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Short Communication

An unusual long-term outcome of a child with primary myelofibrosis harboring a *JAK2* mutation☆

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ABSTRACT

We report an extremely rare case of a female child who presented the onset of primary myelofibrosis (PMF) harboring JAK2 (Janus Kinase 2 gene) mutation (JAK2V617F) when she was 15 months old. She was monitored over 25 years, a period in which she was treated with spleen radiotherapy and recombinant interferon α. She also underwent splenectomy when she was 13 years old, due to massive splenomegaly, anemia and various infection disease episodes. The longstanding evolution of the patient enabled us to verify that there were no complications related to post-splenectomy events and/or blast transformation. To the best of our knowledge, this is the first reported case of severe PMF with JAK2 mutation in a child. We provide evidence that a better quality of life and long survival in pediatric PMF may be provided by splenectomy.

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1. Introduction

Primary myelofibrosis (PMF) is an entity that belongs to the group of clonal stem cell chronic myeloproliferative neoplasm (MPN). PMF has an unknown etiology, and it is characterized by bone marrow (BM) fibrosis, extramedullary hematopoiesis, and a variety of clinical manifestations, mainly marked splenomegaly [1,2]. The median age of PMF in adults is 60 years and the incidence is approximately 1.3/100,000/year [2]. Pediatric PMF is an extremely rare disease [3]. An acquired *JAK2* mutation (*JAK2 V617F*) has not been detected in children, but has been demonstrated in approximately 50% of adults with PMF [3–5].

2. Case report

The case reported herein shows the clinical, hematological and molecular characteristics, and long-term evolution, in a 15-month-old non-white female child with a history of pallor and a progressive increase in abdominal volume beginning at birth. The patient was referred to the National Cancer Institute (INCA), Rio de Janeiro, Brazil, in June 1989. Her birth weight was 2.4 kg. There was no history of maternal illness during pregnancy or genetic familial diseases. Additionally, there was no previous history of infection. Physical examination revealed pallor, massive splenomegaly reaching the left iliac fossa, and hepatomegaly 5 cm below the right costal margin (Fig. 1). The first laboratory testing revealed hemoglobin 72 g/L; white blood cells 4.4×10^9/L; and platelets: 70×10^9/L. Routine laboratorial investigation tests were all normal. An abdominal ultrasound showed hepatomegaly and splenomegaly. The complete skeleton radiographs and chest X-ray were normal. Due to dry tap bone marrow (BM) aspirate, cytogenetic analysis was not performed. BM histopathology revealed diffuse reticulin fibrosis and increased myeloid and megakaryocytic lineages and a decrease in erythrocytic lineage cells. There was a slight megakaryocytic atypia. BM histopathological review found World Health Organization (WHO) classification criteria for PMF [6]. Incisional liver biopsy histopathology revealed hepatic fibrosis and myeloid metaplasia, represented by erythroid, myeloid and megakaryocytic cells. The patient was initially

Abbreviations: BM, bone marrow; MPN, myeloproliferative neoplasm; CMD, chronic myeloproliferative disease; DIPSS, dynamic-IPSS; EC, endothelial cells; HSCT, hematopoietic stem cell transplantation; INCA, Instituto Nacional de Câncer; IPSS, International Prognostic Scoring System; JAK2, Janus kinase tyrosine protein kinase 2; JAK-STAT, Janus kinase-signal transducer and activator of transcription pathway; PMF, primary myelofibrosis; OS, overall survival; WHO, World Health Organization.

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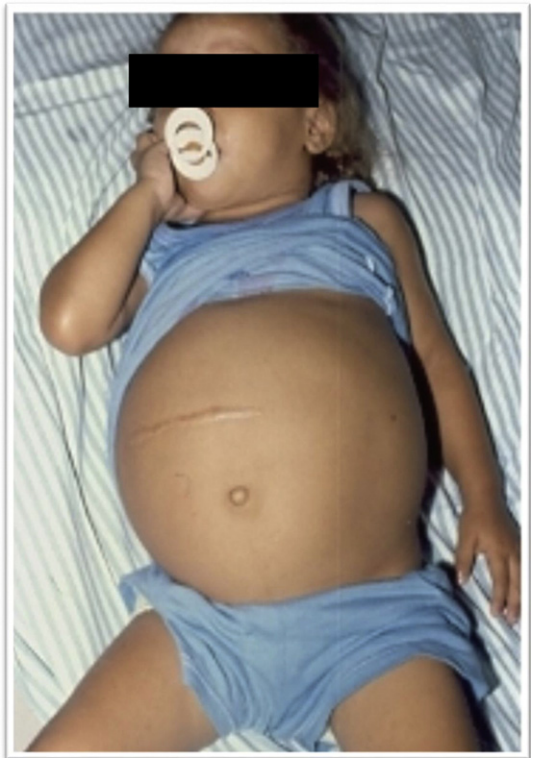

Fig. 1. Patient at 2 years old. The child's picture showing the increased abdominal volume and the scar of hepatic biopsy.

treated in a palliative manner, with red blood cell and platelet transfusions associated with hydroxyurea. At 3 years, splenic irradiation was performed with 3.5 cGy in 3 fractions, with toxicity limited to pancytopenia.

In June 1994, the patient was treated with recombinant interferon α (three million IU s.c. twice a week) but was given an irregular dose schema due to myelotoxicity and pneumonia. These procedures led to the partial reduction of spleen size (12 cm below the left costal margin) that was confirmed by ultrasonography. The patient was followed-up expectantly. Thereafter, a gradual increase in spleen size was observed and the patient developed recurrent episodes of infection, including pneumonia (n = 7), urinary infection (n = 1), otitis (n = 1) and tonsillitis (n = 2). The laboratory evolution is depicted in the Fig. 2A, B, and C. The splenectomy was performed when the girl was 13 years old. The spleen weight was 910 g. This approach improved her life quality considerably. No abnormality was found in her hematologic tests, as well as in abdominal ultrasonography, in the following 13 years. She had two healthy children born four years and eight years after the splenectomy. In June 2014, after 25 years of follow-up, her last peripheral blood count revealed 4.5 × 109/L erythrocytes, 8.3 × 10/L leucocytes and 375 × 10/L platelets. The mutation status of *JAK2* was investigated using genomic DNA from the spleen which was extracted using 2 sections of 20 μm from tissue fixed in formalin and embedded in paraffin, using QIAamp DNA FFPE Tissue Kit (Qiagen, Valencia, CA, USA). To detect the *JAK2V617F* mutation, a pre amplification step based on the protocol previously described by our group was performed using two pairs of primers and simultaneous amplification of normal and mutated alleles. Following the pre-amplification, the PCR product was diluted 1:10 and loaded into TaqMan Q-PCR assays performed according to our previously reported protocol [7]. The presence of mutant $JAK2^{V617F}$ allele was detected in the spleen sample (Fig. 2D, E, F). This study was approved by the institutional review board of INCA (number 062/08).

Our patient met all three major plus two minor criteria established by WHO 2008. The WHO classification system for PMF requires clinical histopathological and laboratory features [6]. The presence of *JAK2*, as well *MPL W515* or *CALR* mutations, reinforces but is not essential for the PMF diagnosis [6,8]. The low age of the patient at diagnosis was similar to the median age that was previously reported [3]. On the

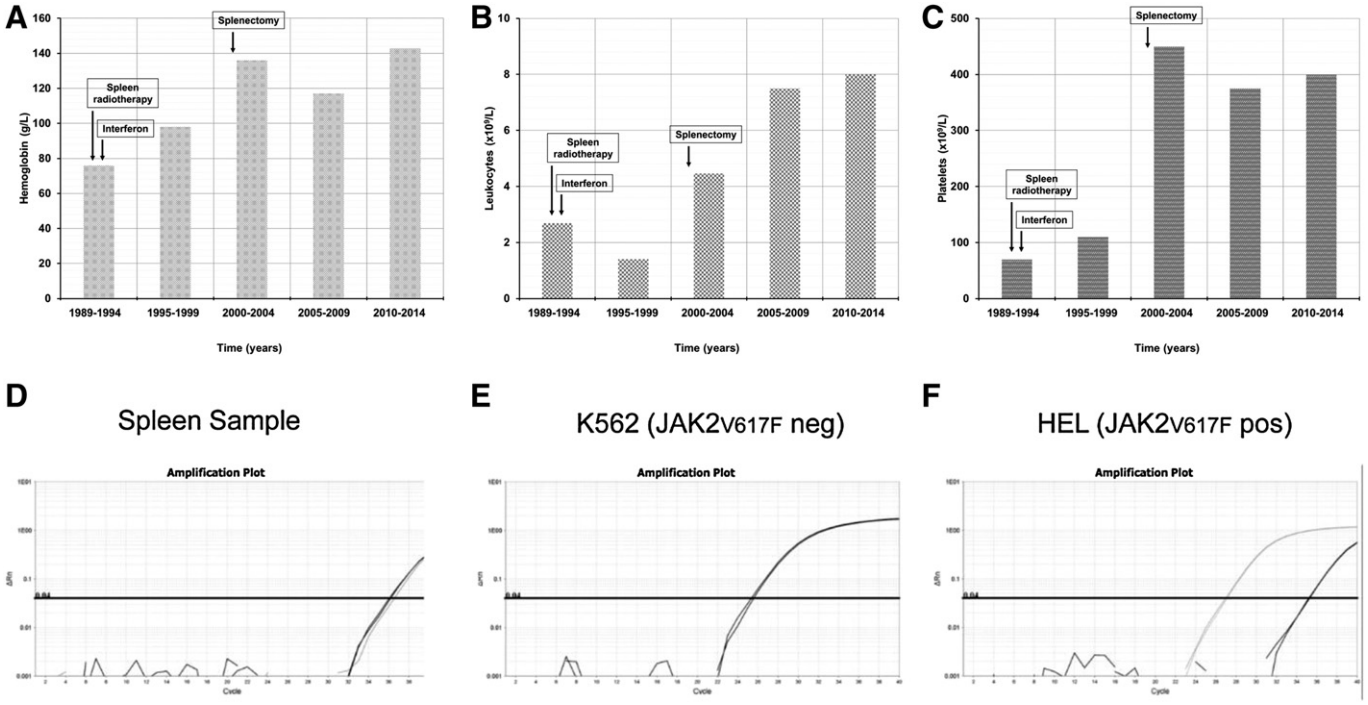

Fig. 2. Hematologic tests evolution during 25 years. A, B and C represent hemoglobin, leukocytes and platelets values, respectively. Each bar express the mean value the hematologic tests that were analyzed by period of each five years. Allele-Specific PCR for detection of *JAKV617F* mutation. D, DNA sample from the spleen patient biopsy. E, K562 and F, HEL cell lines used as negative (neg) and positive (pos) controls, respectively. Gray lines represent the amplification of the mutant JAKV617F allele while black lines represent the amplification of the wild type/non mutated *JAK2* allele.