CASE REPORT

A rapid increase in the normal white cell counts without blasts as the initial presentation of T-cell acute lymphoblastic leukaemia

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SUMMARY

A 5-year-old girl with multiple enlarged cervical lymph nodes consistent with Epstein-Barr virus infection showed a rapid increase in the white blood cell counts (myeloid cells and lymphocytes) without blasts over a week period. Bone marrow evaluation performed after a week's observation unexpectedly showed replacement of the marrow with T lymphoblasts. A presentation of T-cell acute lymphoblastic leukaemia (T-ALL) in this fashion is very unusual. We postulate that the T-lymphoblasts may have been secreting granulocyte colony stimulating factor like substance. We are unable to find a similar case report in the literature, and thus we wish to report this case. The patient has been treated with Children's Oncology Group T-ALL protocol, and has been in continuous remission.

BACKGROUND

'The leukemoid reaction' was defined in the 'Haematology of Infancy and Childhood' as 'the elevation of total leucocyte count to greater than 50×10^3 cells/ μ L, and the peripheral blood often has increased numbers of immature myeloid cells, including occasional myeloblasts and promyelocytes'.¹ It is most often seen not only in infections but also in other clinical conditions such as in patients with burns or with metabolic disorders,¹ or patients on certain antiepileptic medications.² Childhood lymphoid leukaemia either presents with leukopenia and neutropenia, or leucocytosis due to an increase in leukaemic blasts. It is very unusual, however, for acute leukaemia to present with what appears to be leukemoid reaction (extreme leucocytosis without blasts) as the initial haematological feature. Recently, we have experienced a child who developed a 10-fold increase in the normal white cell count over a week's period without presenting with any leukaemic blast cells in the blood. We postulate that leukaemic cells may have produced granulocyte colony stimulating factor (G-CSF) like stimulants to drive the initial leucocytosis.³

CASE PRESENTATION

A 6-year-old white girl presented to the hospital with a history of recurrent sinus infection with cough, congestion and intermittent fever for 1 month. She was treated with various oral antibiotics without improvement. The patient was noted to have neck swelling that progressively increased in size during preceding 2 days before admission.

The swelling was mildly tender. She has not reported of sore throat, joint pain or joint swelling or rash. Physical examination showed bilaterally enlarged tonsils without exudates, multiple enlarged cervical nodes, the largest one measuring 2×2 cm in the posterior cervical triangle matted together with other smaller nodes. There was no other lymph node enlargement. The spleen was palpable 3 cm below the left costal margin. A CT scan of the chest showed a slightly enlarged thymus gland, but otherwise normal chest. No tracheal narrowing or deviation was detected.

INVESTIGATIONS

The initial complete blood count (CBC) showed white blood cells (WBC) of $10.4 \times 10^3/\mu$ L, hemoglobin (HGB) of 13.9 g/dL and platelet count of $329 \times 10^3/\mu$ L. The differential showed 46% polymorphonuclear neutrophils, 42% lymphocytes, with monocytes and eosinophils as the remaining white cells. The patient was treated for bacterial lymphadenitis, though blood cultures and throat cultures did not yield any organisms. Viral workup showed evidence of reactivation of Epstein-Barr virus (EBV) infections. Anti-EBV viral capsid antigen antibodies IgM was negative, but IgG was positive. Anti-EBV early antigen and early antigen and nuclear antigen IgG antibodies were elevated at 11.5 and 185 U, respectively.

Bartonella henselae IgM and IgG and cytomegalovirus IgG and IgM antibodies were not detected. *Mycobacterium tuberculosis* skin test was negative. During the next 7 days, daily CBC showed explosive increase in the total WBC counts (see table 1 and figure 1).

The increase was due to lymphocytes and myeloid cells, but not blasts. Daily inspection of the blood smear failed to detect any leukaemic blast cells until day 9 of admission when there were many blasts observed. Subsequently, there was a progressive increase in the lymphoblasts in the blood smear. The bone marrow aspiration performed on day 8 of the hospital stay showed very cellular marrow. Eighty percent of the cells were lymphoblasts. Immunophenotypic marker study showed T-lymphocyte immunophenotypes (CD2, CD3, CD7, CD5 positive, CD19, CD10, CD117 negative).

DIFFERENTIAL DIAGNOSIS

- Infectious mononucleosis
- Leukemoid reaction due to an infection of unknown organism

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Table 1 Serial complete blood count and differential

Day	WBC	HgB	Platelet	Blast	Myelo	Meta	Band	Seg	Eo	Lymph	Mono	NRBC
1	10.4	13.9	329	0	0	0	0	45	2	45	7	0
3	28.7	13.5	354	0	1	4	3	61	4	24	3	0
4	33.1	13.0	356	0	0	7	3	56	2	30	2	0
5	53.8	13.6	332	0	2	1	12	48	2	34	1	0
6	42.7	12.5	238	0	1	1	6	38	0	49	5	6
7	59.3	13.4	198	0	0	8	17	23	6	41	5	1
8	75.8	12.5	177	25	0	2	9	16	0	42	6	2
9	101.1	13.0	120	27	2	2	5	16	1	41	3	3
10	160.3	12.5	107	47	0	0	6	15	1	31	0	2

The figures in the differential of WBC are percent. T

Day, day of admission; Eo, eosinophils; HgB, haemoglobin g/dL; Lymph, lymphocytes; Meta, metamyelocytes; Mono, monocytes; Myelo, myelocytes; NRBC, nucleated red blood cells; Platelet, platelet count; $\times 10^3/\mu\text{L}$, Seg, segmented neutrophils; WBC, white blood count; $\times 10^3/\mu\text{L}$. Note that blasts were not observed until day 8.

- Chronic myelocytic leukaemia
- Acute lymphoblastic leukaemia

TREATMENT

The patient was registered and started on Children's Oncology Group (COG), AALL (COG protocol number) 0434 therapeutic protocol for T-cell acute lymphoblastic leukaemia (T-ALL).

OUTCOME AND FOLLOW-UP

Currently she has been in remission, and doing well.

DISCUSSION

This patient presented with two unique features. One is a clear evidence of reactivation of EBV infection which may have played a role in the development of leukaemia and the other is the typical leukemoid reaction one would see in patients with bacterial infections. EBV infection as a triggering event of acute leukaemia has been frequently described in immune compromised hosts, typically poststem cell transplant. It is almost always B-cell lymphoma or leukaemia. Development of T-cell leukaemia or lymphoma with EBV infection has been much less commonly reported.⁴ Thus, this patient is unique in this respect as well.

The initial clinical presentation of cervical lymphadenopathy, fever and splenomegaly was highly suggestive of EBV infection. The serology for EBV infection clearly supported that diagnosis. However, daily progressive increase in the total white cell counts together with 'shift to left', the classical leukemoid reaction, is extremely unusual for an EBV infection. The blood smear showed mostly mature lymphocytes and very few 'atypical lymphocytes'.

The leukemoid reaction suggested a possibility of chronic myelogenous leukaemia (CML), though there were many features that are not typical of CML such as normal haemoglobin, normal platelet count (not increased), absence of eosinophilia and lymphocyte predominance during the latter half of the hospital days. The bone marrow aspiration performed to rule out CML unexpectedly showed a picture diagnostic of ALL. The flow cytometry showed the lymphoblasts to be of T-cell origin. Cytogenetic and fluorescence in situ hybridization study did not detect any bcr/abl rearrangement.

We postulate that the leukemoid reaction may have been due to G-CSF like substance produced by the leukaemic cells, though we did not do G-CSF assay before the treatment. Two reports in the literature described G-CSF production by leukaemia/lymphoma cells. One is by leukaemic cells from five patients

Figure 1 Numbers on the x-axis represent month and day. The figures on the y-axis represent number of white blood cell counts (WBC) ($\times 10^3/\mu\text{L}$). The numbers on the trend line are actual WBC counts on that day.

with adult T-cell leukaemia.⁵ It is postulated that in adult T-cell leukaemia (ATL), human T-cell leukaemia virus (HTLV1) Tax protein transactivates cytokine genes leading to production of G-CSF in ATL cells.⁵ It is therefore very unlikely that the leukaemic cells in our patients produced G-CSF by this mechanism, since our patient does not have ATL, and though not tested, she would be negative for HTLV1 infection. The second case was described by Ohtsuki *et al.*² A 71-year-old woman developed leucocytosis of unknown aetiology. This patient had immunoblastic lymphoma like T-cell malignant lymphoma. The patient's lymphoma was demonstrated to produce G-CSF. It is possible that our patient's leukaemic cells produced G-CSF analogous to the case described above.

In summary, we described a rare observation regarding a child who initially developed marked leukemoid reaction followed by a diagnosis of T-ALL. It is also quite unique that her T-ALL may have been triggered by reactivation of her EBV infection.

Learning points

- ▶ On occasions a complete blood count needs to be performed daily to gauge the tempo of the disease.
- ▶ Spectacular daily rise in the white cell counts may mean a leukaemia rather than leukemoid reaction.
- ▶ When the diagnosis is uncertain, close moment to moment observations are crucial in arriving at a correct diagnosis.

Contributors SI cared for the patient, developed case presentation concept and wrote the final form. JS managed the patient as a resident physician, and wrote the first draft of the manuscript. NO cared for the patient as attending physician, and read the manuscript.

Competing interests None.

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