





## Case Report

# Cholecystectomy in a man with hemophilia A and inhibitor on emicizumab prophylaxis: A case report

Paula Cella Giacometto <sup>a,b</sup>, Marcello Tortelli Bavaresco <sup>a,c,d</sup>,  
Juliana Alvares-Teodoro <sup>e</sup>, Ricardo Mesquita Camelo <sup>e,\*</sup>

<sup>a</sup> Hospital Regional Universitário da Universidade Estadual de Maringá (HU UEM), Maringá, PR, Brazil

<sup>b</sup> Centro de Hematologia e Hemoterapia do Paraná (HEMEPAR), Maringá, PR, Brazil

<sup>c</sup> Hospital Santa Casa de Maringá, Maringá, PR, Brazil

<sup>d</sup> Faculdade de Medicina UniCesumar, Maringá, PR, Brazil

<sup>e</sup> Faculdade de Farmácia da Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil

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## Introduction

Inherited hemophilia A is a rare bleeding disorder due to absent/reduced activity of the clotting factor VIII (FVIII).<sup>1</sup> Therefore, its treatment is based on regular FVIII infusions to prevent (i.e., prophylaxis) or treat (i.e., on demand) bleedings.<sup>1</sup> The most impacting complication of this treatment is the development of anti-FVIII antibodies (i.e., inhibitors).<sup>1</sup> Inhibitors reduce/abolish the clotting activity of FVIII, rendering the patients with the previous or worse bleeding phenotype, which ultimately leads to increased morbimortality.<sup>1</sup>

Although bypassing agents (recombinant activated factor VII [rFVIIa] and partially activated prothrombin complex [aPCC]) can be prescribed for both prophylactic and on-demand treatments, the current recommended prophylactic drug in such cases is the humanized bispecific antibody emicizumab.<sup>1,2</sup> Emicizumab mimics the clotting effect of FVIII and, since its structure is not similar to the FVIII structure, anti-FVIII inhibitors have no effect on its clotting activity.<sup>1,2</sup> There are few reports about the hemostatic effectiveness and safety of this biopharmaceutical on major non-orthopedic surgeries.<sup>3–5</sup> In addition, since the introduction of emicizumab in the armamentarium for hemophilia treatment in Brazil, in 2018, no major surgical procedures have been reported in Brazilian patients on emicizumab prophylaxis. Herein we described a man with severe hemophilia A and high-responding inhibitor under emicizumab prophylaxis who was submitted to open

\* Corresponding author at: 1020/101 Padre Eustáquio, Belo Horizonte, MG, Brazil, CEP30.730-170.

E-mail address: [rmcamelo@hotmail.com](mailto:rmcamelo@hotmail.com) (R.M. Camelo).

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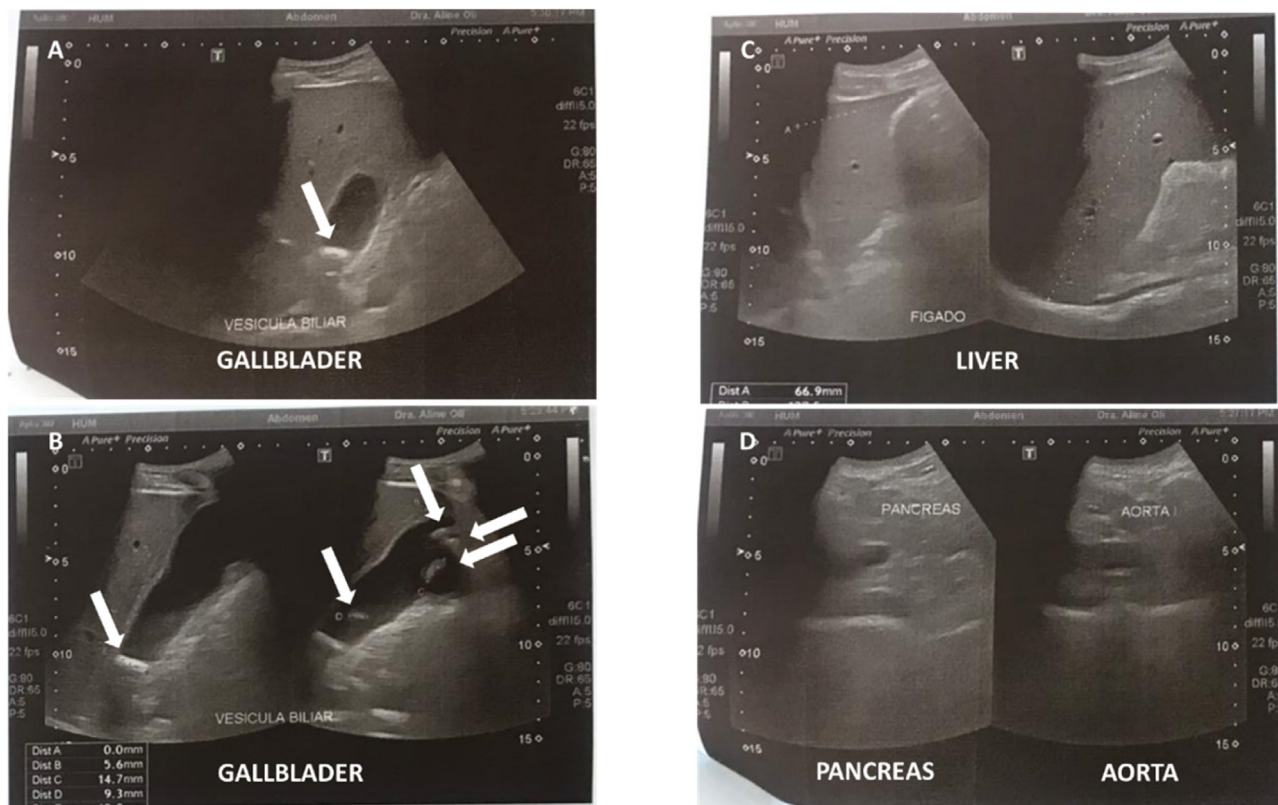
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cholecystectomy due to acute-on-chronic calculous cholecystitis. This report was approved by the local Committee on Ethics on Research (May/29/2019). The patient signed the Consent Form before his data was reviewed on the hospital medical files.

### Case report

A 32-year-old man first visited the Emergency Department complaining severe diffuse abdominal colic unresponsive to oral analgesics, in the last 7 h. He denied fever, nausea, and diarrhea. He had severe hemophilia A with high-responding inhibitor. He was under prophylaxis with emicizumab (1.5 mg/kg weekly). He had been submitted to several abdominal surgeries (appendicectomy, midgut volvulus, and abdominal trauma). Physical examination was unremarkable. Aspartate and alanine aminotransferases were mildly elevated (56 and 83 U/L, respectively). He was discharged home after ameliorating with symptomatic drugs. He came back 4 days later, with the same complaints. He had a positive Murphy's sign and a negative Blumberg's sign. Blood tests were unremarkable. The gallbladder had a normal wall thickness (0.6 cm) with several mobile calculi (from 0.9 to 1.8 cm) by abdominal ultrasound, without dilation of the biliary tract, alteration of the pancreas/pancreatic duct, or lymphadenomegaly (Figure 1). He declined hospitalization for probable

surgical assessment, but he returned 5 days later, after having discussed with his Hematologist. Emicizumab was maintained throughout the described period. Before the procedure, he received intravenous rFVIIa 93  $\mu$ g/kg and tranexamic acid (TxA) 1 g. rFVIIa was maintained each 2 h, during the first 24 h. The procedure was performed under general anesthesia. Videolaparoscopic cholecystectomy was withheld, due to adhesions precluding peritoneal inflation. Upon a right subcostal (Kocher) incision, a hydroptic gallbladder was removed. Anatomopathological analysis confirmed acute-on-chronic calculous cholecystitis. A purified pigskin sterile absorbable gelatin sponge was placed on his hepatic bed, before closing the surgical wound. The surgeon reported above-the-usual bleeding during the procedure (estimated blood loss of 500 mL against usually minimal blood loss). Ceftriaxone and metronidazole were prescribed throughout the hospitalization. rFVIIa 77  $\mu$ g/kg was scattered daily: every 2 h until every 12 h along 1 week (total 2400  $\mu$ g/kg). TxA 1 g every 8 h was prescribed during the same period. He had mild hematic drainage (less than 30 mL on the post-operative day and decreasing in the following days). This was judged as good hemostasis by the surgeon. The drain was removed on the 4th post-operative day. Hemoglobin decreased from 13.7 g/dL on the day of the procedure to 9.4 g/dL the day before discharge (lowest 8.9 g/dL) (Table 1). No blood transfusion was required throughout the hospitalization. He was discharged home 1 week after surgery. No bleeding event was reported



**Figure 1 – Abdominal ultrasound performed on the 5th day of symptoms. (A and B) Several mobile calculi (from 0.9 to 1.8 cm) were identified inside the gallbladder. White arrows point the calculi. (C) Both liver echotexture and intra- and extra-hepatic canaliculi were normal. (D) Pancreas echotexture was normal.**

**Table 1 – Hemoglobin (Hb) and hematocrit (Ht) variation from before to several times after the surgery.**

Time	pre-surgery	immediately after surgery	1st post-operative day	2nd post-operative day (morning)	2nd post-operative day (evening)	5th post-operative day
Hb (g/dL)	14.1	13.7	12.5	8.9	9.8	9.4
Ht (%)	45.4	44.0	39.1	28.5	30.4	29.0

during the outpatient follow-up within 3 weeks. No symptoms nor signs of thrombosis were reported.

## Discussion and conclusion

To the best of our knowledge, this is the first report of a Brazilian man with severe hemophilia A and high-responding inhibitor under prophylactic emicizumab who was submitted to major non-orthopedic surgery. Worldwide, the experience on major surgical procedures on people with hemophilia A under emicizumab prophylaxis largely involves orthopedic surgeries,<sup>3–5</sup> which are the most prevalent surgical procedures to which these patients are submitted.<sup>1</sup> There are few reports on major non-orthopedic surgeries in such cases. In the pivotal studies of efficacy and safety of emicizumab prophylaxis, among 18 major surgical procedures, five were non-orthopedic, of which one was cholecystectomy.<sup>3</sup> Among inhibitor-positive patients, the authors reported that the hemostasis provided by the concomitant use of emicizumab and bypassing agent was good.<sup>3</sup>

While emicizumab is a prophylactic agent, hemostasis to treat bleeding among inhibitor-positive individuals should be accomplished with bypassing agents.<sup>1</sup> aPCC is not recommended as first-line therapy due to the risk of thrombosis when used concomitantly with emicizumab.<sup>1</sup> However, concomitant use of rFVIIa and emicizumab has a safe profile and there are recommendations for their prescription during major orthopedic surgeries.<sup>1,6,7</sup> For major orthopedic surgeries, an expert group recommended rFVIIa 90–120  $\mu\text{g}/\text{kg}$  and TxA pre-operatively and de-escalating rFVIIa frequency every 2 days, based on published evidence and personal experience.<sup>7</sup> For non-orthopedic surgery hemostasis without emicizumab coverage, some experts advocate a bolus dosing of 120  $\mu\text{g}/\text{kg}$  and maintenance dose of 90–120  $\mu\text{g}/\text{kg}$  every 2 h, de-escalating daily by increasing the time between infusions, until there is no sign of bleeding and the wound is normally healing.<sup>8</sup> We opted to use the lowest-dose regimen since the patient was under emicizumab prophylaxis. Although there was a minimal bleed and a significative drop on the patients' hematimetry, no transfusion was required.

The incorporation of emicizumab as a prophylactic therapeutic for people with hemophilia A and high-responding inhibitor resulted in an effective reduction of breakthrough bleeding as well as less hemorrhage after low-to-moderate trauma.<sup>2</sup> However, its effectiveness as a hemostatic agent in overall major surgeries remains to be elucidated.<sup>3</sup> Finally, we would like to reinforce the importance of an interdisciplinary approach as the best option to manage surgery among people with hemophilia, despite severity, inhibitor status, and

product in use. In conclusion, the concomitant use of emicizumab and rFVIIa was effective and safe for a man with severe hemophilia A and high-responding inhibitor submitted to open cholecystectomy.

## Authors' contributions

P.C.G. was responsible for the conceptualization, data curation, investigation, and writing – review & editing. M.T.B. was responsible for the investigation and writing – review & editing. J.A.-T. was responsible for the conceptualization, formal analysis, methodology, project administration, supervision, visualization, writing – original draft, and writing – review & editing. R.M.C. was responsible for the conceptualization, data curation, formal analysis, methodology, project administration, supervision, visualization, writing – original draft, and writing – review & editing.

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## Conflicts of interest

P.C.G. declare financial support to participate in scientific meetings from Takeda, NovoNordisk, and Roche. R.M.C. declare personal fees as speaker and financial support to participate in scientific meetings from Bayer, NovoNordisk, Takeda, and Roche. M.T.B. and J.A.-T. have nothing to disclose.

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