Erythrocytosis and thrombocytosis secondary to hyperandrogenism caused by ovarian Leydig cell tumor

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Abstract
Both erythroblasts and megakaryocytes contain androgen receptors, and testosterone regulates their expression. However, the exact mechanisms of testosterone’s hematopoietic effects are poorly understood. We report a case of perimenopausal women with severe hyperandrogenism caused by pure Leydig cell ovarian tumor accompanied by concomitant erythrocytosis and thrombocytosis. Substantial, immediate, and persistent decrease in both red blood cell count and platelet count after testosterone-secreting tumor removal in our patient suggests testosterone’s synergistic effect on erythropoiesis and thrombopoiesis. Further studies are worthy and might help to enlighten testosterone’s hematopoietic effects.

Key words: Testosterone; hematopoiesis; erytrocytosis; trombocytosis; Leydig cell tumor

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DOI: 10.21040/eom/2017.3.4.6

Received: June 04th 2017
Accepted: June 18th 2017
Published: June 30th, 2017

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Funding: None.

Conflict of interest statement: The authors declare that they have no conflict of interest.

Patient consent: Patient gave her written consent for this case study.

Data Availability Statement: All relevant data are within the paper.
1. Introduction

Both erythroblasts and megakaryocytes contain androgen receptors, and testosterone regulates their expression [1,2]. However, the exact mechanisms of testosterone's hematopoietic effects are poorly understood. We report a case of perimenopausal women with severe hyperandrogenism caused by pure Leydig cell ovarian tumor accompanied by concomitant erythrocytosis and thrombocytosis.

2. Case Report

A 53-year-old woman presented with androgenic alopecia (Figure 1a), hirsutism (Figure 1c and 1e) (Ferriman–Gallwey score of 31), facial redness, and hoarse voice, all of which progressed after her last menses 2 years ago. Endocrinological evaluation disclosed serum testosterone level of 34.8 nmol/L (normal range 0.1–1.4) and suppressed follicle-stimulating hormone and luteinizing hormone levels. Blood routine disclosed erythrocytosis and thrombocytosis. The patient had red blood count (RBC) of 5.6 × 10^{12}/L (normal range: 3.86–5.08), hemoglobin level of 170 g/l (normal range: 119–157), hematocrit level of 0.552 (normal range: 0.356–0.470), mean corpuscular volume of 93.1 fl, and platelet count (PC) of 465 × 10^9/L (normal range: 158–424). White blood cell count, erythrocyte sedimentation rate, and C-reactive protein were all within the normal ranges. Abdominal and pelvic computed tomography, transvaginal ultrasonography, and pelvic magnetic resonance imaging failed to localize testosterone-secreting tumor. Normal dehydroepiandrosterone levels and normal adrenal glands indicated ovarian origin of hypertestosteronemia. Laparoscopic bilateral ovariectomy was performed. Focal tumor mass was not found on macroscopic examination of surgical specimens. Microscopic examination disclosed a part of tumor tissue in the hilus of the left ovary. Tumor was torn apart and cauterized during surgery. Tumor tissue consisted of acidophilic cells containing lipid pigment (Figure 1b) and stained positively for inhibin (Figure 1d) and calretinin (Figure 1f). The diagnosis of hilus Leydig cell tumor was established. On 14th post-operative day, testosterone level normalized (1.7 nmol/l) erythrocyte count (4.8 × 10^{11}/L), hematocrit level (0.450), hemoglobin level (141 g/L), and thrombocyte count (388 × 10^9/L) were within normal ranges. Testosterone levels, RBC, and PC remained normal 3 months after the surgery.

3. Discussion

This is the first reported case of erythrocytosis and thrombocytosis secondary to hypertestosteronemia. Ovarian Leydig cell tumors are exceedingly rare and present 0.2% of hyperandrogenism cases [3]. Their association with erythrocytosis was reported in two cases [4,5]. Besides in myeloproliferative disorders, concomitant erythrocytosis and thrombocytosis are rarely found. Thrombocytosis was observed in anemic hemodialysis patients receiving erythropoietin therapy [6]. This effect is poorly understood, but it is confirmed that iron deficiency has a great role in thrombocytosis pathogenesis [6]. Studies on animal models disclosed that acute erythropoietin administration increases both RBC and PC, but its chronic high-dose administration is associated with thrombocytopenia [7]. Testosterone

Figure 1. Female patient diagnosed with ovarian Leydig cell tumor presented with androgenic alopecia (a) and excessive hirsutism (c and e). Tumor tissue consisted of acidophilic cells containing lipid pigment (hematoxylin and eosin, ×400) (b). Immunohistochemistry showed positive expression for inhibin (×200) (d) and calretinin (×200) (f)
has a dose-dependent stimulatory effect and does not increase erythropoietin levels [8]. Testosterone was also found to be effective therapy for thrombocytopenia in patients with myelodysplastic syndrome [9]. Synergistic effect of testosterone has never been studied in humans, although Sullivan reported that castration decreases both thrombopoiesis and erythropoiesis in mice [10]. Substantial, immediate, and persistent decrease in both RBC and PC after testosterone-secreting tumor removal in our patient suggests testosterone’s synergistic effect on erythropoiesis and thrombopoiesis. Further studies are worthy and might help to enlighten testosterone’s hematopoietic effects.

Author contributions:
GM gave an idea for the case study, participated in drafting the article and gave the final approval. DB performed the surgery and was engaged in patients follow-up, and gave the final approval. IK reviewed the previously published literature, wrote the article and gave the final approval. MV participated in drafting the final version of the manuscript and gave the final approval.

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