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Hematologic Complications of Tick Bites and Tick-Borne Illness: A Brief Narrative Review

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ABSTRACT

Introduction: Tick-borne illnesses are rising in the United States, and tick bites can result in hematologic complications including anemia, thrombocytopenia, pancytopenia, and even life-threatening sequelae like disseminated intravascular coagulation. While case reports and brief reviews exist for specific ticks, there is a lack of review on the known hematologic complications after various tick-borne illnesses.

Methodology: This narrative review examined over twenty articles on hematologic complications of tick-borne illnesses published from 2000 onwards. A comprehensive search of electronic databases, including PubMed and Google Scholar, was conducted to identify relevant literature published between 2000 and 2024. Inclusion criteria comprised articles available in English and those describing hematologic consequences of tick-borne illnesses. Exclusion criteria included duplicates, unpublished works, and studies not directly related to the topic. A total of over twenty articles were screened based on title and abstract for eligibility.

Discussion: Tick bites can cause various hematologic complications, including anemia, leukopenia, thrombocytopenia, pancytopenia, and disseminated intravascular coagulation by various mechanisms. While it can cause marrow suppression, tick bites can also cause leukocytosis. Clinically, patients can present with profuse bleeding or bruising in some cases or severe diseases like disseminated intravascular coagulation. Workup for these various hematologic pathologies can include complete blood counts and peripheral blood smears.

Conclusions: Early identification of hematologic abnormalities related to tick-borne illnesses can be important for clinical management.

Introduction

Tick-borne illnesses are increasing in incidence in the United States, and diagnosis can be challenging given many do not recall a tick bite in the history.[1] Part of the rising number of cases may be related to increasing rates of certain tick-borne illnesses in older adults secondary to age-related decline in immunity, as is reported regarding babesiosis in the literature.[2] Regarding diagnosis of tick-borne disease, initial symptoms can be similar and nonspecific, and diagnostic tests may have poor sensitivity early in a tick-borne illness course. Untreated disease can result in various lab abnormalities, including hematologic sequelae, as ticks are hematophagous parasites.[1,3]

While hematologic sequelae have been reported in the literature, there remains a lack of a comprehensive review of hematologic complications of tick-related infections. The aim of this article is to provide a comprehensive review of hematologic complications associated with tick-borne illnesses. More specifically, we seek to provide a resource summarizing understanding of the hematologic consequences encountered in patients with tick-borne illnesses, facilitating early recognition, accurate diagnosis, and optimal management of these potentially life-threatening complications.

This project was designed as a narrative review. A literature review was performed for articles related to hematologic complications of tick-borne illnesses. PubMed and Google Scholar were used to search for articles published between 2000 and 2022. The followed keywords were utilized: "tick-borne, tick bite, hematologic, complications."

We surveyed articles and information published between 2000 and 2024, published works that were available in English, and articles describing hematologic complications of tick-borne illnesses. Exclusion criteria included duplicates, unpublished works, or works not related to the topic at hand. See Figure 1 for details regarding the query, study selection, and exclusion criteria for the literature review. Over 25 articles were reviewed for the creation of the narrative review, with 20 total articles used to provide this brief review.

Our article aims to highlight some of the hematologic consequences of tick-borne illnesses based on the most recently published literature and provide a useful resource to help guide further research and clinical management. Delineation of some of these resulting hematologic feature can guide future research into diagnostic frameworks and initial workup to help quickly identify these possibly deadline complications.

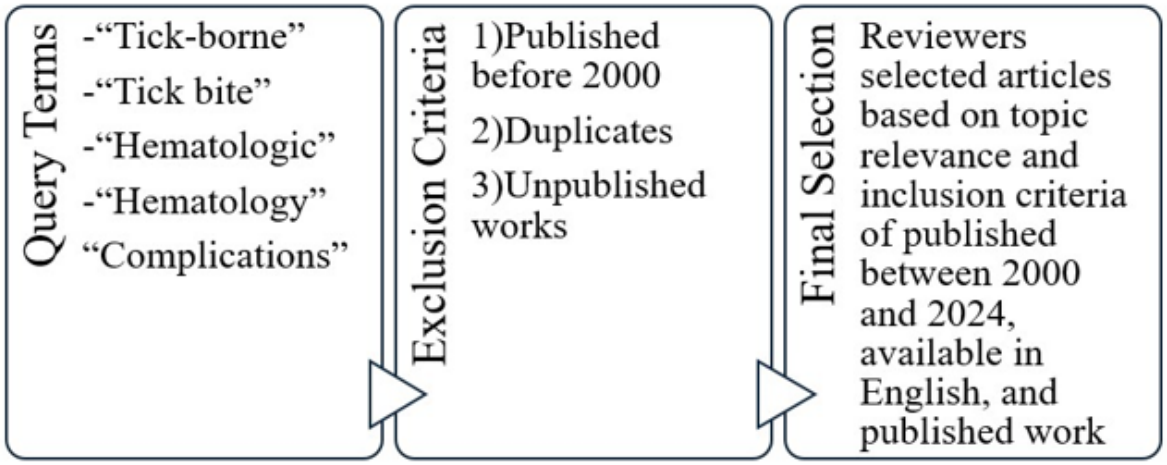

Figure.1 Details regarding the query, study selection, and exclusion criteria for the literature review.

A BRIEF INTRODUCTION TO TICK-BORNE ILLNESSES AND SUBSEQUENT HEMATOLOGIC SYNDROMES

Ticks can transmit bacterial, viral, and parasitic pathogens. Diseases caused by ticks include Lyme disease, human granulocytic anaplasmosis, human monocytic ehrlichiosis, babesiosis, B. mayonii infection, B. miyamotoi infection, tick-borne encephalitis, Crimean-Congo hemorrhagic fever, severe fever with thrombocytopenia, Heartland virus disease, E. ewingii infection, Powassan encephalitis, Bourbon virus disease. Understanding the various hematologic presentations these illnesses can have may help clinicians quickly identify and treat them.

ANEMIA

Anemias can be found across a variety of tick-borne illnesses, such as with ehrlichiosis.[4] Mild anemia has also been reported in cases of human anaplasmosis.[4] Mild cases of anemia were reported in a study of hematologic parameter changes related to African tick bite fever.[5] Severe anemia can also result from tick-borne illnesses, including relapsing fever as was diagnosed in several cases in the Middle East give hematologic lab abnormalities including severe anemia.[6] Babesiosis can also result in severe anemia.[7]

One etiology of anemia in patients with tick-borne illnesses includes hemolytic anemia. For example, babesiosis can result in a hemolytic anemia through protozoal invasion of human erythrocytes with subsequent lysis.[8] As a result of hemolysis, patients can present with hematuria and jaundice.[8]

LEUKOPENIA

Leukopenia is a known possible consequence of of tick-borne illnesses. For example, leukocyte counts are reported to have dropped to a nadir noted around day 5 or 6, with subsequent count rising around day 11-14 in a study of African tick bite fever.[5] During the first ten days of illness with African tick bite fever, leukopenia was

noted in 8.8% of patients in one study.[5] One systemic review found low leukocyte counts in over 30% of cases of Rickettsia africae that were reviewed.[9]

This low cell count can also be seen in ehrlichiosis, specifically in human monocyte ehrlichiosis caused by Ehrlichia chaffeensis with findings notable as early as one week into the disease course as well as disease from Ehrlichia ewingii.[4] In some cases, the pancytopenia associated with ehrlichiosis has resulted in bone marrow biopsies, which are typically normocellular or hypercellular.[4,10] Human anaplasmosis, or human granulocytic anaplasmosis, can also cause leukopenia.[4]

More specifically, lymphopenia can also result secondary to tick borne illnesses, including the African tick bite fever and Ehrlichia muris-like agent ehrlichiosis.[4,5] Cases of leukopenia have also been reported in human granulocytic anaplasmosis from blacklegged tick bites.[11]

Regarding pathophysiology, in studies of bone marrow in patients with severe fever with thrombocytopenia syndrome (SFTS), changes in bone marrow noted on patients noted heteromorphic lymphocytes and hemophagocytosis, which was reported to be more prevalent in patients who did not survive compared to those who did survive in a study of mortality of SFTS.[12]

LEUKOCYTOSIS

Leukocytosis can also result from tick-borne illnesses. Leukocytosis was found in 3.2% of patients with African tick bite fever in one study of hematologic sequelae related to the infection.[5] Regional lymphadenopathy has also been reported with African tick bite fever.[9] Additionally, cases of Rocky Mountain spotted fever have also had normal to slightly increased white blood cell counts but with increased immature neutrophils.[4]

THROMBOCYTOPENIA

Thrombocytopenia is also a known possible consequence. Unfortunately, though, thrombocytopenia can contribute to mortality and morbidity in patients with tick-borne illnesses.[3] Various infections have been described with concurrent thrombocytopenia. Severe fever with thrombocytopenia syndrome was first described in 2010 and is a hemorrhagic fever that is caused by a phlebovirus.[13] It was first described in rural China but has had reported cases in other countries including Korea and Japan and has a known complication of thrombocytopenia.[13] The average case fatality rate of the virus is 7.3%.[13] Rocky Mountain spotted fever, rickettsiosis, human anaplasmosis and ehrlichiosis can also result in thrombocytopenia.[4] More specifically, thrombocytopenia has been reported to be more notable as disease advances in tick-borne illnesses.[4]

In one case of human granulocytic anaplasmosis from a tick in North America, an important part of workup was evaluation of immunoglobulin G-specific antibiotics on immunofluorescence assay. Of note, this patient presented with tachycardia with further evaluation showing anemia, thrombocytopenia as well as leukopenia with lymphopenia.[11] Smear evaluation and laboratories studies were used to rule out other etiologies of the patient's presentation, which was arguably important in ultimately establishing the diagnosis.[11] Treatment with doxycycline resulted in improvement in thrombocytopenia in the aforementioned case.[11]

Babesiosis can also result in parasitemia which has been reported to result in thrombocytopenia, with one case report discussing thrombocytopenia to the 60,000-range secondary to parasitemia from babesiosis discovered on a peripheral smear.[14]

Cases of thrombocytopenia in tick-borne illnesses can be acquired in their pathophysiology, such as in cases of primary immune thrombocytopenia (ITP) after tick bites. Rocky Mountain spotted fever has been reported to be an inciting factor for cases of ITP in the literature.[15] The pathophysiology of this is hypothesized to be related to molecular mimicry, as infection may result in amino acid sequences that may be structurally similar to regions of platelet glycoproteins, so antibodies directed against the pathogen may result in thrombocytopenia through cross-reaction with the glycoproteins.[15]

Beyond acquired pathophysiology, the pathogenesis has been reported to be related to hypo-proliferation from the marrow, hypersplenism, consumption due to widespread endothelial damage, and consumption due to disseminated intravascular coagulation.[3] Decreased production can be a result morulae and granuloma infiltration in the marrow of patients with pancytopenia, such as in cases of ehrlichiosis.[3] Direct invasion of platelets can also occur, such as with Ehrlichia platys infections and Lyme disease.[3]

Sequelae of infection-related thrombocytopenia includes serious thrombosis, profuse bleeding and, ecchymoses.[3] Some of these have been seen in Crimean-Congo hemorrhagic fever and in babesiosis occasionally.[3]

PANCYTOPENIA

Acute pancytopenia may also be the presenting hematologic sequela of tick-borne illnesses. In cases where patients present with acute pancytopenia, the differential is initially broad, including other infections such as HIV, EBV, CMV, drug side effects, nutritional deficiencies, bone marrow infiltration from another progress, or new hematologic primary pathology.[16,17] Pancytopenia may be due to the production of chemokines that are myelosuppressive, resulting in decreased proliferation and differentiation in the bone marrow.[17]

One case in the literature reports a tick-borne illness treated with doxycycline trial presenting with acute pancytopenia, which is an atypical initial presentation of tick-borne disease, in a patient with known Lyme disease, which very rarely causes pancytopenia independently but has been reported to do so in setting of co-infection.[16] Bone marrow analysis in this case showed reactive but non-specific changes.[16] The patient was empirically treated for suspected tick-borne disease with doxycycline with improvement.

Blood smears should be considered in evaluation of patients with new-onset acute pancytopenia as part of the diagnostic workup, given that pancytopenia is generally less frequently encountered as a presenting pathology compared to other hematologic complications

like hemolytic anemia.[17] Of note, a lack of organism of the peripheral smear does not totally rule out parasitic illness as an etiology, as morulae are only detected in about 60% of cases of anaplasmosis, for example.[18]

DISSEMINATED INTRAVASCULAR COAGULATION

DIC is a serious and potentially deadly sequala of tick-borne illnesses. Severe fever with thrombocytopenia syndrome can result in disseminated intravascular coagulation (DIC) with multi-organ dysfunction.[12] One study of non-survivors with severe fever with thrombocytopenia syndrome found that they had increased prothrombin times, activated partial thromboplastin time, and lactate dehydrogenase compared to those that survived.[12] Disseminated intravascular coagulation has also been reported in cases of CCHF, with one woman presenting with DIC and reporting a tick bite several days prior with post-mortem analysis via PCR showing significant viral load of the CCHF virus.[19]

DIC and rarely hemophagocytic lymphohistiocytosis has been reported in cases of babesiosis. Treatment includes red blood cell exchange apheresis in some cases. Research on babesiosis causing DIC, which has been predominantly in animal and veterinary studies, has suggested that the Babesia species enters and shears cells, causing erythrocyte sludging and can result in hypoxic injury and vascular endothelial damage.[20] This then stimulates the intrinsic clotting pathway.[20] Additionally, mechanical destruction of invaded erythrocytes can result in intravascular hemolysis, which leads to the release of thromboplastin and activates the extrinsic clotting pathway.[20] Thromboplastin release causing DIC is also related to platelet injury.[20] Finally, there may be a contribution of reticuloendothelial system blockade resulting in DIC.[20] In summary, there are several mechanisms that may be contributing on a pathophysiologic level to DIC related to babesiosis.

Rocky Mountain spotted fever has also been reported to present with DIC, with symptoms of this tick-borne illness usually starting five to seven days after the tick bite occurs.[21] Patients may initially present with a rash, but it is imperative to remember this possible deadly consequence of the illness. If there is clinical concern for Rocky Mountain spotted fever, literature suggests that treatment with doxycycline should be started within five days of symptom onset.[21]

Tick-borne hemorrhagic fevers can also result in DIC.[22] Tick-borne hemorrhagic fevers can be caused by infection tick bites and crushing infected ticks as well as direct contact with blood or tissues that are infected with the virus.[22] These syndromes can be marked by fevers and general malaise but can have other significant exam findings such as hepatomegaly, petechiae and purpura in the days following that may reflect another worrisome process occurring.[22] In terms of diagnosis, it is important to consider evaluation of hemoglobin, platelet count, coagulation studies, and fibrinogen in patients with tick bites and signs or symptoms that might suggest DIC.[23] Although it is overall reported to be rare with some tick borne illnesses like babesiosis, keeping DIC on the differential in patients with new physical exam findings and recent tick bites or tick-borne illnesses can help guide further investigation into this potentially deadly complication.[24]

IMPLICATIONS IN THE CLINICAL SETTING

As discussed, there are several hematologic sequelae that can result from tick-borne illnesses. Based on our findings and review of the literature, important steps in evaluation for suspected tick-borne hematologic pathologies can include not only complete blood counts but peripheral blood smears. The ruling out of other pathologies by peripheral smear and laboratories studies can be an important part of the diagnostic workup.[11] Quick identification and management can be important in hematologic pathologies related to these illnesses, in life-limiting sequelae like pancytopenia and DIC.

Limitations

While this review provides information on the various known hematologic sequelae of tick-borne illnesses, there are limitations to the current review. First, the review was conducted as a narrative rather than systematic review of the literature, and a systematic review would have a more rigorous and detailed methodology to literature search; therefore, some articles or studies that cover the topic in question may not be included. Further work in this area could include a systematic review to better understand the entire literature of the subject matter. Additionally, our article encompasses a surveying of articles over the last two decades, and systematic review with more specific methods might provide a more comprehensive encompassment of the entire landscape of the literature.

Conclusion

Tick-borne illnesses can have several hematologic consequences, including anemia, thrombocytopenia, and pancytopenia. Complications of this can be life-threatening if not identified and treated. Early recognition and treatment of the etiology and management of these can help guide clinical management of both the hematologic pathology and of the tick-related disease, especially since there has been increased presence of ticks since the start of the twentieth century.[25]

Conflict of Interest:

The authors have no conflicts of interest to declare.

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