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Arthritis related to parasitic infections

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ABSTRACT

Various parasitic infections can manifest with symptoms resembling inflammatory rheumatic diseases. Parasitic arthritis is uncommon, and the literature concerning rheumatic manifestations of specific parasitic infections tends to be limited to case reports. Despite its rarity, parasitic infections should always be included in the differential diagnosis of rheumatic presentations when there is a history of risk factors, particularly in patients from endemic regions and in atypical rheumatic presentations. Specific treatment of the parasitic infection often leads to significant improvement or resolution of symptoms. This account discusses various parasites that have been reported to be associated with arthritis and other related musculoskeletal manifestations.

1. Introduction

A parasite is an organism that lives on or in a host organism and derives its nutrients at the expense of its host [1]. Three main classes of parasites can cause disease in humans: protozoa, helminths, and ectoparasites.

Parasitic infections due to protozoa and helminths cause substantial morbidity and mortality worldwide. In 2023, an estimated 263 million malaria cases were found in 83 countries, with 597,000 deaths due to malaria [2].

Soil-transmitted helminth (STH) infections are among the most common infections worldwide, accounting for an estimated 1.5 billion infected people, or 24 % of the global population. The most common species of STHs are *Ascaris lumbricoides, Trichuris trichiura,* and hookworms (*Necator americanus* and *Ancylostoma duodenale*) [3].

Infectious diarrhoea is the third leading cause of death in children below 5 years of age. A significant number of infectious diarrhoeas are caused by intestinal protozoa, the commonest being *Cryptosporidium*, *Giardia*, and *Entamoeba* spp [4].

These infections are more common in tropical and subtropical countries, particularly in communities with limited access to clean water and sanitation. Due to widespread international travel and human migration, these diseases are also being encountered in communities where they are usually not endemic.

Various parasitic diseases may present with rheumatic manifestations such as inflammatory arthritis, myositis, and vasculitis. Parasitic infections are rarely considered in the differential diagnosis of rheumatic complaints. However, in patients with relevant risk factors, it is important to consider these infections in the differential diagnosis of rheumatic syndromes so that they can be appropriately treated.

A study involving stool examination performed in patients having unexplained rheumatic pain attending the rheumatology and rehabilitation outpatient clinic in a university hospital in Egypt showed that 50 of 107 patients with unexplained rheumatic pain had a parasitic infection. *Cryptosporidium* was the most common (48 %), followed by *Cyclospora cayetanensis* (32 %), *Giardia lamblia* (24 %),

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Blastocystis hominis (20 %), and *Entamoeba histolytica* (8 %). 16 of the 50 patients (32 %) fulfilled the criteria of parasitic rheumatism, and it was most commonly due to *Giardia* infection, followed by *Cryptosporidium*, *Cyclospora cayetanensis*, *Entamoeba histolytica/dispar*, and *Strongyloides stercoralis* [5].

Rheumatic complications of parasitic diseases may also be under-recognized and under-reported in literature. A retrospective matched cohort of individuals from a large administrative claims database in the United States showed that giardiasis was associated with a 51 % increase in claims for arthritis or joint pains [6].

This review focuses on arthritis related to parasitic infections. The possible pathogenesis involved in parasitic arthritis and the various parasitic infections causing arthritis and related musculoskeletal manifestations are reviewed.

2. Pathogenesis of arthritis in parasitic infections

Parasitic arthritis can occur by various mechanisms. Arthritis in parasitic diseases can occur due to the presence of the parasite itself inside the joint or due to a focus of infection in the vicinity of the joint. In *Echinococcus* infection, arthritis has been reported to occur as a result of parasitic cysts occurring within the joint, leading to granulomatous synovial inflammation [7,8].

Sometimes, arthritis due to *Echinococcus* occurs due to a focus of infection in the bone near a joint with secondary extension to the joint [9,10].

Synovial biopsies performed in patients presenting with arthritis due to *Schistosoma* infection identified the presence of parasite ova with synovial inflammation and vasculitis. This inflammatory response to *Shistosoma* eggs is characterised by a cell-mediated delayed-type hypersensitivity reaction [11].

Adult worms and larvae were also demonstrated inside the knee joint in cases of arthritis caused by *Dracunculus medinensis* [12].

Often, arthritis in various parasitic infections occurs without evidence of demonstrable organisms in the joint. Such sterile inflammatory arthritis is believed to be a reactive arthritis.

Reactive arthritis has been reported in infections by parasites such as *Amoeba, Giardia, Cryptosporidium, Strongyloides*, *Schistosoma and Echinococcus*.

Immune complex-mediated mechanisms may underlie the reactive arthritis caused by parasitic infections. Circulating immune complexes (IC) were demonstrated in serum and synovial fluid with immunoglobulin and complement deposits in synovium in a patient diagnosed with *Strongyloides stercoralis* and another patient with *Taenia saginata* infection who presented with polyarthritis [13].

Circulating immune complexes were also demonstrated in several reports of arthropathy in *Schistosoma* infection [14,15]. Bebars et al. compared the immune complex levels in the sera of 100 individuals using ELISA. They were divided into four groups: 40 cases with schistosomiasis and arthropathy, 20 with schistosomiasis without arthropathy, 20 with rheumatoid arthritis (RA), and 20 apparently healthy individuals. IC levels were higher when schistosomiasis was associated with arthropathy. Furthermore, IC levels in the joint fluid were higher than in the blood, pointing to a possible pathogenic role of ICs in this arthritis [15].

Autoimmune mechanisms also underlie some of the other complications of certain parasitic infections.

For example, malaria has been associated with the development of autoimmunity in patients and mice models, inducing the generation of antibodies against a variety of self-antigens, such as erythrocytes cytoskeletal and membrane proteins, enzymes, DNA, and phospholipids [16].

Autoantibodies recognising the membrane lipid phosphatidylserine (PS), erythrocyte membrane protein band-3, and spectrin are implicated in the autoimmune haemolysis of uninfected erythrocytes during malaria, thus contributing to the pathogenesis of anaemia in malaria [16].

In nephropathy caused by *Plasmodium malariae* infection, immunofluorescence has demonstrated endothelial deposits with IgG, IgM, C3, and parasite antigens, supporting the role of immune-mediated mechanisms in the pathogenesis of kidney injury in *P. malariae* infection [17].

The presence of *Schistosoma* antigens in the glomerular basement membrane and the detection of ICs containing these antigens supports a hypothesis of IC-mediated glomerulonephritis in *Schistosoma* nephropathy [18].

The presence of the HLA-B27 genotype is a well-known risk factor for developing reactive arthritis. HLA-B27 is a class 1 surface antigen which presents antigenic peptides to cytotoxic T cells. The exact pathogenetic role of HLA-B27 in reactive arthritis is unknown. The arthritogenic peptide hypothesis proposes that some HLA-B27 subtype alleles bind a specific arthritogenic peptide that is recognized by $CD8^+$ T cells. The primed T cells then cross-react with self-peptides due to molecular similarity (molecular mimicry) [19].

HLA-B27-associated reactive arthritis shares common features with the spondyloarthritides (SpA), such as the absence of rheumatoid factor and characteristic extra-articular features such as urethritis, uveitis, conjunctivitis, enthesitis and mucocutaneous lesions [20].

In the case of reactive arthritis caused by classical reactive arthritis-associated organisms such as enteric bacteria and chlamydia, HLA-B27 has been reported to be positive in 50–80 % of cases [21].

While HLA-B27 positive cases have been reported in reactive arthritis associated with parasitic infections [29,42,107,108], with some of them presenting with features of SpA such as uveitis, conjunctivitis, urethritis, keratoderma blennorrhagicum, enthesitis, there is no data on the prevalence of HLA-B27 positivity in parasitic reactive arthritis. Most reported cases of reactive arthritis in parasitic infections are HLA-B27 negative.

Parasites have evolved mechanisms to evade the host's protective responses to ensure their survival. These include encapsulation within a fibrous tissue reaction as in cystic echinococcosis, residing within the gut lumen as occurs in *Ascaris* or acquiring host antigens

as displayed by *Schistosoma* and inhibiting the host's immune responses [22].

Helminthic infections are characterised by skewing of the immune response towards a predominantly Th2 type response, which involves IL-4, IL-5 and IL-13 that induce B-lymphocytes to switch to IgE antibody production and induce proliferation and activation of eosinophils that help to reduce parasite burden and limit host tissue damage. Helminths also can induce down-regulation of T- and B-cell responses via the induction of regulatory T cells or the anti-inflammatory cytokines such as IL-10 and transforming growth factor beta (TGF-β) in the chronic phase of infection [23].

Such immune modulation by helminths could affect the host's ability to respond to pathogens such as *Mycobacteria* and HIV, reduce the efficacy of vaccines against other pathogens, and alter the expression of allergic and autoimmune diseases [23].

3. Parasites linked with rheumatic manifestations

3.1. Protozoan infections

3.1.1. Entamoeba histolytica

Entamoeba histolytica has been recovered worldwide and is more prevalent in the tropics and subtropics than in cooler climates. Amoebiasis is mainly caused by ingesting food or water contaminated with faeces containing *E. histolytica* cysts [24]. (Fig. 1).

Approximately 90 % of infected individuals are asymptomatic carriers, and 4-10 % develop invasive disease. Invasive disease can present as intestinal disease with amoebic colitis or extraintestinal disease. The commonest extraintestinal involvement is amoebic liver abscess [25].

Rare case reports have described amoebic colitis or amoebic liver abscess presenting with reactive arthritis. The arthritic involvement in these cases was mainly oligoarticular arthritis involving large joints, which responded well to anti-parasitic treatment [26,27].

In a single case of knee arthritis, *E. histolytica* cysts were identified by microscopy and immunocytochemistry from the synovial fluid aspirate. The patient's knee arthritis resolved after treatment with metronidazole [28].

3.1.2. Blastocystis species

Blastocystis is an enteric protozoan parasite of humans and many animals. It has a worldwide distribution and is often the most commonly isolated organism in parasitological surveys [29]. Contaminated water is implicated as a source of *Blastocystis* infection [30].

Blastocystis infection is more common in patients with HIV and other immunocompromised states [31]. The commonest symptoms associated with *Blastocystis* infection are abdominal pain and diarrhoea. Eosinophilia and urticaria are also reported [29].

Few case reports have described reactive arthritis in relation to gastroenteritis and the isolation of *Blastocystis hominis* from stools. Joint involvement in these patients was mainly asymmetrical polyarthritis or oligoarthritis, predominantly involving the lower limbs [32–34].

A peripheral spondyloarthropathy, including bilateral uveitis with heel pain and monoarthritis of the knee, occurred in an HLA-B27-positive patient with *Blastocystis* infection [35]. Anti-protozoal treatment with or without anti-inflammatory drugs resolved arthritis in these patients, suggesting a possible link between *Blastocystis* and reactive arthritis.

In a single reported case, *Blastocystis* was identified from the knee synovial fluid aspirate of a 29-year-old female with RA who developed acute left knee synovitis and diarrhoea. Stool examination also revealed large numbers of *B. hominis* organisms. Diarrhoea and left knee inflammation resolved after a course of metronidazole [36].

3.1.3. Cystoisospora belli

Cystoisospora belli is a coccidian parasite of humans with a direct faecal-oral transmission cycle. It is globally distributed but mainly

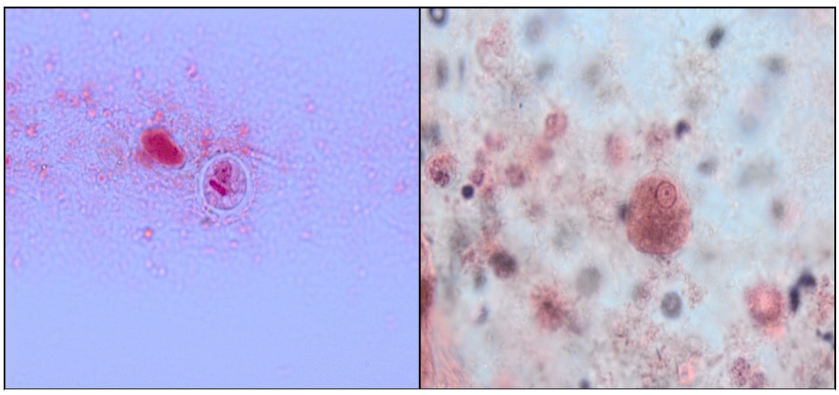

Fig. 1. Cyst of *Entamoeba histolytica* (left) and trophozoite of *Entamoeba histolytica* (right)
(Courtesy of Department of Parasitology, Faculty of Medicine, Universiti Malaya).

found in tropical and subtropical areas. Common symptoms of *C. belli* infection include profuse diarrhoea, abdominal discomfort and weight loss. Immunocompromised people can experience more severe disease with extreme diarrhoea [37].

Symmetrical polyarthritis similar to RA involving bilateral wrists and MCP joints was reported in an HIV-positive patient who developed chronic diarrhoea. *C. belli* were isolated from the stools. The diarrhoea and arthritis resolved upon treatment with oral trimethoprim/sulfamethoxazole and diclofenac [38].

3.1.4. *Cryptosporidium species*

Cryptosporidium is a protozoan that infects various animals and humans, causing gastroenteritis. Globally, *Cryptosporidium* infection was ranked fifth among the 24 most important food-borne parasitic infections by a joint Food and Agriculture Organization (FAO)/ World Health Organization (WHO) expert committee in 2012 [39].

Cryptosporidium has a wide range of host animals. *C. parvum* and *C. hominis* species account for most cases of human cryptosporidiosis. Transmission of oocysts occurs by the faecal-oral route directly by poor hygiene or indirectly through contaminated drinking or recreational water [40].

Cryptosporidiosis can range from an asymptomatic infection to acute or persistent diarrhoea in immunocompetent individuals. In acquired immunodeficiency syndrome (AIDS), chronic or fulminant infection can occur [41].

Cryptosporidium infection has been rarely associated with reactive arthritis [42–46].

3.1.5. *Giardia lamblia*

Giardia lamblia is distributed worldwide and is estimated to cause 280 million cases of diarrhoea annually [47]. The ingestion of infectious cysts initiates giardia infection. The parasite is non-invasive and replicates attached to the intestinal epithelium [48]. Giardia infection can be asymptomatic or cause severe acute or chronic diarrhoea with weight loss [48].

The association of giardiasis with acute arthritis was first described in 1977 in a case series consisting of 66 children between 2 and 15 years of age diagnosed with giardiasis. An acute arthritis was observed, mostly involving large joints of the lower extremities (knees, ankles and hips). Wrists, elbows, and shoulders were also significantly involved. In 90 % of these children, joint symptoms resolved with anti-parasitic treatment [49].

In a systemic review of 16 studies involving 115 patients, reactive arthritis caused by giardiasis was more commonly reported in children and adolescents than adults. The most frequently affected joints were the knee and ankle, followed by the hip, wrist, elbow, shoulder and axial skeleton. Small joints were involved much less frequently [50].

A retrospective matched cohort of individuals from a large administrative claims database in the United States showed that giardiasis was associated with a 51 % increase in claims for arthritis or joint pains [6].

Other reported extra-intestinal manifestations, which are presumably immune-mediated, include ocular manifestations such as retinal lesions (salt and pepper retinopathy), uveitis and retinal vasculitis [51–53]. Cases of erythema nodosum have also been

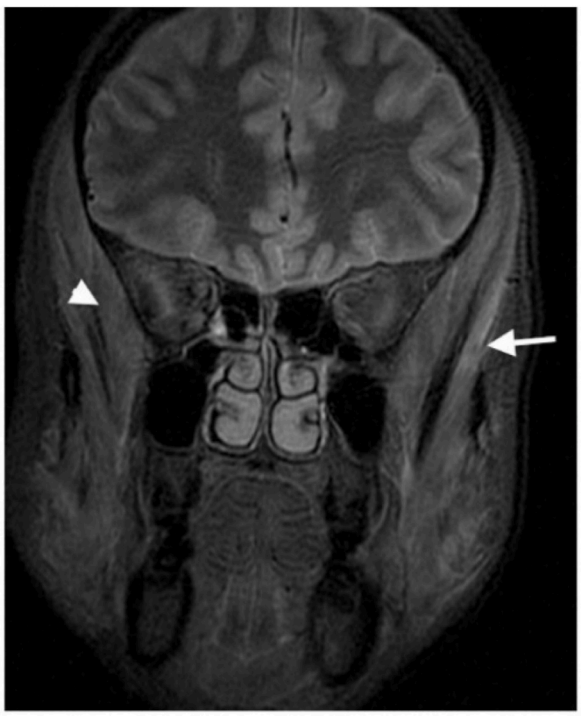

Fig. 2. Coronal STIR MRI demonstrating bilateral asymmetrical high signal in deep (arrow head) and superficial (arrow) temporalis muscles [57].

described [54,55].

3.1.6. Sarcocystis species

Sarcocystis species are found worldwide. The life cycle involves two hosts: an intermediate or prey host, in which cysts (sarcocysts) containing infectious zoites are present in the muscles, and a definitive or predator host that ingests these cysts and develops intestinal-stage parasites which release infective oocysts or sporocysts into the environment.

Humans are accidental intermediate hosts for *Sarcocystis nesbitti*, which has a reptilian definitive host and possibly other unidentified hosts. Infection is acquired by ingesting oocysts and sporocysts from faeces-contaminated food or water [56].

These ingested oocysts or sporocysts release sporozoites in the small intestine, which invade through the gut epithelium and disseminate throughout the body. They eventually infect the skeletal muscles, cardiac muscles and less commonly smooth muscles, becoming sarcocysts containing multiple bradyzoites.

Until the 21st century, muscular sarcocystosis was only rarely reported. Most cases were found as incidental findings on biopsy or autopsy specimens in tropical countries. 50 % of these were reported from Malaysia [56].

The largest reported outbreak of human muscular sarcocystosis involved 92 persons who attended a retreat on Pangkor Island in Malaysia in 2012 [57]. The onset of symptoms occurred within 26 days after the retreat and consisted of fever, myalgia, headache and arthralgia. Some of the patients developed facial muscle swelling and calf muscle swelling. Elevated creatinine kinase (CK) levels and eosinophilia were observed in some of the patients. MRI of skeletal muscles revealed myositis and muscle biopsies demonstrated sarcocysts with muscle inflammation and focal necrosis. *S.nesbiti* was confirmed by ribosomal DNA sequencing (Fig. 2). and (Fig. 3).

Another outbreak attributed to *S.nesbiti* involved foreign tourists who had vacationed on Tioman Island in Malaysia in 2011 and 2012. 68 patients met the case definition with myositis, eosinophilia and negative trichinellosis serology [58].

Figs. 2 and 3 reproduced from Ref. [57]. Licensed under CC BY.

3.1.7. Microsporidia species

Microsporidia are intracellular parasites related to fungi. They are found worldwide and infect a wide variety of invertebrates and vertebrates. Human infections occur primarily through ingesting microsporidia spores in contaminated food and water [59].

Microsporidia are mainly opportunistic pathogens causing disease, particularly in HIV-infected and other immunocompromised persons. *Microsporidia* may also cause disease in immunocompetent persons [60].

Chronic diarrhoea is the most common manifestation in immunocompromised patients. Other presentations in immunocompetent and immunosuppressed persons include encephalitis, sinusitis, keratitis and myositis [59].

In a review of 20 cases of myositis caused by *Microsporidia*, an immunocompromised state was the predominant risk factor for infection. Half of these cases occurred in HIV-positive patients, whereas the remaining occurred in other immunocompromised states. Myositis occurred either as an isolated involvement or as a component of disseminated infection involving pansinusitis, keratitis, myocarditis, or encephalitis [61].

Microsporidia myositis presents with fever, diarrhoea, joint pains, generalised myalgia and muscle tenderness with limb or bulbar muscle weakness. CK levels are elevated with myopathic changes on electromyography [62–64].

3.1.8. Plasmodium species

Four species of *Plasmodium*, *P. falciparum, P. vivax, P. ovale, and P. malariae,* are considered true parasites of humans and cause malaria. However, simian malaria parasites, mainly *P. knowlesi,* have been reported in humans [65] (Fig. 4).

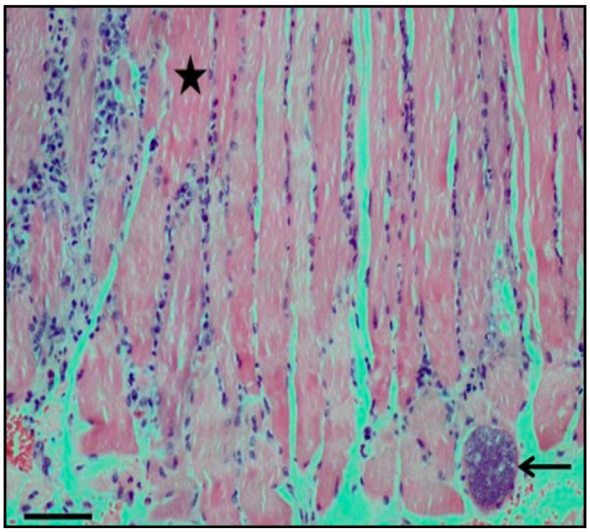

Fig. 3. A single sarcocyst (arrow) within a muscle fibre. Typically, there is mild myositis (★) near the sarcocyst [57].

In 2023, an estimated 263 million malaria cases were found in 83 countries, with 597,000 deaths due to malaria [2].

P. vivax infection is the most common but is rarely fatal, whereas *P. falciparum* is responsible for severe and potentially fatal infections [66].

Malaria is transmitted through the bite of an infected female *Anopheles* mosquito. The inoculated sporozoites undergo cycles of asexual multiplication in the hepatocytes (exoerythrocytic schizogony) and red blood cells (RBCs) (erythrocytic schizogony). Some of the parasites differentiate into sexual erythrocytic stages, the gametocytes, which are then ingested by the mosquito during its blood meal. The parasite undergoes sexual reproduction inside the mosquito's gut, producing sporozoites that ultimately reside in the mosquito's salivary glands [65].

Sequestration of parasitised RBCs in various organs, such as the heart, brain, lung, kidneys, and placenta, is a characteristic of *P. falciparum* infection. Although arthralgia and myalgia can occur in malaria, well-defined rheumatic syndromes are rare.

Severe malaria can cause rhabdomyolysis by sequestering parasitised RBCs in striated muscle capillaries, leading to microcirculatory obstruction. This sequestration is mediated by interactions between parasite-derived proteins expressed on the RBC surface and host endothelial cells. Rhabdomyolysis can lead to acute kidney injury [66,67].

In a study of 58 children with *P. falciparum* infection, where patients were divided into three groups: 14 were admitted with vomiting but otherwise non-severe disease, 23 with obtundation and 21 because of coma (cerebral malaria); overall, 28 % had abnormally elevated CK levels and 45 % had high myoglobin levels. CK and myoglobin levels showed a significant relation with the severity of illness as measured by neurological status, even for children without seizures, suggesting that skeletal muscle damage is common in falciparum malaria and proportional to the severity of infection [68].

Malaria has been associated with the development of autoimmunity in patients and mouse models, inducing the generation of antibodies against various self-antigens, such as RBC cytoskeletal and membrane proteins, enzymes, DNA, and phospholipids.

Autoantibodies against the membrane lipid phosphatidylserine (PS), RBC surface proteins band-3 and spectrin are implicated in autoimmune haemolysis of uninfected RBCs during malaria, thus contributing to the pathogenesis of anaemia in malaria [16].

Immune-mediated mechanisms also contribute to acute kidney injury in malaria, in addition to volume depletion and RBC sequestration in the renal microvasculature [16,17].

3.1.9. Leishmania species

Leishmania spp. are protozoa belonging to the family Trypanosomatidae. In 2023, ninety-nine countries were considered endemic, with 272,098 new cutaneous leishmaniasis (CL) cases and 11,922 new visceral leishmaniasis (VL) cases being reported to the WHO [69] (Fig. 5).

Over 20 species of the *Leishmania* parasite exist and are transmitted by 70 different types of phlebotomine sandflies. Leishmaniasis is mainly a zoonosis. The parasite is found in two morphologic forms. The form introduced into the skin of the mammalian host by the sand fly is the promastigote. The organism is engulfed by reticuloendothelial cells (RE cells), where the parasite transforms into the intracellular amastigote form (Leishman-Donovan body).

The three main phenotypic categories of disease are cutaneous leishmaniasis (CL), mucosal leishmaniasis (ML), and visceral leishmaniasis (VL). In CL, the amastigotes remain confined to the skin, causing skin lesions such as raised papules or ulcers. Visceral leishmaniasis involves bone marrow, lymph nodes, liver, and spleen, causing hypertrophy of the liver and spleen with cytopenias.

Arthritis has rarely been reported in leishmaniasis in human hosts [70–73]. Presentation in the form of acute or relapsing monoarthritis of knees or chronic symmetrical polyarthritis has been described. Leishmania amastigotes were identified in synovial fluid aspirate or from synovial biopsy in these patients.

Autoantibodies may be detected during the course of leishmaniasis. A Greek study examined 16 patients infected with VL with no clinical symptoms of autoimmune disease such as arthralgia or cutaneous vasculitis. Of note, elevated serum ANA were reported in 88 % of patients, positive RF in 63 %, whereas complement factors C3 and C4 were decreased in 13 % and 50 %, respectively. In addition,

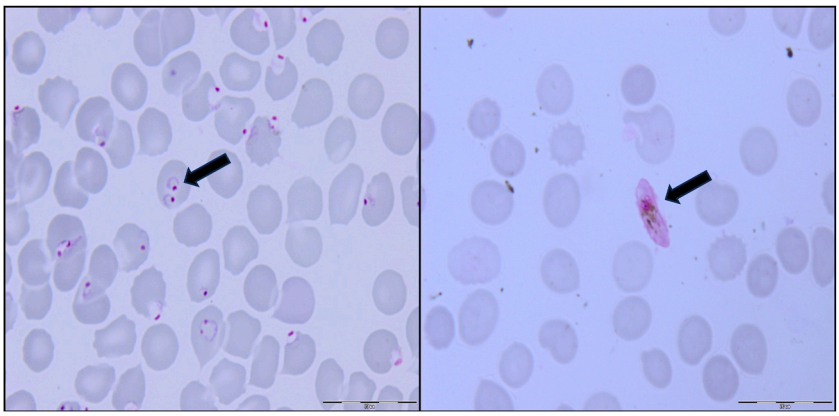

Fig. 4. Ring forms of *Plasmodium falciparum within red blood cells* (left) and gametocyte of *Plasmodium falciparum (right)* (Courtesy of Department of Parasitology, Faculty of Medicine, Universiti Malaya).

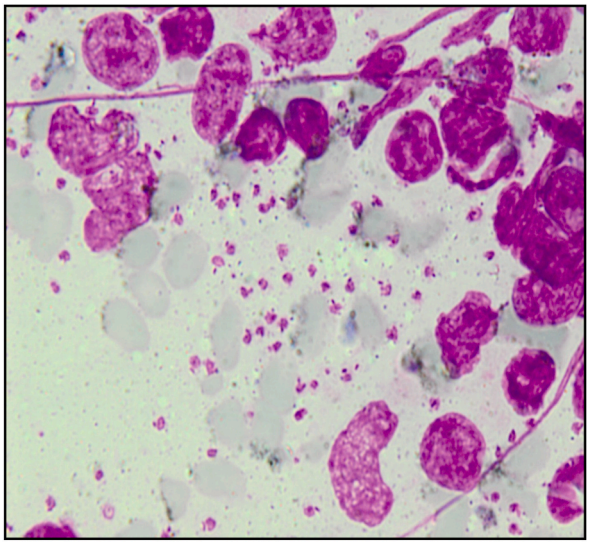

Fig. 5. *Leishmania donovani* amastigotes.
(Courtesy of Department of Parasitology, Faculty of Medicine, Universiti Malaya).

cryoglobulins were detected in 50 % of patients. These laboratory findings had resolved in all the patients who were re-evaluated three months after treatment [74].

Leishmaniasis can mimic a new onset of SLE or a flare of SLE when patients present with intermittent fever, arthralgia, pancytopenia, and visceromegaly with positive anti-nuclear antibodies [75,76].

A dermatomyositis-like eruption without muscle weakness, characterised by erythemato-violaceous maculopapular lesions or plaques on the face, upper eyelids, bony prominences, and upper back and periungual erythema was reported in a case series of 3 HIV positive patients with leishmaniasis. ANA and other immunological tests were negative in these patients. *Leishmania* amastigotes were identified from biopsies of the skin lesions [77].

A dermatomyositis-like eruption with severe myalgia, elevated CK levels, and a muscle biopsy suggestive of dermatomyositis was reported in another patient with visceral leishmaniasis [78].

Cryoglobulinaemic vasculitis has also been reported in leishmaniasis [79,80].

3.1.10. Toxoplasma gondii

Toxoplasma gondii is a protozoan parasite that is estimated to infect one-third of the world's human population [81]. Members of

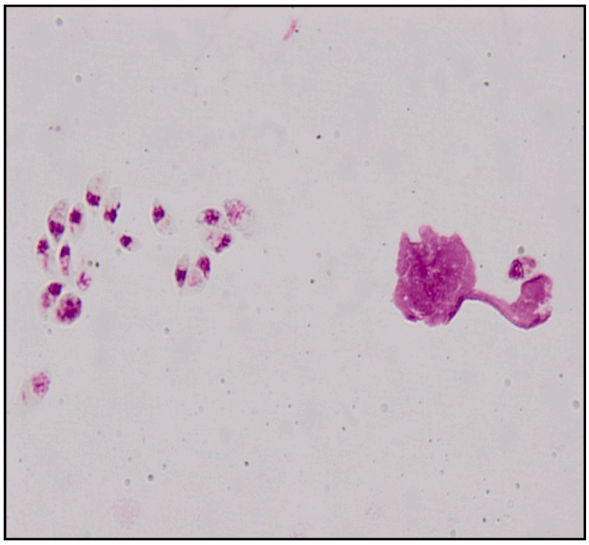

Fig. 6. Pseudocyst and zoites of *Toxoplasma gondii*.
(Courtesy of Department of Parasitology, Faculty of Medicine, Universiti Malaya).

the family *Felidae,* including the domestic cats, are the definitive hosts where sexual reproduction (gametogony) occurs, leading to the formation of oocysts, which are excreted in their faeces. Most warm-blooded mammals, birds, and humans are intermediate hosts where tissue cysts containing bradyzoites are found (Fig. 6).

Ingestion of bradyzoite-containing cysts in raw or poorly cooked meat or infectious oocysts in contaminated food and water are the major infection sources for humans. Also, congenital transmission to the fetus can occur via the placenta during maternal infection in pregnancy.

Acquired infections in immunocompetent individuals are asymptomatic in 90 % of cases. However, 10–20 % of patients with acute infection may develop painless cervical lymphadenopathy. Rarely, healthy persons can develop disseminated disease, myocarditis, pneumonitis, hepatitis, myositis or encephalitis. These are most often seen in immunocompromised individuals. In immunocompromised patients, toxoplasmosis most often occurs because of the reactivation of chronic infection. They are at high risk of encephalitis or disseminated disease [81].

Clinical studies and several case reports have suggested that infection with *T. gondii* is associated with polymyositis and/or dermatomyositis. In a study of 58 patients with polymyositis/dermatomyositis, 24 % had positive *Toxoplasma* IgM titres indicative of recent infection, which was a significantly high proportion compared to the general population [82].

There are two proposed mechanisms by which *Toxoplasma* may cause myositis: direct invasion of the muscle or indirectly by altered immune responses. Response to anti-protozoal treatment is variable, with early anti-protozoal therapy associated with a better response.

A case of adult-onset Still's disease (ASOD) has been reported in association with toxoplasma infection [83].

3.2. Nematode helminths

3.2.1. Filarial nematodes

Filarial nematodes that infect humans include *Wuchereria bancrofti*, *Brugia malayi,* and *Brugia timori,* which cause lymphatic filariasis; *Onchocerca volvulus,* which causes dermatitis and eye lesions; and *Loa loa,* which causes subcutaneous swellings (Calabar swellings) and allergic manifestations. As of 2018, globally, 51 million people were infected by lymphatic filariasis, a 74 % decline since the start of WHO's Global Programme to Eliminate Lymphatic Filariasis [84]. (Fig. 7).

Mosquitoes of the genera *Aedes, Anopheles, Culex, or Mansonia* are the intermediate hosts and vectors of lymphatic filariasis. The adult worms in lymphatic filariasis reside in the lymph nodes and lymphatic channels, and female worms produce larvae called microfilariae. Inflammation and fibrosis cause lymphatic obstruction, causing lymphoedema, elephantiasis, and hydrocele. Depending on the immune response, some patients with severe manifestations may not have peripheral microfilaremia, while others may have heavy microfilaremia but may be asymptomatic [85].

Large joint arthritis has been described in lymphatic filariasis. A study involving 33 adults with possible filarial arthritis from a bancroftian filariasis endemic zone in Sri Lanka and another study involving 19 children from a bancroftian filariasis endemic zone in India showed similar findings of mainly large joint involvement, the knee joint being the most common, with the majority having associated pain and effusion. Recurrent episodes were noted. More than two large joint involvements and small joint involvements were not seen. Filarial antibodies against *W. bancrofti* were present in 84–90 % of these patients. However, microfilaria was seen only in one of these patients [86,87]. Similar clinical findings were reported in another study of 19 adult patients from a filaria-endemic

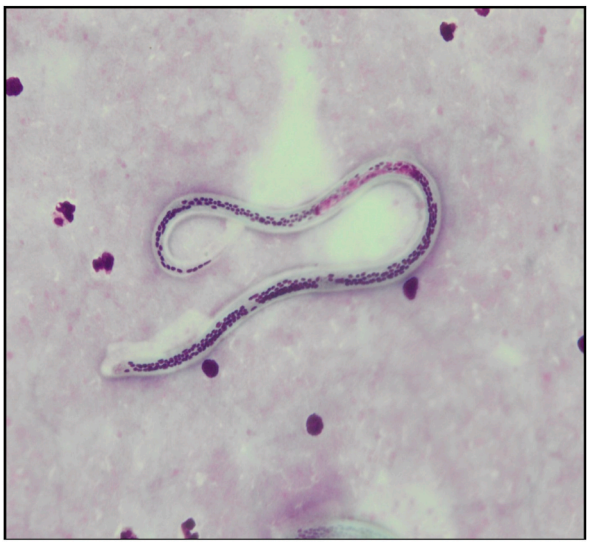

Fig. 7. Adult worm of *Wuchereria bancrofti.*
(Courtesy of Department of Parasitology, Faculty of Medicine, Universiti Malaya).

area in Papua New Guinea who presented with arthritis symptoms. Microfilaria were detected in the blood of all these patients [88].

In these studies, patients who were treated with diethylcarbamazine citrate (DEC) showed a good response.

Lymphatic filariasis can also cause a chylous arthritis. In one study, there were 25 cases of arthritis with chylous effusion affecting the knee joint. These patients presented with painful swelling of the knee joint associated with fever. Most of these patients had unilateral involvement of the knee joint. One of these patients had moderate elephantiasis, and another had a history of chylous hydrocele. Microfilaria were detected in the blood in eight of these patients, and synovial fluid cultures were negative for bacteria. The mechanism for chylous arthritis was suggested to be obstruction of lymphatic vessels leading to lymphangiectasia, lymphatic fistulation, and extravasation of chyle into the joint space. They were noted to develop recurrent effusions and chronic arthritis [89].

Rare cases of arthritis have also been reported in *Loa loa* infection. Arthritis in these cases typically involved large joints of lower limbs. Microfilariae of *Loa loa* were identified in the synovial fluid in some of these cases [90,91]. Leukocytoclastic vasculitis was reported in a single patient [92].

3.2.2. *Dracunculiasis*

Dracunculiasis, also called Guinea worm disease, is caused by the nematode helminth *Dracunculus medinensis*. It affects people in rural, deprived, and isolated communities who depend mainly on open stagnant surface water sources such as ponds for drinking water.

During the mid-1980s, an estimated 3.5 million cases of dracunculiasis occurred in 20 countries. Since then, the number of worldwide cases has reduced drastically due to global eradication efforts led by WHO. The number of reported cases fell to less than 10,000 cases for the first time in 2007. Since 2015, human cases have remained in the double digits. Currently, 5 countries (Angola, Chad, Ethiopia, Mali, and South Sudan) are considered endemic [93].

Human infection usually occurs by drinking water from stagnant water sources such as ponds contaminated with copepods containing Guinea worm larvae. These larvae penetrate the stomach and intestinal wall and migrate to the abdominal and retroperitoneal connective tissue, where they develop into the adult stage and mate. The female worm migrates to the surface of the skin, usually of the lower extremities, causing the formation of a painful blister which ulcerates, enabling the worm to release larvae on contact with water. These larvae must be ingested by copepods for further development into infective forms.

Guinea worm infection has been associated with monoarthritis, with the knee joint most commonly affected [94]. Untreated infections cause ankylosis and joint deformities [95].

Various mechanisms of arthritis are described in dracunculiasis. In some cases, the arthritis is caused by direct invasion of the joint by *D. medinensis* or the presence of the larvae in the joint.

In four cases of acute severe monoarthritis of the knee joint with joint effusion reported from the South India region in 1968, larvae of *D. medinensis* were demonstrated in joint fluid microscopy accompanied by negative bacterial cultures. Arthrotomy revealed the presence of the adult worm within the joint cavity in all four patients [12].

Septic arthritis, sometimes associated with cellulitis, is also reported. In these patients, ulceration of the skin adjacent to a joint provides a route for bacterial infection of the joint. Patients presenting late may develop severe joint deformities [94].

A reactive arthritis has also been described with no demonstrable larvae in the joint fluid but temporally associated with the appearance of a Guinea worm ulcer in the affected limb [94]. In a series of 350 cases of Guinea worm infections, 7 cases of acute monoarthritis of the knee joint were seen. In all these cases, Guinea worm was seen near the knee joint. However, joint aspirate

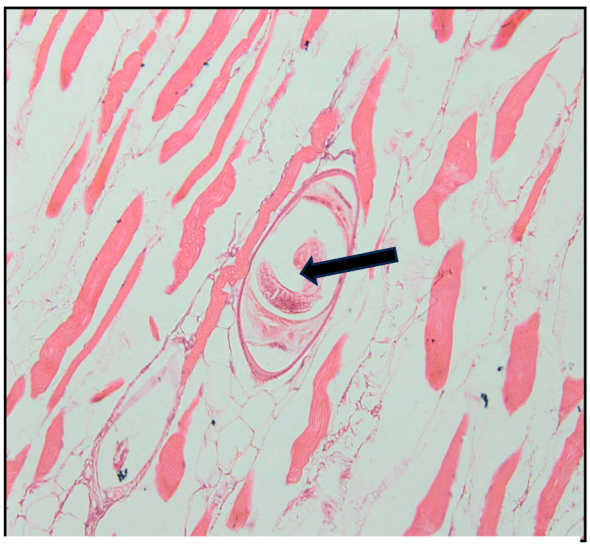

Fig. 8. Encysted larvae of *Trichinella spiralis* within skeletal muscle.
(Courtesy of Department of Parasitology, Faculty of Medicine, Universiti Malaya).

microscopy did not reveal larvae, and bacteriological cultures were negative [96].

Sometimes, the presence of a calcified dead worm in the vicinity of a joint may also lead to a sterile chronic monoarticular arthritis. In a prospective study of 100 people with evidence of calcified guinea worms, 10 patients had chronic arthritis attributable to a periarticular calcified worm. Among them, 8 had arthritic involvement of the knee [97].

3.2.3. *Trichinella species*

Trichinella has a global distribution. Among the 8 species, *Trichinella spiralis* is the most important etiological agent to cause human disease [98] (Fig. 8).

Infection of humans occurs with the ingestion of *Trichinella* larvae that are encysted in the muscle tissue of domestic or wild animal meat. The most important source of human infection worldwide is the domestic pig. After ingesting raw or undercooked meat, gastric digestion releases the parasite larvae, which develop into adult stages within the intestinal mucosa. Adult worms mate and release newborn larvae, which disseminate to striated muscle via the bloodstream and lymphatics. In muscle cells, parasite larvae encapsulate themselves and can survive for years [98].

Musculoskeletal manifestations are frequently seen in *Trichinella* infection.

In three large outbreaks involving *Trichinella nelsoni* from Northern Italy (150 patients), *Trichinella britovi* from Turkey (98 patients), and *Trichinella spiralis* and *Trichinella britovi* from Bulgaria (72 patients), myalgia was the most common presenting symptom, reported in 88–97 % of patients. Joint pains were seen in 32 %–84 % of cases; however, synovitis or tenosynovitis was not observed. Eosinophilia was reported in 84–97 % of cases, and elevated levels of CK suggesting myositis were seen in 62–82 % of patients. Patients in the *T.nelsoni* outbreak were managed symptomatically without steroids or anti-helminthic drugs, whereas patients in the *T.spiralis* and *T.britovi* outbreaks were treated with anti-helminthic drugs with corticosteroids in addition in the case of severe symptoms. Complete resolution of musculoskeletal complaints was reported in all these patients [99–101].

The long-term outcome of most cases of trichinellosis is favourable. However, life-threatening manifestations may occur in approximately 2 % of cases and are related to cardiac and CNS involvement [102].

3.2.4. *Toxocariasis*

Toxocariasis is caused by the nematodes *Toxocara canis* or *Toxocara cati*. Their definitive hosts are the domestic dog and cat, where the adult worms live within the lumen of the small intestine. Infected definitive hosts excrete the eggs of *Toxocara* in their faeces. Human infection occurs via ingestion of contaminated water, food, and soil.

In the small intestine, the larvae are released from the eggs, penetrate the intestinal wall, and travel via the circulatory system to various organs, including the lungs, liver, muscles, and brain. Except in the definitive hosts, these larvae do not mature but can arrest in development within tissues for many years [103].

Rarely, cases of arthritis, myositis, and vasculitis have been described in association with Toxocara infection [104–109].

3.2.5. *Strongyloides stercoralis*

Strongyloidiasis is a soil-transmitted infection caused mainly by *Strongyloides stercoralis* and, to a lesser extent, by *Strongyloides fuelleborni*. The infection is estimated to affect 300–600 million people globally [110] (Fig. 9).

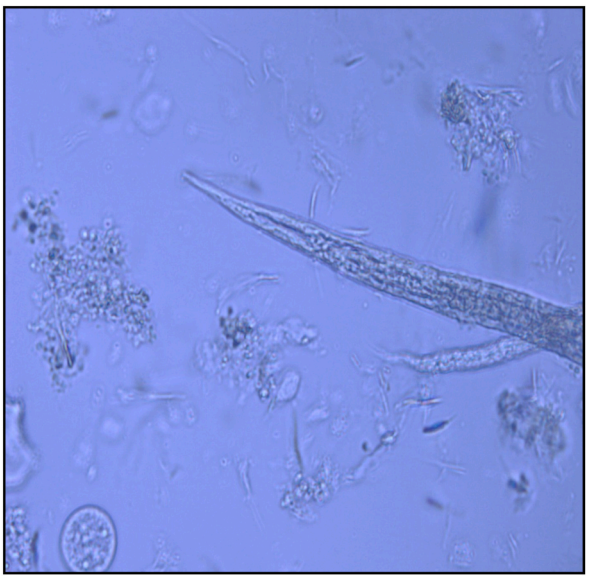

Fig. 9. Adult worm of *Strongyloides sterocoralis*.
(Courtesy of Department of Parasitology, Faculty of Medicine, Universiti Malaya).

Adult female *Strongyloides* lay eggs in the small intestine of infected humans. These eggs become rhabditiform larvae and are passed in the stool. Human infection occurs mainly by the transcutaneous route. After infective larvae penetrate the skin, they travel to the lungs via the bloodstream and lymphatics and then migrate to the gut. In the small intestine, they develop into parasitic adult females that reproduce asexually. Some rhabditiform larvae transform into filariform larvae within the gut and re-infect the host by invading the intestinal wall or the perianal skin. This auto-infection enables *Strongyloides* to complete its entire life cycle within the human host and can give rise to the persistence of infection [111].

Chronic infection is mostly asymptomatic. 75 % of infected persons may have eosinophilia or raised IgE levels [109]. When symptomatic, these can include abdominal pain, diarrhoea, constipation, pruritis ani, weight loss, non-specific urticarial rash, larva currens (pruritic, urticarial, linear streaks located along the buttocks, groin, abdomen and trunk), and rarely, arthritis [112].

In a review of 9 cases of arthritis in *Strongyloides* infection, 8 of these patients had a history of travel to a *Strongyloides* endemic area. Joint involvement was in the form of oligo- or polyarthritis, with knee joints most frequently involved. Eosinophilia was frequently present. *Strongyloides* larvae were identified in the synovial biopsy in one patient. HLA B27 antigen was negative in the tested patients [113].

Oligoarthritis, keratoderma blenorrhagicum, ulcerative keratitis, and eosinophilia were reported in an 11-year-old HLA-B27 positive child who was diagnosed with Strongyloidiasis. Her symptoms responded well to oral ivermectin along with NSAIDs and topical steroid treatment for her eyes and skin [114].

Corticosteroid treatment is known to increase the risk of acquiring strongyloidiasis as well as inducing a state of hyperinfection in patients with strongyloidiasis. Such severe *Strongyloides* infection is characterised by a massive invasion of filariform larvae in the bowel and often in the lungs, with disseminated infection leading to a high mortality risk [112].

Hence, in the case of strongyloidiasis, corticosteroids should not be used before receiving anti-helminthic therapy [115].

Reactive arthritis has also been very rarely reported with other nematode infections such as *Enterobius vermicul*aris, *Necator americanus* (New World hookworm) and *Anisakis simplex* infections [116–118].

3.3. Cestode helminths

There are four medically important cestodes (tapeworms). These are *Taenia solium, Taenia saginata, Diphyllobothrium latum*, and *Echinococcus granulosus*.

Among these, the most well-described rheumatic involvements are seen with *Echinococcus granulosus* infection, which causes cystic echinococcosis (hydatid disease). This disease is globally distributed [119].

Dogs and other canids are the definitive hosts and harbour this parasite's intestinal tapeworm stage. Several herbivores and omnivores act as intermediate hosts that become infected by ingesting the parasite eggs. These eggs develop into larval stages as echinococcal cysts in the viscera of these intermediate hosts. The inner layer (germinal layer) of these fluid cysts produces multiple protoscolices by asexual division. The cysts are surrounded by a granulomatous tissue reaction produced by the host. The definitive hosts become infected by the consumption of viscera of intermediate hosts containing these cysts. The sheep strain of the parasite is the most associated with human infections. Practices such as feeding dogs with the viscera of slaughtered sheep facilitate the transmission of this strain. Humans are accidental intermediate hosts. Human infection with *E. granulosus* produces one or more slow-growing cysts (hydatid cysts), most commonly in the liver (65 %), followed by the lungs (25 %), and less commonly in other organs [120].

Hydatid disease of bones and joints is rarely reported, occurring only in 1–2 % of echinococcosis infections [9].

Hydatid synovitis may develop due to direct parasitic infiltration or as an immune-mediated reactive arthritis.

Most commonly, hydatid synovitis occurs due to a bone hydatid cyst located in the vicinity of a joint with secondary extension to the joint [8–10,121].

A rare case of primary and isolated echinococcal arthritis involving the knee joint was reported in a 63-year-old woman who presented with a 1-month history of monoarthritis of the knee joint. A CT scan, in this case, showed a synovial cystic lesion without any adjacent bone lesion or visceral cysts. Synovial biopsy showed synovitis with a foreign body-type giant cell reaction to remains of hydatid germinal membrane fragments with no bone involvement [7].

Reactive arthritis has been rarely reported with hydatid cysts of the liver presenting with large joint oligoarthritis or asymmetrical polyarthritis. Interestingly, surgical removal of the hydatid cyst was followed by complete resolution of the arthritis [122–124].

Hydatid disease rarely occurs in muscle, even in endemic areas. Intramuscular hydatid disease may mimic a soft tissue tumour [125].

Human cysticercosis caused by infection with the larval stage of *Taenia solium* (pork tapeworm) can cause muscular involvement. The parasite more commonly infects the central nervous system, causing neurocysticercosis. Muscular cysticercosis is mostly asymptomatic and often seen incidentally as dot-shaped or ellipsoidal calcifications in the thighs or arms. A massive parasite burden can cause muscular pseudohypertrophy [126].

3.4. Trematode helminths

Trematodes, or flukes, are parasitic flatworms. They include schistosomes, intestinal flukes (e.g., *Fasciolopsis*), liver flukes (e.g., *Fasciola, Clonorchis, Opisthorchis*), and lung fluke (*Paragonimus*).

Among the trematodes, the most well-described rheumatic manifestations are reported in *Schistosoma* infections. Three main species of schistosomes infect humans- *Schistosoma haematobium, Schistosoma mansoni,* and *Schistosoma japonicum* (Fig. 10).

Schistosomiasis is prevalent in poor communities in tropical and subtropical areas without access to safe drinking water and

adequate sanitation. Schistosomiasis transmission has been reported in 78 countries, with at least 90 % of those requiring treatment for schistosomiasis living in Africa [127].

Adult male and female *Schistosoma* worms live inside the veins of the infected human host, where they mate and produce fertilised eggs. Due to poor hygienic practices and improper sanitation, people infected with schistosomiasis can contaminate freshwater sources with faeces or urine containing parasite eggs. These eggs hatch, releasing free-living miracidia that infect suitable snails where they undergo asexual reproduction, giving rise to cercaria, which are released into the water. Human infection occurs by the transcutaneous route.

Host pathology and organ damage are driven by granulomatous inflammation directed against the eggs of the adult worms. The clinical presentations depend on where the species resides, such as the gastrointestinal tract or genitourinary tract. Symptoms include abdominal pain, diarrhoea, rectal bleeding, ascites, oesophageal varices, haematuria, obstructive uropathy, and squamous cell carcinoma of the urinary bladder [128].

In a large cohort of patients from Egypt, which is endemic for *S.mansoni* and *S.Haematobium,* joint involvements were assessed in 124 male patients aged 10–30 years who were infected with schistosomiasis and complained of joint pains. The duration of joint pains varied, lasting from a few days to three years. Musculoskeletal involvement was mainly in the form of knee arthritis, sacroiliitis, and enthesitis of the heels. Radiographic changes were seen in sacroiliac X-rays and heels in 41 % of patients. HLA-B 27 was not assessed. *Schistosoma* eggs were demonstrated in the synovium in 3 out of 11 patients who underwent synovial biopsy. Synovitis with vasculitis was the main pathological finding [11].

In another study from Egypt involving 96 patients with active *Schistosoma mansoni* infection diagnosed with the finding of *S. mansoni* eggs in rectal biopsy, 72 of these patients had prominent musculoskeletal complaints, out of which the majority had a combination of arthritis and enthesitis confirmed on physical examination. The pattern of arthritis was predominantly a symmetrical polyarthritis. There was no clinical evidence of vasculitis or extraarticular manifestations, and no radiological abnormalities were found in the affected joints. Rheumatoid factor was positive only in 5 patients with musculoskeletal involvement. HLA-B 27 was not assessed. For most patients, joint pains were alleviated within one month of treatment with praziquantel [129].

Circulating immune complexes were demonstrated in some reports of arthropathy in *Schistosoma* infection, which supports a role of immune complex-medicated mechanisms in the pathogenesis of reactive arthritis in this infection [14,15].

3.5. Parasitic treatment associated syndromes

The Mazzotti reaction is a potentially life-threatening inflammatory reaction triggered by the rapid release of parasite antigens during the killing of microfilaria. The reaction most often occurs when diethylcarbamazine citrate (DEC) is used to treat onchocerciasis [130].

This reaction is characterised by fever, urticaria, arthralgias, tender lymphadenopathy, tachycardia, hypotension, oedema, and abdominal pain, which occurs within seven days of treatment of microfilariasis. The underlying mechanism is thought to be mediated by eosinophil activation, and the risk is also related to the parasitic load [130]. The risk of Mazzotti reaction is significantly lower (10 %) with the use of Ivermectin.

Due to the high risk of Mazzotti reaction, DEC is contraindicated in treating onchocerciasis or in treating lymphatic filariasis when there is coinfection with onchocerciasis. DEC should be used with caution in treating loiasis [131].

Praziquantel used for the treatment of schistosomiasis does not cause the typical Mazzotti reaction; however, in patients with a very high parasitic load, high rates of adverse reactions characterised by fever, urticaria, and abdominal pain have been reported [131].

Albendazole, used in treating several parasitic infections, has not been linked to Mazzotti reaction [131].

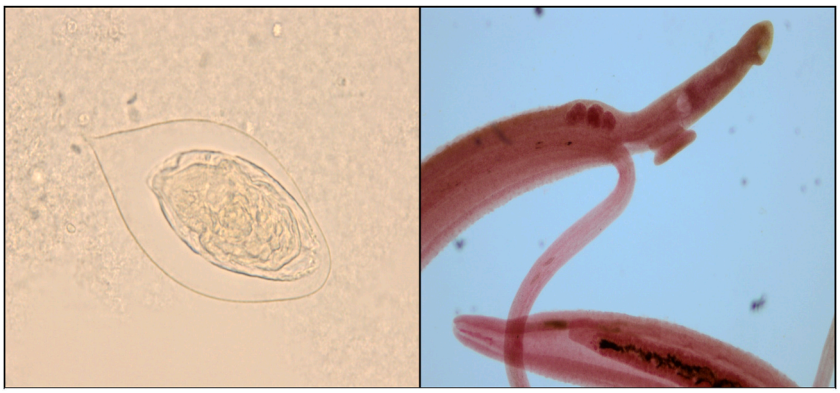

Fig. 10. Egg of *Schistosoma haematobium* (left). Adult worm of *S. haematobium* (right). The thin female resides in the gynaecophoral canal of the thicker male.
(Courtesy of Department of Parasitology, Faculty of Medicine, Universiti Malaya).

3.6. Diagnosis of parasitic arthritis

Diagnosis of parasitic arthritis can be difficult to establish. Clinicians should always include parasitic infections in the differential diagnosis of rheumatic symptoms in regions where parasitic infections are endemic. It should also be considered in immigrant populations from endemic areas or when there is a travel history to such locations, as well as in immunocompromised individuals who are at an increased risk of various protozoal infections.

A history of consuming undercooked or raw meat or fish may suggest a parasitic infection in the diagnosis. A history of similar illness in others who have eaten the same food raises the likelihood of an infectious cause.

In patients presenting with rheumatic symptoms, the presence of additional clinical features such as diarrhoea, abdominal pain, bloating, fever, malaise, and myalgia may indicate an infectious aetiology. The presence of leucocytosis, elevated C-reactive protein, ESR, or CK are clues to a diagnosis of an underlying infection. Although not specific, the presence of eosinophilia could provide a valuable diagnostic clue to an underlying parasitic infection.

The definitive diagnosis of parasitic infections relies on microscopic examination of stool, urine, blood, other body fluids, tissue, serological tests, molecular techniques, and radiological imaging (Table 1).

There are no validated criteria to diagnose parasitic arthritis. A set of criteria proposed in 1975 included 6 criteria for diagnosing parasitic rheumatism [133] (Table 2).

These criteria may eliminate parasitic pathologies that may cause joint erosions, such as dracunculiasis, cystic echinococcosis, and schistosomiasis, and eliminate patients who may respond partially to anti-inflammatory therapy. Parasitic arthritis cases reported in the literature were mainly diagnosed based on the demonstration of the parasitic infection and the resolution of arthritis with anti-parasitic treatment.

The differential diagnosis of parasitic arthritis includes other infectious arthritis, septic arthritis, crystal arthropathy, early-onset spondyloarthritis, and connective tissue diseases such as rheumatoid arthritis and SLE.

3.7. Management of parasitic arthritis

The literature on arthritis related to parasitic infections is scarce and limited to case reports or small case series. Clinical studies evaluating treatment strategies in parasitic arthritis are lacking. Hence, an evidence-based management approach to parasitic arthritis is currently unavailable.

Treatment of suspected parasitic arthritis is directed towards treatment of the specific parasitic infection (Table 1). NSAIDs or corticosteroids may be used to alleviate inflammation. However, corticosteroids should not be used in *Strongyloides* infection before anti-helminthic treatment due to the risk of corticosteroid treatment causing disseminated strongyloidiasis. Characteristically, parasitic arthritis responds to specific anti-parasitic treatment often when anti-inflammatory drugs such as NSAIDs have not been effective.

In certain circumstances, such as when a parasitic infection is suspected in an immunocompromised person, a clinical microbiologist or infectious disease specialist should be consulted for advice regarding the most appropriate tests and treatment options. In specific clinical scenarios, such as diarrhoea in an immunocompromised individual, the laboratory should be alerted to the potential diagnosis of organisms like *Cryptosporidium* to perform specific tests. Routine stool microscopy may not reveal these organisms, and the diagnosis may be otherwise missed (Table 1).

Gastrointestinal protozoal infections often cause significant diarrhoea. Hence, monitoring hydration status and replacing fluids and electrolytes is critical in managing these infections.

Immunocompromised patients are particularly predisposed to infections from certain protozoa, such as *Cryptosporidium* spp, *Blastocystis* spp, *Microsporidia* spp, *Toxoplasma gondii*, and *Cystoisospora belli*. In these cases, in addition to anti-parasitic treatment, it is important to restore immune function to achieve sustained eradication of these infections. This may include initiating anti-retroviral therapy as soon as possible in patients with HIV or adjusting immunosuppressant therapy for those who are on immunosuppressant medications.

In cases where outbreaks are suspected, public health authorities should be informed, as investigations will be necessary to identify the source of the outbreak and implement interventions to control it.

3.8. Prevention and control of parasitic infections

The basic principles of prevention of parasitic infections are:

1. Avoiding ingestion of infective cysts, eggs, larvae, or intermediate hosts infected with larvae.
2. Preventing contact of bare skin with infective larvae.
3. Avoiding bites of infected vectors.

At the individual level, preventive measures involve drinking safe water; practicing adequate hand washing, particularly after using bathrooms and latrines and before food preparation; and properly cleaning and cooking when preparing food. Swimming in freshwater rivers or lakes should be avoided in areas where schistosomiasis is endemic. People should not walk barefoot in areas where *Strongyloides* or hookworms are found. Measures to avoid insect bites in endemic areas include wearing long-sleeved clothing, applying insect repellents to exposed skin, treating clothing with permethrin, and using bed nets impregnated with permethrin or other insecticides. Residents of non-endemic areas should use prophylactic antimalarial medications when travelling to malaria-endemic

Table 1
Diagnosis and treatment of common parasitic infections [132].

Parasitic agent	Diagnostic tests	Treatment
Entamoeba histolytica	• Stool microscopy for identification of *E. histolytica* cysts and/or trophozoites (Minimum 3 different specimens on different days to optimise detection). • Antigen detection from stools and serum. • PCR from stools, tissue or liver abscess aspirates. • Serology to detect antibodies against *E. histolytica* (serology cannot distinguish between current and past infection, especially in endemic areas).	• Asymptomatic intestinal colonisation is treated with intraluminal agents paromomycin or diloxanide furoate. • Amoebic colitis or extraintestinal amoebiasis is treated with systemic therapy with nitroimidazoles such as metronidazole or tinidazole. Following systemic therapy, an intraluminal agent, either paromomycin or diloxanide furoate is given for intraluminal elimination of *Entamoeba*. • Amoebic liver abscess occasionally requires image-guided therapeutic aspiration as an adjunct to antiparasitic therapy.
Giardia lamblia	• Stool microscopy for detection of cysts and trophozoites (sampling a minimum of 3 different specimens on different days increases the sensitivity to > 90 %). • *Giardia* antigen detection from stools. • PCR from stool.	• Tinidazole is the drug of choice. • Alternatives include Metronidazole and Nitazoxanide.
***Blastocystis* spp**	• Stool microscopy for detection of cysts (microscopic identification is difficult due to variable forms and sizes of *Blastocystis)*. • PCR from stool (highly sensitive and specific).	• Metronidazole, trimethoprim-sulfamethoxazole, nitazoxanide, paromomycin.
Cystoisospora belli	• Stool microscopy for identification of oocysts using modified acid-fast stain (multiple stool examinations may be required). • PCR testing from stool assay is highly sensitive and specific.	• Trimethoprim-sulfamethoxazole is the drug of choice. • Alternative antibiotics include ciprofloxacin, pyrimethamine together with folinic acid or nitazoxanide.
***Cryptosporidium* spp**	• Stool microscopy for identification of oocysts using modified acid-fast stain (multiple stool examinations may be required). • Visualisation with immunofluorescence microscopy. • Molecular techniques such as PCR from stool.	• Restoration of immune function is necessary for effective treatment (this may include starting ART in patients with AIDS or reducing immunosuppressants in patients who are on these medications). • In AIDS, anti-parasitic treatment is reserved for severe symptoms or persistent symptoms despite anti-retroviral therapy. • Nitazoxanide is the first-line agent. Paromomycin is used as an alternative agent. Data regarding the efficacy of these drugs is mixed. • Immunologically competent patients usually have self-limited illness with spontaneous recovery.
***Sarcocystis* spp:**	• MRI of clinically affected muscles. • Skeletal muscle biopsy for identification of sarcocyts in muscle tissue and demonstration of inflammation of muscle. • PCR from muscle tissue is used for species identification. • Serology using Western blot assay (positive serology is suggestive of previous exposure, but is not diagnostic for acute disease.	• Symptomatic infection is generally self-limited. • The optimal treatment is uncertain; trimethoprim-sulfamethoxazole has been effective in several cases. • Corticosteroids for symptomatic relief in cases of acute myositis.
***Microsporidia* spp**	• Stool microscopy (using chromotrope or chemifluorescent staining) for gastrointestinal microsporidiosis. • Specimens such as urine, conjunctival scrapings, nasal scrapings, and CSF are examined in disseminated microsporidiosis. • Skeletal muscle biopsy for identification of microsporidian spores and muscle inflammation. • PCR from stools, urine or tissue allows species identification. • Electron microscopy from tissue allows species identification.	• Albendazole is effective against most microsporidia species. • Restoration of immune function is necessary for effective treatment (this may include starting ART in patients with AIDS or reducing immunosuppressants in patients who are on these medications).
***Plasmodium* spp**	• Light microscopy of thick and thin blood smears using Giemsa staining is the gold standard. • Rapid diagnostic tests (RDTs) based on plasmodium antigen detection can be used in situations where microscopic examination is delayed or difficult to obtain.	• The approach to anti-malarial therapy should take into account local guidelines, drug sensitivity patterns, and drug availability. Please refer to WHO guidelines for malaria [135].
***Leishmania* spp**	• Light microscopy of Giemsa-stained smears to visualise *Leishmania* amastigotes on bone marrow aspirates (preferred specimen, sensitivity 60–95 %) or splenic or lymph node aspirates. • Culture. • PCR from whole blood (sensitivity 93 %, specificity 96 %). • Serology to detect antileishmanial antibodies.	• Amphotericin B formulations such as liposomal amphotericin B. • Pentavalent antimony compounds such as sodium stibogluconate (SSG) or meglumine antimoniate. • Miltefosine. • Paromomycin.
Toxoplasma gondii	• Serology for detection of *T. gondii* IgM and IgG antibodies. • CT or MRI brain in *T. gondii* encephalitis (demonstrates multiple ring-enhancing lesions). • PCR for detection of *T. gondii* DNA in body fluids and tissues. • Histopathology for visualisation of tachyzoites and bradyzoites in tissue sections or body fluids (e.g., CSF, amniotic fluid, or BAL).	• Pyrimethamine plus sulfadiazine plus folinic acid (preferred regimen). Alternative regimes include: • Pyrimethamine plus clindamycin plus folinic acid, • In patients with sulphonamide allergy, atovaquone can be used.

(*continued on next page*)

Table 1 (*continued*)

Parasitic agent	Diagnostic tests	Treatment
Lymphatic filariasis (*W. bancrofti, B.malayi*)	• Blood smear examination for detection of microfilariae (sample should be obtained at night during peak density of parasitaemia). • Circulating filarial antigen assays for detection of *W. bancrofti* antigens (allows point-of-care detection of active infection in the absence of microfilaremia). • Doppler ultrasonography can detect adult worms in lymphatic vessels.	• Diethylcarbamazine is highly effective at eliminating microfilariae but has modest activity against adult worms.
Dracunculus medinensis	• Clinical diagnosis by appearance of the skin blister and identification of the emerging whitish filamentous worm as the blister ruptures. • Calcified worms may sometimes be seen adjacent to an arthritic joint by X-rays.	• Symptomatic treatment with analgesics and application of wet compresses to the affected skin. • No anthelmintic drugs are known to be effective. • Topical antibiotics to prevent secondary bacterial infection. • Gentle extraction of the worm over a period of several days using a small stick to avoid breaking the worm.
***Trichinella* spp**	• Serology for detection of *Trichinella*-specific antibodies (Seroconversion usually occurs by 3 weeks after infection).	• Systemic corticosteroids in conjunction with mebendazole may be used in severe illness.
***Toxocara* spp**	• Serology for detection of IgG antibodies to *Toxocara* excretory/secretory antigens. • CT or MRI of the brain, liver or lungs may demonstrate lesions due to toxocariasis.	• Mild symptoms are self-limited and do not require specific therapy. • Albendazole or mebendazole, or diethylcarbamazine with corticosteroids are used in severe respiratory, myocardial or central nervous system involvement.
Strongyloides stercoralis	• Stool microscopy for detection of *S. stercoralis* larvae (seven different stool examinations may be needed). • Stool PCR.	• Ivermectin.
***Echinococcus granulosus* (cystic echinococcosis)**	• Ultrasonography, CT or MRI for visualisation of hydatid cysts. • Serology to detect antibodies against *E. granulosus*.	• Guidance of the WHO-Informal Working Group on Echinococcosis (WHO- IWGE) recommends an image-based, stage-specific approach with the following options [136]: • Percutaneous treatment of the hydatid cysts with PAIR (Puncture, Aspiration, Injection, Re-aspiration) technique, • Surgical resection to remove the cyst in toto, • Anti-infective therapy with albendazole or mebendazole, • Watch and wait.
***Schistosoma* spp**	• Stool or urine microscopy for detection of *Schistosoma* eggs • Antigen detection from serum or urine • Serology to detect antibodies against *Schistosoma* spp. • PCR from stool, urine or serum	• Praziquantel.

PCR: Polymerase Chain Reaction; MRI: Magnetic Resonance Imaging; CT: Computed Tomography; BAL: Bronchoalveolar Lavage; CSF: Cerebrospinal fluid; IgG: Immunoglobulin G; IgM: Immunoglobulin M; AIDS: Acquired immunodeficiency syndrome; ART: Antiretroviral therapy.

Table 2
Doury criteria for articular impairment due to parasitic infection (Criteria 1–6 are essential for diagnosis).

1.	Inflammatory oligo-mono-or polyarthropathy
2.	Living in an endemic area
3.	Parasitic documentation on samples (stool, urine, serology)
4.	No X-ray lesions
5.	No efficacy of anti-inflammatory treatments
6.	Efficacy of anti-parasitic treatments
7.	Biological inflammation (raised ESR)
8.	Eosinophilia
9.	Inflammatory joint fluid, but no parasites in the fluid

regions.

Public health interventions at the community level include providing clean water and sanitation, implementing hygienic food production practices to prevent the contamination of meat, fish, and vegetables, vector control measures, and preventing or treating infections in domestic animals. Providing health education is crucial to create awareness about endemic diseases and personal preventive measures.

Global efforts to prevent and control parasitic infections include various global programs led by WHO and supported by governments and non-government organisations.

The Guinea worm eradication program is a global program that involves surveillance for prompt detection and reporting of human or animal infections, provision of safe water, vector control measures such as regular application of temephos to stagnant water to kill infected copepods, and community education aimed at spreading awareness and promoting community participation [93].

Global Programme to Eliminate Lymphatic Filariasis involves stopping the spread of infection through large-scale annual treatment of all eligible people in endemic areas by using a combination of two filaricidal drugs (albendazole plus either diethylcarbamazine or

ivermectin) delivered once yearly. This reduces microfilaraemia in the blood of infected persons to levels that can no longer sustain transmission by mosquito vectors to new hosts [84].

Mass drug administration is also a key intervention in global programs to control schistosomiasis and soil-transmitted helminthiases along with improved access to water, sanitation, and hygiene [134].

4. Summary

Various parasitic infections may present with rheumatic manifestations (Table 3). Furthermore, some parasitic infections temporarily produce various autoantibodies, which, along with rheumatic symptoms, can easily mimic well-known autoimmune diseases. Although rare, parasitic infections should always be considered in the differential diagnosis of rheumatic presentations such as arthritis when there is a history of exposure to risk factors, especially in patients from endemic regions and in atypical rheumatic presentations. The efficacy of specific antiparasitic treatment is a characteristic feature of parasitic arthritis.

Practice points

1) Parasitic infections should always be included in the differential diagnosis of arthritis when the patient has risk factors for parasitic infections.

Table 3
Rheumatic manifestations associated with parasitic infections.

Parasite	Rheumatic manifestations and pattern of joint involvement
Entamoeba histolytica	• Reactive arthritis (Oligoarticular pattern with predominantly large joint involvement) [26,27] • Infectious arthritis [28]
Blastocystis spp	• Reactive arthritis (asymmetrical polyarthritis or oligoarthritis predominantly involving the lower limbs) [32–34] • Infectious arthritis (organism demonstrated in synovial fluid) [36] • Uveitis [35] • Enthesopathy [35]
Cystoisospora belli	• Reactive arthritis (symmetrical polyarthritis like RA involving bilateral wrists and MCP joints) [38]
Cryptosporidium spp	• Reactive arthritis (mainly oligoarthritis involving large joints) [42–46] • Uveitis [42] • Plantar fasciitis [42] • Reiter's triad of arthritis, urethritis, and conjunctivitis [46]
Giardia lamblia	• Reactive arthritis (oligoarthritis with predominant involvement of large joints of the lower extremities) [49,50] • Uveitis [53] • Retinal lesions (salt and pepper retinopathy), retinal vasculitis [51,52] • Erythema nodosum [54,55]
Sarcocystis spp	• Infectious myositis [56–58]
Microsporidia spp	• Infectious myositis [61–64]
Plasmodium spp	• Arthralgia and myalgia • Rhabdomyolysis [66–68] • Autoimmune haemolytic anaemia [16] • Immune-mediated glomerulonephritis [16,17]
Leishmania spp	• Monoarthritis or chronic symmetrical polyarthritis [70–73] • Dermatomyositis-like or polymyositis-like presentation [77,78] • Cryoglobulinaemic vasculitis [79,80]
Toxoplasma gondii	• Polymyositis, dermatomyositis [82]
Wuchereria bancrofti	• Large joint monoarthritis or oligoarthritis predominantly involving knees [86,88] • Chylous arthritis of the knees [89]
Loa loa	• Large joint oligo arthritis of lower limbs [90,91] • Leukocytoclastic vasculitis [92]
Dracunculus medinensis	• Infectious arthritis or reactive arthritis (monoarthritis, predominantly of knee joint) [12,94–97]
Trichinella spp	• Infectious myositis [99–101]
Toxocara spp	• Reactive arthritis [104,105] • Infectious myositis [106,107] • Systemic vasculitis [108] • Cutaneous vasculitis [109]
Strongyloides stercoralis	• Reactive arthritis (oligoarthritis or polyarthritis predominantly involving knees) [113–115] • Keratoderma blenorrhagicum, ulcerative keratitis [114]
Echinococcus granulosus (cystic echinococcosis)	• Infectious monoarthritis [7–10,121] • Reactive arthritis (large joint oligoarthritis or asymmetrical polyarthritis) [122–124] • Intramuscular hydatid cyst can present as a soft tissue tumour [125]
Taenia solium	• Muscular pseudohypertrophy seen in massive parasitic burden [126]
Schistosoma spp	• Oligoarthritis predominantly of knees, sacroiliitis, enthesitis [11] • Symmetrical polyarthritis, enthesitis [129]

2) ANA and other autoantibodies are observed in certain parasitic infections, including leishmaniasis, malaria, and toxoplasmosis. In patients exhibiting clinical features of SLE, vasculitis, or myositis, it is essential to consider and rule out these parasitic infections in endemic areas.
3) Parasitic infections such as trichinellosis, microsporidiosis, and toxoplasmosis should be considered in the differential diagnosis of myositis, especially in the presence of eosinophilia, risk factors like immunosuppression, and atypical features such as negative autoimmune myositis serology.
4) Identifying certain parasites in the laboratory can be challenging and requires specialised techniques. Routine microscopy might overlook these infections. Therefore, in certain clinical scenarios, such as evaluating diarrhoea in an immunocompromised patient, it is advisable to consult with the laboratory or an infectious disease specialist for recommendations on the most appropriate tests.
5) Corticosteroids should be avoided before anti-helminthic treatment in patients with *Strongyloides* infection to prevent the risk of causing disseminated strongyloidiasis, which can be severe and life-threatening.
6) Due to the high risk of Mazzotti reaction, diethylcarbamazine citrate (DEC) is contraindicated for the treatment of onchocerciasis or in cases of lymphatic filariasis when there is coinfection with onchocerciasis. It should be used with caution in treating loiasis.

Research agenda

1. Much of the current knowledge about reactive arthritis is based on the classical reactive arthritis-causing pathogens such as enteric bacteria. Further research is required to clarify the pathogenic mechanisms involved in reactive arthritis caused by parasites.
2. Clinical studies are needed to determine evidence-based treatment approaches for the management of parasitic arthritis.
3. Despite the common occurrence of various parasitic infections and the high prevalence of rheumatic complaints in the community, few studies have assessed the association between parasitic infections and rheumatic syndromes. Further research will provide valuable data for studying the association. This could have implications for clinical practice.

CRediT authorship contribution statement

Shaheed Ahmed: Writing – original draft, Methodology, Conceptualization. **Jasmin Raja:** Writing – review & editing, Methodology, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used [GRAMMARLY] in order to [improve the grammar and language only]. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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