Essential thrombocythemia transforming into acute biphenotypic leukemia in a patient on hydroxyurea monotherapy

We describe a rare event of acute biphenotypic leukemic (BAL) transformation of a patient with essential thrombocythemia (ET) being treated with hydroxyurea (HU).

Our patient was a 78-year-old African-American female who was diagnosed with ET in 1996. Her platelet count was 1500 × 10^9/l and bone marrow was diagnostic for ET. The same year she suffered a stroke. The patient received HU for the next 13 years and remained asymptomatic. In December 2009, she presented with a 2-week history of generalized weakness.

On presentation, she was febrile to 100.5°F, had severe pallor and no organomegaly. Laboratory analysis revealed white blood cell count of 0.5 × 10^9/l (4 × 10^9/l to 10 × 10^9/l), hemoglobin 8.9 g/dl (12 g/dl to 16 g/dl), hematocrit 25% (36%–46%), platelets 100 × 10^9/l (140 × 10^9/l to 440 × 10^9/l) and a retic count of 0.35%. Mean corpuscular volume was 106 fl with normal B12 and folate levels. No blasts were noted in the peripheral smear. She had high fibrin split products (>20) and low fibrinogen level (128 mg/dl). The initial diagnosis was HU-related pancytopenia associated with neutropenic fever and disseminated intravascular coagulation. HU was discontinued. Leukemic transformation was also in the differential diagnosis. The patient was started on i.v. antibiotics and transfused for symptomatic anemia. The following day, the patient continued to have a low-grade fever (100.1°F). Antifungal agent was added to broaden the coverage. No focus of infection was found even on extensive investigation.

Bone marrow was done to rule out leukemic transformation. Review of aspirate revealed blasts comprising 82% of nucleated bone marrow cells. Immunohistochemistry showed that the majority of the blasts stained with myeloperoxidase, CD43 and leukocyte common antigen and BCL-2. However, 10% of the blast also co-expressed weak cytoplasmic CD3 and terminal deoxynucleotidyl transferase (TdT) in addition to the myeloid markers. Flow cytometry demonstrated myeloid differentiation with blasts expressing surface myeloid antigens (CD13, CD33) and CD34, CD117, CD38, CD56 and dim CD19. Cytoplasmic positivity for CD3 and TdT was confirmed in a minor subset.

Based on these immunohistochemistry and flow cytometry results, the leukemia was classified as biphenotypic leukemia (Figure 1). Bone marrow cytogenetics showed 46, XX, del (3) (p13p14), add (5) (q22) and add (11) (q25) in all the 15 metaphases observed.

A day after the bone marrow, the patient’s condition acutely worsened, and she developed shock with respiratory distress requiring intubation. Unfortunately, despite aggressive management in the intensive care unit, the patient died the next day.

Leukemic transformation in untreated ET is a rare event. Interferon, anagrelide and HU are the commonly used therapeutic agents. The overall risk of drug-related transformation to acute leukemia in cases of ET varies from 0.7% to 5.3% in retrospective series and from 8% to 12% in some prospective studies. Though studies in the past have reported no leukemic transformation with HU, the average risk is anywhere between 3.5% and 5% [1]. Transformation is commonly to acute myeloid leukemia, less commonly to acute lymphoblastic leukemia and rarely to BAL [1]. Of these, BAL has the worst prognosis. To date, there has been only one reported case of drug-related BAL transformation in a patient with ET [2]. She had received HU, anagrelide and interferon, in different combinations and varying doses for a period of 4.5 years, before BAL transformation. It was therefore difficult to evaluate with certainty whether HU was the main leukemogenic agent, although the author’s suspicion was high for the same, given the better safety record of interferon and anagrelide [3]. Martin and Della Valla [4] have reported a case of BAL transformation in an untreated patient of ET. However, the reported patient had a Philadelphia positive chromosome on cytogenetics that our patient lacked.
In conclusion, HU may rarely cause BAL transformations in ET patients. Aleukemic leukemia can be an atypical presentation of BAL transformation.

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