Human Pathology (2005) **36**, 120–127

ELSEVIER

Human PATHOLOGY

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Erythropoietin and erythropoietin receptor system in a large uterine myoma of a patient with myomatous erythrocytosis syndrome: possible relationship with the pathogenesis of unusual tumor size

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Received 27 October 2004; accepted 29 October 2004

Keywords:
Erythropoietin;
Erythropoietin receptor;
Erythrocytosis;
Leiomyoma

Summary The rare condition of women with erythrocytosis and a concurrent myomatous uterus has been classified as "myomatous erythrocytosis syndrome". Substantial myoma size has been noted as a common denominator in this condition in which recent evidence have confirmed erythropoietin (Epo) production by myoma tissues themselves. Apart from its primary endocrine role in controlling erythropoiesis, Epo has been demonstrated to mediate several cellular processes such as angiogenesis, mitogenesis, and inhibition of apoptosis by autocrine and paracrine mechanisms. Recently, Epo and its receptor (Epo-R) have been shown to be involved in the growth, viability, and angiogenesis of several malignant tumors including human female reproductive organ malignancies. In this paper, we researched on Epo and, as a first in the literature, Epo-R immunoexpression in a large uterine myoma of a term pregnant patient suffering from the myomatous erythrocytosis syndrome. Eight nongravidic leiomyomas and 8 gravidic leiomyomas were used as control group samples. Apart from confirming Epo production by myoma smooth muscle cells in the myomatous erythrocytosis syndrome, we reveal in this pathologic condition a characteristic strong Epo-R expression in myoma endothelial cells and a weak and sporadic Epo-R expression in myoma smooth muscle cells. The striking presence of Epo-R within myoma tissues in the case of the myomatous erythrocytosis syndrome allows us to speculate that myoma Epo production, besides determining erythrocytosis through systemic effects, may contribute, acting by autocrine and paracrine mechanisms, in determining the large myoma size almost always observed in this condition. Finally, we confirm a less but specific immunostaining for Epo in uterine myomas of patients without erythrocytosis and, as a first in the literature, we prove a weak and sporadic

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0046-8177/$ – see front matter
doi:10.1016/j.humpath.2004.10.009

Epo-R expression in these lesions. These last results may contribute to knowledge of the yet unclear etiopathogenesis of the most common human gynecologic neoplasm.

1. Introduction

The rare condition of women with erythrocytosis and concurrent myomatous uterus (almost exclusively large myomas) has been classified as "myomatous erythrocytosis syndrome" [1,2]. Restoration and maintenance of normal hematological values after hysterectomy are the third feature characterizing this pathologic condition [3]. According to LevGur and Levie [1], less than 40 cases of myomatous erythrocytosis syndrome have been reported in the English language literature since the first case was described in 1953 by Thomson and Marson [4]. The exact pathophysiology of this condition is unclear; a number of theories have been proposed [1]. Particularly, recent evidence confirmed erythropoietin (Epo) production by myoma tissues of patients with associated erythrocytosis [5,6]. Erythropoietin is a low-molecular-weight (30 kd) glycoprotein hormone mainly produced by the liver in the fetal life and by the kidney in the adult life [7]. This hormone, regulated by oxygen concentration, stimulates erythropoiesis by promoting the proliferation and differentiation of erythroid precursors [8,9]. Erythropoietin elicits its actions binding a specific receptor (Epo-R), which belongs to a family of cytokine receptors that have no tyrosine kinase domain [7]. For many years, Epo was thought to be solely involved in erythropoiesis. This assumption was challenged when Epo and Epo-R were found to be expressed in numerous other tissues aside from the liver and the kidney and in several nonerythroid physiological and pathological compartments including central nervous system cells [10], trophoblast cells [11], human female reproductive organs [12-14], endometriosis [15], malignant tumors of female reproductive organs [16,17], breast cancer [18], and numerous other human malignancies [19]. Moreover, Epo is able to stimulate proliferation and interfere with the differentiation of the myoblasts [20]. Apart from its endocrine function in controlling erythropoiesis, evidence of several autocrine and paracrine activities of Epo elicited by a range of cellular responses including angiogenesis, mitogenesis, chemotaxis, mobilization of intracellular calcium, and inhibition of apoptosis [21] have been provided by all these reported findings. In the uterus, autocrine and paracrine Epo/Epo-R systems have been demonstrated, with Epo taking an important place in angiogenesis via Epo-R expressed in the vascular endothelial cells of the endometrium [13]. Surprisingly, Epo production in uterine tissue is estrogen dependent, revealing a new Epo regulation that is different from oxygen concentration [13]. Furthermore, recent evidence confirmed Epo production in large myomas of patients with associated erythrocytosis [5,6]. Bearing in mind all reported Epo/Epo-R properties (uterine expression and activity, angiogenic and mitogenic actions, hypoxia and hormone inducibility, and involvement in the development and progression of tumors of female reproductive organs), it is supposable that the autocrine or paracrine Epo/Epo-R system may play a role in the unusual large size of uterine myomas of patients with myomatous erythrocytosis syndrome. In the present study, we investigated Epo and, as a first in the literature, Epo-R immunoexpression in a large uterine myoma of a patient suffering from the myomatous erythrocytosis syndrome. Through the demonstration of Epo-R expression, we could speculate that Epo effectively acted on the unusual size of this myoma. Furthermore, investigating for Epo and Epo-R immunoexpression in control samples of myomas with a diameter of less than 10 cm from patients without erythrocytosis, we could supply new evidence that might contribute to knowledge of the yet unclear etiopathogenesis of the most common human gynecologic neoplasm.

2. Materials and methods

The myoma samples used in this study were from a patient with myomatous erythrocytosis syndrome at 38 weeks of gestation (case patient) and from 16 otherwise healthy women (control subjects). In the control group, 8 case subjects were term pregnant women. Upon admission, each patient gave a signed written consent to the use of surgical samples for scientific aims.

The patient with myomatous erythrocytosis syndrome was 34 years old. Her obstetric history was significant for one previous cesarean delivery. She was admitted in our division of prenatal medicine for diagnosis of a large uterine myoma at end pregnancy. Ultrasonography evaluation reported a regular ongoing pregnancy in the uterus with a large round, solid, heterogeneous, and well-circumscribed posterior mass measuring 29 × 20 × 11 cm; this mass, confirming all previous instrumental evaluations, was consistent with a large posterior uterine myoma arising from the isthmocervical uterine region. Laboratory results were normal, except for the hemoglobin level of 15.40 g/dL (normal, 11.6-14.9), the hematocrit of 48.3% (normal, 35.0%-44.5%), and the red blood cell count of 5.75 million/μL (normal, 3.89-5.2); these values were consistent with the diagnosis of erythrocytosis, mostly considering the physiological hemodilution during pregnancy. A serum Epo level of 17 mU/mL was observed (normal, <20). Although this parameter is within the reference range, it was inappropriately high on account of erythrocytosis. An obstetric consultation decided for a cesarean delivery. Because of the large size of the mass and the possible need