LETTER TO THE EDITOR
Persistent Elevation of Fetal Hemoglobin Following Chemotherapy in Sickle Cell Disease

To the Editor: Regulation of fetal hemoglobin (HbF) production is complex [1]. Our experience of persistent HbF elevation during a 7-year follow up in a child with homozygous sickle cell disease (SCD) who underwent chemotherapy for Wilms tumor (WT) adds to the complexity of the regulatory mechanisms in HbF production.

An 8-year-old African–American female homozygous SCD patient with metastatic WT was treated with vincristine, doxorubicin, and actinomycin D. After 6 months of therapy, she underwent nephrectomy; histology showed focal anaplasia. Interim, she developed a metastatic right liver lobe nodular lesion. She then received radiation to abdomen and lungs followed by ifosfamide, carboplatin, and etoposide chemotherapy. The treatment was completed in 26 months and her creatinine level remained normal. She did not require hospitalization for SCD complications and has had baseline hemoglobin of 9–10 g/dl. At the age of 3, her HbF was 17.6%. Her parents do not have elevated HbF levels ruling out hereditary persistence of HbF. Six months following treatment, her HbF was 33% along with increased red blood cell mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH). Despite MCV and MCH remaining stable, HbF trended down to 20.8% (Fig. 1). This may be secondary to age-related increase in average MCV and MCH levels in children irrespective of the HbF. F cells shown by flow cytometry were 95 and 82% at 6 months and 6 years after the completion of chemotherapy, respectively.

Following chemotherapy, persistently high MCV has been reported in long-term follow up; however, HbF values have not been reported [2]. The relation between HbF and F cells in our case was within expected age-related distribution in SCD patients [3]. Elevation of HbF and MCV in this case is reminiscent of stress erythropoiesis. However, increased HbF persistence has been far long-lived in the absence of chemotherapy in contrast to the dependence of HbF elevation on the continuous administration of hydroxyurea in SCD. In addition to alterations in chromatin structure or kinetics of erythroid differentiation, alternative mechanisms have been identified in HbF induction [4,5]. Increased HbF is seen in juvenile myelomonocytic leukemia, which is associated with acquired mutations in the Ras/MAPK pathway. Stem cell factor induces adult erythroid growth and HbF production through Ras/MAPK pathway [6]. Elevated EPO is unlikely, since increases of EPO levels are transient following nephrectomy in kidney donors [7]. Hemoglobin levels were stable in our case.

The current case is unique in the prolonged elevation of HbF. Persistent chemotherapy-related bone marrow microenvironment and cytokine milieu alterations may be an explanation. Emergence of an altered stem cell population secondary to acquired genetic or epigenetic changes resulting in a stress erythropoiesis-like reaction might also be possible. In conclusion, prospective evaluation of similar cases may add to our knowledge of the regulation of HbF production.

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Received 10 August 2011; Accepted 23 January 2012
Fig. 1. Fetal hemoglobin (HbF), mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH) changes over time. The patient’s age in years is depicted on the x-axis. The values while the patient was undergoing chemotherapy were not included due to frequent packed red blood cell transfusions.

REFERENCES