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Case Report **Internal Medicine**

Osler-Weber-Rendu Disease: Two New Successes of Bevacizumab and Literature Review

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Abstract

Osler-Weber-Rendu syndrome (OWRD) is a rare vascular dysplasia of genetic origin and of autosomal dominant transmission, the pathophysiology of which involves the vascular endothelial growth factor (VEGF), a major growth factor of angiogenesis. Bevacizumab is an anti-VEGF monoclonal antibody that has demonstrated its interest in this indication. Two patients, with a personal and familial history of haemorrhagic syndrome, who had an OWRD detected in recurrent epistaxis, cutaneous-mucosal telangiectasia, and complicated visceral arteriovenous malformations with an iron deficiency anemia. Due to the persistence of the symptomatology despite a transfusion support, the treatment with bevacizumab was started and allowed a favorable outcome. Bevacizumab appears to be very well tolerated and represents a therapeutic advance in OWRD.

Keywords: Osler-Weber-Rendu disease, epistaxis, telangiectasia, bevacizumab.

INTRODUCTION

Osler-Weber-Rendu syndrome OWRD or hereditary hemorrhagic telangiectasia(HHT) is a rare inherited disorder characterized by malformations of various blood vessels potentially resulting in bleeding(hemorrhaging) and shunting of blood .Chronique nosebleeds are the first malformation sign of various blood vessels .They may result in abnormalities affecting the lungs, brain,spinal cord and liver [1]. Nasal telangiectasias are responsible for epistaxis. In this research, the diagnosis is mainly clinical and is based on the existence of, at least, three criteria among the following: recurrent epistaxis, multiple cutaneous-mucous telangiectasias, family history and the existence of visceral arteriovenous malformations [2].

OWRD is linked to a state of imbalance between antiangiogenic factors and proangiogenic factors such as vascular endothelial growth factor (VEGF). This condition is secondary to mutations in 3 genes ENG (encoding endoglin), ACRLV1 (encoding activin receptor-like kinase 1) and MADH4 (encoding Smad 4 or Mothers against decapentaplegic homolog 4). These genes have an important role in the angiogenic balance. The coexistence of a disturbance of the angiogenic balance and a neoactivation of angiogenesis remains a plausible pathophysiological hypothesis for ORD [3, 4].

Therapeutically; the use of anti-VEGF antibodies could inhibit the activation of angiogenesis and therefore return to a quiescent state of angiogenesis. Bevacizumab, an anti-VEGF monoclonal antibody, has demonstrated its major contribution in this indication, and could represent a very promising alternative [3-9]. We report two new observations successfully treated with bevacizumab.

PATIENTS AND OBSERVATIONS

Observation 1

A 35-year-old woman, with a history of iterative epistaxis once every 2 days for 6 years with chronic anemia under iron .She also has two brothers presenting chronic epistaxis. She was admitted for abundant nasal hemorrhage and with difficulty in breathing. Her hemoglobin level was 6 g / dl justifying an emergency blood transfusion of 4 red blood cells and anteroposterior tamponade. Her clinical examination noted: skin pallor, telangiectasias involving the nostrils, the soft palate, and the inner face of the cheeks and the tip of the tongue. A lesion assessment, in particular a thoraco-abdominal CT angiography, revealed thrombosis of the portal trunk with cavernoma by

arterio-portal fistula (figure 1), associated with a dilation of the hepatic veins, the inferior vena cava, the renal veins and the splenic vein. The brain angiography and digestive endoscopy were without abnormalities. The genetic study carried out in our patient showed a pathogenic heterozygous mutation of the ALK1 gene. The patient had undergone several ENT laser mechages and cauterizations.

Faced with recurrent epistaxis affecting the quality of her life, with relapsing anemia sometimes severe and non-response to symptomatic treatment and risks of repeated transfusions not resolved .Treatment with bevacizumab was decided at a dose of 5 mg / kg every 15 days with a total of 6 injections and 60mg / of iron supplementation. This treatment allowed an improvement in the quality of her life with a marked decrease in the frequency of epistaxis once a month, a normalization of the hemoglobin level (13 g / dl) and a stabilization of the radiological lesions with a follow-up of 12 months.

Observation 2: A 20-year-old patient was admitted to the internal medicine department for investigation of anemia. Interrogation noted in her history several epistaxis episodes (once / 2 days) as well as a sister who died from severe epistaxis. The patient had a history of three months with the onset of a severe anemic syndrome consisting of asthenia, dizziness, palpitations and severe headaches. The patient initially admitted to the emergency room where she was transfused with 4 red blood cells (the hemoglobin level was 5.8 g / dl), then transferred to our department for further treatment. On clinical examination, the patient was pale, slightly discolored conjunctivae, and presented with telangiectasias in the perioral region, soft palate, fingertips and digital hippocratism. An etiological assessment, in particular an eso-gastro-duodenal fibroscopy, revealed diffuse angiodysplastic lesions. Cerebral angio-MRI revealed a superficial right parietotemporal arteriovenous malformation (figure 2). The thoraco-abdominal angio-CT showed several pulmonary arteriovenous fistulas: on the right side-basal and left postero-basal (figure 3). The diagnosis of ORD disease was retained. Genetic analysis was not performed in this patient. Faced with recurrent epistaxis requiring repeated urgent transfusions, the patient was treated with 6 courses of bevacizumab at 5 mg / kg 15 days apart with a total of 6 injections and iron supplementation (80 mg / dl). The course was marked by a marked decrease in the frequency of epistaxis (once / month), normalization of hemoglobin (13 g / dl) and stabilization of the radiological lesions, with a follow-up of 12 months.

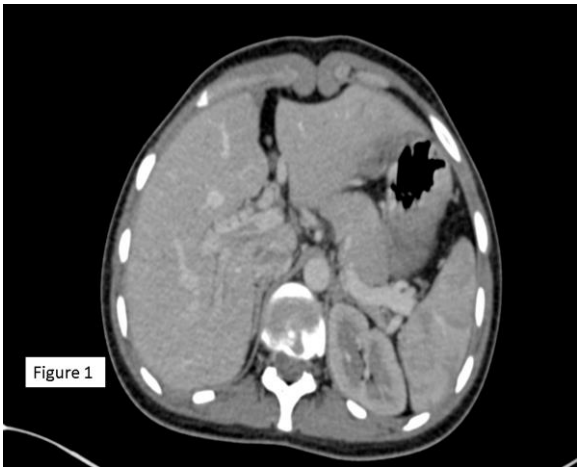

Fig-1: Axial abdominal CT : portal trunk thrombosis with portal cavernoma by arterio-portal fistula

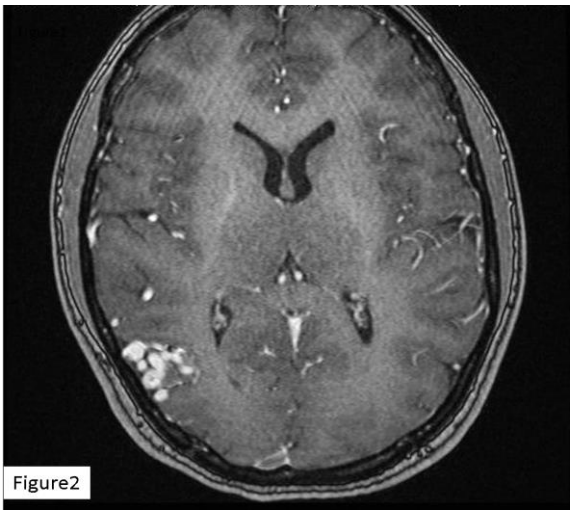

Fig-2: Axial MRI of the brain: right parietotemporal arteriovenous malformation

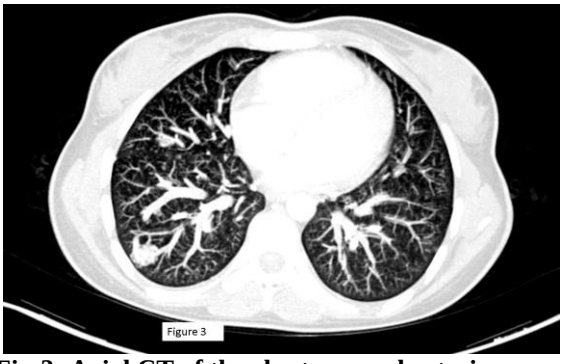

Fig-3: Axial CT of the chest: several arteriovenous malformations

DISCUSSION

ORD is a very rare disease that affects one in 5,000 to 8,000 people [10]; it is characterized by the presence of recurrent epistaxis, cutaneo-mucous telangiectasia with an autosomal dominant mode of transmission. It is expressed primarily heterozygous,

with homozygosity being lethal in utero or in early childhood. The three genes identified in the disease (ENG, ACVRL1, MADH4) encode proteins involved in the TGFβ (Transforming Growth Factor β) signaling pathway in the endothelial cell causing endothelial hyperproliferation [10].

The management of patients with ORD is mainly based on screening for arteriovenous and visceral malformations and symptomatic measures. However, the angiogenic nature of this pathology suggests an interesting therapeutic possibility via the use of modulators of angiogenesis [3, 5]. The reference center for ORD based in Lyon in collaboration with 12 competence centers across France as part of the "rare diseases" plan, has enabled the drafting of a French national protocol for diagnosis and treatment. The aim of such protocol is to optimize the management of these patients [10].

Among the symptoms of ORD, epistaxis are the main clinical expression of telangiectasias, they are spontaneous, repeated, irregular, diurnal or nocturnal. They concern more than 95% of patients, and are readily anemic and the source of a significant professional, social and psychological impact. The monthly frequency of epistaxis is extremely variable [1]. In the 2 cases that we have described, recurrent epistaxis with haematological repercussions was the main reason for consultation leading to the diagnosis of the disease.

The pathophysiology of ORD is probably based on an imbalance in the balance between pro-angiogenic factors such as VEGF and anti-angiogenic factors such as the bone morphogenetic protein (BMP9 for bone morphogenetic protein 9) [5]. Thus bevacizumab, an anti-VEGF monoclonal antibody, has been proposed in the management of this pathology.

Several studies on the efficacy of this molecule, used systemically or topically in epistaxis [6-8, 11] or anemic syndrome [13] of ORD have been reported. A phase 2 trial studying the efficacy of bevacizumab (5 mg / kg every 2 weeks for a total of 6 injections) in 25 patients with hepatic impairment responsible for high-output heart failure showed that cardiac output and duration epistaxis are significantly improved, respectively, three and six months after the start of treatment [5]. The usual dose of bevacizumab in ORD reported in the majority of studies is 5 mg / kg every 2 weeks but lower doses (2 mg / kg every 3 weeks) have been used successfully [13]. Another study in a limited series of eight patients where bevacizumab was used by injection directly into the nasal mucosa showed a significant improvement in the intensity and frequencies of epistaxis as well as the quality of life from four years onwards. Weeks of treatment [11]. Treatment with bevacizumab by injection at a dose of 5 mg / kg every 2 weeks with a total of 6 injections was very effective in our two patients with a marked decrease in the frequency of epistaxis, a normalization of hemoglobin levels. and stabilization of the radiological lesions with a follow-up of 12 months.

For improved use and reduced side effects; a local nasal spray form was evaluated. This form seems to be much better tolerated but less effective than the injectable form. Indeed, during a phase 1 trial published in 2014; the authors studied the effectiveness of bevacizumab nasal spray in 40 patients with ORD and concluded that the treatment was not effective [6]. Similar results were found in phase 2 and 3 trials regarding the effectiveness of treatment in reducing the frequency [7] and duration [8] of epistaxis in ORD.

Side effects associated with the use of bevacizumab are mainly in the form of grade 3 hypertension, which can occur within 30 days of starting treatment and which may not be treated without difficulty [5, 12]. Headache, signs of digestive intolerance such as nausea, vomiting, diarrhea, abdominal pain, asthenia, as well as arthromyalgia have also been reported [5, 12, 14]. Severe side effects such as thrombosis or hemorrhage or gastrointestinal perforation have been described by some authors [14]. In our patients, no adverse effects attributable to bevacizumab were reported during the treatment and observation period.

CONCLUSION

Modulators of angiogenesis, such as bevacizumab, clearly appear to be an interesting therapeutic advance in ORD. This is an off-label prescription for the treatment of severe anemia secondary to epistaxis or digestive hemorrhage and / or heart failure secondary to liver damage. Improvement is described in about two thirds of patients. Maintenance treatment is sometimes offered although there is no recommendation.

Conflicts of interest: The authors declare no conflict of interest

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