

# Myomatous erythrocytosis syndrome: further proof for the pathogenic role of erythropoietin

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## ABSTRACT

**Background:** Myomatous erythrocytosis syndrome is defined by the combination of erythrocytosis, myomatous uterus and persistent restoration of normal haematological values after hysterectomy. A pathogenic role of erythropoietin is suggested by clinical and experimental data.

**Case report:** A postmenopausal patient is described with the classical clinical signs of the myomatous erythrocytosis syndrome. During hysterectomy we demonstrated a large gradient between the erythropoietin levels in the uterine vein and artery, providing direct evidence for *in vivo* erythropoietin production by the myomatous uterus.

**Conclusion:** While erythropoietin and its receptor are consecutively expressed in normal and myomatous uterine tissue, it is amazing that erythrocytosis occurs so rarely in such a frequent disorder as uterine myomatosis. We strongly advocate cytogenetic examination of the myomatous tissue of subsequent patients with this entity.

until 1968, when the presence of erythropoietin in an extract of a myomatous uterus was proposed by increased radioactive iron incorporation in a hypoxic polycythemic mouse model. Since then, the presence of erythropoietin has been demonstrated in tumour extracts by functional assays, and a variety of immunological and molecular techniques. Although the preoperative erythropoietin activity or levels were only occasionally absolutely increased, a decrease in the serum erythropoietin activity or level after hysterectomy was found in most, but not every patient. We present a case with the typical features of the myomatous erythrocytosis syndrome and provide further evidence for the pathogenic role of erythropoietin by demonstrating direct *in vivo* production of erythropoietin by the myomatous uterus.

## CASE REPORT

## KEYWORDS

erythrocytosis, erythropoietin, myoma, uterus

## INTRODUCTION

The combination of erythrocytosis, myomatous uterus and persistent restoration of normal haematological values after hysterectomy is defined as the myomatous erythrocytosis syndrome.<sup>1</sup> Since the first description in 1953 more than 40 cases have been reported. Already in 1955, a causative role of erythropoietin produced by the myomatous uterus was hypothesised, but analytical problems hampered the demonstration of erythropoietin production in the tumour

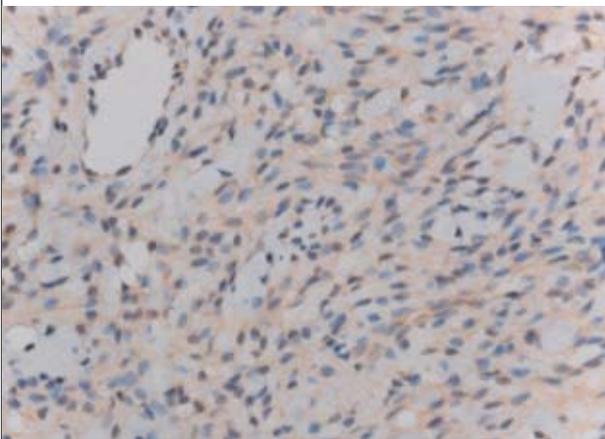
A 45-year-old female was admitted because her haemoglobin (Hb) level had increased from 8.8 mmol/l (reference interval 7.4 to 10.1) to 10.8 mmol/l in five years. The relevant medical history revealed endometriosis of the left adnex treated by adnexectomy, mild uterine myoma and hypertension. For two years she had been taking tibolone because of climacterial symptoms. On physical examination her blood pressure was 140/90 mmHg. The patient was mildly obese (weight 74 kg, height 172 cm) with moderate hypertrichosis. The spleen was not enlarged. Laboratory examination showed a haematocrit (Ht) 0.53 l/l (RI: 0.36 to 0.47), erythrocyte count 5.69 x 10<sup>6</sup>/l (RI: 3.9 to 5.6), while the platelet and leucocyte counts were normal. An extensive biochemical profile, including serum cobalamin and overnight dexamethasone

suppression test, was within the reference interval. The O<sub>2</sub> saturation of 97% (RI: 96 to 100), the pulmonary function tests and chest X-ray were normal. Abdominal ultrasound revealed normal-sized kidneys and spleen. The serum erythropoietin level was 8.9 pmol/l (RI: 4.5 to 19.6). The measured total erythrocyte volume was 1850 ml (24.6 ml/kg), which was 118% of the calculated volume of 1570 ml ( $[1.06 \times \text{age}] + 822 \times \text{m}^2$  body surface area). Bone marrow examination showed mildly increased but otherwise normal erythropoiesis with normal megakaryopoiesis and myelopoiesis. At pelvic examination the gynaecologist noticed that the myomatous uterus had increased in size, despite the postmenopausal status. During the follow-up period the Hb level increased to 11.9 mmol/l and Ht to 0.57 l/l while the erythropoietin level increased to 17 pmol/l. Because the uterus also increased in size during this period of time, it was decided to perform a hysterectomy. During the operation samples were drawn from the uterine vein and artery. The erythropoietin level was 12.7 pmol/l in the uterine artery while the concentration was 40 pmol/l in the uterine vein. A 1235 gram uterus was removed with multiple myomas, the largest diameter being 8 cm. Sample suspensions of the myomatous tissue and normal endometrium were made by homogenising 4 mm<sup>3</sup> tissue in 2 ml PBS using a Potter's homogeniser. The erythropoietin concentration in the supernatant of the homogenised myomatous tissue was 50 pmol/l while the concentration was <1.0 pmol/l in the supernatant of the normal myometrium. Immunohistochemical staining with monoclonal antibody against erythropoietin (Santa Cruz Biotechnology, Santa Cruz, CA, USA) showed the presence of erythropoietin in myomatous tissue cells (figure 1) while the staining was negative in the normal myometrium cells (figure 2). After hysterectomy the Hb and Ht persistently returned to normal values and the serum erythropoietin level decreased to 6.3 pmol/l.

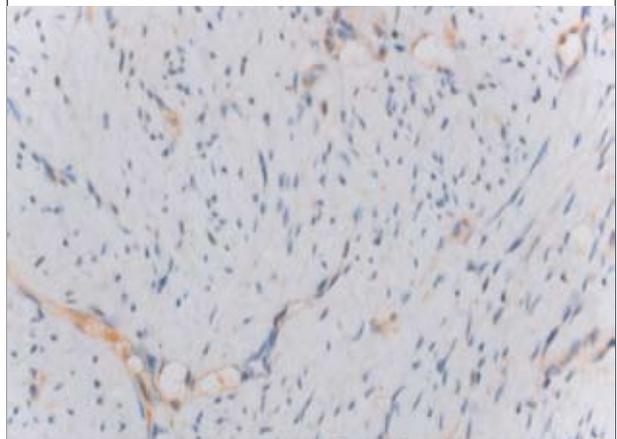
## DISCUSSION

In this patient all three diagnostic criteria of the myomatous erythrocytosis syndrome are met. This is to our knowledge the first case in which direct evidence is provided for *in vivo* production of erythropoietin by the myomatous uterus by the demonstration of an erythropoietin level gradient between the uterine vein and artery of 27.3 pmol/l with a ratio of 3.1. As others, we found increased production of erythropoietin in the myomatous tissue *in vitro* and the presence of erythropoietin in the myomatous tissue was confirmed by immunohistochemical staining. Based on these findings the pathogenic role of erythropoietin in the myomatous erythrocytosis syndrome is undoubted. Erythropoietin is primarily produced by cells of the renal cortex and stimulates growth and differentiation of the erythrocyte progenitor cells.<sup>2</sup> Recent studies indicate that both erythropoietin and erythropoietin receptor (Epo-R) are expressed on a great variety of tissues including the female reproductive organs. There is emerging evidence that in premenopausal women the cyclic expression of erythropoietin in normal endometrial cells is regulated by oestrogen and progesterone.<sup>3,4</sup> During the female reproductive life cyclic formation of new blood vessels (angiogenesis) occurs in the normal uterus. Experimental data may indicate that an oestrogen-induced-erythropoietin-Epo-R signalling pathway stimulates angiogenesis.<sup>5,7</sup> Uterine myoma affects 30% of reproductive women with an estimated incidence of 70 to 80% at the age of 50.<sup>8</sup> The pathogenesis of uterine myoma is not fully elucidated. Myomata are oestrogen and progesterone hormone dependent and many cytokines and growth factors may foster myoma growth through paracrine and/or autocrine mechanisms.<sup>9</sup> The causative role of erythropoietin and Epo-R in myoma and especially in the erythrocytosis myomatous syndrome is speculative. Erythropoietin and Epo-R are expressed

**Figure 1.** Immunohistochemical staining for erythropoietin in uterine myoma, erythropoietin is expressed in the myoma and the vascular endothelial cells (40 x)



**Figure 2.** Adjacent normal myometrium, erythropoietin is not expressed in the normal myometrial cells, but is in the vascular endothelial cells (40 x)



in normal and myomatous tissue while in patients with the erythrocytosis myomatous syndrome the level of erythropoietin and/or Epo-R expression in the myoma is (strongly) elevated compared with myoma in patients without erythrocytosis and, as in our case, normal adjacent myometrium. It has been hypothesised that erythropoietin may contribute to myoma growth by stimulating angiogenesis. In the erythrocytosis myomatous syndrome the oestrogen-induced erythropoietin production may be further augmented by local hypoxia due to the rapid growing myomatous tissue, or by paracrine and/or autocrine mechanism.<sup>1</sup> However, theoretically the increased expression of erythropoietin and Epo-R may be explained alternatively. Despite the benign nature of uterine myomas chromosomal abnormalities can be demonstrated in up to 40 to 50% of the patients.<sup>10-12</sup> The aberrations are both nonrandom and tumour-specific and include t(12;14)(q15;q23-q24) and del(7)(q22.q32), while other rearrangements are less frequent. The 7q deletion, encompassing roughly band q22-q32 occurs frequently (17%) and is highly specific for myoma.<sup>12-14</sup> The 7q22 band appears the critical region of rearrangement. An infrequent cytogenetic aberration in myoma are gains on chromosome 19 with the minimal region of overlap mapped to 19p13.3 and 19p13.1 or 19p13.2.<sup>15</sup> Notably the gene encoding erythropoietin is located on 7q22 while the Epo-R gene is located on 19p13.3-p13.2 ([www.ncbi.nih.gov](http://www.ncbi.nih.gov)). Gene profiling studies of genes involving the erythropoietin and Epo-R genes in uterine myoma are lacking and cytogenetic studies in patients with the myomatous erythrocytosis syndrome have not been performed. In view of the high incidence of uterine myoma and the consecutive expression of erythropoietin and/or Epo-R in normal and myomatous endometrium, it is amazing that the myomatous erythrocytosis syndrome occurs so infrequently. Further studies in subsequent patients are needed to clarify whether the increased production of erythropoietin is caused by a fortuitous local deregulation or by a unique cytogenetic aberration involving a specific region of the 7q22 and/or 19p13.3-p13.2 bands.

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