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PERSPECTIVE

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Scurvy: A treatable forgotten fatal differential diagnosis and potential etiology of leukemia and aplastic anemia in pediatric population

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Abstract

Scurvy is a rare nutritional deficiency disease which is less likely to be suspected and it mostly lead to delayed diagnosis. It can present with features which can mislead clinicians to misdiagnose the condition as leukemia or aplastic anemia. This can subject patients to the wrong management which leads to poor outcome and increased preventable morbidity and mortality. Vitamin C deficiency is still prevalent among pediatric population even in the modern days and should no longer be considered as historical condition. Chromosomal fragility has been greatly accounted for the development of leukemia and aplastic anemia secondary to various triggers. The role of vitamin C toward DNA stability, prevention, and control of mutations have been documented. Vitamin C plays a vital role in hematopoiesis by controlling regulation and prevent dysfunction of hematopoietic stem cells. Scurvy deficiency has been a silent growing clinical problem which needs a high index of suspicion for a clinician to pick it. It should be considered as one among potential differential diagnosis of leukemia and aplastic anemia especially in the pediatric population. History of any dietary restriction should be obtained and addressed properly. Serum vitamin C should be among the essential laboratory workout in diagnosis of both leukemia and aplastic anemia. All patients suspected to have such conditions should be screened and supplemented for vitamin C deficiency irrespective of positive confirmatory test results of leukemia or aplastic anemia since the probability of co-occurrence is likely also. Moreover, studies should be conducted to explore the clinical link, if any, between vitamin C deficiency or insufficiency and development of leukemia and aplastic anemia among the pediatric population given its physiological and genomic role in hematopoiesis. Furthermore, the potential pharmacological therapeutic use of vitamin C in treatment of leukemia and aplastic anemia should be determined clinically.

KEYWORDS

aplastic anemia, leukemia, pediatric, Scurvy, vitamin C

1 | INTRODUCTION

Globally, leukemia and aplastic anemia cases among pediatric population have been reported to increase abruptly recently in different regions especially in sub-Saharan countries including Tanzania[1,2] This increase poses epidemiological implications of either there has been an increase of exposure factors, increase of hosts' susceptibility to develop such conditions or both. On the other hand, improved healthcare provision and awareness of such conditions might have enabled more patients to seek for healthcare services, hence increase in statistics of the conditions.

Moreover, the clinico-pathological manifestations similarity of other conditions like scurvy which can mimic such conditions or co-occurrence of vitamin C deficiency as the etiological factor might have confounded such an abrupt increase of cases recently. Scurvy is a rare nutritional deficiency disease which is less likely to be suspected and it mostly lead to delayed diagnosis.[3] In some circumstances when severe, can present with features which can mislead clinicians to diagnose the condition as leukemia, aplastic anemia, coagulopathies, septic arthritis, rheumatoid diseases, osteomyelitis or as other malignancy cases.[4–6] These misdiagnoses subject patients to the wrong management which leads to poor outcome and increased preventable morbidity and mortality.

Vitamin C deficiency is still prevalent among pediatric population even in the modern days and should no longer be consider as a historical condition.[3,7–9] A study in Mexico in 2014 among school-aged children, revealed that 38% and 23% had hypovitaminosis C and vitamin C deficiency respectively.[10] Dietary restriction in conditions like avoiding restrictive food intake disorder (ARFID) is one among factors which predispose children to develop scurvy.[6,7,11] Scurvy has been found to exist even in healthy children with no apparent risk factors even living in wealthy families.[3,12] While the treatment of scurvy is simple with good prognosis just within few days, treatment of leukemia and aplastic anemia is very expensive, with more treatment complications, very demanding to both clinician and a patient and most of the time with poor prognosis especially in low resource settings.[3,13,14] Fortunately, in pediatric population, vitamin C supplementation even at higher doses have showed no to very few tolerable adverse effects.[15]

This perspective article highlights on why there is a need for screening and supplementing for vitamin C among suspected cases of leukemia and aplastic anemia in a pediatric population so as to enhance better outcomes in management of such patients in case of independent or co-occurrence with vitamin C deficiency.

1.1 | Vitamin C and hematopoiesis

Hematopoiesis refers to the physiological process which results into formation of blood cellular components from hematopoietic stem cells (HSC) in the bone marrow since embryonic development and throughout life.[16] These components involve 10 blood lineages which are erythrocytes, platelets, neutrophils, eosinophils, basophils, monocytes, T and B lymphocytes, natural killer cells, and dendritic cells.

Vitamins like vitamin C are essential during hematopoiesis.[17] Vitamin C plays a pivotal role in differentiation of progenitor cells in hematopoiesis since embryonic development and is required to sustain the process especially during cellular stress conditions.[18] Vitamin C deficiency impair hematopoiesis significantly and cause hypo-cellular bone marrow which is associated with dysfunction and reduction in HSCs, multipotent progenitors, and hematopoietic progenitors.[18,19] Vitamin C supplementation have been found to suppress and reverse this effect.[18,19]

2 | LEUKEMIA AND APLASTIC ANEMIA CLINICO-PATHOLOGICAL MIMICRY OF VITAMIN C DEFICIENCY

Scurvy can present with similar manifestations as in autoimmune conditions, infections, and different anaplastic conditions in terms of clinical, histopathological, hematological, and imaging findings.[20] In pediatrics, scurvy can present with several symptoms like fever, generalized body malaise, lack of appetite, abdominal pain, vomiting, irritability, musculoskeletal complaints (such as generalized or localized myalgia and arthralgia mostly in lower limbs, limping, refusal to walk), mucosal involvement which presents with gingival bleeding and hyperplasia, epistaxis, pulmonary symptoms, cutaneous lesions like ecchymosis, petechiae, perifollicular hemorrhage, hyperkeratosis, dry skin, psychological changes (including hypochondriasis), corkscrew hair, nail findings such as koilonychia and splinter hemorrhages and poor wound or ulcer healing occasionally.[3,8,21] Gastrointestinal bleeding cases secondary to scurvy has been reported more in adult compared to pediatric population.[21] While bleeding tendencies in scurvy is secondary to thrombocytopenia and impaired collagen production which lead to blood vessels incompetence,[3,20] in leukemia and aplastic anemia is mainly secondary to thrombocytopenia.[13,14]

On addition to some of the fore-mentioned clinical manifestation, hematological features like pancytopenia, imaging, and histological findings like osteopenia and bone marrow hypo-cellularity or hyper-cellularity are mostly among the key diagnostic features of leukemia and aplastic anemia.[13,14] Surprisingly, the same features of pancytopenia, osteopenia, bone marrow hypo-cellularity, or hyper-cellularity has been reported in scurvy patients. One case report documented a scurvy case which mimicked acute leukemia with pancytopenia in a 14-year-old boy.[6] Another one reported a scurvy case with myelodysplastic syndrome (MDS)-like bone marrow manifestations with pancytopenia and bone marrow hypo-cellularity.[22] Another scurvy case of a 17-year-old child presented with pancytopenia and bone marrow hyper-cellularity.[23] A case report of a 15 years old female with scurvy reported gelatinous bone marrow transformation with MRI findings of dark T1 and bright T2 signals which were consistent with leukemia or lymphoma diagnosis.[24]

In the review article discussing 15 articles which included 166 pediatric scurvy cases which were published between 2000 and 2015, it was reported that[3]: 11 articles reported the delay of diagnosis from clinical manifestation ranging from 2 weeks to 2 years, 18% of patients underwent invasive diagnostic exams include bone marrow aspiration and biopsy, bone and muscle biopsy, and lumbar puncture. One or more than one provisional misdiagnosis was made before reaching the scurvy diagnosis. At first, among other misdiagnoses, of 52% and 10% were misdiagnosed as oncological conditions of leukemia and bone neoplasia respectively based on clinical manifestation, hematological, histopathological, laboratory, and imaging investigations.

3 | VITAMIN C GENOMIC INFLUENCE ON LEUKEMIA AND APLASTIC ANEMIA DEVELOPMENT

Chromosomal fragility has been greatly accounted for the development of leukemia and aplastic anemia secondary to various triggers.[13,14] This genetic instability makes host cells susceptible to develop the conditions under different environmental factors. Occurrence of leukemia likelihood increases in patients with pre-existing bone marrow damage as in aplastic anemia and cases of leukemia which presented as aplastic anemia at first in pediatric and adult have been documented.[25–29] Different culprits such as exposure to ionized radiations, infections, chemotherapy, benzene exposure, and congenital genetic defects can trigger and induce mutagenic changes to susceptible genes in the bone marrow.

One study on the genetic features of myelodysplastic syndrome and aplastic anemia in pediatric and young adult patients revealed pathological mutations were found in DKC1, MPL, and TP53 genes among the aplastic anemia (AA) cohort, and in FANCA, GATA2, MPL, RTEL1, RUNX1, SBDS, TERT, TINF2, and TP53 among the myelodysplastic syndrome (MDS) cohort while only 5.1% of AA and 13.6% of MDS patients carried mutations in known inherited genes.[30] Acquired mutations play a big role. The study identified the failure to determine ascertainment of pathogenicity for a given variant as one among the challenges in genetic studies.

Despite the fact that evidence are still accumulating, the possibility of long-term vitamin C deficiency to induce genetic changes and trigger phenotypical presentations for those already with inborn genetic mutation susceptibility should not be underestimated when dealing with genetic changes related diseases like leukemia and aplastic anemia. The role of Vitamin C toward DNA stability, prevention, and control of mutations have been documented. It has been reported to enhance epigenetic regulation of genomic stability through promotion of DNA methylation by complementing the activity of ten-eleven translocation (TETs) enzymes as their co-factor.[31,32]

Dysregulation of DNA methylation cause aberrant stem cell function and cellular transformation since it plays a crucial role toward hematopoiesis in controlling proper HSC regeneration and lineage differentiation.[33] Studies have shown that vitamin C regulates HSC activity and suppresses leukomogenesis by modulating TETs functioning.[18,34] It was found also that restoration of TETs functioning by vitamin C treatment blocks aberrant self-renewal and leukemia progression.[35] This makes vitamin C to be among potential pharmacological therapeutic agents in fighting leukemia, other hematological disorders like aplastic anemia and various cancers which involves dysregulation of DNA methylation.[34,36–39]

Moreover, one study showed that Vitamin C supplementation of 1 g daily reduced significantly bleomycin-induced chromosomal damage in lymphocytes.[40] Moreover, Vitamin C have been found to prevent DNA mutation secondary to oxidative stress exposure.[41,42]

3.1 | Potential benefits of vitamin C supplementation in leukemia and aplastic anemia

Vitamin C supplementation has been found to alleviate cancer and chemotherapy related symptoms like fatigue, insomnia, loss of appetite, nausea, pain and improve overall health including cognitive, physical, emotional and social functioning.[43] These symptoms are prevalent also among leukemia and aplastic anemia patients who are on or not in treatment. However, in case of misdiagnosis or co-occurrence of scurvy and leukemia or aplastic anemia, vitamin C supplementation might reduce both morbidity and mortality and improve clinical manifestations of anemia among these patients.

Moreover, vitamin C plays a vital role in modulating immune system and have shown to possess the ability to act as a broad spectrum antimicrobial agent against both bacterial, viral, parasitic, and fungal infections even with resistant strains.[44] Since there is immune suppression aspect in both leukemia and aplastic anemia condition as the consequences of both the disease and the treatment of the conditions using immunosuppressive agents, vitamin C supplementation will enhance immunity and protection against infection. This might reduce the extensive prophylactic use of antimicrobials in such patients.

4 | CONCLUSION AND RECOMMENDATION

Scurvy or vitamin C deficiency has been a silent growing clinical problem which needs a high index of suspicion for a clinician to pick it up especially in conditions which resembles it in clinical manifestations. It should be considered as one among potential differential diagnoses of leukemia and of both inherited and acquired aplastic anemia especially in the pediatric population. History of any dietary restriction should be obtained and addressed properly. All patients suspected to have such conditions should be screened for vitamin C deficiency irrespective of positive confirmatory test results of leukemia or aplastic anemia since the probability of co-occurrence is likely also given the genetic influence of vitamin C at the DNA

level. Hence, serum vitamin C should be among leukemia and aplastic anemia essential workout panels or laboratory investigations.

Ruling out vitamin C deficiency by testing or supplementing empirically all suspected or confirmed patients with different hematological conditions will not only reduce overtreatment and unnecessary side effects of drugs but also will prevent patients from developing into critical condition and death in case it is scurvy or co-occurrence.

In clinical settings where serum vitamin C levels can't be checked, empirical treatment with scurvy dose (100 mg thrice a day) can be initiated for a month while the patient is under the standard management of a confirmed or suspected leukemia, aplastic or fanconi anemia diagnosis. Despite the fact that vitamin C have shown to possess no to mild toxicity even at high doses in pediatric population, even with the assumption that the supplemented patients have no deficiency, still vitamin C supplements will be helpful in improving the patients' immunocompromised and other clinical symptoms presented in leukemia and aplastic anemia.

Moreover, studies should be conducted on the prevalence of vitamin C deficiency among patients diagnosed with leukemia and aplastic anemia and to explore the clinical link between vitamin C deficiency or insufficiency and development of leukemia and aplastic anemia among the pediatric population given its physiological role in hematopoiesis, enhancement of DNA stability, prevention and control of mutations. The genetic and histopathological influence of vitamin C to the bone marrow suggests the pathophysiological possibility of vitamin C deficiency etiological link toward development of different hematological conditions like leukemia and aplastic anemia. Furthermore, the potential pharmacological clinical use of vitamin C in treatment of leukemia and aplastic anemia should be investigated.

AUTHOR CONTRIBUTIONS

Harold L. Mashauri: Conceptualization; data curation; methodology; project administration; supervision; validation; writing—original draft; writing—review and editing.

CONFLICT OF INTEREST STATEMENT

The author declares no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study. Data are available on request from the authors.

TRANSPARENCY STATEMENT

The lead author Harold L. Mashauri affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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