case report

inv (4)(p13q13) in patient with essential thrombocythemia: A case report

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The inv (4)(p13q13) cytogenetic abnormality is uncommon in hematologic malignancies. So far, it has not been previously reported in patients with essential thrombocythemia (ET). We report a first case of ET with inv (4)(p13q13) karyotype in a 69-year-old female patient who developed myelofibrosis at follow up. Conventional cytogenetic analysis from a bone marrow sample showed 46, XX, inv (4)(p13q13) [3]/46, XX [4] at diagnosis and subsequent analysis revealed the same abnormal karyotype during the myelofibrosis phase (46, XX, inv (4)(p13q13) [13]/46, XX [26]). The prognostic significance of this chromosomal abnormality is unknown.

KEYWORDS: Essential thrombocythemia; Myeloproliferative disorder; inv (4)(p13q13)

Essential thrombocythemia (ET) is an acquired myeloproliferative disorder characterized by an increased number of platelets ($>450 \times 10^9$/L) in the circulating blood. ET shares clinical, phenotypical and pathological similarities with other myeloproliferative neoplasms (MPNs), particularly polycythemia vera (PV) and primary myelofibrosis (PMF). ET is diagnosed by excluding the presence of other MPNs, and by excluding causes of reactive thrombocytosis. The incidence is approximately 1.5–2.5 per 100,000 population. The median age at diagnosis is 65–70 years, but the disease may occur at any age. The female to male ratio is approximately 2:1.[1–4] The most common complications are vascular complications, including a tendency for thrombosis, microvascular disturbances, and hemorrhage.[5] Survival of ET patients does not substantially differ from that of the general population. However, the main causes of morbidity are vascular complications. Transformation to myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) is an uncommon complication of ET, especially following therapy with alkylating agents or radioactive phosphorus.[5,6]

ET is a Philadelphia-negative classical myeloproliferative neoplasm, having much in common with other myeloproliferative neoplasms such as polycythemia vera and primary myelofibrosis.[5] The Janus kinase 2 gene (*JAK2*) V617F mutation is detected in approximately 50% of patients diagnosed with ET.[7,8] The incidence of clonal cytogenetic abnormalities in ET is approximately 5%, but no specific abnormality has been reported to date.[9] We report a patient with essential thrombocythemia, presenting with the chromosomal abnormality: inv (4)(p13q13).

CASES REPORT

In June 2012, a 69-year-old female patient was admitted to the internal medicine outpatient clinic with a complaint of excessive fatigue. Microcytic anemia and thrombocytosis (Hb: 6.6 g/dl, MCV: 72 fl,

WBC: 9.7×10^9/L, 1165×10^9/L) were detected in complete blood count. Microcytic anemia was consistent with iron deficiency anemia (IDA). Gastrointestinal blood loss was investigated as a possible cause of IDA. Colonoscopy and biopsy were consistent with the diagnosis of Crohn's disease. IDA was successfully treated. During this period salazopyrine was started for Crohn's disease. In retrospective analysis, thrombocytosis (approximately 1000×10^9/L) was determined to have been present for about 5 years. Despite successful treatment of IDA and Crohn's disease, persistent thrombocytosis was observed, and a chronic myeloproliferative neoplasm was subsequently investigated. No other causes of reactive thrombocytosis were found. *JAK-2* mutation analysis and t(9; 22) were negative in the peripheral blood. Hypercellular bone marrow and abundance of mature megakaryocytes and platelet clumps were observed. No significant increase in the erythroid and myeloid series and no other malignant infiltrations were observed. The patient's karyotype was determined with conventional cytogenetic analysis in the bone marrow sample and was designated as 46, XX, inv (4)(p13q13) [3]/46, XX [4] according to the ISCN (International System for Human Cytogenetic Nomenclature) 2013 (Fig. 1). Our patient was diagnosed with essential thrombocythemia according to World Health Organization (WHO) 2008 criteria; and because of high-risk ET, acetylsalicylic acid and hydroxyurea therapy were initiated. The platelet count decreased with this treatment but due to the ensuing neutropenia it was discontinued and anagrelide (1 mg/day) was started. The patient was asymptomatic and her complete blood count was normal, except for mild anemia over a period of 1 year with this treatment. After this period, severe anemia occured and there were no causes to explain this anemia. She became transfusion-dependent and a leukoerythroblastic blood film was observed. At the same time, splenomegaly was observed with abdominal ultrasonography. A bone marrow biopsy was performed and this revealed grade III reticular myelofibrosis. The same cytogenetic abnormality was detected (46, XX, inv (4)(p13q13) [13]/46, XX [26]). She was diagnosed with post-essential thrombocythemia myelofibrosis (post-ET MF). She remains transfusion-dependent at follow up.

DISCUSSION

ET is a chronic myeloproliferative neoplasm characterized by a persistent elevated platelet count in the peripheral blood and proliferation of enlarged megakaryocytes in the bone marrow.[10] Cytogenetic abnormalities in ET patients are very rare at diagnosis. Approximately 5% of ET patients show cytogenetic abnormalities which are non-specific. The most frequent cytogenetic abnormalities are trisomy 8, trisomy 9, and deletions of 13q and 20q.[11,12] The role of these chromosomal abnormalities as prognostic indices in disease transformation is not sufficiently studied.

In our case, persistent thrombocytosis was observed and a chronic myeloproliferative neoplasm was investigated. None of the cytogenetic abnormalities mentioned above in ET patients were detected in our patient. We observed a 46, XX, inv (4)(p13q13) [3]/46, XX [4] karyotype in our case with conventional cytogenetic analysis. This change is considered a clonal cytogenetic abnormality in ET because it is determined in 49% of metaphases.

To our knowledge, an inv (4)(p13q13) cytogenetic abnormality has not been previously reported in patients with ET. Although these pericentric inversions of chromosome 4 have not been described in other myeloproliferative disorders, they have been observed in AML. The breakpoints determined in our case are different from inversions of chromosome 4 previously described in cases with AML.[13–16] On the other hand, the same abnormality has been reported in only one case who has recurrent pregnancy loss.[17]

The breakpoint involved in the short arm of chromosome 4p13 in our case contains the *RhoH/TTF* (*ARHH*) gene. The *RhoH* gene encodes a member of the Ras superfamily of small GTPases and is restrictively expressed in hematopoietic cells and tissues.[18] Its function in myeloid cells is unknown. Activation of this gene with mechanism of inversion may have an important role in the pathogenesis of ET or hematological malignancy. The inv (4)(p13q28) karyotype was previously reported in two patients diagnosed with AML [13]. One of the breakpoints of the short arm of chromosome 4 (4p13) is the same as the breakpoint of our case. This finding may be associated with a transformation risk of ET patients to secondary myelofibrosis. This chromosomal abnormality was detected 2 years after the diagnosis, at which time post-ET MF had developed. As far as we know, the other breakpoint of inversion (4q13) does not contain any gene that has been associated with ET or hematological malignancies as yet.

This is the first reported case of inv (4)(p13q13) karyotype in ET. The prognostic significance and transformation to myelofibrosis or AML, associated