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Article

OCULAR INFECTIONS CAN BE CAUSED BY BACTERIA, VIRUSES, FUNGI, OR PARASITES, LEADING TO AN IMMUNE RESPONSE AND INFLAMMATION

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ABSTRACT

Ocular infections can be caused by microorganisms that provoke an innate and adaptive immune response, inflammation, and tissue damage. Microorganisms recognize pathogen-associated molecular patterns (PAMPs) and activate nuclear factor kappa B (NF- κ B) and type I interferon (IFN) signaling, with the production of cytokines. Microorganisms can activate the complement fractions C3 and C5a, which cause opsonization of the pathogen and cell lysis. In the adaptive immune response, CD4⁺ helper cells and CD8⁺ cytotoxic cells are activated, which help eliminate the infection caused by the pathogen. Microorganisms initiate inflammation in ocular infections that is mediated by the cytokines TNF, IL-6, and IL-1 β , which cause severe tissue damage. In addition, they activate macrophages and neutrophils to produce reactive oxygen species (ROS) and nitric oxide (NO) to kill the pathogens, which causes damage to tissues. Infection by pathogenic microorganisms is fought by immune cells, including mast cells (MCs). These are cells that normally mediate allergic reactions through Fc ϵ RI receptors, but in the conjunctiva, cornea, and other ocular tissues, they play an important role in the pathophysiology of infections. Activation of MCs leads to phosphorylation of Syk kinase, triggering MAPK, PI3K, and NF- κ B, with production of inflammatory cytokines. Inflammatory mediators released by MCs cause vasodilation, increased vascular permeability, and immune cell recruitment. Vascular endothelial growth factor (VEGF) contributes to neovascularization and worsens keratitis, while TNF is a cytokine that takes part in the inflammatory network. In viral conjunctivitis, viruses use certain receptor proteins, such as integrins, to enter the cell and activate the immune system. Activation of receptors triggers the NF- κ B, IRF3, and IRF7 pathways, with production of IFN α and γ and inflammatory cytokines. Super-inflammation leads to epithelial damage and can cause conjunctivitis. Bacterial conjunctivitis is mediated by the activation of TLR2 and 4 and inflammatory cytokines. Infectious keratitis is mediated by HSV-1, which enters the cell via nectin-1 and activates TLR3 and RIG-I, causing a TH1 immune response. Therapy includes NF- κ B inhibitors, MAPK inhibitors, and MC stabilizers. The use of anti-inflammatory cytokines can certainly be helpful for treatment, although they are still under investigation.

KEYWORDS: *Ocular infection, microorganism, inflammation, immunity, keratitis, conjunctivitis, allergy*

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INTRODUCTION

Ocular infections can be caused by bacteria, viruses, fungi or parasites, which provoke an immune and inflammatory response (1). These reactions cause damage to ocular tissues that can be more or less severe depending on both the virulence of the microorganism and the immune response of the host (2) (Table I). Microorganisms can activate the innate and adaptive immune response (3). In the innate immune response, microorganisms recognize pathogen-associated molecular patterns (PAMPs), activating nuclear factor kappa B (NF- κ B) and type I interferon signaling, which leads to the production of cytokines such as IL-1 β , IL-6, IL-8, TNF (4). In NOD-like receptor (NLR) activation, inflammasomes are activated, promoting the release of IL-1 β and IL-18, two potent cytokines that induce inflammation (5).

Table I. Some common infectious eye diseases.

| | | |
|--|----------------------------------|---|
| <i>Viral Infections:</i> | Viral Conjunctivitis (Pink Eye) | Often caused by <i>Adenovirus</i> . |
| | Herpes Simplex Keratitis | Caused by <i>Herpes Simplex Virus (HSV-1)</i> . |
| | Herpes Zoster Ophthalmicus | Caused by <i>Varicella-Zoster Virus</i> (shingles in the eye). |
| | Molluscum Contagiosum | Viral skin infection that can affect the eyelid. |
| | Cytomegalovirus (CMV) Retinitis | A severe infection in immunocompromised individuals, such as those with HIV/AIDS. |
| <i>Bacterial Infections:</i> | Bacterial Conjunctivitis | Caused by bacteria like <i>Staphylococcus aureus</i> , <i>Streptococcus pneumoniae</i> , or <i>Haemophilus influenzae</i> . |
| | Blepharitis | Inflammation of the eyelids, often due to <i>Staphylococcus</i> infection. |
| | Keratitis | Infection of the cornea, often caused by <i>Pseudomonas aeruginosa</i> or <i>Staphylococcus aureus</i> . |
| | Endophthalmitis | Severe bacterial infection inside the eye, often after surgery or trauma. |
| <i>Fungal Infections:</i> | Fungal Keratitis | Often caused by <i>Fusarium</i> , <i>Aspergillus</i> , or <i>Candida</i> species. |
| | Endophthalmitis (Fungal) | Can be caused by <i>Candida</i> or <i>Aspergillus</i> . |
| <i>Parasitic & Protozoal Infections:</i> | Acanthamoeba Keratitis | Caused by <i>Acanthamoeba</i> , often linked to contact lens use. |
| | Toxoplasmosis | Caused by <i>Toxoplasma gondii</i> , affecting the retina (ocular toxoplasmosis). |
| | Onchocerciasis (River Blindness) | Caused by <i>Onchocerca volvulus</i> , transmitted by blackflies. |
| <i>Chlamydial & Other Infections:</i> | Trachoma | Caused by <i>Chlamydia trachomatis</i> , a leading cause of preventable blindness. |
| | Ophthalmia Neonatorum | Severe neonatal conjunctivitis due to <i>Neisseria gonorrhoeae</i> or <i>Chlamydia trachomatis</i> . |
| | Syphilitic Uveitis | Caused by <i>Treponema pallidum</i> (syphilis). |
| | Leprosy-related Eye Disease | Caused by <i>Mycobacterium leprae</i> , affecting the eyelids and cornea. |

Microorganisms activate complement fractions C3 and C5a, which together with membrane attack complexes (MAC), contribute to pathogen opsonization and cell lysis (6). In the adaptive immune response, CD4+ helper T cells (Th1, Th2, Th17) and CD8+ cytotoxic cells are activated, which help eliminate the infection caused by the microorganism (7). The acquired response also involves B cells with the production of IgA, IgG and IgM antibodies that neutralize pathogens and prevent adhesion to ocular surfaces (8). Tear antibody load increases in vaccinated patients (9).

Some pathogens induce specific infectious mechanisms, such as bacterial infections by *Pseudomonas aeruginosa*, or *Staphylococcus aureus*, where α -haemolysis and exotoxins are used to destroy the corneal epithelium (10). Viral infections such as Herpes Simplex Virus and Adenovirus use the host DNA replication machinery and induce apoptosis via interferon-stimulated genes (ISG) (11). SARS-Cov-2 enters conjunctival macrophages via the ACE-2 receptor or P2X7R (12). and activates the intracellular caspases by cross-talk with the NPL3 inflammasome, inducing the cytokine storm in the lung alveoli (13).

DISCUSSION

Microorganisms activate biological mechanisms of inflammation in ocular infections, such as the cytokines TNF, IL-6, and IL-1 β that can cause a cytokine storm, leading to inflammation with severe tissue damage (14) (Fig.1). In addition, the production of reactive oxygen species (ROS) and nitric oxide (NO) induced by macrophages and neutrophils to kill pathogens can damage host cells (15). Released matrix metalloproteinases (MMPs) also contribute by damaging the extracellular matrix, causing corneal ulcers, as evidenced in bacterial keratitis (16).

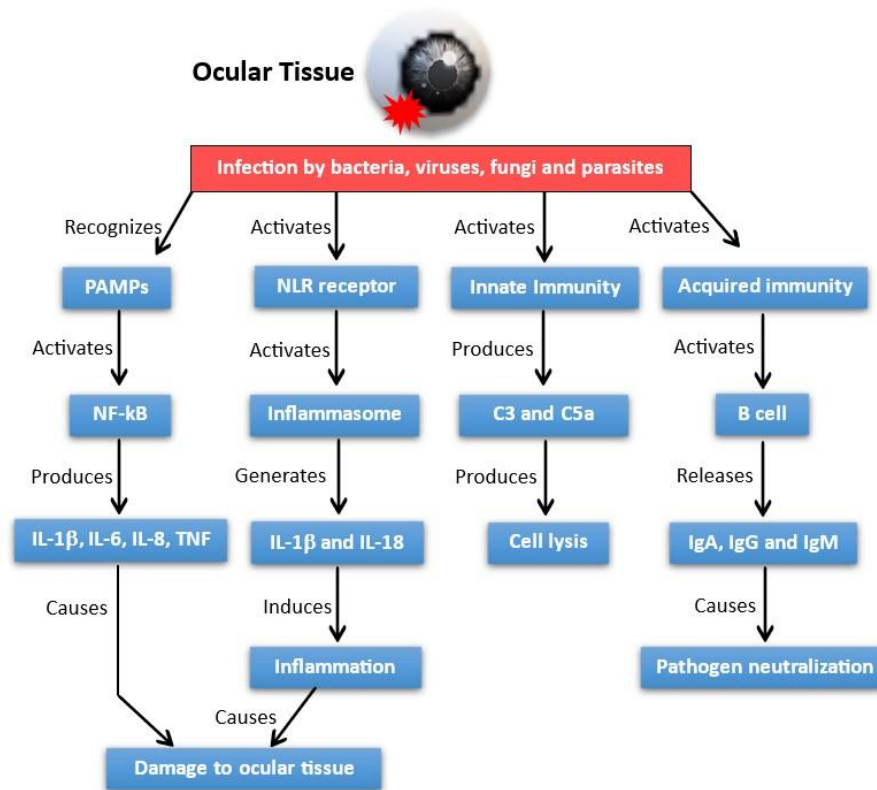


Fig. 1. The biological mechanisms of inflammation in ocular infections induced by bacteria, viruses, fungi, and parasites.

Fungal infections, such as *Candida*, activate the Dectin-1/Syk/CARD9 pathways, leading to chronic inflammation (17). In parasitic infections, particularly in *Acanthamoeba*, autophagy and excessive immune activation can be induced, which leads to serious keratitis (18). Microbial invasion triggers activation of immune cells, including mast cells (MCs) (19).

Role of mast cells (MCs) in eye infection

MCs are activated via Fc ϵ RI receptors when allergens cross-link IgE antibodies. MC activation leads to phosphorylation of Syk kinase, triggering downstream pathways such as MAPK, PI3K, and NF- κ B, which mediate inflammatory responses (20). Preformed mediators such as histamine and tryptase are released within seconds to minutes, while prostaglandins, cytokines, and chemokines, such as IL-4, IL-5, IL-13, IL-1, IL-33, TNF, and CCL2 (MCP-1), are released later (after hours) and promote the recruitment of eosinophils and Th2 cells (21).

MCs are tissue immune cells located in the conjunctiva, cornea, and other ocular tissues that play an important role in the pathophysiology of infections by mediating the inflammatory response (22). They are activated in response to pathogenic microorganisms such as bacteria, viruses, fungi, and parasites (23). MCs possess Fc ϵ RI receptors that bind allergens and lead to degranulation with the release of inflammatory mediators. Pathogenic microorganisms bind to Toll-like receptors (TLRs) on MCs, generating and releasing pro-inflammatory cytokines (24). MCs contribute to the defense of the organism but can also cause damage to the body by releasing compounds that are harmful to tissues. Through TLRs, MCs recognize pathogens such as viruses and bacteria and become activated. Activation can lead to immediate degranulation with the release of inflammatory mediators such as histamine, and proteases, or to a delayed release with synthesis of pro-inflammatory cytokines and lipid mediators such as prostaglandins and leukotrienes (25). The

arachidonic acid cascade generates prostaglandins (including PGD₂, PGE₂) and leukotrienes (LTC₄, LTD₄, LTE₄), amplifying inflammation.

Inflammatory mediators released immediately after seconds cause vasodilation, increased vascular permeability and recruitment of immune cells (26). Vascular endothelial growth factor (VEGF) contributes to neovascularization, worsening keratitis (27). TNF is a cytokine that can be stored in secretory granules and released immediately but can also be generated through protein synthesis and released later (28). All mediators released by MCs amplify the inflammatory response. The mitogen-activated protein kinase (MAPK) pathway is activated through TLR and cytokine receptors (29). These reactions lead to the production of pro-inflammatory cytokines (TNF, IL-6, IL-1 β) and chemokines. The NF- κ B pathway is activated by TLRs, with transcription of genes encoding inflammatory mediators.

PI3K-Akt regulates cell survival and inflammatory responses, and influences MC degranulation and cytokine release, while the JAK-STAT pathway activates cytokines IL-4 and IL-13 in allergic eye diseases (30). Other cytokine-producing cells, such as neutrophils, macrophages, and lymphocytes, are attracted to the site of infection, further amplifying the inflammatory state. Persistent inflammation can lead to systemic tissue damage and can also cause corneal damage and induce conjunctivitis or keratitis (31). Activated MCs not only mediate allergic conjunctivitis and keratitis, but are also involved in molecular and biological pathways, and can aggravate infections by viruses, bacteria and bacterial products, and fungi (32).

Conjunctivitis and keratitis are inflammatory eye diseases that affect the conjunctiva and cornea, respectively. They can be triggered by various infectious (bacterial, viral, fungal, parasitic) and non-infectious causes (allergic, autoimmune, chemical) (33). These diseases involve complex molecular and biological pathways that regulate inflammation, immune responses, and tissue damage. In infectious keratitis, MCs help recruit neutrophils and macrophages via TNF and IL-6, while in non-infectious keratitis (e.g., dry eye syndrome, autoimmune conditions), MCs contribute to chronic inflammation via the TGF- β and IL-17 pathways, leading to corneal damage (34). In allergic conjunctivitis, MC degranulation leads to vasodilation, vascular permeability, and itching, and activation of the histamine H1 receptor on the conjunctival epithelium and nerve endings, which also causes redness, swelling, and itching (35).

In viral conjunctivitis, viruses, including adenovirus, utilize CAR (Coxsackievirus and adenovirus receptor) and integrins for cell entry (36). Herpes simplex virus (HSV-1) binds to nectin-1 and heparan sulfate proteoglycans for entry, causing an immune and inflammatory response (37). Activation of pattern recognition receptors (PRRs) such as TLR3 for dsRNA, triggers the NF- κ B, IRF3, and IRF7 pathways (11). These reactions induce type I interferons (IFN- α , IFN- β) and pro-inflammatory cytokines such as IL-6, IL-8, TNF, IFN- γ , while activation of dendritic cells enhances T cell responses (Th1, Th17) (38) (Fig.2).

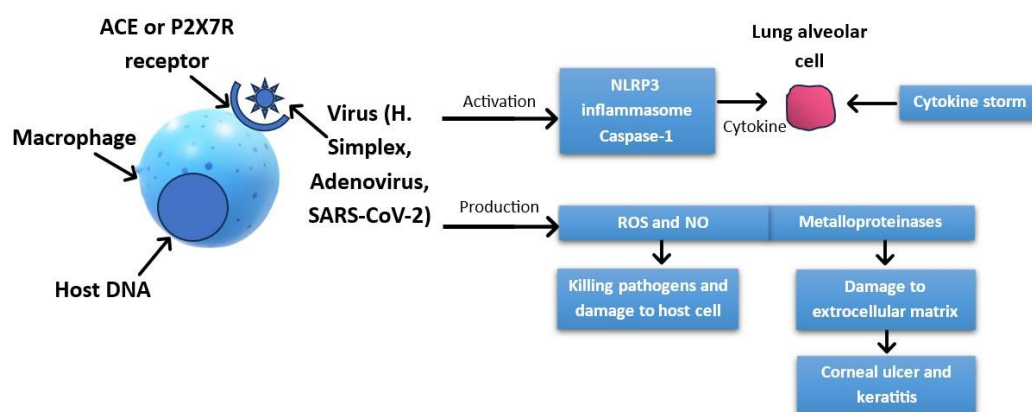


Fig. 2. In viral conjunctivitis, macrophages can be activated through ACE or P2X7R receptors. This activates the NLRP3 inflammasome and caspase-1, which are precursors for the production of cytokines which cause a cytokine storm in the lungs. In addition, macrophage activation produces reactive oxygen species (ROS) and nitric oxide (NO) that kill pathogens but also damage the host cell. Metalloproteinases are generated by macrophages and damage the extracellular matrix and can cause corneal ulcers and keratitis.

Overactive inflammation leads to epithelial damage and can cause pseudomembranous conjunctivitis (39). Bacterial conjunctivitis can be caused by several pathogens, including *S. aureus*, *S. pneumoniae*, *H. influenzae*, and *C. trachomatis* (39). These pathogens bind to their receptors via TLR2 and 4 and adhere to and invade tissues. Fimbriae, pili, and adhesins mediate bacterial attachment to the conjunctival epithelium, while *Chlamydia trachomatis* invades epithelial cells and forms intracellular inclusions (40).

In infectious keratitis due, for example, to HSV-1 or VZV enters via nectin-1, which establishes latency in the trigeminal ganglion (41). This leads to the activation of TLR3 and RIG-I which detect viral dsRNA (42). The hyperactive immune response via Th1 (IFN- γ , TNF) leads to corneal scarring, while type I IFNs (IFN- α , IFN- β) attempt to suppress viral replication. In bacterial keratitis due, for example, to *Pseudomonas aeruginosa* or *Staphylococcus aureus*, there is cell adhesion and biofilm formation (43). The bacteria use fimbriae and adhesins (e.g. type IV pili in *Pseudomonas*) for corneal adhesion. Biofilm formation via quorum sensing (LasR, RhlR) protects the bacteria (44). Bacteria can bind to TLR2 and TLR4, resulting in activation of the NLRP3 inflammasome (45).

The immune response is also mediated by Th17 cells that generate IL-17 and IL-22, cytokines that recruit neutrophils that fuel inflammation and lead to corneal damage (46). In neurotrophic keratitis, there is loss of corneal nerves, reduction of nerve growth factor (NGF), and delayed or failed healing.

Therapeutic targets may be inhibitors of NF- κ B, MAPK, and MC stabilizers such as sodium cromoglicate, which may help modulate inflammation (47). Furthermore, anti-inflammatory cytokines including IL-10, TGF- β , IL-37 and IL-38, and regulatory pathways and lipid mediators such as lipoxins (products of the arachidonic acid cascade) may help improve the inflammatory state (48). Again, targeting MCs by blocking the H1 receptor or inhibiting them with sodium cromoglicate, results in a reduction of degranulation and, therefore, inflammation (35). VEGF inhibitors may help prevent corneal neovascularization in severe keratitis (49) (Fig.3). Inhibitors of inflammatory cytokines such as IL-37 and IL-38 are still the subject of clinical trials that need to be confirmed (50).

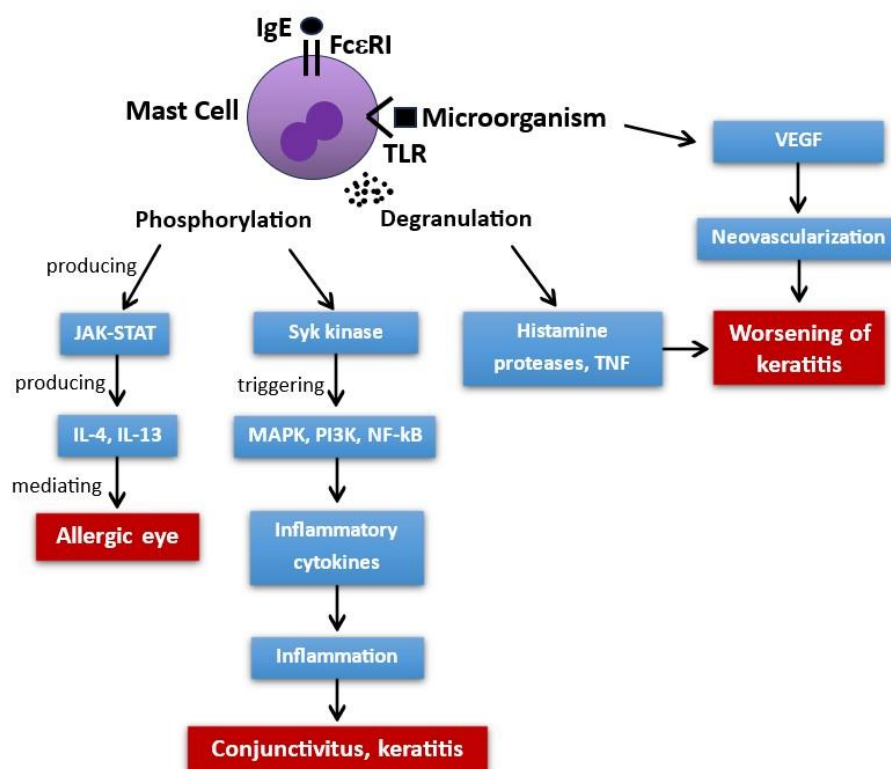


Fig. 3. Mast cells (MCs) can be activated through several receptors including Fc ϵ RI and Toll-like receptors (TLRs). IgE binds Fc ϵ RI and induces MC degranulation within seconds, while the binding of microorganisms to the TLR causes the production of VEGF, which mediates neovascularization and leads to the worsening of keratitis. Following phosphorylation, MCs produce inflammatory cytokines that mediate allergic eye, conjunctivitis, and keratitis.

CONCLUSIONS

Infectious ocular diseases involve complex interactions between pathogens, host immune responses, and tissue damage pathways. While viral infections are largely driven by IFN, bacterial infections rely on TLR-NF- κ B signaling and immune cell recruitment. Fungal infections trigger Dectin-1/Th17 pathways, and allergic conjunctivitis follows a Th2-IgE-MC axis. These immune and inflammatory reactions can be regulated by cytokine inhibitors and immune modulators that can help target novel therapeutics and design new treatments.

Conflict of interest

The authors declare that they have no conflict of interest.

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Letter to the Editor

INFECTIONS IN ORTHOPEDICS IMPACT PATIENT OUTCOMES, RECOVERY, AND PROSTHETIC IMPLANTATION: PREVENTION, DIAGNOSIS, AND TREATMENT

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KEYWORDS: *Infection, orthopedics, clinical, immune system, pathogen*

INTRODUCTION

Infections are very common in orthopedics and a constant concern for the physician (1). Infections by microorganisms can impact patient outcomes, create prolonged recovery periods, and complicate the potential for implant failure (2). The molecular mechanisms of these infections are complex and involve the host immune system, microbial virulence, and inflammation. Infections can be of various types and can involve the bone tissue inside of a joint or a periprosthetic joint used for implants in orthopedics (3). In addition, soft tissue infections can also occur. The pathogens involved in these infections vary, however, the most common are *Staphylococcus aureus*, *Staphylococcus epidermidis*, Gram-negative bacteria, and anaerobic bacteria (4).

DISCUSSION

Different mechanisms are utilized by microbes during infection, including the formation of biofilms, which is a particular concern in periprosthetic joint infections. Biofilms form a protective shield around the bacteria which protects from immune cell attacks and antibiotics (5). Bacteria regulate biofilm formation through chemical signals, while exotoxins, such as those expressed by alpha-toxin in *S. aureus*, damage host tissues. Capsule, protein A, and other protective systems help the bacterium evade the immune system (for example, phagocytosis). Efflux pumps also contribute to antibiotic resistance by expelling drugs from bacterial cells.

The immune response against bacteria causes the release of innate immune cytokines, such as IL-1, TNF, IL-6, and IL-18 (6). The inflammatory response aims to fight the invading microorganism but also impairs patient outcomes, recovery, prosthetic implantation, and treatment. Pathogenic microorganisms can induce osteoclastogenesis via receptor activator of nuclear factor kappa-B ligand (RANKL) signaling, leading to bone depletion and loss (7). Infection attracts neutrophil granulocytes that arrive at the inflamed site to phagocytose and destroy bacteria, but this biological effect causes neutrophils to degranulate, resulting in exacerbation of inflammation. Bacterial antigens bind to Toll-like receptors (TLRs) linked to pathogen-associated molecular patterns (PAMPs) and activate the immune response. In these reactions, nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 (NLRP3) is activated, which leads to the generation of a major inflammatory cytokine, IL-1 β . The immune and inflammatory response induces the activation of NF- κ B and JAK/STAT signaling, which modulates immune cell activity and cytokine production (8).

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Infections have diagnostic and therapeutic implications. In clinical pathology, elevated levels of biomarkers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and procalcitonin are useful for indicating infection. Pathogens can also be identified by next-generation gene sequencing. Antimicrobial therapy may include various strategies such as targeting biofilms with novel drugs or using nanoparticles for targeted drug delivery. Therapies may include inhibition of inflammatory cytokines with medication or even with novel anti-inflammatory cytokines such as IL-37 and IL-38. In addition, therapy may involve immune stimulation against pathogenic microorganisms.

CONCLUSIONS

Infections in orthopedics are a concern for the clinician and can impact patient outcomes, prolonged recovery periods, and potential implant failure. The molecular mechanisms of these infections are complex and involve the immune system and microbial virulence. In bacteria, biofilms form a protective shield from immune cell attacks and antibiotics, exotoxins damage host tissues, and the bacterial capsule helps evade the immune system. The anti-microbial immune response causes the release of pro-inflammatory cytokines and can induce osteoclastogenesis via RANKL signaling with bone depletion and loss. Treatment of infections in orthopedics certainly helps to improve the postoperative status and psychopathological recovery of the patient.

Conflict of interest

The author declares that they have no conflict of interest.

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COMPLICATIONS OF ANGIOKERATOMAS

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KEYWORDS: *Angiokeratoma, angiogenesis, infection, skin, bacteria*

INTRODUCTION

Angiogenesis is a normal physiological process of new blood vessel formation which is essential for growth and diverse functions of the body, including wound healing and embryogenesis. Angiogenesis plays a crucial role in tissue development, function, and repair (1,2). During embryonic development, angiogenesis provides cells with adequate oxygen and nutrients for proper growth. In pathological conditions, angiogenesis helps to restore blood supply and aid recovery, and in malignant tumors, such as glioblastomas, angiogenesis sustains rapid growth. Targeting excessive blood vessel growth in tumors limits their progression.

Angiogenesis is a key physiological process in tissue growth, wound healing, and immune responses. The development of angiogenesis can be significantly influenced by infections through various biological and biochemical mechanisms involving pathogen-derived signals, immune responses, oxidative stress, and endothelial cell remodeling (3). Pathogens, immune responses, and host factors interact to regulate vascular growth, sometimes promoting and sometimes inhibiting angiogenesis.

Angiogenesis can sometimes alter the dilation of blood vessels in the papillary dermis, which contributes to the formation of lesions called angiokeratomas. Angiokeratomas are benign vascular lesions of the superficial dermal blood vessels. They are often associated with hyperkeratosis and form dilations of the superficial blood vessels, causing thickening of the skin with spots (4). They can appear as solitary lesions with a diameter that usually ranges from 1 to 3 mm or multiple lesions and vary in color from dark red to brown. Angiokeratomas have been associated with some genetic conditions, such as Fabry disease.

Angiokeratomas are small blood-filled vesicles that are not infectious, but they can be susceptible to secondary infections. Hyperkeratosis and vascular abnormalities can create an environment where microorganisms can easily proliferate (5). *Staphylococcus aureus* and *Streptococcus pyogenes* contribute to bleeding during infections through various mechanisms (hemolysins, coagulases, proteases, and inflammatory mechanisms) that disrupt vascular integrity.

DISCUSSION

Angiokeratomas are normally benign but they may be prone to secondary infections. Fabry disease-related angiokeratoses results in an accumulation of phospholipids or deficient α -Galactosidase A with the accumulation of globotriaosylceramide (Gb3) in multiple cell types, particularly in the vasculature, which can lead to end organ failure. This disease is caused by mutations in the GLA gene which encodes the enzyme α -Galactosidase that is responsible for

catalyzation in many processes, including the cleavage of glycoproteins, glycolipids, and polysaccharides. Angiokeratomas of Fordyce affect the scrotum or vulva and may be caused by increased local venous pressure.

There is an increase in oxidative stress and abnormalities of the vascular system caused by the endothelial dysfunction in angiokeratomas. This leads to an inflammatory response with activation of the NF- κ B pathway and the release of cytokines. In addition, there is an increase in vascular endothelial growth factor (VEGF) that promotes vascular ectasia, and activation of transforming growth factor-beta (TGF- β) that contributes to fibrosis and the formation of lesions (6). Dysregulation of nitric oxide (NO) can also occur with the formation of microvascular and endothelial abnormalities.

In angiokeratomas, hyperproliferation and differentiation of keratinocytes and mTOR and activation of the PI3K/AKT pathways results in the increased proliferation of keratinocytes and hyperkeratosis. Furthermore, dysregulation of the Wnt/ β -catenin pathway contributes to epidermal thickening. Microtrauma can cause lesions and/or ulcerations of the vesicles with subsequent bleeding and bacterial infection, most commonly from *S. aureus* or *S. pyogenes*.

S. aureus is a human pathogenic bacterium that is responsible for many infections and can cause life-threatening systemic infections and/or superficial skin diseases. Infections caused by *S. aureus* can be complicated by hemorrhages due to tissue damage, as occurs in angiokeratomas. *S. aureus* has several virulence factors that contribute to tissue damage, inflammation, and disruption of hemostasis, leading to hemorrhages (7).

S. aureus utilizes diverse biological mechanisms to evade immune responses, which contribute to inflammation and bleeding. Immune evasion occurs through the binding of protein A to the Fc region of IgG which prevents opsonization and phagocytosis, while superantigens, such as toxic shock syndrome toxin-1, cause excessive immune activation, leading to systemic inflammation and capillary leakage. Lipoteichoic acid and peptidoglycan inactivate pro-inflammatory cytokines IL-1, IL-6, and TNF, increasing vascular permeability and bleeding. The hemolysins A, B, and G form pores in host cell membranes to cause endothelial damage and red blood cell lysis. Targeted treatments could certainly ameliorate the infection and prevent excessive bleeding.

S. pyogenes is a Gram-positive, facultative anaerobic bacterium which is capable of forming colonies of 1-2 mm with β -type hemolysis after 24 hours when grown *in vitro*. This bacterium is capsulated, non-motile, and asporogenous, with homolactic metabolism and negative catalase. It is a highly virulent bacterial pathogen that is responsible for a variety of infections, ranging from pharyngitis to life-threatening sepsis. One of the main pathological effects of pyogenic bacterial infections is bleeding, which can occur due to vascular damage, intravascular coagulation, and disruption of endothelial integrity.

Vascular damage is caused by hemolysins or streptolysins O and S. Streptolysin O is a cytotoxin that causes cell lysis and increased vascular permeability by targeting endothelial cells and immune cells; streptolysin S is responsible for β -hemolysis on blood agar, contributing to erythrocyte lysis and tissue damage. *S. pyogenes* alters the balance between coagulation and fibrinolysis through streptokinase, promoting fibrin degradation and increasing the risk of bleeding.

CONCLUSIONS

Angiokeratomas are benign skin vesicles, but their potential complications (infection, bleeding) and their complex biochemical mechanisms require special attention. Angiokeratomas do not usually require treatment, although in some cases of frequent bleeding, they can be removed by laser or cryotherapy. In subjects with these vascular lesions, there is often psychological damage as well.

The presence of angiokeratomas, especially in the genital area, can cause discomfort and embarrassment and fear of malignancy or social stigma often contributes to emotional distress. Misinterpretation of the lesions as serious conditions such as melanoma can result in excessive medical consultations and anxiety.

Conflict of interest

The author declares that they have no conflict of interest.

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PANDEMICS AND EPIDEMICS: EMPHASIS ON COVID-19

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ABSTRACT

A pandemic is a contagious infection that spreads globally throughout the world population, without any border, while an endemic is an infection that extends to just a part of the world population. An epidemic results from the rapid spread of a disease to a large number of people in a given population in a short period of time. In this century, there have been several pandemics and epidemics that have afflicted humanity such as coronavirus disease of 2019 (COVID-19), Ebola, Zika, Middle East respiratory syndrome (MERS), and H1N1, also known as swine flu. These contagious infections activate both the innate and adaptive immune systems. The excessive immune response can cause severe inflammatory damage that can lead to death of the patient. Here in this paper, we review the pandemics and endemics which occurred in the 21st century and discuss the vaccinations used to prevent them.

KEYWORDS: *Pandemic, endemic, epidemic, infection, COVID-19*

INTRODUCTION

A pandemic is an epidemic that spreads rapidly and extends on a very great scale to involve a large part of the world's population. The word pandemic derives from the ancient Greek word πανδημία, or pandēmios, which means “of all people”. An endemic is a disease that is constantly present or very frequent in a population or territory for various causes, while an epidemic is defined by the rapid spread of a disease to a large number of people in a given population in a short period of time (1) (Table I). The term pandemic applies only to contagious diseases or conditions. A human pandemic occurs when there is a lack of immunity to a highly dangerous pathogen.

Table I. *Pandemics and epidemics since the 19th century.*

| | | | |
|-----------|--|------|---------------------------------------|
| 1817-1823 | First cholera pandemic | 1957 | Asia flu pandemic |
| 1823-1829 | Full cholera pandemic | 1961 | Seventh cholera pandemic |
| 1829-1831 | Second cholera pandemic | 1968 | Hong Kong flu |
| 1852-1859 | Third cholera pandemic | 2000 | HIV/AIDS epidemic (33 million deaths) |
| 1863-1875 | Fourth cholera pandemic | 2003 | SARS epidemic |
| 1881-1896 | Fifth cholera pandemic | 2009 | Swine flu |
| 1899-1923 | Sixth cholera pandemic | 2012 | MERS epidemic |
| 1894-1940 | Third plague pandemic (15 million deaths) | 2019 | COVID pandemic (27 million deaths) |
| 1918-1920 | Spanish flu pandemic (50-100 million deaths) | | |

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In the 21st century, several pandemics have occurred, such as coronavirus disease of 2019 (COVID-19) (the most recent), along with other global or regional outbreaks, such as H1N1 (also known as swine flu), Ebola, Zika, and Middle East respiratory syndrome (MERS) (2).

In pandemic or endemic diseases, viral infection activates innate and adaptive immunity (3). Innate immunity mediated by phagocytic cells is the body's crucial first line of defence in combatting infections and adaptive immunity is activated afterwards with viral activation of T and B lymphocytes.

DISCUSSION

Innate and adaptive immunity play a key role in slowing and stabilizing pandemics towards endemics (4). Natural immunity and vaccines reduce severity, although reinfections remain likely. The study of anticipating pandemics and endemics helps us prevent these pathologies that could emerge, evolve or become serious.

The most recent pandemic that has occurred is COVID-19, which was initiated in China in December 2019 by the SARS-CoV-2 virus. Adaptive immunity is characterized by the participation of antibodies and T cells that generate memory, but with SARS-CoV-2, sterilizing immunity against infection declines faster than protective immunity. The immunological aspects of the pandemic have played an important role in influencing the generation of vaccines and improving already existing therapies. The rapid development of a vaccine has highlighted the importance of long-term immune memory that provides protection. During COVID-19, many young adults presented more severe symptoms due to a more vigorous immune response, even if the incidence of mortality was lower than in the elderly. Some elderly individuals showed partial immune protection due to previous exposures to similar viruses (5). During the pandemic, significant attention was paid to COVID-19, neglecting other pathologies that occurred in the hospital, which affected human immunodeficiency virus (HIV) patients regarding the execution of clinical tests and diagnosis. HIV prevention is crucial and the Centers for Disease Control and Prevention (CDC) recommends that all adolescents and adults from 13 to 64 years of age be tested at least once and patients who are at increased risk for HIV should be rescreened.

The SARS-CoV-2 virus responsible for COVID-19 disease has caused more than 12,000 deaths in Africa, surpassing the total number of people who died during the Ebola epidemic. Ebola virus and SARS-CoV-2 originated from zoonotic spillovers (transmission from animals to humans), with natural reservoirs in bats (6). For Ebola, the intermediate vehicles are primates and rodents, while for SARS-CoV-2, it is the pangolin (not yet confirmed). Ebola is a disease caused by a negative-stranded RNA filovirus, that causes massive vomiting and diarrhea and spreads among individuals who have close contact. Ebola causes severe immune system dysfunction with tissue damage and systemic inflammation. Treatment involves the use of viral vector vaccines and immunotherapy with monoclonal antibodies as emergency treatment.

COVID-19 has often resulted in an excessive and damaging immune response with the formation of inflammatory cytokines which cause a cytokine storm that is mostly mediated by TNF, IL-6 and IL-1. mRNA vaccines are one of the most relevant scientific innovations of the 21st century. COVID-19 vaccines were mainly produced by Pfizer-BioNTech and Moderna and were approved by the Federal Drug Administration (FDA) and the European Medicines Agency (EMA) for global use against SARS-CoV-2. Patients with Ebola and long COVID-19 can develop similar chronic complications such as neurological disorders, anxiety/depression, joint pain, hearing problems, psychological disorders, fatigue and others (7).

Vaccines are one of the best public health tools ever developed and their usefulness is extraordinary. However, immunity does not guarantee the disappearance of the virus, which will continue to evolve and will require targeted vaccinations, genomic surveillance and sensitivity to antigenic dynamics (8). Vaccines prevent serious or fatal diseases, such as polio, measles, hepatitis B, meningitis, tetanus, whooping cough and COVID-19. As immunity increases (from infections or vaccines), transmission slows and an endemic equilibrium with seasonal oscillations is reached. COVID-19 appears to be becoming endemic, with regional outbreaks underway, but its future trajectory remains unpredictable. Vaccines protect against complications such as pneumonia, encephalitis, paralysis, and permanent damage, and reduce hospitalizations and mortality, especially among the elderly and fragile patients. During COVID-19 vaccination, it was noted that the vaccine works faster and is more effective with two doses in the same arm, compared to vaccination in both arms (9).

Once common diseases, such as smallpox or polio, have been eradicated or almost eliminated thanks to vaccination programs used globally (10). Diseases such as the plague and smallpox that were once endemic have been eradicated or controlled thanks to vaccines and public health measures. Vaccines are safer than natural infection, provide effective and long-lasting protection, even at the community level, and prevent illnesses, complications, and deaths, saving social and economic resources.

CONCLUSIONS

In conclusion, both pandemics and epidemics are transmissible infections that recur cyclically and affect various population groups. Infections activate the immune system and inflammation to cause serious local and systemic damage, as well as health and social distress.

Conflict of interest

The author declares that they have no conflict of interest.

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CAR-T THERAPY FOR LYMPHOMAS ASSOCIATED WITH INFECTIONS

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ABSTRACT

Lymphomas are blood cancers which are divided into Hodgkin and non-Hodgkin lymphomas. There has been significant progress treating lymphomas with the advent of immunotherapy, including chimeric antigen receptor T cell (CAR-T) therapy. This therapy allows engineered lymphocytes to directly and selectively eliminate tumor cells. CAR-T therapy is a new personalized technique approved for some aggressive B-cell lymphomas, which express the CD19 target. CAR-T therapy is significantly improving the life expectancy of lymphoma patients. Viral or bacterial infections can increase the risk of developing some types of lymphoma. For example, Epstein-Barr virus (EBV) is associated with Burkitt's lymphoma and Hodgkin lymphoma, while *Helicobacter pylori* is associated with mucosal lymphoma. Although EBV does not often cause serious damage, it can cause some lymphomas in immunocompromised individuals. Specific CAR-T can be used against viral antigens such as those expressed by EBV, although more research is needed.

KEYWORDS: *CAR-T therapy, lymphoma, CD19 target, immunotherapy, infection*

INTRODUCTION

Every year in industrialized countries, the number of individuals diagnosed with blood cancers such as leukemia, myeloma, and lymphoma is increasing (1). Lymphomas are divided into two main categories: Hodgkin's lymphoma and non-Hodgkin's lymphoma (2). Thanks to advances in research, the outlook for lymphoma patients has improved significantly. Until a few years ago, chemotherapy was the classic treatment for blood cancers, including lymphomas. Today, this strategy can be combined with immunotherapy (3), a completely different approach from chemotherapy that consists of stimulating the immune system to recognize and fight tumor cells. This can be done thanks to three new categories of drugs: immunotherapeutics, bispecific antibodies, and chimeric antigen receptor T cell (CAR-T) therapy (4).

Immunotherapeutics work by strengthening the immune system to make it more effective in recognizing and attacking cancer cells (5). Bispecific antibodies are drugs that represent a further evolution of immunotherapy (6). They bind to the tumor and healthy T lymphocytes at the same time, putting them in direct contact. This stimulates the targeted response that allows the lymphocytes to directly and selectively eliminate tumor cells.

The arrival of new, increasingly effective and targeted therapies, such as CAR-T immunotherapy and new bispecific antibodies has reduced the risk of relapses and has increased survival and the chances of recovery (7). So, in recent years, research has transformed therapeutic strategies with the advent of immunotherapy. CAR-T therapy and bispecific

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antibodies are significantly improving the outlook for patients (8). For large B-cell lymphomas, which represent approximately 30% of non-Hodgkin's lymphomas, new options are available that can reduce the risk of disease progression and increase the likelihood of recovery (9). Progress continues even for patients with relapsed or refractory forms (10).

DISCUSSION

Bacterial or viral infections can trigger the development of lymphoma (11,12). Epstein-Barr virus (EBV) is implicated in infectious mononucleosis and is associated with some lymphomas such as Burkitt and Hodgkin lymphoma, as well as the aggressive human immunodeficiency virus 1 (HIV-1). *Helicobacter pylori*, a bacterium that infects the stomach, can induce gastric lymphoma determined by mucosa-associated lymphoid tissue lymphoma (MALT), (13) which is a type of non-Hodgkin B-cell lymphoma that arises in mucosal sites (14).

EBV infection is very common and often does not cause serious symptoms, but in certain individuals with a weak immune system, the virus can cause some lymphomas including Burkitt's lymphoma (15). This lymphoma is very aggressive, although today it responds well to therapy if treated promptly. Lymphoma caused by EBV is very common in Africa and is associated with malaria (16). To date, there is no specific drug for treating lymphoma, so chemotherapy, immunotherapy, stem cell therapy, and CAR-T therapy are used (17).

CAR-T therapy

CAR-T therapy is a personalized and innovative technique (18) used to treat B-cell lymphomas, such as diffuse large B-cell lymphoma (19) (Table I). EBV and HIV-associated lymphomas arise in settings where a chronic infection plays an important role in the development of the tumor (20). For example, this can occur in Burkitt lymphoma and some extranodal lymphomas associated with EBV, or in lymphomas of immunosuppressed patients such as those infected with HIV-1 (21).

Table I. *A brief methodology scheme for CAR-T gene therapy.*

-
- Peripheral blood sampling
 - T-cell sampling
 - Genetically modified T-cells (chimeric antigen receptor)
 - CAR-T cell generation
 - CAR-T cell expansion
 - CAR-T cell infusion
 - Target (cancer cell destruction)
-

HIV-1 is the fastest and most aggressive form of HIV infection, while HIV-2 infection can remain controlled for years without the need for therapy. When we simply speak of AIDS virus we mean HIV-1, the most widespread globally, while HIV-2 is slower, less contagious, and less aggressive (22).

In these lymphomas, CAR-T therapy could be useful, but must be used with caution to reduce side effects (23). Patients infected with HIV and are therefore immunosuppressed, have shown an improvement after CAR-T therapy, compared to untreated patients (24). For EBV-positive lymphomas, there are also experimental approaches that use T cells modified against specific viral proteins.

CAR-T therapy is currently approved in some aggressive B-cell lymphomas, regardless of cause, including some types associated with infections, as long as they express the CD19 target (19). For example, patients with EBV-positive lymphoma who express CD19 may be candidates if they meet the clinical criteria (25). In HIV immunodeficiencies, there are studies that demonstrate that CAR-T therapy could be effective and safe, but case-by-case evaluations and caution are still needed (26). Today, specific CAR-T treatment programs are being developed that target viral antigens such as those expressed by EBV. Although these treatments are promising, especially for post-transplant lymphomas or in cases of resistance to current therapies, continued research is needed to perfect these therapies.

CAR-T treatments are built with a series of steps that combine advanced biotechnology and immunology (27). The patient's T cells are collected through a process called leukapheresis, which involves separating white blood cells from the peripheral blood (28). The T cells are genetically modified in the laboratory through receptor engineering (29). A gene

that codes for a chimeric antigen receptor (CAR) is introduced into the T cells (30). The CAR is designed to recognize specific antigens on the surface of tumor cells, such as CD19 in B-cell lymphomas (31). This procedure is done using transfection or viral transduction techniques, often using viruses such as retroviruses or lentiviruses, which act as vectors to transfer the gene to the T cells to be expanded (32). After inserting the CAR, the modified T cells are cultured to obtain a sufficient number of CAR-T cells for treatment (33). When the number of modified T cells is deemed sufficient, they are infused into the patient. The CAR-T cells bind to target tumor cells that express the target antigen, such as CD19, and destroy them (34). The engineered cells that are injected into patients undergoing CAR-T cell therapy cause systemic inflammation with possible severe side effects. After infusion, the patient is monitored for possible side effects, such as cytokine-release inflammatory syndrome and neurotoxicity, which are classic complications of CAR-T therapy (35).

CONCLUSIONS

Viral or bacterial infections can increase the risk of developing certain lymphomas. To date, there is no specific drug for treating lymphomas, so chemotherapy, immunotherapy, stem cell therapy, and CAR-T therapy are used. CAR-T therapy is an interesting, new method for treating lymphomas linked to infections, and cancer in general. However, due to inevitable side effects, which can be severe, more studies need to continue to allow for safer and more efficient treatment.

Conflict of interest

The authors declare that they have no conflict of interest.

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Case Report

INTRACRANIAL BLEED AND CEREBRAL VENOUS SINUS THROMBOSIS IN A 35-YEAR-OLD FEMALE: A RARE PRESENTATION OF TUBERCULAR MENINGITIS

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ABSTRACT

Tubercular meningitis (TBM) is a life-threatening manifestation of *Mycobacterium tuberculosis* infection of the central nervous system. Complications such as cerebral venous sinus thrombosis (CVST) and intracranial haemorrhage (ICH) are rare but catastrophic consequences of TBM. We present a case of a 35-year-old immunocompetent female with confirmed TBM who developed CVST complicated by a frontal lobe intracerebral haemorrhage. Neuroimaging revealed Focus of late subacute bleed in right superior frontal region with mild surrounding oedema, multiple thrombi in superior sagittal sinus and transverse sinuses and diffuse prominence of bilateral sulci-gyral pattern, prominent ventricular and extraventricular CSF spaces. She was managed with antitubercular therapy, corticosteroids, antiepileptics and anticoagulation following neurosurgical consultation. This case highlights the importance of recognising rare vascular complications of TBM and instituting timely interventions to improve neurological outcomes..

KEYWORDS: *Tubercular meningitis, cerebral venous sinus thrombosis, intracranial haemorrhage, hydrocephalus, TBM complication*

INTRODUCTION

Tubercular meningitis (TBM), the most severe form of extrapulmonary tuberculosis, often presents subacutely and is associated with significant morbidity and mortality. The pathogenesis involves hematogenous spread of *Mycobacterium tuberculosis* to the meninges, causing basal exudates, inflammation, and vasculopathy (1). While hydrocephalus and infarction are known complications, cerebral venous sinus thrombosis (CVST) and intracranial haemorrhage (ICH) remain under-recognised. CVST results from thrombosis of dural sinuses, leading to impaired venous drainage, raised intracranial pressure, and hemorrhagic infarcts. ICH in TBM is rare and often results from vasculitic rupture or venous infarction with hemorrhagic transformation (2). This report presents an unusual case of TBM complicated by CVST and ICH in an immunocompetent adult, emphasising the need for early neuroimaging and comprehensive management.

CLINICAL PRESENTATION

A 35-year-old previously healthy female with no known family or personal history of tuberculosis presented with a seven-day history of fever, headache, vomiting, and loss of appetite, followed by altered sensorium for one day. There

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was no history of seizures, visual disturbances, trauma, or immunosuppressive conditions. The patient was initially evaluated at a nearby hospital and subsequently referred to our tertiary care centre for further evaluation and management.

On admission, the patient was drowsy but arousable, with a Glasgow Coma Scale (GCS) of E4V1M4. She was afebrile, with stable vital signs: pulse 88/min, blood pressure 124/80 mmHg, respiratory rate 18/min, and SpO₂ 98% on room air. Neurological examination revealed bilateral papilledema, neck stiffness and bilateral extensor plantar reflexes.

INVESTIGATIONS

Initial blood work showed hemoglobin 9.5g/dL, leukocyte count 10300/mm³, and platelet count 2,24,000/mm³. Liver and renal function tests were within normal limits. Serum sodium 133mEq/L, serum potassium 3.5mEq/L, serum calcium: 8.9 mg/dL, serum magnesium: 2.56 mg/dL, serum phosphorus: 4.9 mg/dL. Blood sugar was 104 mg/dL. Tests for malaria, dengue, enteric fever, rickettsial diseases, HIV, hepatitis B, and C were negative.

Cerebrospinal Fluid (CSF) Analysis revealed Total leukocyte count: 10 cells/mm³ (90% mononuclear, 10% polymorphs), protein: 500 mg/dL, glucose: 105 mg/dL (serum glucose ~170 mg/dL), ADA: 11.1 U/L, CBNAAT: Positive for *Mycobacterium tuberculosis*, rifampicin-sensitive, Fungal culture: Negative, Gram stain: Negative, TB culture: Awaited at time of admission

MRI of the brain with contrast revealed Focus of late subacute bleed in right superior frontal region with mild surrounding edema. Multiple thrombi in superior sagittal sinus and transverse sinuses, Diffuse prominence of bilateral sulci-gyral pattern, prominent ventricular and extraventricular CSF spaces.

TREATMENT AND OUTCOME

On the second day of admission, her sensorium deteriorated (GCS E2V1M2), necessitating endotracheal intubation. She was transferred to the intensive care unit (ICU) for ventilatory support. During the ICU stay, she experienced multiple episodes of generalised tonic-clonic seizures, which were managed effectively with optimisation of antiseizure medications. Electrolyte imbalances and serum metabolic parameters were monitored closely and corrected as required. She was started on standard four-drug antitubercular therapy (Isoniazid, Rifampicin, Pyrazinamide and Ethambutol) and intravenous dexamethasone. Neuroimaging findings consistent with cerebral venous sinus thrombosis (CVST) and subacute intracerebral haemorrhage were reviewed with the neurology and neurosurgery teams, and the patient started on anticoagulation with low molecular weight heparin (LMWH), and antiepileptics were initiated under close neurosurgical and neurological supervision. After 5days, she was transitioned to oral Warfarin. The patient was maintained on mechanical ventilation for a period of seven days, during which supportive care, including fluid management, nutritional support, and prevention of ICU-related complications, was ensured.

By the end of the first week, her sensorium began to improve, and she was successfully extubated. Oxygen supplementation was continued via face mask and gradually tapered down as her respiratory effort normalized. Over the course of her hospital stay, there was progressive neurological recovery, with GCS improving to E4V5M6. She became fully conscious, oriented to time, place, and person, and began oral intake. She was discharged on ATT, oral anticoagulation, tapering steroids and antiepileptic drugs with outpatient follow-up scheduled.

DISCUSSION

This case represents a rare but important complication of TBM—cerebral venous sinus thrombosis with intracerebral haemorrhage. TBM-related CVST is believed to result from a hypercoagulable state due to inflammation, endothelial injury, and sluggish cerebral venous flow caused by basal exudates. Additionally, vasculitis and direct invasion of the venous sinus by mycobacteria can contribute to thrombus formation (3).

Hemorrhagic infarction is often the first radiological clue in TBM patients with altered mental status or focal deficits. In one case series, CVST was reported in 3–4% of TBM cases, with a significant number developing venous infarcts or ICH (4). Recognition is difficult due to overlapping features with hydrocephalus or vasculitic infarcts.

Anticoagulation in TBM-associated CVST is controversial due to the risk of bleeding, especially in the presence of infarcts. However, most guidelines suggest that benefits outweigh the risks in cases with confirmed thrombosis and stable hemorrhagic lesions (5). In our patient, early anticoagulation was associated with neurological recovery and no worsening of the haemorrhage.

Hydrocephalus is the most common complication of TBM, present in up to 80% of cases. In communicating hydrocephalus without significant mass effect or decline in consciousness, medical management with serial monitoring may suffice (6).

This case highlights the need for multimodal imaging including CEMRI Brain/MRV in TBM patients with atypical neurological signs, and for a multidisciplinary approach incorporating ATT, steroids, and anticoagulation where indicated.

CONCLUSIONS

Intracranial haemorrhage and cerebral venous sinus thrombosis are rare but serious complications of tubercular meningitis. High clinical suspicion and early neuroimaging, particularly with MRI Brain/MRV, are essential for diagnosis. A combined approach of ATT, corticosteroids, and cautious anticoagulation can lead to favourable outcomes in selected patients. Clinicians should be vigilant for vascular complications in TBM, especially when patients exhibit sudden neurological deterioration.

Conflict of interest

The authors declare that they have no conflict of interest.

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IL-6 AND IL-11 IN INFECTION

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ABSTRACT

Cytokines are secreted by the immune system and regulate immune and inflammatory responses. Interleukin (IL)-6 and IL-11 both belong to the IL-6 cytokine family and play crucial, but distinct, roles in infections and the immune response. IL-6 is a pro-inflammatory cytokine produced in response to pathogenic microorganisms by cells such as macrophages, dendritic cells, T lymphocytes, and endothelial cells. IL-6 plays a key role in the acute-phase response, helping the body react to infections and tissue damage and stimulates the liver to produce acute-phase proteins such as C-reactive protein (CRP), fibrinogen, and serum amyloid A. IL-6 also promotes B-cell maturation and antibody production, and supports T-cell differentiation and Th17 responses, which are important in bacterial and fungal infections. IL-11 regulates inflammation and has both pro- and anti-inflammatory potential. It can reduce the production of pro-inflammatory cytokines such as tumor necrosis factor (TNF) and IL-1 β , and promotes cell survival and tissue regeneration and repair, as well as stimulating hematopoiesis. Both IL-6 and IL-11 are important regulatory cytokines of the immune and inflammatory response.

KEYWORDS: *IL-6, IL-11, cytokine, infection, inflammation*

INTRODUCTION

Cytokines are proteins secreted by immune system cells that regulate immune and inflammatory responses. During an infection, a cascade of cytokines is activated, stimulating the immune response to fight the infectious agent. Cytokines activate the vascular endothelium, promoting fever and the production of other cytokines, and anti-inflammatory cytokines limit the immune response to prevent tissue damage.

Interleukins (ILs) belong to the cytokine family and are important chemical messengers for the immune system, but when they increase excessively, they induce inflammation (1). Today, we know that there are also anti-inflammatory cytokines that could potentially be used to treat inflammatory diseases. Cytokines are capable of performing various functions and signaling, performing endocrine, autocrine and paracrine effects.

In the state of sepsis, many harmful molecules are produced, including inflammatory cytokines, which are important for the course of the disease (2). The first cells to intervene are macrophages which engulf the microorganisms. One of the soluble products released by Gram-negative bacteria is lipopolysaccharide (LPS), which activates macrophages to produce cytokines *in vivo* and *in vitro*. These cytokines are not only specifically activated by septicemia, but can also be released after trauma, transplant rejection, ischemia, inflammation, hepatitis, myocarditis, and other diseases (3).

IL-6 and IL-11 both belong to the IL-6 cytokine family and play crucial roles in infections and the immune response. IL-6 is a pro-inflammatory cytokine produced by various cells such as macrophages, dendritic cells, T lymphocytes, and

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endothelial cells in response to pathogenic microorganisms such as bacteria and viruses. IL-6 plays a key role in the acute-phase immune response, helping the body react to infections and tissue damage. It stimulates the liver to produce acute-phase proteins such as C-reactive protein (CRP), fibrinogen, and serum amyloid A, which are biomarkers for inflammation. Furthermore, IL-6 promotes B-cell maturation and antibody production, and supports T-cell differentiation, particularly Th17 responses which are important in bacterial and fungal infections. IL-11 plays an important role in several physiological and pathological processes, including the immune response to infections. It regulates inflammation with an anti-inflammatory effect, reducing the production of pro-inflammatory cytokines such as tumor necrosis factor (TNF) and IL-1 β . However, IL-11 may also have pro-inflammatory effects, such as those seen in the ageing process. IL-11 promotes cell survival, tissue regeneration and repair, and also stimulates hematopoiesis.

DISCUSSION

IL-6 participates in infectious processes by playing a role in host defence against microorganisms and is produced by many cell types, including macrophages. IL-6 does not induce the pro-inflammatory prostaglandin prostaglandin E2, but in hepatocytes *in vitro*, it can release serum amyloid A, an acute phase synthesis protein (4). In humans, low administrations of IL-6 (30 μ g/kg) do not cause hypotension, while 100 ng/kg does. It has been found that high levels of IL-6, but not TNF, can be fatal in septicemia. However, in certain pathologies, IL-6 can be a non-inflammatory, protective cytokine (5).

The biological functioning of IL-6 occurs through its binding to the gp130 receptor. Therefore, cytokines of the IL-6 family (which has four α -helix bundle structure), use the common signaling glycoprotein of the 130 kDa receptor subunit (gp130), expressed by all cells of the body. Members of the gp130 cytokine family induce the Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) pathway, such as STAT3 and to a lesser extent, STAT1 (5). In some infectious diseases, IL-6 and IL-11 activate gp130, causing biological effects (6). The biological effects of IL-6 include the proliferation and differentiation of T lymphocytes, the induction of acute phase proteins, and the induction of immunoglobulin production in B cells.

For now, eight cytokines involved in the pathophysiology of B cells belong to the gp130 cytokine family (7). Blocking the activity of IL-6 with a monoclonal antibody (an effect similar to blocking TNF) is a strategy that is used in the therapy of some autoimmune diseases. Members of the IL-6 family share 4 helices with structural homology extending to cytokine receptors. Therefore, all cytokines of this IL-6 family that use the gp130 receptor have similar biological characteristics, but with different activities. IL-6 cannot be activated in the absence of its gp130 receptor (8).

The levels of IL-6 in the peripheral blood are approximately 3-6 pg/ml which increases up to many thousands in inflammatory states and in severe cases of septicemia (9). In humans, the IL-6 gene is located on chromosome 7 and the protein has a molecular weight of 20-30 kDa and shows a certain homology with granulocyte colony-stimulating factor. The IL-6 receptor has a short intracytoplasmic region and, when activated by IL-6, does not induce signal transduction (10). The soluble IL-6 receptor, which increases under inflammatory conditions induced by infection, binds to the cytokine IL-6 and stimulates the membrane receptor gp130.

IL-6 deficiency in mice can induce a high susceptibility to bacterial infections, dysregulated haematopoiesis and may contribute to liver dysfunction, even if the mice appear phenotypically normal (11). Mice with alteration of the gp130 receptor are more sensitive to LPS and can develop gastric tumors and pulmonary emphysema (12). These results demonstrate a protective activity of this cytokine and show the importance of IL-6 in infections and other pathologies.

The cytokine IL-11 is part of the IL-6 family and is a monomeric protein that has pleiotropic effects (14). This cytokine induces signaling through an IL-11 α receptor complex and the gp130 β subunit (15). In several infections, IL-11 has been seen to be immunomodulatory by regulating pro-inflammatory cytokines. However, overexpression of IL-11 induces inflammation (mainly mediated by lymphocytes) and fibrotic remodelling (16).

IL-11 belongs to the IL-6 family and can activate pro-inflammatory signals such as JAK-STAT3, ERK-mTORC1, and NF-kB. IL-11 is upregulated in older people and is a marker of ageing (17). IL-11 stimulates platelet precursor megakaryocytes, promoting the production of platelets and is a multifunctional cytokine with significant roles in immune response modulation and haematopoiesis (18). IL-11 uses the gp130 receptor (even in the absence of the IL-6 receptor) and has inflammatory effects; when produced in excess, it increases the levels of inflammation in several disease.

IL-11 has been shown to be effective in mucosal protection and repair of the mucosal lining of the gastrointestinal tract and modulates the immune response, preventing tissue damage during infections (19). Some research suggests that IL-11 levels may correlate with the severity of certain infections, indicating its potential as a biomarker. However, the role of IL-11 in viral infections is less clear.

It has been observed that some metalloproteinases cleave the IL-11 receptor bound to the cell membrane, generating the soluble IL-11 receptor capable of activating the gp130 receptor with biological effects (20). Although it can help

modulate the immune response, its overall effect can vary depending on the type of microorganism and the context of the infection. Its inflammatory properties make it a molecule of interest in the context of infections, where on the one hand, it could help control excessive inflammatory responses by protecting tissues, and on the other, it could increase inflammatory levels.

Proteins damaged during ageing are recognized by the immune system as if they were microorganisms and therefore non-self, and the immune system attacks them, causing inflammation. The triggered inflammatory process aggravates the pathological state and contributes to the formation of new diseases, including cancer. It has been seen that IL-11 is more abundant in older mouse tissues, including fat, skeletal, muscle, and liver tissue (13).

CONCLUSIONS

The cytokines IL-6 and IL-11 mediate hematopoiesis, immunity, and inflammation, and both share a signaling pathway via the gp130 receptor subunit. IL-6 is produced by macrophages, dendritic cells, fibroblasts, T lymphocytes, and B lymphocytes in response to viruses and bacteria and plays an important role in inflammation. IL-11 is generated primarily by fibroblasts, epithelial cells, and stromal cells, and can have both anti-inflammatory pro-inflammatory effects, along with providing tissue-protection and promoting the survival and regeneration of epithelial cells in the intestine and lungs.

Complications from streptococcal infections can induce the synthesis of pro-inflammatory cytokines and cause a high mortality rate (21). IL-6 has a pathophysiological action and is protective in macrophages treated *in vitro* with endotoxins. Using IL-11, another cytokine that utilizes the same subunit of the signal transduction receptor as IL-6, it was noted that the latter also has its own protective potential (22). Treatment of laboratory animals with an anti-IL-6 antibody increases mortality, demonstrating the ability of this cytokine to have a protective action against death. In these experiments, IL-11 was also protective against toxic shock syndrome (23).

IL-11 is mainly used in the therapy of chemotherapy-induced thrombocytopenia, in which low platelet counts occur, but its role in infectious diseases is still under research. IL-11 is a protein implicated in the ageing process. As recently reported in the medical literature, blocking IL-11 and its molecular partners appears to have a positive impact on longevity, but these studies still need to be confirmed (13). Therefore, in many international research laboratories, drugs that block this cytokine are being studied and are being tested against various diseases such as cancer, fibrosis, and chronic infections. According to a recently published article, IL-11 appears to counteract tissue ageing and impact lifespan (24). However, these results were observed in mice and may be different in human clinical trials. Ongoing research is exploring the potential therapeutic applications of IL-11 in infectious and inflammatory diseases.

Conflict of interest

The authors declare that they have no conflict of interest.

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DIAGNOSTIC, IMMUNOLOGICAL, AND PATHOGENETIC ASPECTS IN HIV-INFECTED CHILDREN

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ABSTRACT

Human immunodeficiency virus (HIV)-infected women have an approximately 30% increased risk of transmitting HIV infection perinatally. Positive screening tests such as enzyme immunoassay (EIA), immunofluorescence, and Western blot are essential for accurate diagnosis of HIV infection in infants. After infection, the first antibodies appear within a few weeks, while antibodies to other HIV antigens are produced later. Infants born to HIV-infected mothers have IgG antibodies to HIV from the placenta and may remain positive for about 18 months of age whether or not they are infected with HIV. Because IgA cannot cross the placenta, the presence of IgA antibodies to HIV is an experimental method in the evaluation of HIV infection. The measurement of p24 antigen in serum, a modified test that would consist of the dissociation of the immune complex, could be another valid diagnostic method although the polymerase chain reaction (PCR) method that reveals viral DNA has a higher sensitivity. Children infected with HIV have an inhibition of the immune system that facilitates the onset of opportunistic infections due to a decrease in the number of CD4⁺ cells necessary for the activation of B cells to produce antibodies. Measurement of the absolute number and percentage of CD4⁺ lymphocytes remains an effective diagnostic method. In infected patients, the presence of gp120 antibodies is present in the serum. These antibodies damage CD4⁺ cells, prevent their binding to major histocompatibility complex (MHC), and cause immunodeficiency. Lymphocytes from HIV-infected patients undergo apoptosis or cell death with the participation of gp120-anti gp120 complexes, or by gp120 expressed on HIV-infected cells. Improved diagnosis and therapy of pediatric patients infected with HIV is necessary in the treatment of this infection.

KEYWORDS: *HIV infection, children, human immunodeficiency virus, diagnosis, immune dysfunction*

INTRODUCTION

A rise in the number of women infected with human immunodeficiency virus (HIV) has led to a parallel increase in perinatal HIV infection (1). Most studies indicate that approximately 30% of newborns born to HIV-infected mothers acquire the virus perinatally, and the World Health Organization (WHO) estimates that 10 million HIV-infected children will have been born by the end of the century (2).

Given this rapid increase in the number of infected children and the possibility of reducing the infection rate, it has become essential to define accurate, rapid, and definitive methods for diagnosing HIV infection as soon as possible after birth for early diagnosis (3).

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The current routine standard requires a positive screening test performed twice with an enzyme immunoassay (EIA), or by immunofluorescence and a confirmatory test performed with a Western blot, immunofluorescence, or another reliable test (4).

The determination of seroconversion after HIV infection depends on the time required for measurable levels of antibodies to the various HIV antigens to occur. The shortest time interval between infection and the first antibodies is found between four and six weeks, while antibodies to other HIV antigens are produced later (5).

Results from a clinical trial with zidovudine (AZT) suggest that a potentially major reduction in this infection rate is possible provided this therapy is available worldwide (6).

DISCUSSION

Children born to HIV-infected mothers result HIV-positive at birth because anti-HIV IgG crosses the blood-placental barrier (7). This poses one of the major problems in the early detection of HIV infection in newborns using commonly accepted serological testing protocols, given that the newborn can result EIA and Western blot positive until approximately 18 months of age, whether infected or not with HIV, as a result of the transplacental passage of anti-HIV IgG (8). Clearly, it is necessary to obtain positive evidence of HIV infection as soon as possible after birth to accurately monitor the immune status, to establish therapy and prophylaxis, and to reassure the parents of uninfected newborns.

Consequently, several alternative methods have been examined that could serve to provide a diagnosis of HIV infection during the very early life of the newborn (9). Since IgA cannot cross the placenta, the detection of anti-HIV IgA antibodies is an experimental method that has proven reliable and technically practical in evaluating HIV infection (10). However, sensitivity in early childhood is not adequate, given that at 10 weeks of age only 10-30% of newborns infected with HIV test positive, and the positivity rate rises to 70-90% by six months.

Measurement of p24 antigen in serum has an even lower sensitivity with only 20-40% positivity at six months. Recent modifications of this test, which consist of the dissociation of the immune complex, have increased the sensitivity to 90-95%, at 6 months (11).

Much greater sensitivity has been achieved by testing for the presence of the virus in culture, by detecting the presence of viral DNA by the polymerase chain reaction (PCR) method, and by *in vitro* antibody production. These methods have a 70-90% positivity rate at two months and reach 95% between three and six months of life (12).

However, these last three methods are very demanding; they require considerable experience and specialized laboratory facilities which makes them very expensive and not optimal for the routine of a hospital laboratory. There is still a need for a reliable and easy-to-perform test to detect HIV infection shortly after birth.

HIV infection leads to a regular and progressive decline in immune function to the point where opportunistic infections occur due to a high degree of immunosuppression. The extent and precise nature of events affected by HIV are important for the integrity of the immune system and are unfortunately not yet fully established. However, it is clear that an important cause of the decline in immune function is the progressive reduction of the number of CD4+ lymphocytes, which are targeted by HIV. These cells are called T helper cells because they help B cells produce antibodies. They are a cellular subpopulation that plays a fundamental role in the regulation of immune functions (13).

It has been universally accepted that the method of choice for carefully evaluating the progression of HIV infection and for instituting therapy is the CD4+ lymphocyte count. For this purpose, the most commonly used method is flow cytometry with monoclonal antibodies labeled with fluorescent substances (14). Very precise quality control guidelines have been defined to ensure the validity of the results of this procedure. Subsequently, other methods for counting CD4+ lymphocytes have been proposed. Some of them are based on simplified flow cytometry methods, while others are based on the use of enzyme immunoassays. If the latter prove to be as reliable, sensitive, and as specific as flow cytometry, they will bring an undoubted benefit to the continuous control of HIV infection in underdeveloped areas.

In recent years, a series of studies have been launched to more accurately define the immune deficits resulting from HIV infection, to establish more precise methods in following the course of the disease and to improve therapy (15). While these studies improve our knowledge of the immune dysfunction caused by HIV, measurement of the absolute percentage number of CD4+ lymphocytes remains the method of choice for following patients (16).

Having clearly established that CD4+ lymphocytes are the main target of HIV, considerable efforts have been focused on understanding the mechanisms by which HIV infection causes a reduction in CD4+ lymphocytes. It is reasonable to believe that the explanation of these mechanisms would contribute to the understanding of the pathogenesis of HIV infection and, at the same time, provide more reliable methods for following the course of the infection. The results of studies in this area have suggested that many mechanisms may be involved in the destruction or depletion of helper T lymphocytes in HIV-infected patients (17).

The direct cytopathic effects of HIV may be responsible for the depletion of CD4+ lymphocytes. Furthermore, it has been shown that *in vitro* syncytia can form between HIV-infected cells and uninfected cells, leading to the formation of giant cells (18). However, this latter mechanism has not been found *in vivo*, and it is not easily understood how the formation of a syncytium can lead to the depletion of T lymphocytes.

The presence of antibodies for gp120, which is found in the envelope of HIV, has been found on CD4+ lymphocytes and in the serum of infected patients. This finding led to the suggestion of two other possible mechanisms for lymphocyte depletion. These antibodies cross-react with type II major histocompatibility complex (MHC) proteins and could block CD4-MHC interactions and interfere with the normal function of CD4 lymphocytes, similarly to a state of anergy (19). It could be induced by gp120 protein-anti-gp120 antibody immune complexes that bind to the CD4 antigen and damage the normal function of CD4 lymphocytes. It has also been proposed that CD4+ lymphocytes may become anergic and reduced in number due to the effect of superantigens. These retrovirus-associated antigens are recognized entirely by the V β region of the T cell antigen receptor (TCR) and therefore, selectively activate and drive clonal proliferation of all V β T cells (20). Since this leads to anergy and death of these lymphocyte clones, a state of immunosuppression would result due to the disappearance of a high number of CD4+ lymphocytes.

The finding that apoptosis is a very important mechanism in the elimination of self-reactive T lymphocyte clones during thymic maturation has stimulated interest in exploring the role played by apoptosis as a possible mechanism of lymphocyte elimination in viral infections (21).

Many studies have shown that lymphocytes from patients infected with HIV undergo apoptosis when stimulated by a series of antigens. Moreover, during HIV infection of cell lines, apoptosis is an important mechanism of cell death. It has also been demonstrated that the cross-binding of the CD4+ antigen on the membranes of lymphocytes by gp120 determines apoptosis following activation of the lymphocyte. Taken together, these observations suggest that uninfected cells may undergo apoptosis as a consequence of stimulation by gp120-anti gp120 complexes or by gp120 expressed on HIV-infected cells, followed by activation by a series of antigenic or other stimuli (22). This could explain the progressive depletion of CD4+ lymphocytes following HIV infection, since it appears that only small numbers of CD4+ lymphocytes are infected by HIV. The finding that *in vitro* mitogen stimulation induces T lymphocytes from HIV-infected patients to undergo apoptosis suggests that evaluation of pokeweed mitogen (PWM)-induced apoptosis may help identify HIV-infected infants (23).

Studies have shown that PWM-stimulated lymphocytes obtained from pediatric patients infected with HIV undergo apoptosis in a higher percentage than uninfected controls. Furthermore, the rapid progressive forms present a higher frequency of apoptosis than the slow progressive forms, although the difference is at the limit of statistical significance. These observations are interesting as they suggest that the evaluation of the frequency of apoptosis induced by PWM may be valid in defining the diagnosis of HIV infection shortly after birth, and even more importantly, it may help in distinguishing between rapid progressive forms and slow progressive forms (24). This would help in establishing therapy and monitoring pediatric patients infected with HIV over time.

CONCLUSIONS

Faced with the scale of the HIV pandemic, it is vitally important to diagnose the infection and follow the best treatment in a timely manner. Considering this situation, efforts must continue to accurately delineate the nature and extent of the immunological alterations that accompany HIV infection, realizing that a better understanding of the immune disorder induced by the virus would help to clarify the pathogenesis, the natural history of the infection, and would allow for the design of more effective therapy (25).

Similarly, success in preventing infection through an effective vaccine relies on a deeper understanding of the interactions between HIV and the immune system. The understanding that the immune system is the main target of HIV has stimulated numerous studies aimed at defining changes in the number and function of natural killer lymphocytes in different lymphocyte subpopulations and in cytokine concentrations, as well as delineating the mechanisms involved in the interaction between HIV and cells and in the depletion of CD4+ lymphocytes which causes immunosuppression (26).

As studies slowly advance our understanding of the natural history and pathogenesis of HIV infection, more effective treatment modalities will be developed to care for pediatric patients. However, only a complete clarification of the natural history of HIV will lead to a complete eradication of this infection.

Conflict of interest

The authors declare that they have no conflict of interest.

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