False Positivity of FDG-PET During Hemophagocytic Lymphohistiocytosis in a Child With Hodgkin Lymphoma in Remission

To the Editor:

We have read with interest the article by Levine et al entitled “Routine use of PET scans after completion of therapy in pediatric Hodgkin disease results in a high false positive rate.”1 The presence of nonmalignant factors, such as infection and inflammation, can make interpretation of positron emission tomography (PET) scans difficult in patients with Hodgkin lymphoma (HL) off therapy, particularly in pediatric patients.2–4 The therapeutic decisions should not be made without histologic confirmation.1 We reported a false-positive PET result, that is related to hemophagocytic lymphohistiocytosis (HLH) in a child with HL in remission.

A 12-year-old boy was admitted to our clinic with pallor and fever. He had been diagnosed as stage IIA nodular lymphocyte predominant type HL, his primary tumor being in cervical and axillary regions. He received 2 courses of ABVD chemotherapy protocol and involved field radiotherapy (25 Gy). After completion of therapy, no clinical or laboratory signs and symptoms, that may suggest a relapse of his tumor, have been noted for 3 years. In the last follow-up visit, pallor, fever, and hepatosplenomegaly were noted. There was not any lymphadenopathy. Complete blood count revealed pancytopenia (hemoglobin, 7.7 g/dL; white blood cells, 1800/μL; absolute neutrophil count, 700/μL; and platelets, 65,000/μL). Peripheral blood smear was normal except for hypo- chromia. Apart from hyperferritinemia (576 μg/L) and hypertriglyceridemia (265 mg/dL), blood chemistry profile was normal. Thoracic and abdominal computed tomography (CT) and abdominal ultrasonogram, that were carried out to rule out an HL relapse, were normal except for hepatosplenomegaly. Bone marrow aspiration and biopsy findings were not suggestive of secondary leukemia, myelodysplastic syndrome, or HL involvement; but histiocytes containing red cells and neutrophils in their cytoplasm were noteworthy (Fig. 1). The patient was

FIGURE 1. Histiocytes showing phagocytosis of normoblasts, neutrophils, and platelets in bone marrow aspirate (arrows: nuclei of histiocytes). Giemsa ×100.

FIGURE 2. The pretreatment PET/CT study shows abnormally increased FDG localization in a nasopharyngeal mass, in multiple lymph nodes (3 to 4 periportal nodes, 1 node in spleen hilum, 1 node between spleen and stomach fundus, and 1 subcarinal node under the right main bronchus and diffusely in the enlarged spleen and bone marrow). CT indicates computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography.
diagnosed as HLH according to the revised diagnostic guideline. Nevertheless, with the suspicion that the clinical picture might be due to an HL relapse, fluorodeoxyglucose (FDG)-PET/CT study was performed. The PET study showed increased FDG localization in multiple lymph nodes (periportal, splenic, subcarinal), diffusely in the enlarged spleen and in a nasopharyngeal mass (Fig. 2). Serologic tests and cultures for possible triggers of HLH, including viral, bacterial, and parasitic pathogens were negative. According to the HLH-2004 Study design, the patient was given dexamethasone (10 mg/m²/d, with a 50% dose reduction every 2 wk), VP-16 (150 mg/m² twice weekly), cyclosporine A (6 mg/kg/d) as a total of 8-week initial therapy. The patient, his fever taken under control and the size of his spleen reducing rapidly, had a normal blood count after 1 week of therapy. Hemophagocytosis in bone marrow disappeared after 2 weeks of treatment. The posttherapy (on day 16 of treatment) PET/CT study demonstrated no foci of abnormally increased FDG uptake and complete response to treatment.

To the best of our knowledge, our patient is the first child in whom false-positivity in PET/CT due to HLH has been reported.

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REFERENCES

Multifocal Osteomyelitis as a Presenting Manifestation of Childhood Acute Myeloid Leukemia

To the Editor:

Multifocal skeletal lesions because of leukemic infiltration are a rarity in acute myeloid leukemia (AML) at presentation. Bilateral symmetrical periosteitis and lytic bone lesions have been described in approximately 12% of children with AML-M7. We report an infant with AML who had multifocal skeletal lesions resulting from osteomyelitis rather than from leukemic infiltration.

An 11-month-old child presented with intermittent fever, painful swelling, and deformity of bilateral forearms of 2 months duration. On examination he had anemia, generalized bony tenderness, an irregular and tender bony swelling over the right forearm, and hepatosplenomegaly. Hemogram showed hemoglobin 6.3 g/dL, white blood cell count 23,500/μL, absolute neutrophil count 15,900/μL, and platelets 89,000/μL; peripheral smear and bone marrow examination confirmed the presence of acute myelomonocytic leukemia. Radiographic evaluation revealed bone destruction with periosteal reaction and new bone formation in right radius (Fig. 1A); periosteal reaction was also seen in left radius and bilateral femur without evidence of bone destruction (Figs. 1B, C), overall features being suggestive of multifocal...
osteomyelitis. The initial blood culture was sterile. Bone biopsy from the right radius showed bony trabeculae, areas of granulation tissue, and chronic inflammatory cell infiltrate consistent with infectious etiology (Fig. 1D); there were no evidence of blasts or any microbiologic organism.

Patient was started on induction regimen with daunorubicin and cytoxane arabinoside combination. On day 3 of induction, the child started having high-grade fever; clinically focus of infection was localized to the multifocal bone involvement. Patient was started on cefoperazone-sulbactam combination with amikacin to which he responded; blood culture at this time showed Klebsiella pneumoniae sensitive to the above antibiotics. On day 9 of induction, the child again had breakthrough fever with no new clinical focus of infection. Vancomycin was empirically added to the ongoing antibiotic regime. Blood cultures, taken at this time and subsequently, revealed Enteroctococcus fecalis and Enterococcus faecium sensitive to vancomycin. The child, however, failed to respond to these antibiotics, which were empirically upgraded to imipenem with addition of amphotericin B. He, however, died of sepsis on day 17 of induction.

In our case, radiologically and pathologically the diagnosis was consistent with multifocal osteomyelitis and not related to direct leukemic infiltration. Such radiographic and histologic findings may also be compatible with fibrotic reaction to old hemorrhage. Further, we had performed the biopsy from only 1 site, which was radiologically most involved; hence the possibility of leukemic infiltration at the other sites cannot be ruled out. Although the initial blood culture was sterile, it is possible that the subsequent bacteremia was related to dissemination from the site of osteomyelitis after initiation of chemotherapy and development of neutropenia. Osteomyelitis is a relatively rare event in children with acute leukemia despite immunosuppression. In an 11-year retrospective study, there were only 6 patients with acute lymphoblastic leukemia (ALL) and 3 with AML who had osteomyelitis; 7/9 were in remission at the time of diagnosis. Multifocal osteomyelitis has been previously described during therapy of ALL and ALL has been known to mimic multifocal osteomyelitis at presentation.

Thus, our case gives an important message that although leukemic infiltration of bones may mimic osteomyelitis at presentation, the reverse may also be true, as was observed in our case.

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REFERENCES

Transient Spontaneous Remission After Tumor Lysis Syndrome Triggered by a Severe Pulmonary Infection in an Adolescent Boy With Acute Lymphoblastic Leukemia

To the Editor:

Tumor lysis syndrome (TLS) is characterized by a set of metabolic abnormalities such as hyperkalemia, hyperphosphatemia, hypocalcemia, and hyperuricemia in association with massive tumor cell lysis in hematologic malignancies. TLS is usually triggered by cancer-directed therapy, especially before initiation of chemotherapy in a patient with acute lymphoblastic leukemia (ALL) has rarely been reported, and the precipitating factors are not clear. Here we report a case of an adolescent boy who presented with lobar pneumonia and ALL. Acute TLS evolved after pneumonia. Spontaneous remission (SR) of ALL was attained without conventional ALL chemotherapy.

The 14-year-old boy was transferred to our pediatric intensive care unit by the emergency service because of impending respiratory failure on February 28, 2008. The boy had experienced constitutional off-and-on fever and fatigue in the preceding 2 weeks. He visited local clinics twice, where he was treated with “cold” medications. However, spiking fever, tachypnea, and cyanosis were noted on arrival, and arterial blood gas data showed severe hypoxemia (PaO2, 18.9 mm Hg). Chest x-ray revealed lobar pneumonia of the right lower lung (Fig. 1A). He was intubated and given ventilator therapy. Although no bacterial growth was noted in a blood sample at diagnosis, cultures from pleural fluids yielded mixed microbial growth including methicillin-resistant Staphylococcus aureus, coagulase-negative Staphylococcus spp., Streptococcus viridans, and yeast. The antibiotics vancomycin, meropenem, and voriconazole were administered, although vancomycin was later replaced by teicoplanin because the patient developed vancomycin-induced “red man” syndrome.

Complete blood count and peripheral blood smear examinations on arrival revealed characteristics of acute leukemia including a white blood cell count of 35.5 × 109/L with 93.5% blasts, hemoglobin concentration of 4.4 g/dL, and platelet count of 14.0 × 109/L. The initial lactate dehydrogenase concentration was 650 IU/L (normal range: 98–207 IU/L). The studies of bone marrow leukemic cells revealed the characteristic precursor B-ALL immunophenotype (CD19+ /CD22+ /CD7+ /HLA R+/CD10+/CD7+ / / cCD22+ / cCD79a+ ) and 46 XY cytogenetic karyotype.

Pneumonia progressed initially with tension pleural effusions requiring drainage by pigtail catheter insertion on day 12 after admission (Figs. 1B, C); these effusions resolved gradually although residual fibrotic lesions remained (Fig. 1D). Other intensive measures included ventilator therapy, fluid and electrolyte therapy, and platelet and red cell transfusions. No chemotherapeutic agents, steroids, or colony-stimulating factors were administered.

However, the patient developed a fulminating course characteristic of TLS. Hyperkalemia (peak potassium, 8.68 mEq/L; normal, 3.5–5.0 mEq/L), hyperphosphatemia (peak phosphorus,
12.0 mg/dL; normal, 2.3-4.7 mg/dL), hypocalcemia (nadir free calcium, 0.67 mmol/L; normal, 1.13-1.3 mmol/L), and hyperuricemia (peak uric acid, 25.96 mg/dL; normal, 2.9-7.0 mg/dL) developed after pneumonia and its treatment (Fig. 2). Transient nonoliguric renal failure was noted: the peak creatinine concentration was 4.7 mg/dL (normal, 0.6-1.3 mg/dL) and blood urea nitrogen concentration was 98 mg/dL (normal, 6-22 mg/dL) on day 4 after admission, despite creatinine and blood urea nitrogen concentrations at diagnosis of 1.1 and 17 mg/dL, respectively. TLS and renal failure resolved finally after supportive treatment including the administration of allopurinol followed by rasburicase. Interestingly, rapid reduction of the leukemic blasts was noted along with complete disappearance in the peripheral blood from day 11 after admission (Fig. 2). In addition, hemoglobin concentration and neutrophil (Fig. 2) and platelet counts also normalized. Repeated bone marrow examinations on March 27, 2008, revealed complete remission, which was also confirmed by flow cytometric analysis showing no detectable cells gated on the “dim CD45/low side scatter” blast fraction.

The status of complete remission was short-lived. He returned to our unit with acute bilateral swelling of the parotid glands on April 11, 2008. The hemograms showed hemoglobin concentration of 10.7 g/dL, platelet count of $247 \times 10^9$/L, and white blood cell count of $11.8 \times 10^9$/L, with 2% blasts. Bone marrow examination revealed relapse of the original precursor B-ALL in 23% of all cells by flow cytometric gating on the “dim CD45/low side scatter” blasts. High-risk ALL induction chemotherapy was started and complete remission was achieved again and documented by bone marrow examination on May 22, 2008. He continued to receive consolidation and maintenance chemotherapy according to the high-risk ALL protocol. Until his most recent follow-up in June 2008, he remained in Remission.
The metabolic profile and renal function remained normal.

The course of precursor B-ALL in this adolescent boy was intriguing. First, TLS developed without the administration of any standard leukemia-killing drugs. Second, TLS evolved immediately after the diagnosis and treatment of the lobar pneumonia. Third, TLS resulted in complete remission of ALL. TLS is triggered mainly by cancer-killing measures (especially chemotherapy), and the reported risk factors for its development include bulky lymphadenopathy, high white blood cell count, elevated serum lactate dehydrogenase concentration, preexisting renal disease, and hyperuricemia. Although spontaneous TLS in untreated ALL has been reported, the precipitating factors leading to TLS are obscure. A pediatric case of transient precursor B-ALL associated with Parvovirus B19 infection has been reported in the journal. In contrast, our patient sustained only short-term remission and exhibited subsequent full-blown relapse. Interestingly, SR of untreated acute leukemia has been reported more frequently in acute myeloid leukemia (AML) than in ALL. The SR in AML is usually short-lived (mean, 7.7 mo) but can last as long as 36 months. The exact mechanism of SR in AML is not well established; but infection and blood transfusion have been proposed as the inducing factors, as in our patient. Cross-activated immunity after infection or transfusion might control the AML leukemic clone successfully, for example, by stimulating the production of cytokines and leukemia-specific T cells. It is interesting to dissect the detailed steps in the inflammatory responses that lead to cancer eradication, as shown in our ALL patient and in AML patients. In contrast, inflammation more often contributes to cancer promotion rather than cancer eradication.

In conclusion, the TLS triggered by severe pneumonia in our patient illustrates a new example of inflammation-induced cancer eradication. How the cross-activated immunity after pneumonia in the patient resulted in complete remission of precursor B-ALL is intriguing because it demonstrates powerful leukemia-killing mechanisms other than those induced by standard chemotherapy.

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REFERENCES
Poor Treatment Compliance in Children With Down Syndrome and Acute Lymphoblastic Leukemia

To the Editor:

Children with Down syndrome (DS) have a 20 to 40 times increased risk of developing acute lymphoblastic leukemia (ALL). Some, although not all study groups, have shown DS-ALL to have an increased risk of relapse, which is somewhat surprising, as at least 3 biologic characteristics of the patients and the disease would suggest a better overall prognosis. First, ALL in DS is of B lineage with only a few T-cell ALL cases having been reported in the literature, the higher-risk t(1;19), t(9;22), and MLL translocations are very rare in children with DS, and trisomy 21 has been linked to a favorable prognosis. Second, DS patients seem to have a higher propensity for apoptosis. Third and most important, DS-ALL has a favorable pharmacology for methotrexate and cytarabine (Ara-C). Smoldering and polarized inflammation in the initiation and promotion of malignant disease. Cancer Cell. 2005;7:211–217.

TABLE 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Risk Group (SR/IR)</th>
<th>Down Syndrome (DS)</th>
<th>Non-DS 231/241</th>
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<tbody>
<tr>
<td>Sex (M/F)</td>
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<td>M</td>
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<tr>
<td>Age (median)</td>
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<td>WBC (median)</td>
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<td>Dose MTX (median)</td>
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<td>Dose 6MP (median)</td>
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<td>TPMT (median)</td>
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<tr>
<td>E-TGN (median)</td>
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<td>Time of medication</td>
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<tr>
<td>(median, 75% range)</td>
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<tr>
<td>mWBC_MT</td>
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<td>5.2</td>
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<tr>
<td>mANC_MT</td>
<td>3.6</td>
<td>3.6</td>
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<tr>
<td>Relapse (pEFS)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Brackets refer to the non-Down patients; risk group: SR = standard risk = B lineage with WBC < 10 × 10⁹/L and age 2.0-9.9 years; IR = intermediate risk = B lineage with WBC 10-49 × 10⁹/L and/or age 1.0-1.9 or 10.0-14.9 years; sex: M = male, F = female; age in years; dose MTX and 6MP (mg/m² per week and day, respectively); E-MTX and E-TGN: average level of erythrocyte methotrexate (including polyglutamates) and 6-thioguanine nucleotides during MTX/6MP maintenance therapy; TPMT: erythrocyte thiopturine methyltransferase activity in IU/mL; time of medication: for each blood samples taken for E-MTX, E-TGN measurements, it was registered whether the patient took MTX and 6MP in the morning (=0), at mid-day (=1) or in the evening (=2). An average was then calculated for each drug and the sum of the 2 was calculated. A final score of 4.00 indicates that both drugs are always taken in the morning; mWBC_MT and mANC_MT is the average white blood cell count and absolute neutrophil count during maintenance therapy. *P < 0.10; **P < 0.05; pEFS indicates probability of event-free survival; WBC, white blood cell count at diagnosis.
6TGN. 17  
vels are the end product and not cytosol  
target, partly because DNA-6TGN le-  
blasts and not erythrocytes are the  
monitoring of maintenance therapy is  
6MP metabolite measurements in  
intensity of maintenance therapy.  
the treating physician to optimize the  
inferior willingness and/or efforts of  
rate for DS-ALL may in part reflect  
data indicate that an increased relapse  
ALL patients included is limited, these  
compliance. 16 The role of E-MTX/  
6MP metabolite measurements in  
monitoring of maintenance therapy is  
still unsolved, partly because lymphoblas-  
ostics and not erythrocytes are the  
target, partly because DNA-6TGN le-  
vels are the end product and not cytosol  
6TGN. 17

Although the number of DS-ALL patients included is limited, these data indicate that an increased relapse rate for DS-ALL may in part reflect inferior willingness and/or efforts of the treating physician to optimize the intensity of maintenance therapy.

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