Case Report

JAK2 V617F Mutation in a Patient With Adrenal Incidentaloma and Essential Thrombocythemia

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Abstract: A 62-year-old woman is incidentally found to have adrenal mass, 24*15 mm in diameter, on abdominal computed tomography for evaluation of acute arterial occlusion. Biochemical screening was negative for a functioning adrenal tumor. Routine blood works were significant for a platelet count of 572,000/mm³. Platelet counts were measured again and it’s found as 1,080,000/mm³. The JAK2 V617F mutation was positive which investigated for the etiology of thrombocytosis. Inappropriate JAK2 signaling causes the survival of some solid tumors and cell proliferation. Our case is the third coexistence of the JAK2 V617F mutation with essential thrombocytosis and non-functional adrenal incidentaloma.

Keywords: JAK2 V617F Mutation; Adrenal Incidentaloma; Essential Thrombocythemia.

INTRODUCTION
An adrenal incidentaloma is a mass lesion greater than 1 cm in diameter, coincidentally encountered by radiologic examination [1]. This entity is the result of technological advances in imaging studies such as computed tomography (CT) and magnetic resonance imaging (MRI). Malignancy is an uncommon cause of adrenal incidentaloma in patients without a known diagnosis of cancer however patients with adrenal incidentalomas should be evaluated for the possibility of malignancy and subclinical hormonal hyperfunction.

The chronic myeloproliferative disorders (CMPD) are classified into several subgroups, of which four are well characterized: chronic myeloid leukemia (CML), polycythemia vera (PV), primary myelofibrosis (PMF), and essential thrombocythemia [2]. Although, CML, PV, and PMF can be diagnosed based on the well accepted clinical and laboratory criteria; ET is diagnosed by excluding the causes of reactive thrombocytosis, and also by excluding presence of the other CMPDs [3]. The V617F somatic mutation in the Janus kinase (JAK) 2 gene, has recently been found in the majority of patients with a myeloproliferative disease. In 50% of patients with ET, the JAK2 V617F mutation was found positive [4]. The JAK2 mutation is a genetic marker that is directly associated with the pathogenesis of the myeloproliferative disorders, and for this reason it is a powerful tool for analysis of the molecular and cellular basis of these disorders. Our case is the third coexistence of the JAK2 V617F mutation with essential thrombocytosis and adrenal non-functional incidentaloma [5].

CASE REPORT
A 62-year-old woman presented to our internal medicine clinic with digital ulcer and unregulated diabetes mellitus. Past medical history included diabetes mellitus, hypertension, and burger disease. Acute arterial occlusion in the left lower extremity due to superficial femoral arter thrombosis treated with thrombectomy and warfarin two years ago and splenectomy due to splenic infarct secondary to splenik ven trombosis. Because of the initial concern regarding acute arterial occlusion, computed tomography scan of the abdomen performed after oral and intravenous administration of contrast material revealed an enhancing nodule, 24*15 mm, in the right adrenal gland region. But Incidental adrenal masses not eximinated whether functional.

She was being treated with intensive insulin regimen, nebivolol 5 mg, nifedipin 60 mg and asetil sasilisik asit 100 mg. The patient's blood pressure was 170/90 mm Hg, her pulse is regular and 85 beats per minute. There was no atrial fibrilation in elektrocardiyography. Echocardiography was normal which taken at another hospital. Rest of the physical examination was completely normal. Levels of serum electrolytes, and the results of tests of renal, liver, and thyroid function were all normal. Routine blood works were significant for a platelet count of 572,000/mm³, WBC of 16 x
10^9/L and hemoglobin 10.4g /dl. The terms of the etiology of digital ulcers antinuclear antibodies and antineutrophil cytoplasmic antibodies were negative. In the foreground, thrombocytosis was connected to the iron deficiency anemia and infected digital ulcers. Platelet counts were measured again and it’s found as 1.080.000 / mm³. No atypical cells were observed in the peripheral blood smear.

Bone marrow aspiration and biopsy was not performed due to patient’s refusal. But arterial and venous thrombosis in patients with a history of digital ulcers and follow-up to be a million due to the increase in the platelet count was considered essential thrombocytosis. The JAK2 V617F mutation was positive which investigated for the etiology of thrombocytosis. Based on thrombocytosis and positivity of the JAK2 V617F mutation, a putative diagnosis of the essential thrombocythemia was established. The incidental adrenal adenoma detected previously drawn with thin-slice computed tomography was confirmed. The dexamethasone suppression test, plasma aldosterone/renin activity ratio, 24-hour urine free cortisol, 24-hour urine collection for epinephrine and norepinephrine and were all normal. She was admitted for follow-up for non-functional adrenal incidentaloma and essential thrombocythemia.

DISCUSSION

Based on this evaluation, the patient was believed to have adrenal incidentaloma and essential thrombocythemia. This case illustrates several important points. The first is the history of acute arterial occlusion and the second is that the occurrence of non-functional adrenal incidentaloma, essential thrombocythemia and JAK2 V617F mutation in a diabetic, hypertensive patient with a diabetic foot and digital ulcer. Before any form of decision is made, several question have to be raised, such as whether adrenal incidentaloma results from JAK2 V617F mutation, and whether a procoagulant state is due to JAK2 V617F mutation. The limitation of our report is the lack of biopsy-proven diagnosis of essential thrombocythosis due to patient refusal.

Based on autopsy studies, adrenal masses are among the most common tumors in humans [6]. Numerous autopsy studies have examined the frequency of incidental adrenal nodules. In a report on 25 studies, the overall frequency of adrenal adenomas in 87,065 autopsies was 6% [2].

The term “incidentaloma” has been used for an adrenal mass that is discovered during diagnostic testing for another condition, rather than testing performed because of the suspicion of an adrenal disorder [6]. This entity is the result of technological advances in imaging techniques [6].

The majority of adrenal incidentalomas are benign and non-functional [7, 8]. Other infrequently reported diagnoses include cortisol-secreting adrenocortical adenoma, pheochromocytoma, adrenocortical carcinoma, and metastatic carcinoma [9].

The optimal diagnostic approach to a patient who has an adrenal incidentaloma has not been addressed precisely [7, 9,10]. However, it is reasonable to start by taking a careful history and performing a physical examination, focusing on the signs, symptoms suggestive of adrenal hyperfunction and tests for malignancy and hormonal hypersecretion [11, 12]. The possibility of malignant disease is the major concern when an incidental adrenal mass is identified.

Among 2005 patients with adrenal incidentalomas, adrenocortical and metastatic carcinoma was found in 4.7% and 2.5% of the patients, respectively [9]. The generally accepted recommendation regarding clinically nonfunctional masses is to excise lesions >6 cm, whereas masses 4 cm without suspect imaging are not generally resected [7].

Cytology from a specimen obtained by fine-needle aspiration (FNA) biopsy cannot distinguish a benign adrenal mass from the less common adrenal carcinoma. It can, however, distinguish between an adrenal tumor and a metastatic tumor [13].

The exact etiology of adrenal incidentaloma remains unclear. Development and function of differentiated pituitary neuroendocrine cells are regulated both by hypothalamic trophic hormones and by intrapituitary cytokines and growth factors. These cytokines have been shown to stimulate the hypothalamic–pituitary–adrenal axis in vivo and pituitary ACTH production [14-16].

This past year marked the 20th anniversary of the discovery of the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway [16]. The JAK (Janus tyrosine Kinase)-STAT (Signal Transducer and Activator of Transcription) pathway represents one such signaling cascade whose evolutionarily conserved roles include cell proliferation and haematopoiesis. The JAK belongs to a family of non-receptor protein tyrosine kinases of approximately 130 kDa that comprises of JAK1, JAK2, JAK3 and TYK2 (non-receptor Protein Tyrosine Kinase-2). STATs are latent cytoplasmic transcription factors. They become activated after recruitment to an activated receptor complex. Seven STAT proteins namely STAT1 to 6, have been identified, including STAT5a and STAT5b, encoded by distinct genes [17, 18]. The valine-to-phenylalanine (V617F) alteration constitutively activates JAK2 that results in increased phosphorylation of its substrates and leading to increased cytokine responsiveness of myeloid cells. Approximately 95% of patients and and in 50 -60% of
those with essential thrombocytopenia or primary myelofibrosis with polycythemia vera have mutated JAK2 V617F [19].

The mutation at JAK2 has changing guanine to thymidine. Most of the cytokine receptors have contact with more than one JAK kinase, but the JAK2-deficient myeloid precursors have no answer to erythropoietin, thrombopoietin or the granulocyte-monocyte colony stimulating factor [20]. Secretion and action of both the corticotropin-releasing hormone and pro-opiomelanocortin depends on JAK2-STAT pathway. It is processed via the adrenocorticotropic hormone [5, 21] acting primarily to promote the glucocorticoid production and secretion. The ACTH/cyclic adenosine monophosphate (cAMP) signaling shows its effect via the JAK2-P13K/Akt-PDE3-cAMP pathway in order to regulate P450scc expression and consequent steroid secretion [5, 22].

CONCLUSION

The efforts made to understand the molecular mechanisms and the elucidation of JAK2-STAT pathway been able to provide many insights into disease mechanisms. It has become the basis for new pharmacologic agents. Thus the knowledge stock about this pathway can provide in which these insights are affecting the practice of medicine [23].

REFERENCES

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