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Case Report

# Postmenopausal Secondary Polycythaemia due to Large Fibroid

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## Abstract

Herewith, we report a 57 year-old postmenopausal Caucasian lady who presented with a large pelvi-abdominal mass and Haemoglobin (Hb) level of 23.5 g/dl. The latter could possibly be the highest Hb level reported in literature secondary to fibroid uterus. She had an HCT of 69.9% and Bilirubin of 37.6 mg/dL. Both ultrasound scan and CT for abdomen and pelvis suggested a large fibroid uterus. A provisional diagnosis of Myomatous Erythrocytosis Syndrome was made, and she was considered for total abdominal hysterectomy + Bilateral salpingo-oophorectomy. The plan was to normalise her Hb and HCT before surgery. While awaiting her surgery the patient developed an episode of rectal bleeding for which she underwent both OGD and colonoscopy. She was diagnosed with Grade 2 oesophagitis, large duodenal ulcer, and diverticular disease. A few weeks later, she was fit for surgery and a total abdominal hysterectomy with bilateral salpingo-oophorectomy was performed. Histology report confirmed fibroid uterus with no evidence of sarcomatous changes. Her haemoglobin remained normal 8 months later.

***Keywords:*** *Polycythaemia; Fibroid; Myomatous Erythrocytosis Syndrome*

## Background

Polycythaemia (erythrocytosis) is an abnormal elevation of haemoglobin (Hb) and/or haematocrit (HCT) in peripheral blood. It is diagnosed at levels of Hb (> 16.5 g/dL in men or >16.0 g/dL in women) or HCT levels (>49% in men or >48% in women) [1].

Polycythaemia can be relative or apparent (absolute) [2]. Relative polycythaemia occurs when the plasma volume is depleted such as in diuretic use, vomiting, or diarrhoea [3]. Absolute polycythaemia on the other hand, may be caused by autonomous production of RBCs (primary polycythaemia) or as a response to elevated serum erythropoietin (secondary polycythaemia). Primary polycythaemia is caused by a mutation (either acquired or inherited) in RBC progenitor cells that results in increased RBC mass. Most commonly, primary polycythaemia is caused by an acquired condition, such as polycythaemia vera (PV) or another myeloproliferative neoplasm (MPN). Examples of inherited germline mutations that cause polycythaemia include Chuvash polycythaemia (mutation of the VHL gene), mutations of the erythropoietin receptor, and other rare conditions [4]. Secondary polycythaemia refers to an increase of RBCs mass caused by elevated serum erythropoietin. The latter could be due to an appropriate physiologic response to tissue hypoxia, or as a result from autonomous erythropoietin production (e.g. an erythropoietin -secreting tumour) [4].

## Case Report

A 57 year-old woman was referred by her GP to our gynaecology clinic with a large pelviabdominal mass and raised Hb of 23.5 g/dl. She was otherwise asymptomatic. Her menopause supervened 5 years before. She was not on any HRT. Her obstetric history reveals 7 full

term pregnancies and a single early miscarriage. She does not smoke or drink alcohol. She is a known hypertensive on medications. Her family history was unremarkable.

On examination the patient looked flushed with plethoric face. She had a large firm pelvic mass extending to above the umbilical level. Per vaginal examination was unremarkable. Her Hb came back as 23.5 g/dl. Her HCT was 69.9% and her bilirubin measured 37.6 mg/dL. Both platelets and white cell count were normal. Her pelviabdominal scan and CT revealed a 25 cm solid mass arising from the pelvis consistent with fibroid uterus. There was no evidence of enlarged lymph nodes or renal obstruction. A provisional diagnosis of polycythaemia secondary to fibroid uterus was made e.g. Myomatous Erythrocytosis Syndrome.

The plan was to perform total abdominal hysterectomy with bilateral salpingo-oophorectomy. However, to reduce the risk of thrombosis perioperatively, the patient was considered for prophylactic innohep and phlebotomy to normalise her Hb and HCT. While in the hospital for phlebotomy, the patient developed an episode of rectal bleeding for which she underwent both OGD and colonoscopy. She was diagnosed with Grade 2 oesophagitis, large duodenal ulcer and diverticular disease. Hence, she was started on triple therapy with amoxicillin, levofloxacin, and PPI (protein pump inhibitor). Surgery was therefore postponed until the healing of her duodenal ulcer. On discharge from the hospital, both phlebotomy and rectal bleeding normalised her Hb and HCT to 14.2 g/dl and 42% respectively.

Eight weeks later, a repeat OGD confirmed that her ulcer had healed. Surgery was planned in 2 weeks time. On the day of surgery, her Hb level had risen again to 18.6 g/dl and her HCT reached 57%. The total abdominal hysterectomy with bilateral salpingo-oophorectomy was performed. Patient made a good recovery and was discharged home 3 days later with an Hb of 13.2 g/dl and an HCT of 38.8%. The histology report confirmed fibroid uterus with no evidence of sarcomatous changes. The eight months postoperative review confirmed that her Hb and HCT remained normal.

## Discussion

Uterine fibroid or leiomyoma is the commonest benign uterine tumour, occurring in about 15 - 20% of women in their reproductive years. As the tumour is oestrogen dependent, it usually decreases in size after menopause. Its occurrence in the postmenopausal age group is rare and if enlargement of the fibroid is noted during this time, the diagnosis of leiomyosarcoma is provisional until proven otherwise [5].

An association of fibroids with polycythaemia has been reported in several series. Such an association is described in the literature as Myomatous Erythrocytosis Syndrome. It is a very rare condition and, although reported first nearly seven decades ago, the aetiology is still unclear [6,7]. Although the incidence of myomas in premenopausal women is 20 - 40%, the occurrence of the myomatous erythrocytosis syndrome ranges from 0.02 - 0.5%. It has been postulated that the real incidence of this syndrome may actually be higher as accelerated erythrocytosis may be obscured by the presence of menorrhagia [8].

In 1957, three diagnostic criteria for myomatous erythrocytosis syndrome were proposed: (1) erythrocytosis, (2) a myomatous uterus, and (3) the restoration and maintenance of normal haematological values after hysterectomy [9]. Our case not only fulfilled these criteria but also reported the highest level of Hb and HCT reported in literature. This case report also presents large duodenal ulcers as one of the most serious complications of polycythaemia.

Despite the fact that the syndrome was first reported in 1953 by Thomson and Marson [10], the aetiology is still unclear. There are, however, several mechanisms that have been proposed. Ectopic production of erythropoietin by the leiomyoma is the most favoured aetiopathogenesis [7]. Ectopic erythropoietin production is known to occur as a complication of various tumours such as renal cell carcinoma, hepatocellular carcinoma, and cerebellar hemangioblastoma. However, it is less well known that it can also occur as a complication

of uterine leiomyoma [6]. Horwitz and Mckelway were the first to propose such excess erythropoietin production by uterine myoma in 1955 [11].

Several studies using immunostaining techniques have confirmed the production of erythropoietin by the myoma tissue [7]. Many studies, through different approaches, have shown increased erythropoietin activity in uterine myoma tissue. While Kohama., et al. detected erythropoietin mRNA in myomatous tissue [12], we find Yoshida., et al. succeeded to demonstrate positive immune-staining for erythropoietin in the cytoplasm of leiomyoma cells [13]. Literature review showed associated cases of erythrocytosis with leiomyoma of the oesophagus and cutaneous leiomyoma, bringing up the theory of myoma cells itself being responsible for inappropriate erythropoietin secretion, regardless of their location [12].

An arteriovenous shunt mechanism was proposed by Horwitz and McKelway in 1955, which would lead to the presence of deoxygenated blood flow in the arterial system, and marrow stimulation to increase RBC production as a result [11]. This was rejected as there is no difference between the microscopic appearance of the fibromyoma associated with polycythaemia and other fibromyomas [8]. There have also been multiple case reports of patients with uterine AV fistulas without concurrent erythrocytosis [12].

Pressure on the diaphragm that interferes with pulmonary ventilation and leads to hypoxia and stimulation of erythropoietin secretion, was suggested by Paranjothy and Vaish as a possible cause [14]. This theory, however, was aborted since many patients with this condition did not show any signs of hypoxia or abnormal pulmonary function tests [15]. We believe that this theory is at a minimum inadequate in explaining erythrocytosis due to fibroids that are not big enough in size to irritate the diaphragm.

Menzies., et al believed that back pressure on the renal parenchyma caused by urinary flow obstruction due to the large fibroid might increase erythropoietin production. They further added that compression of renal vessels might lead to renal hypoperfusion and erythropoietin secretion [16]. This mechanism was supported by Toyama and Mitus who observed an increased haemoglobin production in rabbits when the pressure in their ureters is increased. While Wrigley reported marked erythropoietin activity in uterine fibromyomas, others failed to demonstrate such activity [8].

Untreated polycythaemia can cause significant thromboembolic accidents, which can be fatal [7]. Complications of polycythaemia include major thrombotic events such as the Budd-Chiari syndrome and portal, splenic, or mesenteric vein thrombosis [17]. Peptic ulcer disease, and gastroduodenal erosions are also recognised complications of polycythaemia. The likely explanation of these ulcers is increased histamine release from tissue basophils and alterations in gastric mucosal blood flow due to altered blood viscosity [18]. Our patient was very fortunate to have her first bleeding episode while in the hospital.

Gonadotrophin-releasing hormone (GnRH) analogues are commonly used preoperatively to control anaemia secondary to menorrhagia or shrink uterine fibroids to facilitate surgery. There is no published association between the use of GnRH analogues and hyper erythropoietinaemia [7].

In addition to reporting the second case of Myomatous Erythrocytosis Syndrome in literature, Horwitz and McKelway (1955) were the first to report a case of polycythaemia vera presenting with a large fibroid in which hysterectomy failed to improve her erythrocytosis [11]. As in our case report, removal of the tumour was followed by remission in almost all cases, so far reported. Although, in many of the reports, the period of follow-up has been short. Alternative treatment options such as phlebotomy will normalise Hb and HCT for a short time. In this case report, following phlebotomy the Hb rose sharply from 14.2 g/dl to 18.6 g/dl in only 10 weeks despite some blood loss from existing ulcers.

## Conclusion

Myomatous Erythrocytosis Syndrome is a rare presentation of uterine fibroids, as most women present with menorrhagia and/or anaemia. It is important however, to recognize the rare association between polycythaemia and fibroids to minimize unnecessary investigations. In the clinical setting of polycythaemia, it is imperative to rule out polycythaemia vera that does not only lead to serious, life-threatening thrombosis but also has different treatment than myomatous erythrocytosis syndrome, which resolves after surgical removal. Costly investigations however, especially genetic testing, should be reserved for persistent polycythaemia following hysterectomy/myomectomy.

The exact role of erythropoietin in disease pathogenesis is unknown. As a single factor cannot be accepted in all cases, the aetiology seems most likely multifactorial. Moreover, clinical expression of the syndrome is also poorly understood; while we report the highest Hb level in literature of 23.5 g/dl with only a 3 kg fibroid, Abdul Ghaffar., et al (2008) reported a bigger fibroid of 5.05 kg with an Hb of only 22.1 g/dl [5].

The high frequency of uterine fibroids in women throughout their life does not explain the rarity of this Myomatous Erythrocytosis Syndrome. Together with the uncertainty of the aetiology, more research is needed in the future to shed a light on this rare condition and its aetiology.

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