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A Case of Polycythemia Vera Accompanied with Neurofibromatosis Type 1

Semir PASA[1], Abdullah ALTINTAS[1], Kadim BAYAN[2], Yekta TUZUN[2], Timucin CIL[1], Orhan AYYILDIZ[1]

[1] Dicle University Faculty of Medicine, Department of Hematology
[2] Dicle University Faculty of Medicine, Department of Gastroenterology, Diyarbakır, TURKEY

ABSTRACT

Classical myelofibrosis syndromes (MPS) most frequently occur in adults, but MPS unique to childhood also exist. Such syndromes include juvenile chronic myelomonocytic leukemia (JMML), the MPS of monosomy 7 in childhood, familial chronic myeloid leukemia (CML), the transient MPS of infants with trisomy 21, and childhood forms of myelofibrosis. Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disorder with pigmentary abnormalities and are predisposed to benign and malignant neoplasms, mostly in children. MPSs were disproportionately common among children with NF1. Herein we reported a case of polycythemia vera (PV) accompanied to NF1 in an adult patient. The co-existance of NF1 and childhood MPS is a well known condition. The same relation was not demonstrated in adulthood NF1 patients according to our screening of the literature. Most of the reported cases were define a relation with JMML and monosomy 7 syndrome. Probably this is the first case of PV, a type of classic adult MPS accompanied to NF1.

Keywords: Neurofibromatosis, NF1 gene, Polycythemia vera

ÖZET

Nörofibromatozis Tip 1 ile İlişkili Bir Polisitemia Vera Olgusu

Klasik miyeloproliferatif sendromlar (MPS) daha sık erişkinlerde görülürse de çocukluk çağında da görülebilir. Bu sendromlar içinde jüvenil kronik miyelomonositik lösemi (JMML), çocukluktaki monozomi 7'nin MPS'u, familyer kronik myeloid lösemi, trizomi 21'li infantlarda görülen transient MPS ve miyelofibrozisin çocukluk formları sayılabilir. Nörofibromatozis tip 1 (NF1), pigmentasyon anomalileri, başta çocuklar olmak üzere benign ve malign neoplazi sıklığının artmış olduğu otozomal dominant kalıtılan genetik bir hastalıktır. NF1 hastası çocuklarda daha yüksek sıklıkta görülmektedir. Biz bu yazımızda erişkin bir NF1 hastasında gelişen polistemia vera olgusu sunduk. Çocukluk yaşta NF1 ile MPS' ın birlikteliği iyi bilinen bir durumdur. Benzer birliktelik erişkin hastalarda ise gösterilememiştir. Literatür taramalarımıza göre, JMML ve monozomi 7 ile birliktelikler tanımlanmış olsa da muhtemelen polistemia vera ile ilk saptanmış birlikteliktir.

Anahtar Kelimeler: Nörofibromatozis, NF1 Geni, Polistemia vera

INTRODUCTION

Classic myeloproliferative syndromes (MPS), including adult-type chronic myelogenous leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), and idiopathic myelofibrosis (IMF), are disorders that were initially belived to be pure proliferations of granulocytes, red blood cells, platelets, and fibroblasts, respectively. In 1951, they were grouped together as MPSs by Dameshek, who noted that, in various degree, stimulation of all hematopoietic precursors causing excessive proliferation.

Classic MPSs most frequently occurs in adults, but MPS unique to childhood also exists. Such syndromes include juvenile chronic myelomonocytic leukemia (JMML), the MPS of monosomy 7 in childhood, familial CML, the transient MPS of infants with trisomy 21, and childhood forms of myelofibrosis.[1]

Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disorder with an incidence of approximately 1 in 4000 people. Affected individuals show pigmentary abnormalities and are predisposed to benign and malignant neoplasms that typically arise in cells derived from the embryonic neural crest; include neurofibromas, optic gliomas, and pheochromocytomas.[2] In young children with NF1, the risk of malignant myeloid disorders, particularly JMML (formerly known as juvenile CML) and monosomy 7 syndrome, a childhood variant of myelodisplasia, is 200-500 times the normal risk.[3] Children (but not adults) with NF1 are at markedly increased risk of developing malignant disorders, including brain tumors, rhabdomyosarcomas, JCMML, and acute myelogenous leukemia.[4,5] In 1978, Brader and Miller[6] observed that MPSs were disproportionately common among children with NF1. The MPS associated with monosomy 7 (Mo 7) is clinically and pathologically similar to JMML but is recognized as a seperate chronic MPS in children.[7] Herein we reporte a case of PV accompanied to NF1 in an adult patient.

CASE REPORT

A fourty-year-old female patient who followed-up with a diagnosis of neurofibromatosis type-1 for about 25 years, admitted to our Department of Gastroenterology with stomachache, nausea, vomiting and massive hepatosplenomegaly. She had 13 cafe-au-lait spots over her trunk and extremities. Her mother an one of her sisters had NF1. On laboratory examination the leukocyte count was 15.100/μL, hemoglobin level was 18.1 g/dL, hematocrit was 54%, and platelet count was 803.000/μL. Plasma iron level was 32 μg/dL, iron binding capacitiy was 279 μg/dL, ferritin was 29 ng/mL, erytrocyte sedimentation rate was 2 mm/h, prothrombin time was 21.38 sec, INR was 1.76, vitamin B_{12} was 512 pg/mL, erythropoietin level was 0.91 mIU/mL, oxygen saturation was 96%, and pO_2 was 88 mmHg. The spleen size was 17 cm, and hepatic size was 23 cm on radiologic examination. She hospitalized to evaluate this polycythemic state. Neutrophils were 64%, lymphocytes were 28%, eosinophils were 4% and monocytes were 4% on peripheral blood smear examination. BCR-ABL was negative on PCR. Bone marrow aspiration and karyotypic analyse were normal. The diagnosis of polycthemia vera was established according to these clinical data.

DISCUSSION

The NF1 gene was cloned in 1990, which encodes a protein called neurofibromin that binds to members of the p21ras (Ras) family of signaling proteins and regulates their biochemical activity by accelerating hydrolysis of Ras-guanine nuclotide triphosphate (ras-GTP) to Ras-guanine nucluotide diphosphate (Ras-GDP).[4] A large body of experimental evidence implicates Ras proteins in normal and abnormal hematopoietic cell growth.[8-10] In particular, proliferative responses to many hematopoietic growth factors are associated with increased intracellular levels of Ras-GTP; activating RAS mutations are common in preleukemia and AML; and mutant RAS alleles efficiently transform myeloid cell lines. Biochemical and cell culture studies of leukemic bone marrow cells from patients with NF1 and hematopoietic cells harvested from embrios with homozygous inactivation of the murine NF1 gene have shown elevated levels of Ras-GTP, a decrease in the ability to accelerate GTP hydrolysis on Ras, activation of mitogen-activated protein (MAP) kinase (a downstream effector of Ras), and invitro hypersensitivity to granulocyte-macrophage co-

lony-stimulating factor (GM-CSF).[4] Ras activation is an essential component component of proliferative responses induced after receptor binding by variety of growth factors including IL3, GM-CSF, CSF-1, and stem cell factor (SCF).[5] Taken together, these results support the hypothesis that NF1 functions as a tumor-supressor gene in immature myeloid cells and that neurofibromin negatively regulates hematopoietic growth through its effect on Ras-GTP.

There are many case reports and studies about the pathogenetic relation between NF1 and MPSs. Therefore, the co-existance of NF1 and childhood (but not adulthood) MPS is a well known condition. The same relation was not demonstrated in adulthood NF1 patients according to our literature search. One another differency of our patient is the co-existance of PV. Most of the reported cases were defined a relation with JMML and monosomy 7 syndrome. Probably this is the first case of PV, a type of classic adult MPS accompanied to NF1. Normal karyotype of our patient is suggested that there may be a defect in intracellular signalisation and more investigational studies are needed to define this defect and to clarify this relation.

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Correspondence

Dr. Semir PAŞA

Dicle Üniversitesi Tıp Fakültesi

İç Hastalıkları Anabilim Dalı

Hematoloji Bilim Dalı

21280, Diyarbakır / TURKEY

e-mail: semirpasa@dicle.edu.tr

Tel: (+90.412) 248 82 33

Fax: (+90.412) 248 84 40