

## Leukemoid Reactions in Hematological Malignancies: Report of Three Cases and Review of the Literature

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Leukemoid reactions (LR) are important differential diagnoses in hematological malignancies as they may be misinterpreted as a relapse or a second leukemia. We report 3 pediatric cases including one non-Hodgkin's lymphoma and two acute lymphoblastic leukemias (ALL). One LR resembled chronic myeloid leukemia (CML) and two LR's suggested that a relapse of ALL had occurred, which has major clinical implications. Two of the patients had the LR on more than one occasion (total 6 episodes). CML or relapse were excluded mainly on clinical grounds, by normal bone marrow studies, and in the case of CML by a high score of leukocyte alkaline phosphatase (LAP). No infections could be detected during the episodes of LR.

We reviewed the literature looking for LR's reported during the course of hematological malignancies, and could find very few reports of such cases. We believe the LR's in our cases are due to rebound effects following neutropenia, and possibly due to prednisolone in one episode. We conclude that LR's are possible during the course of hematological malignancies. This possibility should be borne in mind after excluding important differential diagnoses, like infections. The importance of recognizing LR's in hematological malignancies is to avoid a misdiagnosis of a relapse or a second malignancy.

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Leukemoid reaction is defined as a hematological finding which resembles some type of leukemia, but in whom leukemia was not confirmed by the subsequent course of the illness or at autopsy. This involves changes in the white blood cell count, total or differential. More restrictive definitions, such as those that required a certain leukocyte count, or the presence of blasts or other precursors have been proposed, but they are not found to facilitate classification or understanding, and their use excludes some cases that, in fact, simulate leukemia<sup>1</sup>. LR's can resemble acute leukemias, myeloid (AML) or lymphoblastic (ALL). They can also be confused with chronic leukemias, myeloid (CML) or lymphocytic (CLL). In patients with established leukemias blood pictures of LR would lead to major diagnostic challenges. Relapse of an acute leukemia, leukemic transformation of lymphoma, and a second hematological malignancy being the most important differential diagnoses.

Rarely very high counts of well differentiated neutrophils, eosinophils or monocytes are encountered. The latter findings do not cause great diagnostic difficulties in patients known to have a leukemia. Our report of 3 cases of LR's highlights the importance of recognition of these conditions particularly during the course of hematological malignancies.

### CASE NO. 1

SM is a 7 years old girl, who had stage III non Hodgkin's lymphoma, diffuse small non-cleaved cell type diagnosed by node biopsy. On presentation her CBC showed only mild normochromic normocytic anemia. In particular her differential WBC, as well as bone marrow cytology and histology were normal. After initial stabilization chemotherapy was started using a modified COMP-regimen (Fig 1). The patient went into clinical remission and then developed profound leukopenia, mainly neutropenia, but recovered promptly thereafter. She was admitted on day 16 after a delay upon request. Her WBC was found to be 26700/mm<sup>3</sup> with immature precursors mimicking a picture of CML. Chemotherapy was postponed further.

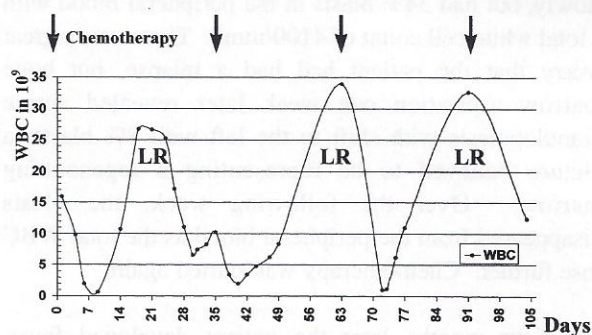


Figure 1. The 3 LR's of case No. 1 in relation to chemotherapy and neutropenia

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In spite of a careful search for infections including tuberculosis, no explanation for this severe leukocytosis was found. The patient remained afebrile. RBC-morphology was normal. Bone marrow aspiration and a trephine biopsy were done. Both were normal. LAP-score was not reduced. Karyotyping was not done.

After discussions, we thought that this is a LR possibly due to a rebound effect after neutropenia. Prednisolone therapy might be contributing. We decided to continue with the chemotherapy. Her WBC returned to normal to show again neutropenic values after further doses of cytotoxic chemotherapy. The event free clinical course following this episode confirmed the benign nature of this leukocytosis. The patient showed two similar pictures during her subsequent follow up. Those 2 episodes were not following prednisolone therapy but both were preceded by marked neutropenia. Clinically there was no evidence suggesting an infection. LAP and bone marrow studies were thought to be not indicated.

#### CASE NO. 2

NE is a girl, who developed at the age of 18 months an acute lymphoblastic leukemia of common type with L2 morphology. She was treated with a modified BFM-protocol. Eight months after starting maintenance therapy she had a period of two months, when she had serious infections of the Hickmann line and the gut. She also developed anal abscesses and had positive blood cultures of staphylococcus epidermis, salmonella enteritidis, and candida albicans. At this stage she was neutropenic, so that chemotherapy had to be stopped. Two weeks later intensive antimicrobial therapy was believed to have led to eradication of those infections. After 4 weeks of neutropenia she started to recover slowly, but had 34% blasts in the peripheral blood with a total white cell count of 4100/mm<sup>3</sup>. There was a great worry that the patient had had a relapse, but bone marrow aspiration one week later revealed active granulopoiesis with shift to the left with 8% blasts, a picture believed to be representing a regenerating marrow. Over the following week, the blasts disappeared from the peripheral blood as the total WBC rose further. Chemotherapy was started again.

Four months later the patient developed fever, pulmonary infiltrates and had positive blood cultures for staphylococcus epidermis from her Hickman line. The

line was removed. Chemotherapy was stopped, because the patient was neutropenic again, and antibiotics were given. The patient improved clinically. During recovery from her neutropenia, she again showed blasts in the peripheral blood (25% of WBC 4600/mm<sup>3</sup>). Some myelocytes were also seen. Bone marrow was done again which showed a normal picture. The blasts disappeared again as her WBC rose to 8500/mm<sup>3</sup>. She has remained in remission and off treatment for one year.

#### CASE NO. 3

IJ is a female patient, who presented at the age of 6 years with an acute lymphoblastic leukemia with a difficult morphology. Immunophenotyping suggested pre B-ALL with weak positive reactions with CD 10. She was treated with a modified BFM-protocol, which was completed in August 1992.

Four months later blasts were seen in her peripheral blood at a low percentage (5% of WBC 3800/mm<sup>3</sup>). This induced a tremendous concern about her and led us to do a bone marrow aspiration which revealed normal findings. Over the next few weeks the blast cells were observed occasionally and then disappeared. She has remained in remission, off treatment, for two years.

#### DISCUSSION

Differentiating between LR's and hematological malignancies, can be difficult. Care must be taken before declaring such an abnormal hematological finding to be an LR, particularly in patients known to suffer from malignant blood disorders. Such LR's during the course of hematological malignancies can be due to various causes. Table 1 lists different etiological factors which might lead to LR's. The most important disorders, which have to be excluded, particularly in hematological malignancies, are infections. In spite of all efforts we could not detect any infections in our three patients at the time they had their LR's.

The subsequent clinical course, in particular the decrease in WBC or the disappearance of blasts without antimicrobial therapy, makes infections very unlikely. There was no evidence of other inflammatory processes. No drugs apart from prednisolone during the first episode of case no.1 could be implicated in relation to LR's in our patients.



Table 1. Causes of leukemoid reactions<sup>2</sup>

<i>Resembling CML:</i>	<i>Resembling AML:</i>
Tuberculosis	Tuberculosis
Metastatic carcinoma	Recovery from agranulocytosis
Pyogenic infections	Alcoholic hepatitis
Burns	
Diabetic ketoacidosis	<i>Resembling ALL:</i>
Poisonings	EBV, or CMV mononucleosis
Rheumatoid arthritis	Infectious hepatitis
	Mumps
	Drug sensitivity

Sweet's syndrome is an important disorder, which should be considered if patients with leukemia develop leukocytosis<sup>3</sup>. However in our cases, no skin lesions suggesting this disease were present.

Our search in the literature using Medline records for the last 20 years revealed only a few cases of LR's in hematological malignancies. In a histopathological comparison between LR and CML, Schmid et al included 2 cases of LR's in non Hodgkin's lymphoma and 4 cases in Hodgkin's disease. No details were given about the type of leukemia mimicked<sup>4</sup>. Ko et al described a patient with paroxysmal nocturnal hemoglobinuria with myelodysplasia who developed a picture resembling AML during a septic episode<sup>5</sup>. Monocytic and eosinophilic LR's were described in patients with myelodysplastic syndrome or angioimmunoblastic lymphadenopathy respectively<sup>6,7</sup>. One AML-patient developed monocytic LR during treatment with granulocyte colony stimulating factor (G-CSF)<sup>8</sup>.

A transient neonatal myeloproliferative disorder resembling CML or acute leukemia is well recognized in Down's syndrome or in phenotypically normal newborns with trisomy 21 mosaicism<sup>1</sup>. Many of these children remit spontaneously, although some develop acute leukemias. Penchansky et al reported a child, who developed overt AML 11 years after having LR during infancy<sup>9</sup>.

The only cause, which could be attributed with a reasonable certainty to LR's in our cases, is a rebound effect after neutropenia. Prednisolone might have played a role during the first episode of case no. 1. Blasts as well as other precursors appear frequently during recovery from neutropenia, but they disappear as the total leukocyte counts approach normal values. Rebound leukemoid reaction is described during

recovery from agranulocytosis. Prednisolone is known to cause neutrophilia, but it is not a recognized cause of LR's. Patients with ALL may show lymphocytosis with increased blasts in their bone marrows after stopping chemotherapy, and this may persist for over a year. The importance of differentiating this from a relapse is emphasized by Lilleyman<sup>10</sup>. However we believe that the presence of such blasts in peripheral blood has not been previously described with normal total leukocyte counts. The real problem is to decide at the time whether or not the cells are truly malignant or merely the result of rapid marrow recovery. For instance if the cells were predominantly CD 10 antigen positive then a recurrence of the leukemia might be assumed, but Hutchinson<sup>11</sup> points out that CD 10 positivity is not leukemia specific and may occur on normal cells. Similarly, lymphoid cells bearing terminal deoxynucleotidyl transferase (TdT) may represent recurrent leukemia but must be differentiated from immature nonmalignant TdT positive cells. Although some authors<sup>12</sup> utilized immunological markers to differentiate between leukemic pictures and LR, they should be interpreted with caution and only after taking into account the clinical situation. Changes in Karyotype might be of more help<sup>13,14</sup>.

## CONCLUSION

The appearance of leukemia like cells in the peripheral blood of a child who is being treated for an acute leukemia usually heralds a relapse. We report three children in whom this phenomenon occurred but as far as we could ascertain were not in relapse, nor have they relapsed since. This is a problem that is quite familiar to many pediatricians and hematologists who have looked after children with leukemia. It used to be seen when a bone marrow aspiration was done some weeks after completing some of the earlier trial treatments, when the number of blasts in the peripheral blood or in the marrow caused confusion. Just waiting would see them gradually disappear. Now it is fairly unusual to do a marrow at this time. The significance of the finding is obvious. Misdiagnosing a relapse commits the child to one or two more years of treatment unnecessarily. Failing to diagnose a relapse may also have sad results. Our three cases illustrates the significance of correct recognition of LR during the course of hematological malignancies.

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