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Letter to Editor (Pages: 137-141)

Risks of Corticosteroid Administration Before Diagnosis in Children With Suspected Hematologic Malignancies: A Clinical Warning

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Abstract,

Childhood hematologic malignancies, particularly acute lymphoblastic leukemia (ALL) and lymphomas, may present with nonspecific symptoms such as fever, pallor, fatigue, bone or limb pain, bruising, petechiae, lymphadenopathy, hepatosplenomegaly, or cytopenias, often mimicking benign infectious, rheumatologic, or immune conditions. Empirical systemic corticosteroid administration before completion of the diagnostic evaluation may mask symptoms, reduce circulating blasts, delay diagnosis and referral, and compromise diagnostic tissue yield in suspected lymphoma. In children with a high tumor burden, corticosteroid-induced cell lysis may also precipitate tumor lysis syndrome. Children with red-flag features should undergo prompt complete blood count with differential, peripheral blood smear examination, and timely referral to pediatric hematology-oncology before corticosteroid initiation. This caution does not apply to life-threatening emergencies or protocol-directed steroid prephase therapy after diagnostic confirmation.

Key Words: Acute lymphoblastic leukemia, Corticosteroids, Delayed diagnosis, Hematologic neoplasms, Pediatric oncology.

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Dear Editor,

Corticosteroids are essential components of standard treatment protocols for acute lymphoblastic leukemia (ALL) and many childhood lymphomas (1, 2). However, empirical corticosteroid administration before completion of the diagnostic workup in children with suspected hematologic malignancy represents an important and potentially preventable diagnostic pitfall. The marked sensitivity of malignant lymphoid cells to glucocorticoids means that even a short course of prednisolone or dexamethasone may temporarily alter the clinical presentation, suppress symptoms, and complicate interpretation of initial findings (3).

Acute leukemia and lymphoma in children do not always present with classic features. Fever, pallor, fatigue, bruising, mucosal bleeding, bone or limb pain, lymphadenopathy, and hepatosplenomegaly are frequent manifestations of childhood hematologic malignancies. A systematic review and meta-analysis of childhood leukemia presentations found that more than half of affected children had hepatomegaly, splenomegaly, pallor, fever, or bruising at diagnosis. Limb pain, fatigue, lymphadenopathy, bleeding or petechiae, and recurrent infections were also relatively common presenting features (4).

In clinical practice, these symptoms may be attributed mistakenly to viral illness, juvenile idiopathic arthritis, other rheumatologic disorders, growing pains, inflammatory conditions, or immune thrombocytopenia. Bone or musculoskeletal pain due to marrow involvement may improve temporarily after corticosteroid exposure; however, such improvement does not confirm a benign or inflammatory diagnosis. Instead, it may create false reassurance for clinicians and families and delay essential investigations, including repeat complete blood count testing, peripheral blood smear review, lactate dehydrogenase measurement, bone marrow evaluation, and referral to pediatric hematology-oncology services (5, 6).

Corticosteroids may cause a transient decline in circulating blasts and alter peripheral blood counts. Therefore, a normal or near-normal complete blood count after corticosteroid exposure does not exclude leukemia, particularly in a child with persistent bone pain, prolonged fever, progressive fatigue, unexplained bruising or bleeding, weight loss, lymphadenopathy, or hepatosplenomegaly. Laboratory findings should be interpreted in the context of clinical history, physical examination, peripheral smear findings, and the overall clinical course, rather than temporary symptomatic improvement alone (4–6).

Another important concern is the potential reduction in diagnostic yield in suspected lymphoma. In children with a mediastinal mass, persistent lymphadenopathy, or an accessible lymphoid mass, corticosteroid administration before biopsy may reduce tumor size, induce necrosis or apoptosis in malignant cells, and disrupt tissue architecture. In a retrospective study of 86 children with mediastinal lymphoma, 23 received corticosteroids before biopsy because of concern for cardiorespiratory compromise. Among these 23 children, prebiopsy corticosteroid exposure was associated with delayed definitive diagnosis, failure to establish a diagnosis, or difficulty in staging in 5 cases (7).

Nevertheless, this observation should not be interpreted as an absolute contraindication to corticosteroid administration in all circumstances. In a child with a mediastinal mass and respiratory distress, impending airway obstruction, superior vena cava syndrome, substantial pericardial effusion, or hemodynamic instability, delaying treatment may be life-threatening. In such situations, the decision to administer corticosteroids should be made urgently by a multidisciplinary team, including pediatric hematology-oncology, surgery, anesthesia, radiology, and pathology specialists. Whenever feasible, the safest and most rapid diagnostic tissue sample should be obtained before or contemporaneously with treatment initiation (7).

The risk of tumor lysis syndrome should also be considered. Glucocorticoids have cytolytic effects on malignant lymphoid cells and may accelerate cell breakdown in children with high tumor burden, marked leukocytosis, bulky mediastinal disease, aggressive lymphoma, or renal dysfunction. Tumor lysis syndrome may result in hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and

acute kidney injury. Therefore, corticosteroids should be initiated with considerable caution in children with a strong clinical suspicion of leukemia or lymphoma when risk assessment, appropriate hydration, baseline laboratory testing, and close monitoring are unavailable (8, 9).

An additional concern is the effect of corticosteroid exposure before diagnosis on the initial evaluation of ALL. In some ALL protocols, early steroid response contributes to assessment of treatment response and risk stratification. Consequently, corticosteroid exposure outside a treatment protocol may influence the presenting white blood cell count, peripheral blast count, and interpretation of early treatment response. However, available evidence does not indicate that prior corticosteroid exposure necessarily or independently results in inferior survival or a higher relapse rate. In a Children's Oncology Group report of children with B-cell ALL, after appropriate adjustment of risk stratification and treatment assignment, no significant difference in event-free survival or overall survival was observed between children with and without prior corticosteroid exposure. Although minimal residual disease positivity at the end of induction was more frequent in the steroid-pretreated group when assessed using a more sensitive threshold, final outcomes were comparable after appropriate treatment modifications (3).

Accordingly, concern regarding corticosteroid administration before diagnosis should not rest on the categorical assertion that it inevitably causes drug resistance or worsens survival. More clinically relevant concerns include masking of disease manifestations, distortion of the initial assessment of disease burden, reduction in diagnostic tissue quality, and interference with risk classification. These issues are particularly important in non-specialist settings, where children may receive empirical corticosteroids for fever, musculoskeletal symptoms, bruising, thrombocytopenia, or presumed inflammatory disorders before referral to pediatric hematology-oncology services.

Children with thrombocytopenia presumed to have immune thrombocytopenia (ITP) also require careful distinction between typical and atypical presentations. In typical ITP, characterized by isolated thrombocytopenia, an otherwise normal physical examination, and no warning signs, routine bone marrow examination is not required. However, unexplained anemia, neutropenia or other cytopenias, an abnormal peripheral smear, bone pain, persistent fever, weight loss, lymphadenopathy, hepatosplenomegaly, or poor general condition should raise concern for marrow malignancy or other important alternative diagnoses. In these circumstances, further evaluation and, when appropriate, urgent pediatric hematology-oncology consultation should precede corticosteroid treatment (10, 11).

To reduce inappropriate early corticosteroid administration, we recommend that primary care clinicians, emergency physicians, pediatricians, rheumatologists, and other frontline healthcare professionals consider the following measures:

1. In any child with persistent or nocturnal bone pain, limping, prolonged fever, pallor, progressive fatigue, weight loss, petechiae, unexplained bruising, mucosal bleeding, lymphadenopathy, or hepatosplenomegaly, a complete blood count with differential and careful peripheral blood smear examination should be performed (4–6).
2. The presence of cytopenias affecting more than one cell line, blasts or abnormal cells on the peripheral smear, markedly elevated lactate dehydrogenase, elevated uric acid, hepatosplenomegaly, atypical lymphadenopathy, refractory bone pain, or constitutional symptoms should prompt deferral of systemic corticosteroids and urgent specialist assessment (4, 6, 8, 9).
3. In a child with apparent ITP, any atypical finding in the history, physical examination, or laboratory evaluation should prompt consideration of leukemia or another marrow disorder. Conversely, fully typical ITP should be managed according to established ITP guidelines (10, 11).
4. In suspected mediastinal lymphoma, diagnostic tissue should be obtained before corticosteroid treatment whenever this can be done safely. However, in the presence of immediate cardiorespiratory compromise, stabilization of the life-threatening condition

through multidisciplinary decision-making takes priority over preservation of the complete diagnostic algorithm (7).

5. Steroid prephase therapy in ALL, administered after diagnostic confirmation and risk assessment within a formal treatment protocol, differs fundamentally from empirical corticosteroid treatment before diagnosis. Prephase therapy should be accompanied by appropriate hydration, monitoring of electrolytes, uric acid, and renal function, and readiness to manage tumor lysis syndrome (8, 9, 12).

CONCLUSION

Systemic corticosteroids should be avoided whenever possible before completion of the diagnostic evaluation in children with suspected leukemia or lymphoma. This precaution is not based on the assumption that prior corticosteroid exposure invariably causes drug resistance or worsens survival. Rather, corticosteroids may produce false clinical improvement, delay appropriate investigation and referral, distort assessment of initial disease burden, and, in selected cases—particularly mediastinal lymphoma—reduce diagnostic tissue yield and complicate staging. Prompt complete blood count testing, peripheral blood smear review, recognition of red-flag findings, and timely referral to pediatric hematology-oncology are practical measures that may help prevent these avoidable consequences.

CONFLICT OF INTEREST: None.

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