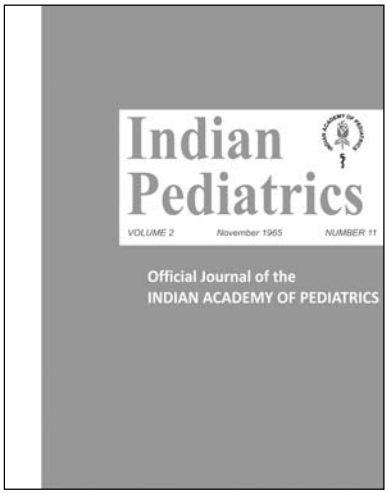
Leukemoid Reaction – A Tale of 50 Years

PIALI MANDAL AND *SHARMILA B MUKHERJEE
*Department of Pediatrics, Lady Hardinge Medical College, New Delhi, India. *theshormi@gmail.com*

In 1965, the 34-paged November issue of *Indian Pediatrics* published three original articles (case series of Familial tuberous sclerosis, Leukemoid reaction and Phenylketonuria, respectively) besides four case reports and the usual current literature, notes and news. Keeping the present day readers in mind, we selected the paper on leukemoid reaction as despite advances in diagnostics, this entity still causes considerable diagnostic dilemma to both clinician and hematologist, and undue parental anxiety in case of misdiagnosis.



THE PAST

This *Case series* by Chandra and Bhakoo [1] comprised of clinical details of 18 cases of leucoerythroblastic (leukemoid) reaction. There were 12 boys and 6 girls ranging from 3 days to 10 years of age. The diagnosis of leukemoid reaction was mainly based on the peripheral smear (presence of myelocytes, myeloblasts, lymphoblasts and normoblasts); a total leukocyte count (TLC) above 50,000/mm^3 was found in only 3 cases: thalassemia (68,000/mm^3), pertussis (56,000/mm^3), and cirrhosis (68,400/mm^3). In the rest, counts ranged from 7900 to 32,000/mm^3. The etiology included 11 infectious, 2 cirrhotic, and 5 other hematological disorders.

In the discussion, the authors focused on the probable etiopathogenesis. They cited the Hill and Duncan classification that attributed leukemoid reaction to three mechanisms; (*i*) bone marrow irritation or stimulation by physical, chemical or allergic agents; (*ii*) response of the bone marrow to an overwhelming demand for leukocytes; and (*iii*) ectopic hematopoesis due to destruction of or encroachment of the marrow space [2]. This was followed by possible illnesses attributable to each; (*i*) infections with bacteria like *S. aureus*, *H. Influenzae*, *M. tuberculosis*, *S typhi* and much less commonly viruses; (*ii*) hemolytic conditions or hemorrhage, increased bone marrow regeneration after hematinics or post bone marrow suppression; and (*iii*) lymphoma or neuroblastoma. The authors stated that leukemia should not be diagnosed merely by peripheral blood smear findings, and concluded by suggesting that the term leukemoid reaction be replaced by 'Leuco-erythroblastic reaction' as it had less ominous implications.

Historical background and past knowledge: The term 'leukemoid reaction' was coined by Krumbhaar, in 1926, to describe the leukemia-like blood picture that was found in several non-leukemic conditions [3]. The diagnostic criteria included a total leukocyte count (TLC) of more than 50000/mm^3 and/or the presence of immature leukocytes (mostly myelocytes or their equivalents) in the peripheral blood smear. These would usually be granulocytic or lymphoid, according to the predominant cell lineage. It was recognized that leukemoid reaction could be mistaken for chronic myeloid leukemia (CML). However, in those days CML was differentiated from leukemoid reaction based on clinical manifestations (rareness in children, slow progression, pallor, bleeding, bone tenderness, lymphadenopathy and massive splenomegaly), hematological smear (mostly immature leukocytes and blasts with abnormal nuclei and cytoplasm with additional thrombocytopenia, eosinophilia and basophilia) and leukocyte alkaline phosphatase (LAP) levels (low or even absent in CML in contrast to increased in leukemoid reaction).

THE PRESENT

Till date the term 'Leukemoid reaction' still hold good. The definition, however has become more elaborate, and now reads as 'a hematological disorder, characterized by a leukocyte count >50,000 cells/µL, significant increase in mature neutrophil counts in the peripheral blood,

accompanied by a differential count showing marked left shift, signs of neutrophil activation in the absence of basophilia and dysplastic changes'. Over the last fifty years, most advances have been in terms of expanding the number of underlying causes as well as the use of alternative diagnostic modalities when standard hematological methods fail to establish the diagnosis.

It is well known that most cases are due to reactive causes operating outside the bone marrow [4,5]. Infective causes are still the commonest, especially bacteria like *B. pertussis*, *C. difficile*, *Shigella*, *Mycoplasma* and *M. tuberculosis*. Others include viruses (EBV, CMV, HIV and parvovirus B19), parasitic illnesses (trichinosis, visceral larva migrans, and malaria) and even fungal infections (mucormycosis, *Tinea capitis*), and scabies. An association of neonatal leukemoid reaction in low birth weight babies has been observed with maternal chorioamnionitis. When an infectious cause is not evident, it is essential to exclude hematological malignancies like CML and chronic neutrophilic leukemia (CNL), a rare myeloproliferative syndrome with poor prognosis. There is a long list of other malignancies associated with leukemoid reaction, which also secrete haematopoeitic stimulating cytokines. These include carcinomas (lung, oropharyngeal, gastro-intestinal, genitourinary, and nasopharyngeal), Hodgkin lymphoma, melanomas and sarcomas. Apart from severe hemorrhage and acute hemolysis (that was recognized earlier), drugs like corticosteroids, minocycline, recombinant hematopoietic growth factors and ethylene glycol intoxication are also known to cause leukemoid reaction.

Usually a good history (including exposure to toxins or drugs), clinical examination and standard investigations (total and differential blood counts, peripheral smear, LAP score, bone marrow aspiration/biopsy) can determine the underlying etiology. However, there may be instances where more targeted testing by advanced diagnostic modalities is required for exclusion. These include cytogenetic testing (chromosome 20 abnormalities seen in some cases of CNL) and molecular analysis (t 9:22 translocation in CML). Immuno-phenotyping is useful in detecting surface antigens like CD13 and CD15 (found in mature neutrophils in leukemoid reaction) and CD34 (in acute leukemia or myelodysplastic syndromes). It may also rule out CML in blast crisis by the presence of HLA-DR [6]. Serum vitamin B_{12} and vitamin B_{12}-binding capacity may be elevated in CML due to increased leukocyte derived B_{12} binding protein levels resulting from the increased leukocyte mass. Clonality studies demonstrate monoclonal cells in myeloproliferative syndromes and polyclonal neutrophils in leukemoid reaction [7]. Imaging studies and biopsies are useful when solid tumors are suspected. This may be substantiated by elevated serum levels G-CSF, GM-CSF and IL-6, indicating the presence of cytokine-producing tumors [8,9].

To conclude, leukemoid reaction is a rare but challenging condition that may require a careful diagnostic work-up. The diagnosis is usually made by a combination of raised TLC, marked mature neutrophilia (but with a left shift), high LAP score and hypercellular bone marrow with intact maturation and morphology of all elements. Rarely, it may require demonstration of absence of cytogenetic abnormalities, mature granulocyte pattern by immunophenotyping and polyclonal neutrophils, or the absence of high levels of hemopoietic growth factors.

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