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Atypical Chronic Myeloid Leukemia in a Patient with Aplastic Anemia

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Acquired aplastic anemia (AA), a bone marrow (BM) failure disease, and atypical chronic myeloid leukemia (aCML), a myelodysplastic syndrome (MDS)/myeloproliferative neoplasm, are both rare diseases. An aCML occurring as a secondary malignancy is a very rare event.

In April 2005, an 18-year-old boy already diagnosed with AA and treated with cyclosporine (CSA) and prednisone (PDN) came to our center. No HLA identical family donor was available. Cytogenetic analysis showed a normal karyotype. Treatment with rabbit anti-thymocyte globulin combined with CSA, methylprednisolone, and granulocyte colony stimulating factor was successfully administered. Forty-four months later, an asymptomatic severe thrombocytopenia was successfully treated with CSA and PDN. The peripheral blood cell count remained normal for 8 years, when a mild thrombocytopenia occurred. Cytogenetic analysis showed 46,XY, del(3)(p13p23)[20]. Nine months later, an increase in white blood cell count with 27% immature dysplastic myeloid cells (promyelocytes, myelocytes, and metamyelocytes) combined with thrombocytopenia and mild anemia was detected. No organomegaly was present. BM hyperplasia with granulocytic dysplasia and no fibrosis were present. No *BCR-ABL1*, *PDGFRA*, *PDGFRB*, or *FGFR1* rearrangements and no *JAK2*, *CALR*, *CSF3R*, *SETBP1*, *TERC*, or *TINF2* mutations were detected. A diagnosis of aCML was made and hydroxycarbamide was started but the clinical and hematologic features worsened. While waiting for a haploidentical stem cell transplant, ponatinib (Ariad Pharmaceuticals Inc., Italy) was administered, based on in vitro sensitivity. Due to disease progression, ponatinib was discontinued and cytarabine, vindesine, and etoposide were given. Unfortunately, the patient developed an acute myeloid leukemia (AML) and died from multi-organ failure. The patient's DNA was then analyzed for genes associated with BM failure, AML, and MDS. Sanger sequencing defined two heterozygous missense mutations in the second zinc finger domain of the *GATA2* gene (p.Thr358Lys and p.Leu359Val).

To date, there are no reported cases of AA evolving into aCML with clonal abnormalities involving chromosome 3. In our patient, the del(3)(p13p23), detected before the onset of aCML, could have been a prodromal sign of clonal evolution.

Cytogenetic abnormalities found in myeloid malignancies have been reported in 4–11% and 20–88% of AA and aCML, respectively [1–3]. To date, no association be-

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tween hematologic diseases and del(3)(p13p23) has been reported. Interestingly, a deletion of the short arm of chromosome 3 revealed by cytogenetics does not correlate with *GATA2* mutation involving the long arm of chromosome 3. *GATA2* germ-line mutations are associated with the "*GATA2* deficiency syndrome" and have also been identified in chronic neutropenia, in pediatric BM failure, and in young adults with AA. Acquired mutations of *GATA2* are reported in MDS/AML [4] and the *GATA2* L359V mutation has been found in CML patients in blast crisis [5]. Unfortunately, due to a lack of biologic samples, we were unable to define whether *GATA2* T358L and L359V mutations, detected in our patient, were germline or acquired. As the patient had never suffered from monocytopenia and infections, we can only hypothesize that the *GATA2* mutations were acquired. The results, hereby reported, suggest that GATA2 mutations should be investigated in all patients with AA.

Statement of Ethics

Informed consent to use the presented data anonymously was given by the patient.

Disclosure Statement

The authors declare no conflicts of interest.

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