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Immune Response in Amoebiasis with Entamoeba Histolytica

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Abstarct: Entamoeba histolytica is a protozoan parasite that causes amebiasis. Amebic pathogens can present clinically in a variety of ways, symptoms can range from being asymptomatic to having severe ones like diarrhea and extra-intestinal abscesses. Only 20% of those affected, like other infectious diseases, are thought to exhibit symptoms, and that the result of infection is determined by both the parasite's and humans' genetic make-up as well as external elements like the microbiome. Amebic pathogenicity involves several crucial stages, including the deterioration of the mucosal layer and infiltration into it, penetration into the tissues, adherence to the intestinal epithelium, and dissemination to other organs. Hepatic amoebiasis, which includes amoebic hepatitis and liver abscesses, is the most prevalent and dangerous effect of intestinal amebiasis. Although the mucosal layer in the digestive tract frequently serves as a main physical barrier against intestinal pathogens, the intestinal immune response is the secondary defense against E. histolytica infection. Mucosal immunoglobulins are the most significant component of the human gut defense system. Host protection against E. histolytica also depends on cell-mediated immune responses.

Key points: Entamoeba histolytica, Immune response, pathogens.

Introduction

Entamoeba histolytica, an intestine protozoan parasite, is the source of amiosis, which also affects humans. Up to 100,000 fatalities each year are attributed to amebiasis, a persistent global health issue (1). Six protozoan species make up the genus *Entamoeba*, of which one is pathogenic and five are non-pathogenic. The pathogenic species are among three of the six species, share the same morphology. The human host is home to the pathogenic *Entamoeba histolytica* as well as *Entamoeba coli, Entamoeba dispar* and *Entamoeba moshkovskii*(2). This genus of amoebae is extensively spread in different ogranisms. They are distinguished by having vesicular nuclei, which include varying numbers of chromatin granules attached to the nuclear membrane in the periphery and a relatively tiny karyosome at or near their centers. Most species are distinguished by morphological features. Although these species share the same size range and are visually indistinguishable, They can be differentiated through the use of monoclonal antibody typing and iso-enzyme analysis(3).

History of the Amoebae

The cytoplasm of amoebas, which separated to an outside ectoplasm and an inner endoplasm, is confined with a single membrane and has no fixed structure. Amoebas are structurally simple protozoa. Ectoplasm pushes forth and is followed by endoplasm flowing inside to create pseudopodia, which are blunt projections. These are used for movement and phagocytosis, the process of ingesting food (3). *Entamoeba polecki*, an intestina amoeba is really cause diarrhea in people. There are types of *Entamoeba*, including the pathogens *E. histolytica, E. gingivalis, E. coli*, and *E. hartmani*. Other commensals include the generally free-living genera' representatives, *E. nana* and *Lodmamoeba butschli*. Human nasopharynx, central nervous system, eyes, and skin have all been found to have Acanthamoeba and Naegleria. Both Acanthamoeba and Naegleria are potential deadly invaders of the CNS (2,4).

Parasitic diseases are more common than any other factor in the burden of illness, sometimes even resulting in death both poor and developed countries which affected, particularly in areas with high-income countries (5). One of the top global causes of morbidity and mortality is amebiasis, mostly in tropical and subtropical regions with poor sanitation and health care systems (6). Serious complications linked to invasive intestinal or extra-intestinal diseases account for the majority of fatalities. After schistosomiasis and malaria, amoebic dysentery is the third leading cause of death from parasite disease globally. Within a year, 4 - 10% of amoeba infection carriers show clinical symptoms (7,5). Even if all deaths may be brought on by invasive E. histolytica infection, data on the prevalence of E. histolytica may be exaggerated because they come from a time before the distinction between the pathogenic and non-pathogenic species of the organism. The prevalence numbers could be affected by both *E. dispar* and *E. moshkovskii* (6,8).

Symptoms and Pathogenesis:

Only until they infiltrate the intestinal tissues do the lumen-dwelling amoebae start to cause sickness. Only 10% of infection-causing agents actually exhibit this behavior; the other 90% are carriers or asymptomatic (9).

a- Intestinal amoebiasis

The incubation time for acute intestinal amoebiasis ranges from one to fourteen weeks, and symptoms include severe diarrhea, numerous tiny stools filled with blood, mucus, and fragments of necrotic mucosa, as well as acute abdominal pain and stiffness. Dehydration, toxaemia, and a leukocytosis of 7000 to 20000 c/mm are unusual symptoms that could indicate a secondary bacterial infection (10). Not all *E. histolytica* strains are invasive or harmful. Only pathogenic strains are able to cling to host cells in vivo and cause the proteolysis of host cell content. There are various ways to distinguish between pathogenic (P) and non-pathogenic (NP) strains, including the utilization of genetic markers, phagocytic activity, and vulnerability to complement-mediated lysis, and the use of monoclonal antibodies. An essential component of P strains' pathogenicity is the amoebic cysteine proteinase, which renders the complement factor C3 inactive. Based on the electrophoretic mobility of six isoenzymes, including acetylglucosaminidase, aldolase, hexokinase, NAD-diaphorase, peptidase, and phosphoglucomutase, *E. histolytica* strains can be separated into at least 22 zymodemes (11). Only nine of these are invasive (P), while the remainder are commensals that are non-invasive (NP). There is a geographic dispersion of the zymodemes. Non-pathogenic zymodemes are much more prevalent than Pones, even in endemic regions, which barely make up roughly 10% of the entire population.NP are now categorized as *E. dispar* in the Lieberkuhn crypts of the colon, the metacyclic trophozoites pierce the columnar epithelial cells. The trophozoite's mobility, which results in discrete ulcers with a pinhead center and elevated margins, and the tissue lytic chemicals secreted by the amoebae, which harm the mucosal epithelium, enhance penetration.

The ulcers are numerous and limited to the colon, with the caecum and the sigmoid-rectal region having the greatest density(12,13). An amoebic ulcer typically has a flask-shaped cross section. Ulcers can infrequently affect the colon's muscular and serous coatings, leading to perforation and peritonitis. Hemorrhage could be brought on by blood vessel erosion. On rare occasions, a chronic

ulcer may take the appearance of a granulomatous growth on the intestinal wall. It's possible to confuse this amoebic granuloma or amoeboma for a cancerous tumor. Recurrent dysentery episodes interspersed with mild to severe gastrointestinal distress and constipation are the hallmarks of chronic amoebiasis(14,15). Localized abdominal discomfort is evident, and long-lasting infections may cause the liver to enlarge and cause psychoneurotic disorders. Cachexia and significant weight loss are side effects of this devastating chronic condition. Diverticula, cancer of the large intestine, and ulcerative colitis must all be taken into account when making a diagnosis. (16).

b- Extra intestinal amoebiasis:

The most prevalent and serious complication of intestinal amoebiasis is hepatic amoebiasis, which includes amoebic hepatitis and liver abscesses. Hepatic amoebiasis results from the infection spreading from the intestinal mucosa into the portal blood stream. An enlarged, painful liver and discomfort in the upper right hypochondrium that may extend to the right shoulder are characteristics of amoebic hepatitis(13,12). Although they are frequently more severe than those of amoebic hepatitis, the signs and symptoms of an amoebic abscess of the liver are remarkably similar to those of amoebic hepatitis. It can be distinguished from viral hepatitis by leukocytosis of 10000–16000/cm mm with 78–80 percent polymorphoncuclear neutrophils(17). There may be an increase in the erythrocyte sedimentation rate. Chills are possible, and fever is typical. The right diaphragm is frequently elevated and immobile, and patients may have mild jaundice. They also frequently have acute discomfort that radiates to the right shoulder. The abscess may burst through the abdominal wall or extend through the diaphragm into the lungs. Chills, fever, leukocytosis, and signs of lung consolidation are symptoms of pulmonary amoebiasis. The typical signs and symptoms of a brain abscess and tumor are present in amoebic infections of the brain. Sadly, these infections have only ever been found after autopsies (16).

Epidemiology of *Entamoeba histolytica*

The distribution of this parasite is international. Infection rates among people are very high in Central and South America, Africa, and India. (17). In tropical endemic places, the frequency might reach 50%. Depending on a person's demographics, socioeconomic level, and surroundings, they can get an infection with *E. histolytica*. The tropics and subtropics are home to many poor and socioeconomically deprived populations where it is extremely endemic (16). 38% of people who visited outpatient clinics in Egypt with acute diarrhea were later diagnosed with amoebic colitis (18). Studies on the seroprevalence of *Entamoeba histolytica* in Mexico found that more than 8% of the population was positive. An investigation into the incidence of intestinal parasites in Yemen found that *E. histolytica* was present in 17.1% of the population (19). The incidence of *E. histolytica,* however, was shown to be as low as 4.6% in Northern Ethiopia in a study to investigate the prevalence of intestinal parasites and their related risk factors (20). Kenya has a prevalence of E. histolytica of about 21% and although though the majority of cases are left untreated because they are asymptomatic (21), this high frequency has a significant impact on amoebiasis. Intestinal protozoan parasite prevalence was found to be 38.9% overall, with *E. histolytica* being the most common.

The transmission and dispersal of intestinal parasite diseases are known to be influenced by environmental, socioeconomic, demographic, and hygiene-related behavior (14). The location of residence, 20-year-old age, consumption of raw vegetables, and the quality of the water were all found to be significant risk factors in a Brazilian study (Benetton)(21). Lack of access to clean drinking water and inadequate sanitation education also contribute to transmission (17). *Entamoeba histolytica* enters the intestines through the mouth after contact with raw vegetables, undercooked food, infected hands, water, or surfaces. Poor personal hygiene, improper trash removal, and improper excreta disposal all contribute to this oral faecal infection (22). Fly-borne infectious cysts from contaminated sites or filthy latrines can contaminate food or water and serve as a mechanical vector for transmission (20). Many tropical developing nations lack an adequate supply of clean drinking water, and because of inadequate sanitation at home or at the water source, contamination may occur (19). The availability and use of restrooms is another risk factor. *E. histolytica* can

contaminate food or water supplies when humans defecate in open cysts that can wash into water bodies or be carried by mechanical vectors like flies. A study on the prevalence of E. histolytica (22) indicates that the illness is widespread and was higher in areas without or infrequently used toilets. Another investigation into the risk of intestinal parasites found a link between unsanitary toilet conditions and the spread of *E. hisolytica*. In a study on risk factors for *E. histolytica* conducted in Vietnam, The correlation between the prevalence of infection and the kind of toilet used (23). The children are more susceptible to infection than adults are because youngsters maintain inferior hygiene habits and have less developed immune systems (24).

Cells of the immune system:

a- Neutrophils:

About 95% of circulating granulocytes are composed of it. They are between 10 and 20 m in diameter and have a distinctive multilobed nucleus. Due to their protein being stored in two different types of granules, such as lactoferrin and hydrolyses enzymes, they become neutral in dye reactions. mostly phagocytic in nature (20). Neutrophil counts can increase due to a variety of inflammatory processes, physical stress, or tissue necrosis that may occur after a severe burn or a myocardial infarction. Granulocytic leukemia also exhibits an increase in neutrophils (23). Neutropaenia is the medical term for a decline in neutrophils; whereas most bacterial infections increase neutrophils, some, such as typhoid fever and brucellosis, as well as many viral illnesses, such as hepatitis, influenza, rubella, and mumps, cause a decline. Neutropaenia can result from a severe infection that depletes the neutrophil population in the bone marrow. Numerous cancer treatments known as antineoplastics cause bone marrow depression and can drastically drop the neutrophil count. Some antibiotics, lithium, phenothiazines, and tricyclic antidepressants are examples of medication classes that can cause neutropenia (24). In instance, polymorphonuclear neutrophil (PMN) degranulation and vasculitis are characteristics of tissue damage in invasive amoebiasis that are similar to those of Wegener's granulomatosis, which is distinguished by the presence of antibodies against neutrophil cytoplasm. Possible reasons include a cross-reacting antibody to an Entamoeba histolytica component or an antibody to PMN components created and maybe altered by the activity of E. histolytica on PMN (25). According to Pudifin (18), it's probable that this antibody has a role in the etiology of invasive amoebiasis.

b- Eosinophils:

When stained with acidic dyes like eosin, eosinophils in human blood typically have cytoplasmic granules and a bilobed nucleus. In healthy, non-allergic people, they make up 2-5% of blood leukocytes and mostly perform phagocytic functions (23). In vitro cultures have demonstrated the effectiveness of eosinophils as effector cells for the parasite-killing process. Eosinophils' in vivo function, however, has been more challenging to establish. Early research revealed a close relationship between eosinophils and injured or dead parasites in histological sections, as well as a statistically significant relationship between parasite resistance and the ability to cause eosinophilia after infection (24).

It has long been known that an infection with helminth parasites is characterized by a rise in the quantity of eosinophils and mast cells. Eosinophils were first believed to have the ability to operate as regulatory cells to control the inflammatory responses brought on by mast cell degranulation. The discovery that pure eosinophils could eradicate Schistosoma mansoni's early schistosomula stage in vitro changed the focus of eosinophil research to an investigation of their function as key effector cells in resistance to parasitic illnesses. Later, it was shown that eosinophils can destroy a range of nematode parasites that are significant to both humans and animals in vitro. Eosinophil-mediated killing was often most efficient against larval stages and necessitated collaboration with antibody and complement for optimal killing potential (25).

c- Basophiles:

Less than 0.2% of leukocytes are basophiles, which are present in very modest quantities in the blood. Heparin and histamine, which are stained by basic dye, are found in the cytoplasmic granules

of these cells. (26) stated that basophils contribute to allergic reactions. It has not yet been determined if basophilia manifests in humans who have parasite infections, Despite the fact that it is regularly seen in parasite infection models in animals. Based on records from 668 individuals with a known parasite infection, 472 patients with only helminthes, 146 patients with only protozoa, 50 patients with both helminthes and protozoa infections, and 50 patients without parasitic infection, the relationship between basophilia and parasitic infection in humans has been examined (22,24). Only four of the 668 patients (0.6%) developed basophilia, and neither the absolute basophil counts nor the proportion of patients with basophilia among the helminth-infected, protozoa-infected, or uninfected group showed any statistically significant differences. Only four individuals had basophils making up more than 3% of the peripheral white blood cell population, according to analysis of relative basophil levels. As a result, basophilia, which only occasionally occurs in human parasite infection, is not a helpful clinical marker in the assessment of suspected parasitic disease. (25,26).

d- Monocytes

CFU-GMs that follow the monocyte pathway first give birth to proliferating monoblasts. These cells eventually develop into mature circulating monocytes from promonocytes. It is thought that tissue-resident macrophages, like lung macrophages, are replaced by circulating monocytes. The mononuclear phagocyte system is made up of the several macrophage subtypes. They make up 2-5% of the blood leukocytes in healthy people. According to (23,26) chronic inflammatory diseases, parasite infections, tuberculosis, and viral infections (such as infectious mononucleosis, mumps, and measles) can all cause an increase in the number of monocytes in the body. The secreted and soluble amoeba (*Entamoeba histolytica*) proteins (SAP) stimulate the production of the chemoattractant monocyte chemotactic protein (MCP) in colonic epithelial cell lines(27).

e- Lymphocytes

The thymus and postnatal bone marrow are the primary or central lymphoid organs and many lymphocytes are created daily. Some of these cells go via the bloodstream and into the secondary lymphoid tissues (lymph nodes, spleen). In a typical blood smear, lymphocytes are divided into two types—cells and T cells—and range in size (6–10 um) and shape. The nuclear to cytoplasmic ratio (N: C) shows differences (23). Epstein-Barr virus-induced infectious mononucleosis is the predominant cause of lymphocytosis, and other viral infections. Atypical pneumonia, the majority of viral upper respiratory infections. Other viral illnesses like infectious hepatitis, the mumps, rubella, and rubeola. a few bacterial illnesses, including syphilis and TB. lymphoma, toxoplasmosis, and acute and chronic lymphocytic leukemia. Graves' illness (21). Following the administration of ACTH and cortisone, burns, trauma, and diseases like lupus erythematosus can all cause lymphopenia (low lymphocyte counts), in long-term uraemia. Many congenital immunodeficiency states, including AIDS, plastic anemia, and tuberculosis, as well as Cushing's syndrome, early acute radiation syndrome, and others. Even though they may be boosted by other chronic infections, lymphocytes are non-specific cells against *E. histolyticea* infection (20). Clinical and experimental research suggests that human cell-mediated immune pathways may offer protective immunity after *Entamoeba histolytica*-induced invasive illness. Human macrophages produced from activated monocytes have the ability to eradicate dangerous axaenic amoebic trophozoites in vitro. Over the course of an 18-hour incubation, amoebae gradually killed non-immune T-lymphocytes without affecting their own survival. Phytohaemagglutinin (PHA)-stimulated T-lymphocytes gradually lowered the vitality of virulent HMI amoebae during the course of an 18-hour incubation. If PHA was taken out beforehand or was only added during the assay, lymphocyte cytotoxicity for amoebae was not present (26,27). PHA-stimulated T-lymphocytes were depleted of T8-bearing cells through complement-mediated lysis, which prevented them from killing amoebas. More PHA-stimulated T cells than unstimulated T lymphocytes adhered to amoebae. Amoebic adhesion is prevented by N-acetyl-D-galactosamine Lectin increased lymphocyte amoebicidal activity and lymphocyte survival while decreasing lymphocyte-amoebic adhesion. It was discovered that cytotoxicity was contact-

dependent when amoebae were suspended in a 10% dextran solution with adherent PHA-stimulated T cells or without them (27).

Immune response in amoebiasis

The best immune responses are influenced by the specific parasite and the stage of the infection, and are usually triggered by a variety of immune defense mechanisms, both antibody- and cell-mediated (24). *Entamoeba histolytica* and *Giardia* are two intestinal protozoa that can endure in an anaerobic setting. The detoxification of reactive oxygen metabolites by host-derived factors, particularly the phagocytosis of bacteria or host erythrocytes (intact or their enzymatic/non-enzymatic components) may present fresh therapeutic options for the treatment of invasive amoebiasis (28). In many compartments connected to the mucosa, *Entamoeba histolytica* cause a local secondary immunological response with the rise of specialized secretary IgA (sIgA) antibodies (25,27). Numerous inflammatory cells entered the intestinal lumen through flattened or damaged epithelium. Amoebae consumed and digested polymorphonuclear leucocytes, eosinophils, and lymphocytes, similar to their well-known consumption of red blood cells. Loss of nuclear stain affinity is one of the first alterations observed in food vacuoles before the loss of exterior membranes, suggesting that ingested inflammatory cells have not yet been detected. The amoebae that cause human dysentery appear to be characterized by their consumption of inflammatory cells (29).

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