Adrenal incidentaloma and the Janus Kinase 2 V617F mutation: A case-based review of the literature

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ABSTRACT

Adrenal incidentaloma was detected in an 81-year-old male patient and a 37-year-old female patient who had been diagnosed with essential thrombocytosis. Each patient’s Janus Kinase 2 (JAK2) V617F mutation was positive, and they were evaluated as having non-functional adrenal incidentaloma. The JAK2 activates the signal transducers and activators of transcription (STAT) proteins which then activate the phosphoinositol-3 kinases, Ras, mitogen-activated protein (MAP) kinases, and transcription. Constitutive activation causes cell proliferation and dysregulation of apoptosis. It is thought that STAT3 activation-mediated JAK family kinases have a central role in the solid tumor cell series. Permanent activation of STAT3 and STAT5 causes tumor cell proliferation, survival, metastasis, and an increase in tumor-mediated inflammation in solid and hematologic tumors. According to our literature screening, irregular JAK signaling, seen at the pathogenesis of many solid and hematologic tumors, has not been previously evaluated with regard to adrenal tumors. As a result, our cases are the first coexistence of JAK V617F mutation with adrenal incidentaloma in the literature. Because of this, we think that JAK2 mutation must be evaluated to clarify the etiology of adrenal incidentalomas.

Key words: Adrenal incidentaloma, essential thrombocytosis, janus kinase 2 V617F mutation

INTRODUCTION

The term “incidentaloma” is used for the adrenal masses that are determined randomly during radiologic or surgical exploration. With the common use of imaging methods, the occurrence of so-called incidentalomas, or clinically silent adrenal masses, has increased. The rate of these coincidental adrenal masses was found to be 6% out of a total of 7065 autopsies in 25 series (1-32%), and the prevalence in abdominal computerized tomographies (CT) performed for non-adrenal-related causes was 2-7%.11 Essential thrombocytosis (ET) is a myeloproliferative disease that is characterized by isolated thrombocytosis and thrombo-hemorrhagic complications and has an incidence rate of 1-2/100,000 annually. The V617F somatic mutation in the Janus kinase (JAK) 2 gene, which causes the substitution of phenylalanine for valine at position 617, has recently been found in the majority of patients with a myeloproliferative disease. In 50% of patients with ET, the JAK2 V617F mutation was positive.21 The relationship between adrenal incidentaloma and the JAK2 V617F mutation has never been defined in the literature; therefore, we present for the first time the combination of the JAK2 V617F, essential thrombocytosis, and adrenal non-functional incidentaloma.

CASE REPORTS

Case 1

An 81-year-old male patient had been undergoing treatment for 12 years after being diagnosed with ET. At the time of diagnosis, his platelet count was 1,700,000/mm3. Reactive thrombocytosis was ruled out. Two years previously, he had been checked for the JAK2 V617F mutation
and was found to be homozygous positive. The patient had a 20-year history of type 2 diabetes mellitus (DM) and hypertension. He was taking metformin (2 g/day), irbesartan (150 mg/day), anagrelide (2 mg/day), and acetylsalicylic acid (80 mg/day). There was no family history of essential thrombocytosis or adrenal incidentaloma. The findings of the physical examination were as follows: Blood pressure, 130/80 mmHg; heart rate, 66 beats/min; and body mass index (BMI), 26.4 kg/m². During patient follow-up, he underwent an upper abdomen MRI because of abdominal pain. An ovoid mass was detected and it was minimally enhancing with intravenous gadolinium. It was approximately 23 × 33 mm at the suprarenal region and was compatible with a well-circumscribed adenoma. The patient was evaluated as having adrenal incidentaloma, and functional evaluations were carried out accordingly. After low-dose dexamethasone suppression cortisol was given, a level of 1 mcg/dl was determined to be normal. The levels of serum dehydroepiandrosterone sulfate (DHEA-S), testosterone, vanillylmandelic acid (VMA) at 24 hrs urine, metanephrine, normetanephrine, and the plasma aldosterone/rennin activity ratio were also normal. The patient was admitted for follow-up for non-functional adrenal incidentaloma, but he died at the 13th month due to myocardial infarction.

**Case 2**

The JAK2 V617F mutation was heterozygous positive for a 37-year-old female patient who was evaluated for thrombocytosis etiology (platelet count was 1,560,000/m³). The patient had been taking medication (anagrelide 2 mg/day and acetylsalicylic acid 80 mg/day) for ET for two years and had no other illnesses. Additionally, she was having regular menstrual cycles. The patient’s mother had hypertension, but there were no other medical concerns in the family history. She was admitted with non-specific abdominal pain, and the findings of the physical examination were as follows: Blood pressure, 110/70 mmHg; heart rate, 80 beats/minute; and BMI, 21.7 kg/m². There was no abdominal tenderness, defense reaction, or rebound. Her complaints were incompatible with premenstrual syndrome or periodic pain syndromes, such as Familial Mediterranean Fever (FMF).

The abdominal ultrasonography (USG), performed due to complaints of abdominal pain, detected a nodular lesion at the left suprarenal region of 1 cm in diameter. The contrast-enhanced upper abdominal tomography performed as a result of the USG findings showed a nodular lesion that was 11 × 8 mm in diameter and minimally-enhanced. This was compatible with a well-circumscribed, regular contoured adenoma. The density of the nodule was 10 Hounsfield units, and it was interpreted as a radiologically benign adenoma. A low-dose dexamethasone suppression cortisol level of 1 mcg/dl was determined to be normal. The levels of serum DHEA-S, testosterone, metanephrine, normetanephrine, VMA at 24 hrs urine, and the plasma aldosterone/rennin activity ratio were normal. The patient was admitted for follow-up for non-functional adrenal incidentaloma, and she experienced no problems over the 15-month follow-up period.

**Discussion**

Adrenocortical tumors, mostly benign adenomas, occur frequently in the general population and nowadays are most often found incidentally. Most of the adrenal masses that are detected by chance consist of adenomas that arise from the cortex, with most showing no hormonal activity.[3] The prevalence increases with age.[8] In our research, 97.4% of all cases were benign, and most of these (89.7%) were non-functional adenomas.[8]

No data exists in the literature regarding the incidence of adrenal adenoma in coexistence with ET or other myeloproliferative diseases.

The JAK2-STAT pathway is essential for the secretion and action of both the corticotropin-releasing hormone (CRH) and pro-opiomelanocortin (POMC), which is processed via the adrenocorticotropic hormone (ACTH).[6] The ACTH acts primarily to promote the production and secretion of the glucocorticoid cortisol. The ACTH/cyclic adenosine monophosphate (cAMP) signaling shows its effect via the JAK2-PI3K/Akt-PDE3-cAMP pathway to regulate P450scc expression and consequential steroid secretion.[6] There have been studies conducted that investigated the etiopathogenesis of adrenal incidentaloma. However, the exact cause could not be defined. Although adrenocortical tumors are mostly sporadic, they can also coexist with hereditary cancer forms like Beckwith-Wiedemann syndrome (11p15.5), Li-Fraumeni syndrome (p53 locus at 17p13), and multiple endocrine neoplasia type 1 (MEN1 at 11q13).[8-11] The Ras proteins (H, N, and K) are membrane-associated proteins which are the most mutated human cancer oncogenes.[11] Oncogenic Ras proteins are different from the normal homologues in that they have only a single amino acid at the 12th, 13th, and 61st position.[13] GTPase activity deficiency in this Ras oncogenic protein may result in irregularity of the normal regulation mechanisms that control cell proliferation.[14] In adrenal tumors, p53 gene mutations are frequently detected, and it has been suggested that there are multigenetic defects at the tumorigenesis. Moreover, the oncogenic effects have been accused of being the cause. In a trial that was conducted on patients with adrenal
tumors, 46% of the tumor tissue was found to have K-ras mutation. In a different study, N-ras mutations in codon 61 were suggested to contribute to adrenocortical tumor formation. In some of the patients with adrenocortical tumors, BRAF/RAS and epidermal growth factor receptor (EGFR) mutations were detected. In patients with activating mutations at the Ras/Raf/MEK/ERK and EGFR pathways, inhibitors can be investigated for the targeted therapies with clinical trials of selected patients. The STAT proteins are activated by JAK2, which then activates the phosphoinositols-3 kinases, Ras proteins, Map kinases, and transcription. Constitutive activation causes cell proliferation and dysregulation of apoptosis. In 2005, four different study groups separately showed a somatic single-point mutation in the valine-phenylalanine at the 617th position (V617F) of the JAK2 kinase. This mutation at JAK2 consists of changing guanine to thymidine. Most of the cytokine receptors have contact with more than one JAK kinase, but it has been shown that the JAK2-deficient myeloid precursors do not answer to erythropoietin, thrombopoietin or the granulocyte-monocyte colony stimulating factor. This data suggests that JAK2 is the dominant JAK kinase in myeloid cell proliferation and differentiation. In myeloproliferative diseases or other human malignancies, no other alternative mutation at this codon has been detected. The JAK2 V617F mutation has been detected in most patients with ET or idiopathic myelofibrosis (IMF), except for those with polycythemia vera. There have been some studies that have conducted evaluations to determine whether the JAK2 V617F mutation causes any other hematologic malignancies or whether it contributes to non-hematologic tumors. Inappropriate JAK2 signaling causes the survival of some solid tumors and cell proliferation. At a trial in which 10507 participants were evaluated for JAK2 mutation, 18 patients (0.2%) had positive results. Despite this low overall frequency, testing positive for this mutation increased the risk of having a myeloproliferative disease or cancer and enhanced the mortality risk when compared with patients who were negative for the JAK2 mutation. The non-hematologic malignancies that were seen in the 18 patients with positive JAK2 mutation were as follows: Two patients had lung cancer, two had breast cancer, and two had non-melanoma skin cancer. Basal cell carcinoma, testis, brain, liver and bladder cancer were each found in one patient, respectively. Two different malignancies were detected in four patients. In a different trial conducted with 618 human cancer patients (486 non-hematologic tumors), the JAK2 V617F mutation was evaluated. In the non-hematologic group, patients that had more than 30 different tumors were included. Signal transducer and transcription activator proteins are one of the families of growth factor answers and cytokine-mediated transcription factors. Permanent STAT3 activation is oncogenic and is very common in various human cancers such as breast, prostate, head/neck, ovarian and is also found in other solid and hematologic tumors. The Janus family kinases (JAK1, JAK2, JAK3, and Tyk2) activate STAT via the cytokines and it is thought that the STAT3 activation-mediated JAK family kinases have a central role in the solid tumor cell series. Permanent activation of STAT3 and STAT5 causes tumor cell proliferation, survival, metastasis, and an increase in tumor-mediated inflammation in solid and hematologic tumors. Pyrazolyl pyrimidine AZD1480 is a strong competitive ATP inhibitor of the JAK2 kinase, and this inhibition can suppress tumor growth over STAT3 activation. This data confirms that the JAK kinase is a molecular target for tumors other than those in the myeloproliferative neoplasm and supports the development of JAK inhibitors for the treatment of solid tumors that host permanent STAT3 activation.

Irregular JAK signalization, seen at the pathogenesis of many solid and hematologic tumors, has not been previously evaluated with regard to adrenal tumors according to our literature screening. Detection of the JAK2 mutation should be an intervention point for targeted molecular treatment. As a result, our cases demonstrate the first coexistence of the JAK2 V617F mutation with adrenal incidentaloma in the literature. Because of this, we think that the JAK2 mutation must be further evaluated to clarify the etiology of adrenal incidentalomas.

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