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CASE REPORT

Maladaptive somatic gene rescue as predisposition to *JAK2* molecular abnormalities? Insights from an Israeli family

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Abstract

Eosinophilia associated with *PCM1::JAK2* fusion and classic Philadelphia (Ph)-negative myeloproliferative neoplasms (MPN) are both clonal disorders caused by a dysregulation of the JAK2 signaling pathway. The myeloid neoplasm with t(8;9)(p22;p24.1) and *PCM1::JAK2* rearrangement is now formally included among the myeloid/lymphoid neoplasms with eosinophilia (M/LN-eo) and tyrosine kinase fusion genes. To date, no data on genetic predisposition to M/LN-eo with *PCM1::JAK2* rearrangement are known, while it is well recognized that a subset of classic Ph-negative MPN segregates within families, suggesting a role for germline predisposition in disease etiology. Here we report the first pedigree with a case of classic Ph-negative MPN and a case of M/LN-eo with *PCM1::JAK2*. Our patient carried two acquired molecular abnormalities involving *JAK2* gene (PCM1::*JAK2* fusion and *JAK2* H531Y) along with a germline mutation (*BLM* Y736fs*5, variant allele frequency VAF 41.7%), whereas his sister had the canonical *JAK2* V617F driver mutation. This particular pedigree could arise the hypothesis of a genetic predisposition to acquire different *JAK2* molecular abnormalities as a maladaptive somatic genetic rescue of an underlying germline predisposition, namely the germline *BLM* Y736fs*5 mutation.

Keywords JAK2 · BLM · Familial · Predisposition · Myeloproliferative

Introduction

Eosinophilia associated with *PCM1::JAK2* fusion and classic Philadelphia (Ph)-negative myeloproliferative neoplasms (MPN) are both clonal disorders caused by a dysregulation of the JAK2 signaling pathway and characterized by uncontrolled production of blood cells.

The myeloid neoplasm with t(8;9)(p22;p24.1) and *PCM1::JAK2* rearrangement was incorporated as a new provisional entity in 2016 among the myeloid/lymphoid neoplasms with eosinophilia (M/LN-eo) [1]. In the revised ICC 2022 classification, it is now accepted as a formal member of this category [2]. Different breakpoint locations affecting *JAK2* and *PCM1* have been reported in the literature in patients with t(8,9), most of them leading to in-frame fusion gene and resulting in a fusion product juxtaposing the coiled-coil domains of PCM1 and the tyrosine-kinase domain of JAK2 [3, 4]. This hybrid protein likely facilitates the oligomerization of the PCM1-JAK2 chimeric fusion, resulting in constitutive activation of JAK2.

Recently, a first case of M/LN-eo with coexistence of PCM1::JAK2 and *JAK2* V617F mutation was reported [5]. To date, no data on genetic predisposition to M/LN-eo with *PCM1::JAK2* rearrangement are known, while it is well recognized that a subset of classic Ph-negative MPN segregates within families, suggesting a role for germline predisposition in disease etiology. Indeed, relatives of MPN patients show five- to seven-fold increased risk of developing MPN [6]. Moreover, 7.6% of apparently sporadic MPN in fact exhibit familial clustering [7].

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The precise etiologic fraction of causative germline variants underlying familial MPN (fMPN) remains largely unknown. To further muddy the waters of germline predisposition in MPN biology, the phenotypic driver mutations established in MPN (*JAK2*, *CALR*, *MPL*) are acquired somatically also in fMPN [7]. This along with phenomena of late-onset and incomplete penetrance make the observation of multiple cases of MPN within a family the most important clinical finding alerting for fMPN suspicion.

In this study, we report a pedigree including two siblings with fMPN, of whom one with M/LN-eo with *PCM1::JAK2* and the other with *JAK2* V617F-mutated essential thrombocythemia (ET).

Methods

JAK2 and *LNK* mutations were evaluated through allelic specific q-PCR and Sanger sequencing as previously described [8, 9]. FISH analysis optimized to detect translocations involving *JAK2* at region 9p24 was used as previously described [10].

Case report

In 2019 a 48-year-old male patient, of Ashkenazy Jews ethnicity, was referred to our department for a second opinion. He was firstly evaluated in Israel in 2017 because of leukocytosis (white blood cells 24.000/mmc) with eosinophilia (eosinophils 45%), increased LDH and splenomegaly. The bone marrow biopsy showed hypercellular marrow (100% cellularity), increased eosinophils, with absence of both blasts and fibrosis. Molecular evaluations excluded *JAK2* V617F mutation, *BCR*::*ABL* rearrangements, *FIP1L1*::*PDGFR* alfa and *PDGFR* beta rearrangements. At that point, a diagnosis of unclassified MPN was made. The patient started a treatment with steroids, with good control of eosinophilia, but then switched to hydroxyurea due to progressive leukocytosis. In 2018, a bone marrow DNA was evaluated with a next-generation sequencing (NGS) panel based assay (FoundationOne Heme panel, USA). The latter includes 406 cancer-related genes, 31 gene rearrangements and RNA-seq of 265 genes. The test identified *a PCM1::JAK2* fusion and a *BLM* Y736fs*5. According to this result and due to the progressive leukocytosis despite hydroxyurea (WBC 150.000/mmc), the patients was given ruxolitinib 15 mg BID, then increased to 25 mg BID.

In July 2019, he then came to our attention. We performed bone marrow evaluation with cytogenetics, revealing 46, XY t(8;9)(p22:p24) in 18/18 metaphases, and FISH analysis which confirmed *JAK2* rearrangement in 20/20 metaphases. Sanger sequencing of all *JAK2* exons on peripheral blood identified a C.1591 C > T pHis531Tyr somatic *JAK2* mutation (lymphocytes were negative). This variant is interpreted as likely benign according to ACMG criteria and VarSome classifiers. Given the recent findings on *LNK* and its potential role in driving fMPN susceptibility, we tested the patient but none of the known gene variants were found [11].

Notably, the familial history of the patient was remarkable for his sister being affected with *JAK2* V617F mutated ET, diagnosed after splanchnic vein thrombosis (Fig. 1).

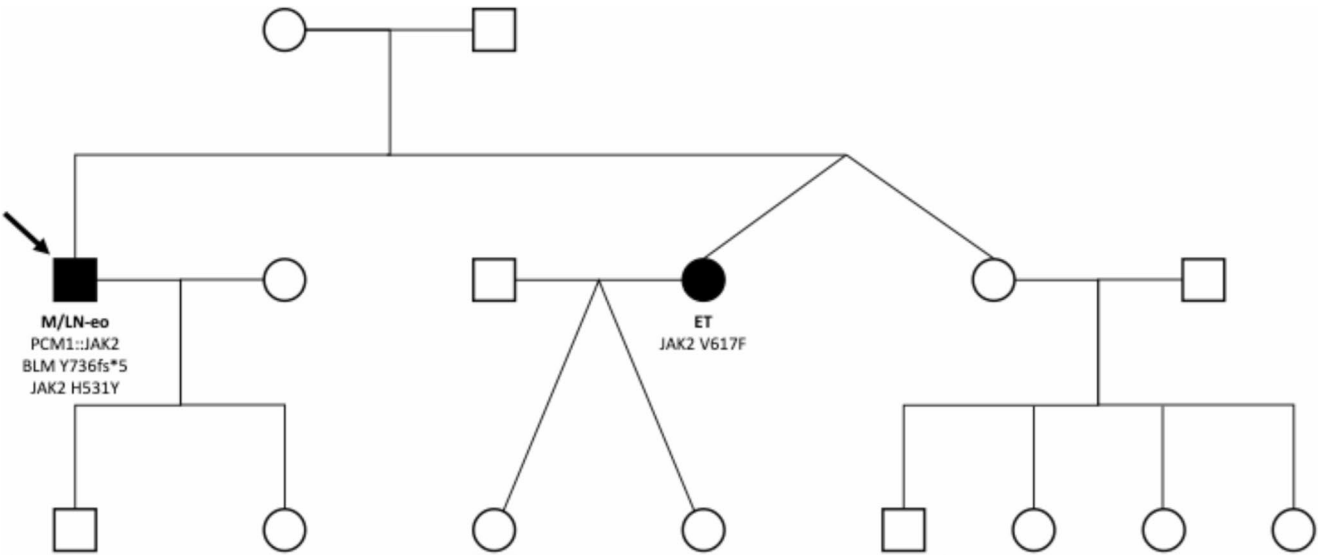


Fig. 1 Pedigree of the family with coexistence of both classic Ph-negative myeloproliferative neoplasm and myeloid/lymphoid neoplasms with eosinophilia with PCM1::JAK2. Filled symbols represent affected members; the arrow identifies the proband. Mutations are reported below each patient. ET: essential thrombocythemia; M/LN-eo: myeloid/lymphoid neoplasms with eosinophilia

At that point, a diagnosis of Myeloid/lymphoid neoplasms with *PCM1::JAK2* was made. Considering that responses on ruxolitinib are usually transient and due to the suspicion of fMPN, we suggested to recur to allogeneic hematopoietic cell transplant (allo-HCT) from an unrelated donor [12]. In February of 2020, the patient underwent allo-HCT from an unrelated donor and he is now in complete cytogenetic remission with full donor chimerism.

Discussion

To the best of our knowledge, this is the first family pedigree with a case of classic Ph-negative MPN and a case of M/LN-eo with *PCM1::JAK2*. Specifically, our patient carried two acquired molecular abnormalities involving *JAK2* gene (PCM1::*JAK2* fusion and *JAK2* H531Y) along with a germline mutation (*BLM* Y736fs*5, variant allele frequency VAF 41.7%), whereas his sister had the canonical *JAK2* V617F driver mutation. Unfortunately, her sister was not evaluated with NGS assay and we do not know whether she carried *BLM* mutations as well.

This particular pedigree could arise the hypothesis of a genetic predisposition to acquire different *JAK2* molecular abnormalities (point mutations and gene rearrangements) as a maladaptive somatic gene rescue (SGR) of an underlying germline predisposition, namely the germline *BLM* Y736fs*5 mutation. *BLM* encodes a RecQ-family DNA helicase protein, which is crucial for maintaining genomic integrity during DNA replication, including resolution of Holliday junctions [13, 14], telomeres attrition [15], and DNA damage response, e.g., in response to double-strand DNA breaks [16]. Homozygous germline mutations in *BLM* cause Bloom Syndrome, an autosomal recessive disorder characterized by growth deficiency, defects in skin pigmentation, chromosomal instability, and predisposition to cancer [17].

The prevalence of pathogenetic *BLM* mutations is particularly high (1%) in people from Ashkenazi Jewish ancestry [18]. Some studies have shown that heterozygotes subjects (carriers of the so-called BLM^{Ash} allele) have an increased risk of cancer compared to the general population [18, 19], although this association was not confirmed by others, and to date remains controversial [20, 21]. *BLM* haploinsufficiency, in which a half dose of the gene product is insufficient for full protein function in the maintenance of genome integrity, may be responsible of an increased mutation rate in the heterozygous cells [18, 19]. We hypothesize that in our patient's family the segregation of a germline *BLM* Y736fs*5 mutation might contribute to susceptibility to fMPN. In this scenario, *JAK2* molecular abnormalities may arise as a result of a maladaptive SGR. This is the process by which somatic cells acquire genetic changes that compensate for or counteract existing germline genetic defects. For Mendelian diseases, the beneficial effect provided by SGR at the cellular level does not necessarily translate into a clinical improvement of the patient; the so-called rescue effect may be neutral or even detrimental (maladaptive) [22]. SGR is most likely to be detected in rapidly expanding cells such as the hematopoietic stem cells. A prototypical example in hematology is SAMD9/9L syndrome [23]. In our patients, a maladaptive SGR might result in the occurrence of *JAK2* point mutations (JAK2 V617F and JAK2 H531Y) and *PCM1::JAK2* fusion. Whether a relation between *BLM* heterozygosity and *JAK2* gene involvement observed in this pedigree really exists or is the byproduct of a serendipitous observation remains an open question. To gain more insights into this, a screening for *JAK2* molecular abnormalities in Ashkenazi Jews carrying the BLM^{Ash} allele would be necessary.

In conclusion, we here reported the first couple of siblings with classic Ph-negative MPN and M/LN-eo with *PCM1::JAK2*, with a suspected fMPN inherited trait. The recognition of such cases is crucial as when allo-HCT is needed, the use of unrelated donors is preferred in order not to incur in the inadvertent transfer of the inherited trait, alike in other myeloid neoplasia settings [24].

Author contributions OB, CG and ER designed research and wrote the paper; DP performed molecular investigations; CG and ER finalized the manuscript. All Authors participated to analysis of data, revision of the draft and final approval.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethical approval This study was approved by the institutional Ethics Committee; procedures were in accordance with the Helsinki Declaration and samples were obtained with written informed consent.

Declaration to publish All authors have agreed with the content of the manuscript for publication.

Competing interests The authors declare no competing interests.

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