Relationship between Characteristics of Genetic Study and Essential Thrombocythemia in Aged Patients

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ABSTRACT

Objective: Essential thrombocythaemia is a rare disease.
Design: A clinical study.
Materials and Methods: An 86-year-old man had marked thrombocytosis, increased leukocyte count and anemia. Analysis of the Janus Activating Kinase 2 (JAK2) V617F (GTC→TTC) gene from his leukocytes demonstrated the JAK2 mutation (V617F GTC→TTC, G1849T, exon 14).
Results: A diagnosis of essential Thrombocythaemia was made.
Conclusions: He has been good in health without chemotherapy since then.

KEY WORDS
essential thrombocythaemia, JAK2 mutation, aged patient

INTRODUCTION

Essential thrombocythaemia is a rare myeloproliferative disorder characterized by a high platelet count without Ph’ chromosome or increased erythrocyte mass1-5). Essential thrombocythaemia is clinically characterized by a near-normal life expectancy4-15). Erythropoietin binds to the erythropoietin receptor on the red cell progenitor surface and activates a JAK2 signaling cascade8,10-12,14-18).

SUBJECTS AND METHOD

A rare case of an 86-year-old male diagnosed with essential thrombocythaemia. He entered our hospital presenting with organic personality disorder.

The present study conformed to the provisions of the declaration of Helsinki in 1995 (as revised in Edinburgh in 2000)19).

RESULTS

From the age of 15 years, he worked in Japanese national railways for 21 years. He married and 2 children. Wandering symptoms and excitability appeared in 1996. He entered our hospital from the age of 65 years in 1996.

Laboratory data: WBC 18650 /μl, RBC 5530000 /μl. Hb 11.5 g/dl, Ht 39.3%, Plt 1212000 /μl. PT% 71%, PT(INR)1.17, APTT 56 s, Fib 474 mg/dl, FDP 11.6 ug/ml, D-Dimer 4.5 ug/ml, Ferritin 326.1 ng/ml.

Course after admission: Splenomegaly was not found. Laboratory data such as WBC 18650 /μl, RBC 5530000 /μl and Plt 1212000 /μl suggested essential thrombocythaemia. We performed gene analysis on the patient.

Genetic study: PCR of share leaf nucleus and circle nucleus of more than 100 cells showed a variant JAK2 V617F (GTC→TTC) gene ++.

Single fusion translocation of Neu Bcr-abl Fish chromosome search of share leaf nucleus and circle nucleus of 100 cells was 0%.

Course to date: During this period, no thrombotic complications were documented and transformation into acute myeloid leukemia, polycythemia vera, or myelofibrosis with myeloid metaplasia did not
occur. He died 86-years-old.

**DISCUSSION**

There was a significant association between the presence of a JAK2 mutation and an older age at diagnosis\(^1\text{a}\text{b}\text{c}\text{d}\). The link between age and a JAK2 mutation incidence, as our case, might represent yet another example of the influence of age on genetic instability.

Most cases of essential thrombocythaemia have survived long-term without liver transplantation. In Japan brain death liver transplantation cases is still not widely performed. Liver transplantation for familial amyloid polyneuropathy type I (transthyretin Met30-associated familial amyloid polyneuropathy, FAP TTR Met30) has been performed in nearly 400 cases worldwide since 1990\(^1\text{e}\text{f}\text{g}\). FAP I demonstrates the mutant transthyretin. We reported a case of FAP I in the resident of Hiroshima Prefecture in 1984. There have been some reports of the late-onset FAP I unrelated to the endemic foci in Japan. We also suspect some role of environmental factors and other genetic factor.

However, it is possible that small defects in transmitting epigenetic information through successive cell divisions, or maintaining it in differentiated cells, accumulate in a process that could be considered as an "epigenetic drift" associated with the aging process. External and/or internal factors can have an impact in the phenotype by altering the pattern of epigenetic modifications and thus modulating the genetic information. Monozygotic twins share a common genotype\(^\text{i}\). There are several possible explanations for these observations, but one is the existence of epigenetic differences\(^\text{j}\). To address this issue, we examined the global differences in a long cohort of monozygotic twin atomic bomb (A-bombing) survivors in Hiroshima\(^\text{k}\). We analyzed 190 of monozygotic twin A-bombing survivors who were exposed to A-bombing at 6th August in 1945 in Hiroshima city in Japan. The number of monozygotic twin in-utero exposed survivors was 14. More than 72 years were passed from exposure\(^\text{a}\text{b}\text{c}\text{d}\text{e}\). In our case of essential thrombocythaemia had no history of A-bombing, only he lived near Hiroshima long after A-bombing. The same identical DNA twin causes the different result of life against the same phenotype of DNA, because DNA methylation arise epigenetic difference because of both external and internal factors\(^\text{g}\text{h}\). A-bombing leukemia occurred in 1948 in Hiroshima and in 1947 in Nagasaki. The one of the biggest external factors is considered exposure of A-bombing.

To clarify the epigenetic drift, we investigated the ontogenic development of calcitonin-gene-related peptide (CGRP) in the rat thyroid and compared with that of calcitonin using the indirect-immunofluorescence method. Parafollicular cells with immunoreactivity to both CGRP and calcitonin first appeared at an early stage of gestation in the central portion of the thyroid. The cells immunoreactive to CGRP and to calcitonin had an almost identical ontogenic appearance. In 14-day-old and adult rats, C-IR cells also exhibited CGRP immunostaining, suggesting that these cells simultaneously produce and store CGRP during ontogeny. Future studies should now address the confirmation of the epigenetic drift of the rat thyroid parafollicular cells and essential thrombocythaemia.

**REFERENCES**