Case Report

Myelodysplastic Syndrome/Acute Myeloid Leukemia Arising in Idiopathic Erythrocytosis

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Received 27 November 2017; Accepted 7 February 2018; Published 22 February 2018

1. Introduction

The causes of erythrocytosis are many and can be broadly divided into either primary or secondary forms. Primary causes are due to a defect intrinsic to the erythroid compartment of the bone marrow which leads to increased red cell generation, whereas secondary causes are due to factors external to the bone marrow that are produced in excess and drive red cell production [1]. The most common cause of acquired primary erythrocytosis is the myeloproliferative neoplasm (MPN) of polycythemia vera (PV) that is molecularly characterized by the JAK2 p.V617F and exon 12 mutations [2]. Mutations of other genes in the erythropoiesis, oxygen sensing, and oxygen transport pathways are known to result in erythrocytosis; however, the underlying causes are unknown in a large number of cases, particularly those recognized as congenital erythrocytosis, and remain classified as idiopathic erythrocytosis (IE) [3]. Several clinical and biological differences exist between IE and PV, including a considerably lower risk of thrombotic events in IE patients compared to PV patients [4] with transformation to acute myeloid leukemia (AML) exceedingly rare in individuals with IE or other molecularly annotated forms of erythrocytosis [5]. A case is described in which application of the myeloid malignancy-targeted, next-generation sequencing (NGS) approach retrospectively provided insights into the molecular appearance of myelodysplastic syndrome (MDS)/AML in a patient with IE.

2. Case Report

An overweight 62-year-old male with hypertension and hyperlipidemia presented with a hemoglobin level of 20.4 g/dL, hematocrit of 0.59, normal white cell and platelet counts, and a mild eosinophilia (Table 1). The patient had no clinical signs of PV, normal spleen size, normal oxygen
from 41, 149, and 161 months. Amplicon libraries covering erythrocytosis and subsequent development of MDS/AML employed to detect mutations possibly contributing to the steroids but died of infection at 161 months.

The karyotype at 159 months was normal. The patient was not
forms, all consistent with MDS progressing to AML (Figure 1).
lymphocytes, dyserythropoiesis with basophilic stippling, and binuclear red cell numbers by both morphological and immunophenotypic
matocrit, the low serum EPO, a mild eosinophilia, and remains throughout the clinical course for a diagnosis of
patients, a high degree of suspicion
JAK2p.V617F or exon 12 mutations in the patient, a high degree of suspicion remained throughout the clinical course for a diagnosis of PV or “PV-like” MPN given the persistently raised hemocrit, the low serum EPO, a mild eosinophilia, and clinically a thrombotic episode (stroke). While NGS confirmed the absence of the JAK2 V617F and exon 12 mutations, several alternative mutations of JAK2 have been identified in sporadic cases of “PV-like” MPN and hereditary erythrocytosis [8–13], yet none were identified by NGS in the bone marrow sample at 161 months. Reinterrogation of sequencing data revealed this CBL mutation to be present a year previously at a VAF of 3.6% (Table 1).

### 3. Discussion

Despite the absence of either the JAK2 V617F or exon 12 mutations in the patient, a high degree of suspicion.
reported in both sporadic and familial MPN, respectively, particularly in those cases and kindred identified with IE [14, 15]. While no somatic mutations were identified within the entire coding region of SH2B3, this patient was heterozygous (T/C) for the common W262R SNP [16]. This SNP and others within SH2B3 have been shown to be associated with an increase in platelets, eosinophils, and elevated hemoglobin and hematocrit levels [17–22]. Furthermore, some recent evidence exists for the T allele of this SNP to be associated with the development of MPN and JAK2 V617F-positive hematopoiesis [16, 21, 22]. Despite in vitro functional analysis of another nonsynonymous SNP (E400K) in a patient with IE indicating no impairment of SH2B3 inhibiting JAK2-STAT5 activation, subtle loss of function induced by SH2B3 SNPs cannot be excluded [23]. While tempting to speculate a causal role for this SH2B3 SNP in the development of erythrocytosis in this patient, no specific evidence exists for such an association, suggesting involvement of additional genetic and/or epigenetic events.

Transformation to AML is a recurrent event in PV with reported risks of 2.3–14.4% at ten years [24]. However, transformation to or development of MDS/AML in other forms of molecularly annotated erythrocytosis or IE is exceedingly rare [25]. A true transformation of the erythrocytosis could neither be confirmed nor excluded in this case due to the absence of a pre-MDS/AML marker of clonality with the possibility that the erythrocytosis and MDS/AML represent two unrelated pathologies. Activating mutations of CBL, a negative regulator of receptor tyrosine kinases, including the p.L380P detected in this case, is recurrent in myeloid malignancies and is associated with progression of MDS to AML [26].

In conclusion, we describe a patient with IE possessing a clinical similarity to PV in which there are persistent erythrocytosis, a thrombotic event, and the acquisition of somatic mutations that resulted in MDS/AML. Employment of an NGS gene panel specifically targeted for investigation of IE has recently demonstrated the benefits of this type of approach [27]. The potential exists for identifying those patients at increased risk of developing a myeloid malignancy, enabling refined counseling and therapeutic decision-making throughout the disease course.

**Conflicts of Interest**

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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