CALR mutations in patients with essential thrombocytopenia diagnosed in childhood and adolescence

After the recent discovery of various mutations of the CALR gene, <10% of adult patients with essential thrombocytopenia (ET) or primary myelofibrosis carry no identifiable molecular markers.\(^1\)\(^2\) More rarely, ET may occur also in children and adolescents.\(^3\) We evaluated, by Sanger sequencing, the mutation status of exon 9 of the CALR gene in 34 ET patients younger than 20 years of age at diagnosis (median age, 15 years; range, 1-19 years). The study was approved by the Institutional Ethic Committees. The median age at diagnosis and the respective follow-up of patients grouped according to their genotype (\(JAK2^{V_{617F}}\) mutated, CALR mutated, and wild type for \(JAK2\), CALR, and \(MPL\)) are summarized in Figure 1A.

\(\text{CALR}\) mutations were found in 8 patients, all \(JAK2\) and \(MPL\) wild type. On the whole, \(CALR\)-mutated ET represented 44% of \(JAK2\) and \(MPL\) wild-type ET and 23% of the entire series. This figure is lower than those reported in large series of adult patients, ranging from 67%...
to 84% of CALR mutations in JAK2- and MPL-negative cases.\(^1,2,4,5\) Among the 26 CARL wild-type patients, 15 were JAK2\(^{V617F}\) mutated (44% of the entire population), whereas 11 were negative for both JAK2 and MPL mutations (32% of the whole series) (Figure 1A). All CARL mutations observed in our patients have been previously reported.\(^1,2\) We found a 5-bp insertion in 3 patients, a 52-bp deletion in 4 patients, and a combined insertion and deletion in 1 patient. The age and hematologic findings at diagnosis were similar among JAK2-mutated, CARL-mutated, or JAK2, CARL, and MPL wild-type patients (\(P = 0.166\) for age, \(0.875\) for white blood cells, \(0.445\) for platelets, and \(0.279\) for hemoglobin concentration) (Figure 1B). Likewise, no differences were found between JAK2-mutated and CARL-mutated patients. Three of the 4 female patients harboring CARL mutations exhibited a monoclonal hematopoiesis (Figure 1B). Because, in these patients, the DNA samples were obtained several years after the diagnosis (14, 10, and 12 years, respectively), this finding might indicate the progressive expansion of the CARL-mutated clone over the years.

CALR-mutated ET in adults seems to have a rather indolent course.\(^1,2,4,5\) In general, children with ET rarely experience thrombosis or evolve to myelofibrosis.\(^6\) However, we found that CARL-mutated or wild patients were more frequently asymptomatic at diagnosis in comparison with patients carrying the JAK2 mutation (\(P = 0.0079\), Figure 1B). On the whole, 2 thrombotic events were recorded, both in patients without JAK2 and CALR mutations. It is noteworthy that the only patient who evolved into a post-ET myelofibrosis was in the CARL-mutated group.

CALR mutations have been recently reported as acquired somatic mutations also among patients with familial ET or primary myelofibrosis.\(^7\) Our series of patients included 2 members of the same family, that is, 2 cousins, male and female, diagnosed at the age of 17 and 18 years, respectively. Interestingly, only the female patient exhibited the CALR mutation, suggesting that the common genetic background is the main driver for developing familial myeloproliferative neoplasms.
To the editor:

Prospective detection of chikungunya virus in blood donors, Caribbean 2014

On December 5, 2013, chikungunya virus (CHIKV) was introduced into the Western Hemisphere. The first cases of autochthonous chikungunya fever were reported in Saint Martin, French West Indies (FWI), demonstrating local transmission.1 As of March 30, 2014, autochthonous cases have been recorded on 9 Caribbean islands, including more than 15,000 suspected cases in FWI.2

Chikungunya fever is an arboviral disease transmitted to humans by Aedes mosquitoes. It is characterized by febrile arthralgia and is responsible for massive epidemics.3

For years, concerns were raised about transfusion-transmitted infections (TTIs) during CHIKV outbreaks,4,5 and attempts were made to estimate the risk.6,7 During the La Reunion outbreak in 2013,6 modeling of TTI risk was based on (1) a proportion of asymptomatic infections of 15%, (2) a 6-day mean duration of viremia after clinical onset in symptomatic patients, (3) a 1.5-day mean duration between the beginning of viremia and clinical onset in symptomatic patients, and (4) a 7.5-day total duration of viremia in asymptomatic patients. Items (1) and (2) were obtained from observational studies,3,6 (3) and (4) being assumed. By using the same model, we estimated that the risk of CHIKV contamination from asymptomatic and presymptomatic viremic blood donors would be roughly equivalent.

In early 2014, the French Blood Agency implemented a strategy to prevent CHIKV TTIs in the FWI that relied on specific CHIKV nucleic acid testing (NAT) combined with postdonation self-reporting of febrile symptoms, accompanied by a 72-hour postdonation quarantine of nonpathogen reduced blood products.

CHIKV NAT screening was performed by using a Biomek NXP Workstation (Beckman Coulter), a NucleoSpin 96 Virus Extraction Kit (MACHEREY-NAGEL), and the RealStar Chikungunya RT-PCR Kit 1.1 (Altona Diagnostics).

Among the first 2149 plasma samples collected from February 24 to April 9,4 were positive (10^5 to 2.0 × 10^6 CHIKV genome-equivalents/mL or 10^3 to 2.0 × 10^5 plaque forming units [PFU]/mL); all were males living in Martinique who had not recently traveled abroad. Two remained asymptomatic (41 and 43 years old), and two reported febrile syndrome 12 to 24 hours postdonation (61 and 66 years old).

The full-length viral RNA genome, which was characterized directly from the plasma of the first patient by using next-generation sequencing, indicated Asian lineage and close similarity to Caribbean sequences described earlier (Figure 1).1,8 These cases are exemplary because they showed that the duration of presymptomatic viremia can be ≥12 hours and, at early stage, the
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