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REVIEW

Malaria and Malignancies- A review

Adarsh Sugathan[1], ✉Shamathmika Rao[2], Nayanatara A Kumar[1], Pratik K Chatterjee[1]

[1] Department of Physiology, Kasturba Medical College Mangalore, Manipal Academy of Higher Education, Karnataka, Manipal, 576104, India

[2] Department of Anatomy, Kasturba Medical College, Manipal Academy of Higher Education, Karnataka, Manipal, 576104, India

Abstract

Introduction: Malaria, a parasitic disease caused by Plasmodium sp. is a substantial threat to global health. In recent years, the association of malignancies and malaria has been an interesting field of research. To date, Burkitt's lymphoma has shown a close association with Malaria in the sub-Saharan nations. The latest research targets the current anti-malarial medicines as a promising approach towards novel anti-cancer therapies. The complicated relationship between malaria, genetics, immune response, and cancer might help in exploring various pharmacological approaches that might help in the therapeutic approach to malaria and cancer. Further, in-depth in-vivo and in-vitro studies are needed to establish the link between malaria infection and cancer progression.

Aims and Objectives: This review aims to explore the key associations of malaria and various malignancies and the possible anti-cancer effects of anti-malarial drugs.

Materials and Methods: A critical review of 53 articles from 1987 to 2023 was conducted.

Conclusion:

• Endemic Burkitt's lymphoma shows a synergy with malaria, but more studies are needed to explore, for correlating the possible associations of malaria with other malignancies.

• Non-hematological malignancies were shown not to have a strong correlation with malaria.

• Anti-malarial drugs displaying anti-cancer properties could be a promising adjunct to current routine cancer treatment

Keywords: Malaria, malignancies

Introduction

Malaria, a parasitic disease, is a substantial threat to global health and a leading cause of mortality [1]. Plasmodium species are the pathogens responsible for malaria [2]. Symptoms of malaria include fever with chills, headache, vomiting, abdominal pain and malaise. [3]. These develop within weeks of infection and may remain dormant for years. The disease is typically diagnosed via peripheral smear although PCR is used to confirm the species of the malarial parasite post microscopy. Malaria can show partial immunity [4] and can easily be prevented by targeting its vector, i.e. female Anopheles mosquito [5]. This is achieved by either preventing the breeding of the vector or avoiding being bit by it via various methods, popularly using mosquito nets. Despite being easily preventable, the disease can cause fatal complications if progressed, especially in children aged less than five years. Cerebral malaria, caused by falciparum species, is the most dreaded complication of malaria. It can lead to seizures, a comatose state or even death. Other complications of malaria include severe anemia, multi-organ failure and pulmonary edema. Chloroquine and Artemisinin combination therapy (ACT) is the treatment offered for uncomplicated and complicated malaria, respectively [6]. Chemoprophylaxis using Doxycycline is recommended for travellers visiting endemic areas [7]. Reports show that in 2021, there were 247 million cases of malaria when contrasted to 245 million cases in 2020. In the year 2021, the projected number of deaths due to malaria was 619,000, compared to 625,000 deaths in the year 2020[8]. The emergence of artemisinin-resilient species and the rapid spread of parasites harbouring deletions of the *pfhrp* (Plasmodium falciparum histidine-rich protein) 2 and 3 genes is a matter of concern [9]. Novel research approaches are in progress to limit the load of this infection. Along with the acute complications of malaria, there is collective evidence of associated long-term effects. In humans it has been found that Plasmodium falciparum is a potential cancer-causing agent [10]. This was more pronounced in hematological malignancies in endemic areas.

It was also noted that certain anti-malarial agents have anti-tumour properties. The present review aims to explore possible co-relations of malaria and its associated malignancies that could provide insight into cancer research and healthcare, contributing to global health and well-being. Sustainable

Development Goal 3 (SDG 3) primarily focuses on "Good Health and Well-being", which targets to have healthy lives and well-being for all ages. Therapeutic targets for cancer and malaria could be well associated with SDG-3.

Malignant neoplasms are abnormal, uncontrolled, and unchecked growing cells which spread to other sites, infiltrating and damaging them [11]. Neoplasms involving lymphocytes are called lymphomas [12]. The symptoms associated with lymphoma include fever, weight loss, lymphadenopathy, malaise, etc. The 5-year survival rate of lymphomas is 85%. Burkitt's lymphoma is a type of B-cell lymphoma which is common in children and has a rapid growth rate [13]. It is commonly seen in African nations. Although well-curable in childhood, despite being rare in adulthood, the disease can be fatal. The linkage between malarial parasites and endemic Burkitt's lymphoma (eBL) has been a topic of study for over 50 years. In the beginning, it was theorised that mosquitoes carrying malaria multiplied the pathogenic agent causing eBL. The quest for this agent resulted in the discovery of human B cell –Epstein Barr Virus (EBV).

Synergism of Malaria and eBL

The origin of eBL is assumed to be from the germinal centre (GC) B cells. Germinal centres are transient structures that form within secondary lymphoid organs. Within these structures, B cells are selected depending on their potential to generate high-affinity antibodies. Upon antigenic provocation, B cells go into the dark zone of GC to multiply and rapidly mutate their immunoglobulin genes. GC reaction requires the biphasic regulation of *c-myc* gene expression [14]. EBV infection leads to deregulated expression of AID (Activation-Induced cytidine De-aminase) that triggers translocation of the *c-myc* oncogene between chromosomes 8 and 14, ultimately leading to eBL. It was noted that P. falciparum targets the B cells in GC and leads to deregulated AID expression along with enhancing EBV infection [15]. Primary infection with EBV might lead to generation of more B-lymphocytes. Falciparum malaria also causes a rise in the EBV-infected B lymphocytes. Increased B-lymphocytes lead to the rise of the abnormal BL cell. The observed rise provides prime evidence related to the origin of abnormal BL cells [16]. Apart from this, macrophages and neutrophils during the malarial infection produce the origin of free radicals, which damage cells and DNA. These free radicals help to destroy parasites. However, the scavenged Reactive Oxygen Species (ROS) in malarial patients might lead to DNA damage in the host cells. Due to non-restoration of DNA, it may lead to the activation of oncogenes eventually leading to the development of cancer [17]. Malaria, thus may act as a triggering factor of eBL, while lymphoma phenotype and onset of eBL are modified through subsequent infection [18]

Factors determining the severity and probability of eBL oncogenesis in malaria

It was found that children with parasitemia (even if asymptomatic, could be the population at risk for eBL [19]. Reports also suggest a link between malarial episodes in childhood and lymphoid neoplasms developing in later life. So, recurrent episodes of malarial infection in childhood are a risk factor for developing malignancies in adulthood. Further, non-hematological cancers in malaria patients were rarely found regardless of their origin [20]. Climatic Factors play a prime role in describing the power of malaria transmission. This is mediated through a mitogen, triggering mitosis or cell division [21]. It has been suggested that abolishing malaria could result in a decline of BL, probably by removing the potential oncogenic mitogen. BL rates and severity were approximately more prevalent in the areas with chronic and enhanced malaria transmission intensity than in those zones with minimal malaria transmission [22]. These observations substantiate that the incidence of malaria has been directly linked to the development and severity of BL. The mortality associated with malaria and cancer depends on the ability of the involved parasite to suppress immune system. Moreover, the transmission of the obscure pathogen by Anopheles mosquito causes mild transient illness in the initial stages, but it might predispose to cancer in the later stage [23,24]. Mosquito-feeding events can activate cancer pathways, and the bite caused by the mosquito might provoke human metabolic pathways [25], leading to oncogenesis or other viral infections. [26-28] Falciparum malaria might deteriorate genomic stability and also lead to Activation-Induced Cytidine De-aminase dependent B cell lymphoma [29].

Laboratory determinants

Anti-Viral Capsid Antigen (VCA) antibodies formed in response to EBV were found to be more common in malaria patients [30]. This suggests that EBV infection and malaria are immunologically correlated to the origin of BL. The characters associated with BL have been described based on the interaction of the disease and host response.

Thrombocytopenia is seen in falciparum malaria, which has an etiological link with eBL [31]. Numerous immunoglobulins were measured from BL patients. However, as opposed to Anti VCA antibodies, Malaria-specific Immunoglobulin-G and Immunoglobulin-M antibody titers were significantly less in the sera from BL patients [32].

Co-relation of Malaria and BL with other diseases and non-hematological malignancies

Splenic lymphoma and hyperactive splenomegaly due to repeated malarial infections have parallel associated features [33], although there are no statistically significant case reports to prove any concrete association.

Reports also show a connection between a genetic mutation in Duffy antigen receptor complex (DARC), which guards against malaria, and a greater incidence of carcinoma prostate [34]. DARC is found on RBCs and is a receptor for plasmodium parasite, but it binds and clears angiogenic chemokines secreted by prostate tumors, preventing the tumor cells from causing angiogenesis. Mutation in DARC is a naturally selected one, seen mostly in African men, as a defense against malaria. However, this can make them more vulnerable to prostate cancer. DARC testing provides information about tumor aggressiveness in patients who are prone to prostate cancer.

Apparently, the shear moduli of RBC were amplified up to ten times during parasitic infection. Reduced deformability of P. falciparum-infected RBCs can lead to massive sequestration in microvasculature, thus crippling the prognosis, similar to the scenario seen in gastrointestinal cancer [35]. Malaria might also negatively affect the outcome of H. pylori infection [36].

It was seen that there is an inverse correlation of BL with sickle-cell anemia [16], along with HbAS conferring some protection against complications associated with malaria [37]. However, to date, no scientific reports have been available to prove this association as statistically significant [16]. More investigations are needed to fully srealise and achieve statistical significance, in these correlations.

In the pediatric population, malaria infection was found to have a higher prevalence (61%) for Kaposi's Sarcoma-associated Herpes Virus (KSHV) cases. In children and adults, increased prevalence of KSHV was associated with lower hemoglobin levels [38]. Malaria was not established to have a causal relation with febrile neutropenia in the pediatric age group with various malignancies in a zone with low malarial endemicity.

Malaria is a major issue in adults with solid organ tumors, leading to various complications and delay in treatment [39], although no concrete causal links have been established to date between malaria and solid organ malignancies.

The association of anti-malarial agents and cancer

Numerous naturally occurring anti -malarials have been proven to have anti-cancer activity [40-43]. Studies have explored the use of nanotechnology to prevent malaria and cancer with a single agent, as well as the potential anti-cancer properties of various substances, including earthworm-mediated silver nanoparticles [44] and metformin [45].

Dihydroartemisinin (DHA) triggers apoptosis in mitochondria and modifies cytokines expression by declining the phosphorylation of STAT3. DHA also causes enhancement in anti-tumor susceptibility in mice through regulating CD8+CTL work by sneutralising IL-10-mediated T-regulatory cell concealment. This could be suggested as an alternative medication for melanoma [46.] Scientific reports also show that the platelets which are activated, comprise both tumor-homing and metastasis-targeting traits via cell adhesion molecules present on thrombocytes and via VAR2CSA protein.

VAR2CSA is the malarial protein which binds to oncofetal chondroitin sulfate. This is overexpressed on cancer cells. Initiated through these, a recombinant VAR2CSA peptide (rVAR2)-modified activated platelet-mimicking nanoparticles (rVAR2-PM/PLGA-ss-HA) with an activated platelet membrane was made. These nanoparticles, after endocytosis, initiated the response to augment intracellular concentration of diminished glutathione, causing their fragmentation and the drugs to slaughter cancer cells. Hence, rVAR2-decorated enacted platelet-targeting nanoparticles with controlled drug release could be a promising conveyance procedure for the effective management of primary and metastatic cancer [47]. The red blood cells which have been infected with malaria parasite protein bind VAR2CSA to chondroitin sulfate (CS) for their placenta-specific affinity. Numerous cancers express a parallel form of CS in this manner named oncofetal CS (ofCS). The particular tropism of malaria-tainted RBCs and the distinguishing oncofetal CS could be a potential tool for targeting cancer [48]. Artemisia argyi treatment restricts both parent and gemcitabine-resistant lung cancer cells by actuating ROS, mitochondrial film sdepolarisation and apoptosis, and decreasing epithelial-mesenchymal transitions. It might be useful as a potent adjuvant to chemotherapy [49]. Conjectural administration of anti-malarials in children with febrile neutropenia is not justified. Pediatric oncologists regularly confront the hurdle of tackling febrile illnesses in immune-deficient cases. Clinicians practicing in areas endemic to malaria can rationally exploit diagnostic tools for malaria for a justified decision. [50]. Enhancement of quality of life and survival of oncology patients will be considerably improved by the evolution of highly efficacious drugs to selectively eliminate malignant cells.

Conclusion

This review suggests a possible association between multiple infections of malaria, which may later lead to development of lymphoid neoplasm. Non-hematological malignancies were shown not to have a strong correlation with malaria; however, in solid organ tumors, malaria is a major comorbidity, as observed in a few studies. In areas endemic to malaria, screening for lymphoid neoplasms would be effective for its prevention. Further comprehensive study is needed in other endemic areas like South India to assess the risk of malaria and neoplasms as most of the reviewed literature was done in Sub-Saharan nations. It was observed that anti-malarial agents had anti-tumor effects, and effective treatment of malaria may prevent malignancies. Activated platelets using modified malarial protein, exhibited metastasis-targeting properties. There is probability for

innovative therapies in the field of parasitology, including possible cancer treatment. Moreover, scientific reports also show the indication of anti-malarial medicines being cytotoxic to various human cancer cell lines. However, though it was effective, only a few clinical studies were conducted. In-depth research in this field on molecular level, xenograft models and human cancer cell lines could help in the robust treatment targets using anti-malarial drugs as a therapeutic approach to cancer therapy with safety and efficacy.

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All authors declared no conflicts of interest.

Declarations Author contribution statement
Adarsh Sugathan- Contributed to conception, data collection, analysis, writing of original draft, editing and finalising the version to be submitted.
Shamathmika Rao- Contributed to writing the original draft, editing, and finalising the version to be submitted.
Nayanatara Arun Kumar- Contributed to the conception of the study, supervised, analysed, wrote the original draft, edited, and finalised the version to be submitted.
Pratik Kumar Chatterjee- Contributed to the supervision of the study, edited and finalised the version to be submitted.
All authors have read and approved the final version of the manuscript to be submitted.

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Data accessibility statement
The datasets generated and analysed during the current study are available from the corresponding author upon reasonable request to the corresponding author.

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