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Coexistence of Essential Thrombocythemia and Pituitary Adenoma: A Case Report of a Saudi Female Patient

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Abstract:

Essential thrombocythemia (ET) is a malignant hematological disease that has the ability to progress to acute leukemia or transform into other myeloproliferative neoplasms (MPNs). The coexistence of ET and other MPNs with pituitary adenoma (PA) is rare. There are no reports of cases of secretory PA of prolactin hormone in combination with ET. This case was reported in a young woman from Saudi Arabia who had the secretory PA present in combination with ET. The 20-year-old patient was treated for a micro-PA with hyperprolactinemia. The patient was referred to the hematological service for thrombocytosis. There was no history of thrombosis, cardiovascular risk factors, or constitutional symptoms. Laboratory tests showed that platelet levels consistently lagged from 700 × 103/μL to 1000 × 103/μL for 1 year. Hemoglobin 13 g/dL, white blood cells (WBCs) 6 × 103/μL, and normal WBC differential. The peripheral blood smear was inconclusive. A peripheral blood sample was sent for the cytogenetic study of myeloproliferative diseases, which came to be positive for c.1849G>T p.(V617F) mutation in the EXON 14 Janus kinase 2 (JAK2) gene. The patient was diagnosed with a MPN, ET with positive exon 14 JAK2, at low-risk category. Evidence suggests that MPNs in combination with endocrinological diseases are rare. However, there is a high incidence of MPN and unrelated tumors such as PA. Further research is recommended to thoroughly investigate endocrine tumors and look beyond secondary thrombocytosis that leads to thrombocythemia as in ET.

Keywords:

Essential thrombocythemia, microadenoma, myeloproliferative neoplasm, pituitary adenoma, thrombocytosis

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Introduction

According to the World Health Organization (WHO), myeloproliferative neoplasms (MPNs) are a group of hematological malignancies that are classified into polycythemia vera (PV), essential thrombocythemia (ET), myelofibrosis, chronic myelocytic leukemia, chronic eosinophilic leukemia, chronic neutrophilic leukemia, not otherwise specified and MPNs-unclassifiable (MPNs-U).[1] ET is a chronic Philadelphia-negative MPN associated with an increase in the number and size of circulating platelets, resulting from one or more mutations in an oncogene that causes increased platelet production. Up to 60% of ET cases being the result of a Janus kinase-2 gene mutation (JAK2 V617F).[2,3] According to the revised international prognostic score for ET (IPSET) classification, the risk of the ET patient is divided into four main classifications: very low, low, intermediate, and high risk based on mutated JAK2/MPL, age (>60 years), having at least one of the cardiovascular risk factors (e.g., smoking, hypertension,

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obesity, dyslipidemia, and diabetes), and a history of thrombosis.[4,5]

The incidence of ET ranges from 0.2 to 2.5/100,000 people per year, a prevalence of 38 to 57 cases per 100,000 people, with approximately 40%–50% of patients asymptomatic at the time of diagnosis. Although the disease can occur at any age, the median age at the diagnosis is between 65 and 70 years, with a female-to-male ratio being approximately 2:1 The clinical picture includes vasomotor symptoms and complications due to thrombosis and bleeding, and thrombocytosis is an incidental finding on routine blood count.[2,3,6] While in a third of cases the disease remains benign and does not lead to complications, it can proceed with thromboembolic and hemorrhagic complications and transform into more aggressive myeloid neoplasms.[6-8]

Pituitary adenomas (PAs), also called pituitary neuroendocrine tumors, are non-metastatic, slow-growing, and benign neoplasms that originate in the pituitary gland.[9,10] PA can be described as microadenoma (<10 mm), macroadenoma (larger than 10 mm), and giant pituitary tumors bigger than 40 mm. Based on their hormone-secreting capabilities, PA can be classified into functional or nonfunctional.[9-11] In patients with functional PAs, the cell type of which they are composed causes increased secretion of one or more anterior pituitary hormones and has endocrine clinical phenotypes associated with varying symptoms of hyperpituitarism or hypopituitarism, depending on the level of secretion of the affected hormones. In patients with nonfunctional PA, hormones are not secreted, but they can potentially compress the surrounding areas of the anterior pituitary gland, leading to hormone deficiency and may exhibit mass effect-related symptoms, such as vision loss and headaches.[10-12]

The pathophysiology of PA and ET is quite distinct and often unrelated, although rare cases have been reported in the literature.[13-15] Thus, an earlier study by Ciresi *et al*. reported a case of growth hormone (GH)-secreting PA, which was associated with the ET-JAK2 V617F mutation.[13] A more recent study by Gupta and Dutta reported GH-secreting PA in hematologic malignancies other than ET, such as PV, chronic myeloid leukemia (CML), thrombocytopenia, acute leukemia, multiple myeloma, and non-Hodgkin's lymphoma.[14] The study of the genetic background of 14 cases (1996–2015) of acromegaly with malignant neoplasms showed that 4 (28.6%) cases were attributed to MPNs (1 ET, 1 CML, and 2 PV), 21.4% of cases were positive for JAK2 V617F mutation with three 3 of the reported 14 cases associated with PA.[14] However, JAK2 V617F-positive mutation as a risk factor for PA is not well understood and ongoing research is required. In addition, there are no reports of cases of secretory PA of prolactin hormone in combination with ET. Thus, this case was reported in a young woman from Saudi Arabia who had secretory PA in combination with ET.

Case Report

This is a case of a 20-year-old unmarried Saudi woman who presented to an endocrinology clinic with complaints of recurrent headaches over the past 4 years, deterioration over the past year, due to general weakness, absence of galactorrhea, regular menstrual cycle, absence of hirsutism, no symptoms of hyper hypothyroidism, and no signs of acromegaly. There was no Cushing's disease or loss of consciousness. After laboratory test and X-ray examination, pituitary microadenoma with hyperprolactinemia was diagnosed. A patient kept on cabergoline 250 μg once a week and was referred to the hematology clinic for a high platelet count of more than 700 × 103/μL, the level re-emerging to 1000 × 103/μL. The patient denied a history of thrombosis, as well as the absence of a recent surgical intervention. The patient had negative B symptoms and a family history of the same health condition.

On physical examination, the patient appeared healthy, without pain or respiratory distress, although underweight with a body mass index of 17.9 kg/m^2. The patient's vital signs were stable: Blood pressure 112/60 mm Hg, pulse 70 beats/min, respiratory rate 20 breaths/min, and oxygen saturation 100% in room air. Head-and-neck examination showed no palpable lymphadenopathy or goiter. Galactorrhea was not detected, although there was slight hyperpigmentation under the breast on the examination of the mammary glands. The patient had minor changes in the respiratory and cardiovascular systems. Abdominal examination revealed no palpable organomegaly.

Laboratory investigation showed hemoglobin 13 g/dL, leukocyte counts 6 × 103/μL with normal differential count, platelet count mean 1000 × 103/μL, MPV 6.6 fl, prolactin level 60.89 ng/mL, follicle-stimulating hormone 5, 6 IU/μL. L, luteinizing hormone 10.38 IU/L, testosterone 1.13 nmol/L, cortisol 168 pmol/L, thyroid-stimulating hormone 2.3 mIU/estradiol 295 pmol/L, progesterone <0.7 nmol/L, ferritin 14.8 ng/mL, iron 18.6 μmol/L, and total iron-binding capacity (TIBC) 49 μmol/L. Liver panel, electrolytes, and kidney panel were normal. An abdominal ultrasound showed mild splenomegaly, an otherwise unremarkable study. In contrast, magnetic resonance imaging showed that the pituitary gland was enlarged, with a smooth bulge measuring 8.0 mm.

According to the WHO, the diagnosis of ET consists of four main criteria: (1) platelet count ≥450 × 109/L, (2)

bone marrow biopsy showing a predominant line of megakaryocytes with hyper lobulated nuclei, (3) presence of JAK2, MPL, or calreticulin (CALR) mutation, and (4) absence of meeting the WHO criteria for other MPNs.[3-5] The patient refused a bone marrow biopsy. Therefore, a peripheral blood sample was sent for the cytogenetic study of myeloproliferative diseases. The result was negative for the Philadelphia chromosome (BCR/ABL), proto-oncogenic thrombopoietin receptor (MPL), and CALR, but a positive c.1849G>T p.(V617F) mutation in the EXON 14 JAK2 gene. The patient was diagnosed with a MPN, ET with positive exon 14 JAK2 V617F at low-risk category. Aspirin 100 mg was administered orally once a day. Since then, the patient has been followed up in the hematology clinic without progression or transformation, and her last platelet count was 530 × 103/μL without additional cytoreduction drugs.

Discussion

ET is a genetic mutation in which megakaryocytes in the bone marrow stimulate the excessive production of platelets into the peripheral circulation.[4] ET risk classification helps to make decisions about the treatment and future risk of thrombosis. In this case, the patient was diagnosed with low-risk JAK 2 mutation-positive ET and was prescribed low-dose aspirin.[3-5] Cytoreductive therapy is recommended for the higher risk categories if symptoms persist, despite taking aspirin or if the platelet count is above a million/μL, which was not appropriate in this scenario.[3,5] Additional evidence suggests the benefit of adding cytoreductive therapy to aspirin in patients with low-risk JAK2-mutated ET.[4] However, there are no data on the indication of cytoreduction therapy in the presence of another tumor (i.e., PA), as in this case. Hence, the prescription was limited to aspirin management.

Thrombosis, bleeding, or transformation to leukemia or other forms of MPNs may complicate the ET. Although the ET transformation to acute leukemia is uncommon and is less frequent than with PV, there is, nevertheless, a <2%/year chance of conversion to leukemia in each case. According to IPSET, the risk of leukemic transformation in patients with ET is associated with advanced age (>60 years), platelet count <1 million/μL and leukocyte count >11 × 109/L, as well as a genetic mutation with the JAK2; population at a higher chance transformation to leukemia than a CALR mutation.[4,15]

This case with exon 14 JAK2 V617F mutated and, thus, was considered a case with a high risk of transformation. Similarly, earlier studies have shown that ET patients are at increased risk of transformation and developing other unrelated tumors.[12,16] For instance, several malignancies have been reported among ET patients, such as breast cancer, gastric cancer, colon cancer, and cancer of the tongue.[17-20] While treatment was individual in all previously reported cases, the majority of ET cases with secondary nonhematologic tumors were JAK2 mutation positive. This raises the question of how the clinicians should deal with V617F JAK2 positive mutated ET patient (s) and indicates the importance of early screening for solid malignancies, such as breast and colon cancer. This observation requires further study and proposal of recommendations for the early detection of malignant neoplasms of organs in the JAK 2 V617F mutation.

Conclusion

Evidence suggests that MPNs in combination with endocrinological diseases are rare. However, there is a high incidence of MPN and unrelated tumors such as PA. Further research is recommended to thoroughly investigate endocrine tumors and look beyond secondary thrombocytosis that leads to thrombocythemia as in ET.

Ethics approval

Our institution does not require ethical approval for reporting the individual cases or case series.

Author contributions

All authors contributed equally.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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