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Case Report

Sirolimus-Induced Severe Hypertriglyceridemia Presenting with Signs of Hyperviscosity Syndrome and as Pink Colored Blood: A Case Report

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Abstract

Background: Inhibitors of the mammalian target of rapamycin have proven as potent immunosuppressive drugs effective in prevention of graft-versus-host-disease (GvHD). However severe disturbances of lipid metabolism are possible with the risk of developing hypertriglyceridemia-induced hyperviscosity syndrome. Clinical experience in the management of this potentially life-threatening complication is limited. **Case presentation:** We report a case of a patient with myelodysplastic syndrome complicated by chronic GvHD after allogeneic hematopoietic stem cell transplantation on second line sirolimus maintenance therapy while developing hyperviscosity syndrome due to severe hypertriglyceridemia of 138mmol/l presenting as pink colored blood. Plasmapheresis was initiated alongside fenofibrates to lower triglycerides. Importantly only serial therapeutic intervention with daily plasmapheresis over five days resulted in persistent therapeutic success. Triglyceride levels dropped to 7.02 mmol/l on day 8 after admission. **Conclusions:** The index case is notable due to symptomatic sirolimus-induced excessive hypertriglyceridemia with signs of hyperviscosity syndrome. Furthermore, we provide evidence that only after repeated plasma exchanges a satisfying decrease of lipid levels is achieved.

Keywords: Hypertriglyceridemia; Pink blood; Sirolimus; Hyperviscosity; Plasmapheresis; Graft-versus-host-disease (GvHD)

Abbreviations: GvHD: Graft-versus-Host-Disease; HSCT: Hematopoietic Stem Cell Transplantation; JAK: Janus-Associated Kinase; MDS: Myelodysplastic Syndrome; MMF: Mycophenolate Mofetil; mTOR: Mammalian Target of Rapamycin; TPE: Therapeutic Plasma Exchange

Introduction

Inhibitors of the mammalian target of rapamycin (mTOR) have proven as potent immunosuppressive drugs that are derived from actinomycete Streptomyces hygroscopius [1]. The most prominent, sirolimus, has entered the transplant field following successful clinical trials that demonstrated effective prevention of graft-versus-host-disease (GvHD) in bone marrow allograft recipients, especially with corticosteroid-dependent or refractory chronic GvHD [2-4]. Mechanistically sirolimus interacts with immunophilins such as FK-binding protein 12 in order to complex with the kinase enzyme mTOR and hereby blocks interleukin-2 synthesis and T-cell proliferation [5,6]. A cell cycle arrest between G1 and S phase is observed in T-cells [7]. Sirolimus expands the repertoire of immunosuppressive armamentarium which is especially needed in transplant medicine with bone marrow and organ transplantation. Given an overall favorable profile of side-

effects, especially no diabetogenic, nephrotoxic and neurotoxic sequelae, and in some cases anticancerogenic effect, sirolimus has become a popular treatment option in patients with comorbidities such as diabetes and refractory arterial hypertension [8-10]. However sirolimus is associated with adverse metabolic reactions concerning lipid metabolism, dose-dependent leukocytopenia and thrombocytopenia and exaggeration of proteinuria [11]. Well-known changes in the lipid metabolism include a steady increase in triglyceride levels accompanied by less pronounced increases in cholesterol levels in long-term sirolimus therapy regimens [12,13]. There are only a few cases in the literature that report on sirolimus-dependent severe hypertriglyceridemia, that is defined as triglyceride level >11.4 mmol/l (> 1000mg/dl) by the Common Terminology Criteria for Adverse Events (CTCAE) from the National Cancer Institute [14]. Urgent therapeutic interventions are indicated in these patients, since due to the highly lipemic blood they are at risk of developing either hypertriglyceridemia-induced acute pancreatitis or hyperviscosity syndrome. There are no general approved guidelines for best management under these conditions. The aim of this case report is to depict a case of a patient suffering from chronic GvHD after bone marrow transplantation developing critical hypertriglyceridemia under sirolimus treatment.

Case presentation

A 28-year-old female patient with history of myelodysplastic syndrome (MDS) underwent allogeneic hematopoietic stem cell transplantation (HSCT) in 2019. MDS has been in complete remission thereafter, but the disease course was complicated by chronic GvHD involving the skin and liver. Since other immunosuppressive medications were not tolerated, the patient received sirolimus as second line therapy. She was started two weeks prior to hospital admission on sirolimus at a starting dose of 1,5 mg per day combined with mycophenolate mofetil (MMF) bid 1000 mg and prednisolone bid 10 mg. The first trough level control was determined at 34 µg/l, thereafter the dose was lowered to 1 mg per day. The patient presented on the day of admission for a regular control in our outpatient hematological ward with nonspecific abdominal discomfort, diminished appetite, slight headache and dizziness. On admission, her medication included acyclovir, allopurinol, amlodipine, amphotericin B, cholecalciferol, cotrimoxazole, levetiracetam, magnesium, metoprolol, mirtazapine, MMF, pantoprazole, posaconazole, prednisolone, quetiapine, ramipril, sirolimus, and torasemid.

On clinical examination her neurologic status did not show focal deficits, however her overall mood was depressed. The blood appeared with a milky opaque pink color (Figure 1). Blood viscosity appeared distinctly increased. Initial laboratory work-up revealed triglycerides >138 mmol/l [ref. range <1.70 mmol/l], total cholesterol levels at 35.4 mmol/l [ref. range <5.2 mmol/l]. High-density lipoprotein and low-density lipoprotein were not measurable under these lipid levels. Over time lipemic blood showed separation into two layers with a milky opaque supernatant resulting triglycerides (Figure 2). Liver enzymes such as aspartate aminotransferase at 0.82 µmol/l [ref. <0.6 µmol/l], amino alanine transferase at 1.68 µmol/l [ref. <0.58 µmol/l], total bilirubin (within normal range), γ-GT 29.9 µmol/l [ref. <0.7 µmol/l] and lipase at 2.2 µmol/l [ref. <1.0 µmol/l] were not markedly altered. Total blood cell counts revealed macrocytic hyperchromic anemia with hemoglobin of 5.2 mmol/l [ref. 7.2 -9.6 mmol/l] due to vitamin B12 deficiency, coagulation was balanced with international normalized ratio for prothrombin time and activated partial thromboplastin time were measured in normal range. Due to the apparent neurological symptoms and suspected hyper viscosity syndrome plasmapheresis was initiated and repeated five times in exchange for albumin. Plasmapheresis decreased triglyceride levels effectively without adverse events. Additionally fenofibrate 200 mg daily was administered, sirolimus discontinued. Triglyceride levels over time dropped to 7.02 mmol/l on day 8 (Table 1). Blood samples thereafter showed no longer the initially depicted hypertriglycerid phenomena. Following discontinuation of sirolimus the patient was put on MMF 1000 mg bid and prednisolone, thereafter the selective Janus-associated kinase 1 (JAK1) and JAK2 inhibitor ruxolitinib was initiated.

Figure 1: Blood appearance on admission day. A bright pink color is seen which contrasts to normal blood appearance with therapeutic plasma exchange. (Colors have not been digitally processed).

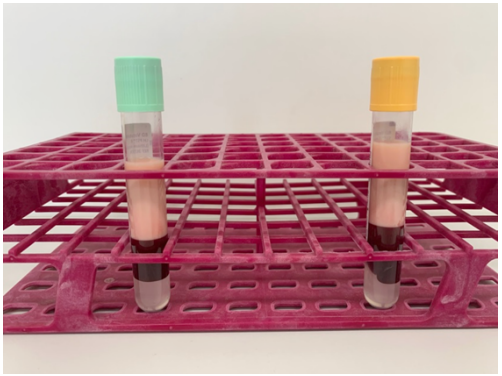

Figure 2: Blood sedimentation into two layers. The milky opaque supernatant results from aggregated triglycerides.

Days after Admission	Triglyceride Level in mmol/l [ref. < 1.7]	Therapeutic Intervention	Triglyceride Removal rate in %	Total Cholesterol in mmol/l [ref. < 5.2]	HDL in mmol/l	LDL in mmol/l
0	138	1. TPE[1], stopping of sirolimus, prescription of fibrates	22	35.4	Unmeasurable[2]	Unmeasurable[2]
1	107	2. TPE[1]	32	38	Unmeasurable[2]	Unmeasurable[2]
2	NA	3. TPE[1]		25.9	Unmeasurable[2]	Unmeasurable[2]
3	72.7	4. TPE[1]	40		Unmeasurable[2]	Unmeasurable[2]
4	44.2	5. TPE[1]	33	NA	NA	NA
5	29.4			NA	NA	NA
6	21.1			NA	NA	NA
7	11.4			NA	NA	NA
8	7.02			22.3	9.03	1.18

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; NA, not available; TPE, therapeutic plasma exchange. 1 Plasma exchange volume 4l. 2 Unmeasurable due to lipemic blood.

Table 1: Lipid panels since hospital admission in relation to therapeutic interventions.

- Lipemia
- Paraproteinemia
- Intoxication (carbon monoxide, cyanide)
- Dyshemoglobinemia
- Hypothermia

Box 1: Differential diagnosis of bright pink colored blood.

Genetic (Primary Hypertriglyceridemias)
• Familial Chylomicronemia Syndrome • Familial Hypertiglyceridemia
Metabolic
• Uncontrolled Diabetes Mellitus • Obesity • Pregnancy • Alcohol
Drugs
• Estrogene • Tamoxifen • Sirolimus • Protease Inhibitors • Interferon • Propofol

Table 2: Selected disorders reported as causative for severe hypertriglyceridemia.

Discussion

Sirolimus-induced hyperlipidemia has been described in up to 50 % of patients [15,16]. Hyperlipidemia is foremost characterized by a prominent hypertriglyceridemia that make up around 50 to 95% of lipids [12,13,17,18]. The pathophysiology of hypertriglyceridemia associated with mTOR-inhibition is not entirely understood. Potential mechanisms relate to interference with lipoprotein lipase activity by antagonizing insulin-dependent effects and diminished apolipoprotein C-III synthesis [19,20]. Additionally the enhancement of hormone-sensitive lipase activity, leading to elevated free fatty-acid release from adipose tissue has been described [21]. Furthermore sirolimus may interfere in lipogenesis by reduction of free fatty acids and expression of key enzymes [22]. Reports on severe hypertriglyceridemia associated with sirolimus treatment are rare, however have to be considered amongst the differential diagnoses (Box 1). Literature searches revealed that levels that high as in our index case have not been observed before [23–25]. Comingling of the red blood cells with the white appearing triglycerides are responsible for the phenomenon of pink colored blood [26].

Other differential diagnoses of severe hypertriglyceridemia include adverse drug reactions (Table 2) [27]. Uncontrolled diabetes mellitus may be accompanied by severe hypertriglyceridemia, however was not present in the index case. Especially the close temporal link with the newly prescribed drug and high trough levels link the excessive hypertriglyceridemia with sirolimus. Potentially aggravating factors elevating additionally lipid levels in this case are chronic kidney disease with mild proteinuria, medication with glucocorticoids and quetiapine [28,29]. Proteinuria leads to renal loss of lipoproteins and hence to hypertriglyceridemia, whereas administration of glucocorticoids increases triglyceride synthesis and stimulates lipoprotein lipase activity [30,31]. There is no generally consented standard of care regime to treat patients with excessive hypertriglyceridemia exceeding 10g/l. Expert opinion and anecdotal case reports provide hints on how to proceed [22]. Kido et al. reported on a pharmacological approach in an index patient without signs of hyperviscosity syndrome [32]. Furthermore triglyceride levels were lower (4425 mg/dl). Repeated laboratory testing in our patient revealed a steady fall of triglycerides following therapeutic plasma exchange (TPE) treatment, as reported in others [33-35]. The procedure is recommended in cases with suspected hyperviscosity syndrome or acute pancreatitis [27,36,37]. In the literature reports on TPE demonstrate lowered triglyceride levels by 66 to 84% after a single session [35,38]. In our reported case this efficacy was not achieved and several sessions had to be performed. This observation may be explained with the hyperviscous blood, which has been demonstrated to reduce the efficiency of triglyceride removal [39].

Conclusion

The index case is notable due to symptomatic sirolimus-induced excessive hypertriglyceridemia with signs of hyperviscosity syndrome. The reddish pink color of the blood and lipid separation in two phases is impressive to the care provider in the dialysis unit as well on the wards. Early and regular testing of the lipid status is mandatory following sirolimus treatment initiation. Furthermore, we provide evidence that only after repeated plasma exchanges a satisfying decrease of lipid levels is achieved.

Declarations

Ethics approval and consent to participate: Ethical approval is not appropriate. The authors obtained patient´s consent to participate.

Consent for publication: The authors obtained informed consent from the patient to publish information on her disease and clinical course.

Availability of data and materials: The authors did not use any datasets, databases, or special software in writing this manuscript.

Authors' contributions: STB collected the patient´s data and drafted the manuscript along with MJG, PRM and CRG. All authors read and approved the final manuscript.

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