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Partial Nephrectomy Allowed by Anti CD_{20} Antibody Treatment for Renal Cancer Associated with Acquired Haemophilia A

Tamas Kullmann[1*], Annick Ankri[2], Marc-Olivier Bitker[3], Serge Herson[1], Olivier Benveniste[1]

[1]Department of Internal Medicine, Pitié-Salpêtrière Hospital, Assistance Publique—Hôpitaux de Paris, Pierre et Marie Curie University, Paris, France; [2]Department of Haematology, Pitié-Salpêtrière Hospital, Assistance Publique—Hôpitaux de Paris, Pierre et Marie Curie University, Paris, France; [3]Department of Urology, Pitié-Salpêtrière Hospital, Assistance Publique—Hôpitaux de Paris, Pierre et Marie Curie University, Paris, France.
Email: *kullmanndoki@hotmail.com

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ABSTRACT

The case of a forty-five year old woman is presented who consulted for spontaneous haematomas of the thighs. The diagnosis of acquired haemophilia A associated to renal cancer was retained. She received anti CD_{20} monoclonal antibody treatment allowing her to undergo partial nephrectomy 4 months later without major complication. One year after surgery there is no sign of tumour recurrence.

Keywords*: *Acquired Haemophilia*, *Rituximab*, *Renal Cancer

1. Introduction

Acquired haemophilia A is a rare bleeding disorder characterised by the presence of auto-antibodies directed against coagulation factor VIII. Bleeding can be often severe and even life-threatening. In about 50% of the cases, it can be secondary to other conditions such as autoimmune disorders, haematologic or cancerous diseases and pregnancy [1].

Treatment consists in two separate objectives: 1) acute control of bleeding and 2) eradication of inhibitor antibodies. The immediate control of haemorrhage can be obtained by FVIII pathway bypassing methods: the administration of activated prothrombin complex or activated FVII. The eradication of inhibitor antibodies can be reached with immunosuppressive treatment. Corticosteroids and cyclophosphamide are currently recommended in first line and rituximab in second line [2].

Rituximab, a chimeric monoclonal antibody specific for human CD20, which targets B lymphocytes, was first developed (and licensed) for the treatment of B-cell lymphoma and is used at a dose of 375 mg/m^2 of body surface area once weekly for 4 weeks. Subsequently it was noted that in patients with lymphoma treated with rituximab and concomitantly suffering from auto-immune diseases such as rheumatoid arthritis or myastenia the latter were improved. Subsequent to these early case reports, rituximab has been used in many auto-immune diseases where B cell seems to play a role. Pivotal studies led to the molecule being licensed in cases resistant to anti-TNF first line therapy (rituximab at the dose of 1 g, on days 1 and 15), but it is also used (off-label) in idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, systemic lupus erythematosus, rhuematoid arthritis, autoimmune haemolytic anaemia, cryoglobulinaemia, polyneuropathies, glomerulonephritis [3].

At date rituximab is not recommended in first line for the treatment of acquired haemophilia. However, certain clinical conditions, for instance the necessity of a surgical intervention in medium term may lead to the preconisation of this option.

2. Methods

We present a case illustrating the dilemmas and a solution to the rare but challenging association of acquired haemophilia to a solid tumour.

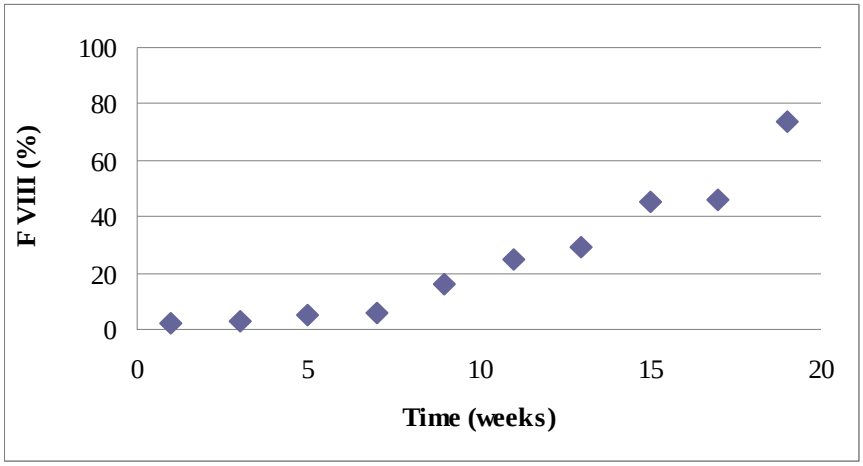
A forty-five year old woman was hospitalised for therapeutic decision for acquired haemophilia A associated with renal cancer. Thyroidectomy, idiopathic urticary and an episode of uretherolithiasis can be noted in her past medical history. She first consulted for recur-

rence of right lumbar pain awakening her from sleep. The pain was completely relieved in some days by simple analgesics. The abdominal ultrasonography identified two renal calculi as being responsible for the pain and revealed a tissular lesion in the controlateral kidney. The lesion was identified by the abdominal computed tomography as a left renal tumour measuring 42 × 30 × 36 mm. She consulted for a second time a week after the onset of the renal colic for two haematomas occurring spontaneously on both thighs. No other bleeding disorder was detected. The laboratory analysis found a prolonged activated partial thromboplastin time (aPTT: 62 s, Normal: 28 s) and subsequently a reduced factor VIII level (FVIII: 2%) with evidence of FVIII inhibitor activity (12 UB/mL) allowing the diagnosis of acquired haemophilia A.

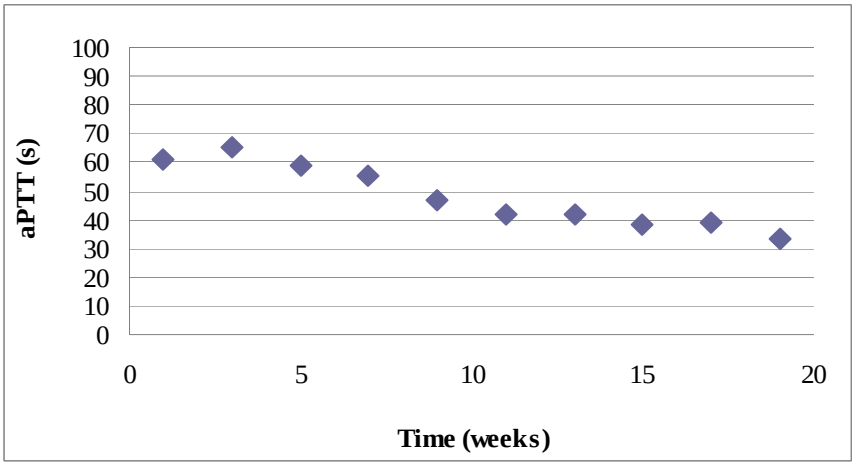
A second interpretation of the computed tomography ruled out the possibility of a renal haematoma secondary to the haemophilia and confirmed the suspicion of renal tumour. No biopsy was effectuated. The PET CT showed no metastasis.

3. Results

A treatment with anti CD_{20} monoclonal antibody (4 cycles of 375 mg/m^2 with one week intervals) was decided. The aPTT and FVIII levels were followed every 2nd week to allow an optimal timing for surgery. A control computed tomography showed no progression of the tumour at 3 months. The patient underwent partial nephrectomy 4 months after the start of anti CD_{20} antibody treatment with normalised aPTT and a FVIII level of 70% (**Figure 1**). The operation was complicated by an intramuscular haematoma that was treated by arterial embolisation. No



(a)



(b)

Figure 1. (a) Level of coagulation factor VIII (%) and (b) activated partial thromboplastin time (s) after the administration of anti CD 20 monoclonal antibodies (week 1-4).

transfusion was needed. Histology showed light cellular renal cancer (Fuhrman 2). The aPTT remained normal and FVIII level became undetectable after surgery.

4. Discussion

The renal cancer of this patient was discovered by chance on the occasion of a controlateral renal colic. At almost the same time she also presented two spontaneous haematomas revealing haemophilia. The association of acquired haemophilia to renal cancer is a rare but not unknown condition [4]. The disappearance of FVIII inhibitor activity after the renal surgery suggests the paraneoplasic origin of the patient's haemophilia.

As on the arrival to our hospital there was no sign of active haemorrhage, the aPTT varied between 62 - 75 s and the level of FVIII was stable at 2% there was no indication to an immediate haemostatic intervention. However, the rapid eradication of the inhibitor antibodies and the correction of haemostasis were necessary to allow a surgical intervention for the renal cancer.

Contrarily to immunosuppressive agents like corticosteroids and cyclophosphamide currently recommended as first line treatment for the eradication of FVIII inhibitors, rituximab has no deleterious effect on postoperative cicatrisation. The relatively low FVIII inhibitor activity and the stability of the patient's cancer allowed the exclusive choice of anti CD_{20} monoclonal antibody. Rituximab needs several weeks to attain its full action. Although lower dose of rituximab has also been described to be efficacious [5], it has 50% risk of failure according to a case review [3], therefore we chose the most commonly used dose of 375 mg/m^2 for four weeks.

The protection against tumour progression by an antiangiogenic treatment until the normalisation of haemostasis can be raised. No antiangiogenic treatment was given, firstly because of the risk of bleeding due to the impaired haemostasis, secondly because it should have been stopped one month before surgery and the intervention was programmed for the normalisation of aPTT and thus the date not known in advance.

To our knowledge this is the first case of renal surgery allowed by the administration of anti CD_{20} monoclonal antibody in context with haemophilia A. One year after surgery the control CT scan does not show any sign of disease recurrence. We believe that our choice allowed a better cicatrisation without influencing the oncologic outcome of the patient. More importantly it contributed to the better conservation of the patient's renal function, who should have otherwise undergo total nephrectomy in case the bleeding time would not have normalised.

5. Conclusions

Rituximab can be an interesting first line treatment option in special cases of acquired haemophilia A.

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