistic agents (Sawada et al., 2009; Silva & Márcio, 2011; Carvalho & Villar, 2018). Estimates indicate that colorectal cancers are among the most aggressive and frequent, and the cause of high mortality, along with stomach cancer (Toychiev et al., 2018). Due to being in an immunocompromised state owing to neoplasia, cancer patients are susceptible to infections by parasites, including commensal and opportunistic intestinal protozoa (Jeske et al., 2018; Esteghamati et al., 2019; Mahmoudi et al., 2020).

The case reports of patients with non-Hodgkin's lymphoma, in Turkey and Italy, presented *B. coli* infection with intestinal and urinary involvement, respectively (Yazar et al., 2004; Maino et al., 2010). This type of lymphoma is a form of cancer originated in the lymphatic system, classified according to the type of cell affected, that is, T or B lymphocytes, the second being the cause of most infections (Rogers, 2006).

Diabetes Mellitus (DM)

Among the reports that include DM, three describe infection by *B. coli* resulting in pulmonary involvement. The studies by Trejo et al. (2014) and Bratta et al. (2018) portray the diagnosis of pneumonia caused by *B. coli* in patients with a history of DM in addition to arterial hypertension. In the first case, the patient's DM was poorly controlled. Sharma & Harding (2003) also report the case of a farmer with a history of insulin-dependent DM who presented a necrotizing lung infection caused by the protozoan. Two other cases involving DM report the case of intestinal and urinary balantidiosis in Bangladesh and Iran, respectively (Cristescu, 2007; Soleimanpour et al., 2015).

DM is part of the group of chronic non-communicable diseases (CNCD), and it can be subdivided into DM type 1 (DM1) and type 2 (DM2). Both forms result in progressive loss of mass and/or function of pancreatic β cells, leading to manifest hyperglycemia, which is harmful to the body (Eizirik et al., 2020). DM1 is characterized as an autoimmune disease in which the immune system attacks and destroys pancreatic β cells. It is caused by environmental and genetic factors that have not yet been fully clarified; the latter usually associated with polymorphisms in the Human Leukocyte Antigen (HLA) molecules in the Major Histocompatibility Complex (MHC). Studies indicate the involvement of CD4 + and CD8 + T lymphocytes, with the release of chemokines and cytokines, macrophages, and specific autoantibodies produced by plasma cells in the autoimmune process in DM1. In DM2, there

is impaired insulin secretion by pancreatic β cells associated with insulin resistance, which can be related to individual lifestyle and the development of the disease (Eizirik et al., 2020; Ilonen et al., 2019).

In addition to the effects generated by autoimmunity, there are consequences regarding the immune dysfunction of DM as it is considered a chronic disease. Hyperglycemia has been seen to cause an increase in the virulence of some pathogens and, therefore, also increases the risk of infections in individuals with DM (Chovancová, 2019). In patients with DM, hypotheses have been raised regarding a decrease in the concentration of components in the complement system, such as the C4 molecule, disturbances in the secretion of cytokines and chemokines, and decreased phagocytic function of polymorphonuclear cells (Chovancová, 2019; Geerlings & Hoepelman, 1999).

Alcoholism

Alcoholism is often mentioned as a factor that favors *B. coli* infection. Studies report *B. coli* peritonitis in France associated with patient alcoholism, hypertension, and moderate asthma (Ferry et al., 2004; Granier, 2004). Another three cases occurred in India. Dhawan et al. (2013) describe a rare case, in which *B. coli* caused cervical osteomyelitis in an alcoholic patient with a compromised nutritional status. This is supposed to be the first case of balantidiosis involving bone and the formation of a vertebral abscess. The report by Kumar et al. (2016) indicates an association between chronic alcoholism, intestinal infection by *B. coli*, and the patient's immunocompromised state due to anti-tuberculosis therapy six months earlier, which may have contributed to the establishment of the ciliate. The report by Kapur et al. (2016) portrays a case of a liver abscess in a patient, probably also associated with alcohol consumption. The effects of alcohol on the body have been studied for some time: changes in immune function due to frequent ingestion and negative implications depend on the intensity, consumption duration and type of drink (Diaz et al., 2002; Romeo & Warnberg, 2010).

Among these alterations, the mechanisms that affect immunity may include leukocyte inability to migrate to the sites of injury and infection, interference in T and B lymphocyte functions, and reduction in their proliferation and of NK cells and monocytes/macrophages, in addition to affecting the balance and production of cytokines and antibodies (Romeo & Warnberg, 2010; Sureshchandra et al., 2019). In a cytokine assay with alcoholics, an inflammatory response profile was noted, with serum concentrations mainly of TNF-α, IL-6, IL-10, IL-12 and IL-13 (Gonzalez-Quintela et al., 2000; Daniluk et al., 2001). The imbalance of the intestinal microbiota was also probably due to the consumption of alcohol, which induces greater permeability of the epithelium enabling tissue invasion by pathogens (Bode & Bode, 2003; Qamar et al., 2019). Therefore, high consumption of alcohol is considered an important

immunomodulator and the cause of a certain degree of immunosuppression, also increasing infection incidence and an inadequate response to invasive agents (Diaz et al., 2002; Romeo & Warnberg, 2010).

Chronic Obstructive Pulmonary Disease (COPD)

Pinheiro & Lima (1991) and Kaur & Gupta (2016) describe fatal reports of balantidiasis associated with COPD: the first with intestinal involvement, aggravated due to the critical nutritional state of the patient, the latter with urinary involvement in a patient under prolonged corticosteroid treatment. COPD presents several pulmonary manifestations, characterized by progressive airflow limitation, associated with chronic inflammation of the airways and/or pulmonary alveoli due to harmful particles or gases, causing narrowing of the airways, destruction of lung parenchyma and decrease in pulmonary compliance (Hattab et al., 2016; Rabe & Watz, 2017).

Smoking is considered one of the main causes of COPD. Exposure to cigarette smoke influences inflammatory cell infiltration at the level of the airways, where local epithelial cells are destroyed. This destruction causes the release of intracellular molecules that are recognized by Toll-like receptors 2 and 4, and cytokines such as TNF-α and IL-8 are released and recruited to the CD, macrophages and neutrophils, constituting the innate immune response (Rabe & Watz, 2017; Decramer et al., 2012). CD4 + and CD8 + B and T lymphocytes are activated via the presentation of released auto antigens, mediating the adaptive response. There is evidence of impaired immune regulation in COPD, due to a reduction in the Treg population and an increase in pro-inflammatory T helper 17 (Th17) in the lungs of these patients. However, the findings of some studies comparing the pulmonary and systemic immune response in COPD are controversial, yet it is believed that there is a small relationship between pulmonary and blood immune alterations (Rabe & Watz, 2017; Decramer et al., 2012; Cruz et al., 2019).

COPD can manifest in different forms and intensities since it is a heterogeneous disease. In cases of disease exacerbation, anti-inflammatory treatment is indicated with inhaled or systemic corticosteroids, depending on the severity of the case. The aggravation is usually due to bacterial or viral infections, as well as a small percentage of non-pulmonary infections, which can be caused by other opportunistic agents that establish the infection more easily due to the immunocompromised state generated by COPD (Hattab et al., 2016; Decramer et al., 2012).

Chronic Renal Failure

Both studies that recorded cases of balantidiasis in patients with acute and chronic renal failure occurred in India (Karuna & Khadanga,

2014; Khanduri et al., 2014). Renal failure can occur acutely, with functional reduction of the kidney in hours or days. This refers to the decrease in the filtration rate, glomerular and/or urinary volume and electrolyte alterations, or in a chronic form as an abnormality in the structure and / or function of the kidney over an extended period of months or years (Weisbord & Palevsky, 2006; Haller & Strauer, 2012).

Due to the functional incapacity of the urinary system, renal failure is accompanied by uremia, that is, the increased presence of urea in the blood causing negative changes in patient immunity, since the kidneys have a fundamental role in the homeostasis of the immune system, removing cytokines and toxins from the body. The retention of these substances not eliminated efficiently activates innate immunity cells and further increases the production of other cytokines. In addition, there is a decrease in lymphocytes and NK cells, as well as functional alterations in phagocytosis and in the count of circulating neutrophils, macrophages and DCs, making the patient functionally immunocompromised and at risk of acquiring infections by different microorganisms, including urinary tract infections (Vaziri et al., 2012; Tecklenborg et al., 2018). Studies have evidenced the dysfunction of the intestinal barrier in the presence of uremia, resulting in the rupture of the epithelial junction and alteration in the permeability and composition of the microbiota (Kurts et al., 2013; Vaziri et al., 2012).

Autoimmune Disease

Three reports were found of balantidiasis in patients with autoimmune disease, a condition in which the immune system loses self-tolerance and body tissues and organs become the targets of the produced autoantibodies. Immunosuppressive drugs have become the standard treatment and are intended to contain the inflammation resulting from autoimmune diseases. However, patients using this type of therapy generally require higher doses of these drugs over time, increasing the toxicity and immunosuppression provided by their use (Proal & Marshall, 2018).

Studies indicate, for instance, that corticosteroids inhibit the secretion of the T lymphocyte growth factor, interfere in the coding and production of various cytokines, such as IL-1, IL-2, IL-3, IL-4, IL- 5, IL-6, IL-8, IL-10, IL-13, TNF-α and IFN-γ, that is, generating a dysregulation in the immune function (Ashwell et al., 2000). Studies also indicate the association between autoimmune diseases in the generation of intestinal dysbiosis, with a decrease in commensal intestinal species and an increase in the proliferation of pathogenic species, resulting in alterations in the mucosa structure and loss of immune balance (Proal & Marshall, 2018; Saadat et al., 2018).

Liyanage et al. (2011) describe the case of a patient with common pemphigus, and diabetes with intestinal balantidiasis. Pemphigus vulgaris is a bullous disorder of the skin and mucous surfaces with an autoimmune characteristic. The target of circulating autoantibodies is mainly keratinocytes and desmoglein proteins 1 and 3, constituents of desmosomes, epithelial adhesion structures (Venugopal, 2011; Melchionda & Harman, 2019). Individuals with pemphigus are known to be susceptible to infections due to their disease and long-term use of immunosuppressants. Although bacterial infections are common, other serious infections can occur due to unusual microorganisms (Liyanage et al., 2011).

In the pathogenesis of pemphigus, dermal layer NK cells stimulate CD4 + T cells to secrete pro-inflammatory cytokines IL-8, IL-6 and IFN- γ. The increase in the secretion of IL-17 and IL-23 has also been documented with a decrease in Treg cells, indicating the influence of Th1 and Th17-type responses to the disease and an unbalanced immune response (Das et al., 2019).

Tanja et al. (2018), in their article report another association between *B. coli* infection and autoimmune skin disease. The report is a case of urinary balantidiasis in a patient in Slovenia, with psoriasis, in addition to other comorbidities, such as hypertension, dyslipidemia, fatty liver disease, chronic gastritis, DM2, left breast carcinoma, urinary incontinence and gouty arthritis. According to the authors, considering the patient presented so many comorbidities, it is likely that all or most of them influenced in some way and more easily triggered the infection by the protozoan.

Psoriasis today is defined as an immune-mediated disease with an autoimmune characteristic. The excessive proliferation and abnormal differentiation of keratinocytes results in erythematous squamous plaques throughout the body, largely mediated by T cells and activation of innate immunity cells, such as macrophages and neutrophils, resulting in inflammation in the epidermal layers. The situation can be aggravated during treatment with immunosuppressive drugs, leading to the suppression of T lymphocytes (Das et al., 2019; Grän et al., 2020).

Martviset et al. (2020) report another finding of *B. coli* in urine as the first case occurring in a patient with SLE and lupus nephritis, in Thailand. SLE is a heterogeneous autoimmune disease, which presents an uncontrolled inflammatory reaction and can affect several organs, causing skin rashes, including butterfly-shaped malar rash, oral ulcers, hemolytic anemia and nephritis (Hagberg & Ronnblom, 2015; Jung & Suh, 2017).

In SLE, cell instability and immune signals occur, and the balance between tolerance and autoimmunity is lost. It is believed that there is an association in the development of SLE with defects in the removal of apoptotic cell fragments by phagocytic cells, being recognized as potentially immunogenic (Shao & Cohen, 2011). Antigen-presenting cells (APCs) present recognized auto antigens to T lymphocytes, leading to the release of pro-inflammatory cytokines,

such as IL-6, IL-17, IL-18 and TNF-α. Plasma cells produce autoantibodies that form immune complexes and damage tissues when deposited. The role of IFN-α is also indicated in the development and pathogenesis of SLE, probably, for example, influencing the suppression of Tregs (Niewold et al., 2010; Lisnevskaia et al., 2014).

Infections are generally reported in patients with SLE, due to the immunosuppressive state generated by the disease itself or by the suppressive drugs used, with greater risks of serious and fulminant manifestations (Braz et al., 2014). In the report in question, the authors suspect that the invasion of the urinary tract occurred due to SLE and worsened after steroid therapy prescription.

Although the large intestine is the most common site of infection by *B. coli,* in certain conditions, extra intestinal sites may harbor the protozoan, as was demonstrated in the review. *B. coli* is not known to produce toxins, but its ability to cause ulcers in the intestinal mucosa is attributed to the hyaluronidase enzyme (Schuster & Ramirez-avila, 2008). Although there are no studies demonstrating the mechanisms of extra intestinal dissemination, these probably occur secondary to colonic balantidiasis (Sharma & Harding, 2003). The protozoan can probably spread to the lungs through the hematological route, lymphatic vessels or through an opening in the diaphragm, and in genitourinary infections, which is believed to occur by direct dissemination of the anal area or by a recto-vaginal fistula caused by *B. coli* (Anargyrou et al., 2003; Vasilakopoulou et al., 2003; Soleimanpour et al., 2015). Regarding the mode of transmission, although direct contact with pigs is recognized, most reports indicate the ingestion of contaminated water or food as the possible infection mechanism.

Few papers have been published demonstrating the mechanisms of the immune response to *B. coli*, and therefore, a number of discoveries in this regard are still pending. Most of the studies include case reports, and do not necessarily elucidate the pathogenesis of the disease and the immunological aspects involved, confirming the need for efforts to elucidate these (Zaman, 1964; Karapetian et al., 2000).

Infection by *B. coli*, although unusual, can present clinical importance in some host immunological conditions, developing a degree of pathogenicity for humans and causing severe fulminant colitis or extra-intestinal disease. The diseases and comorbidities generate imbalance in the innate and adaptive mechanisms of the immune response through persistent systemic inflammation. These circumstances may favor balantidiasis, although this is not restricted to individuals under these conditions, as it is also capable of infection and causing disease in humans with no pre-existing comorbidity. This revision demonstrates that balantidiasis can affect several hosts, emphasizing those with chronic-degenerative diseases or that compromise the immune system, and this manuscript may lead to interest in further research regarding the *B. coli* parasite.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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