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Case Report
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Etoricoxib Induced Thrombotic Thrombocytopenic Purpura

*Rozita Mohd and Lim Kuan Yee**

Nephrology Unit, Medical Department, University Kebangsaan Malaysia Medical Centre, Malaysia

Abstract

Thrombotic Thrombocytopenic Purpura (TTP) is characterized by a pentad of microangiopathic hemolytic anemia, thrombocytopenia, acute kidney injury, neurological symptoms, and fever. It is one of the phenotypes of Thrombotic Microangiopathy (TMA), commonly described in adults. The etiology of TTP is either due to congenital or acquired deficiency of plasma enzyme ADAMTS13 which is associated with female gender, black ethnicity, use of desmopressin, and pregnancy. We describe a rare case of drug induced TTP with selective cyclooxygenase inhibitor etoricoxib that was used for pain control post operation.

Keywords: Thrombotic Thrombocytopenic Purpura (TTP); Microangiopathic hemolytic anemia; Thrombocytopenia; Acute kidney injury; Etoricoxib

Introduction

Thrombotic Thrombocytopenic Purpura (TTP) is characterized by a pentad of microangiopathic hemolytic anemia, thrombocytopenia, acute kidney injury, neurological symptoms, and fever. A deficiency of plasma enzyme ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13) has been identified as the pathophysiology of familial TTP, leading to a reduce in proteolysis of Von-Willebrand Factor (VWF) [1]. The etiology and pathogenesis of acquired TTP, however, remains unknown. Several literatures have postulated that the mechanism of acquired TTP is acquired ADAMTS13 deficiency either due to the presence of antibodies against the enzyme or increased in its clearance [2].

Over the years, there are extensively varieties of drugs being reported to be associated with Thrombotic Microangiopathy (TMA) leading to either TTP or Hemolytic Uremic Syndrome (HUS). TTP-associated drugs have been reviewed in many literatures and are categorized into different groups; however, there is no clear association among these drugs to explain the potential risk of developing TTP [3]. The drugs which have been commonly mentioned include antineoplastic agents, immunotherapy, and antiplatelet drugs [3]. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are rarely been reported to be associated with TTP or HUS. There are only few cases of NSAIDs-induced TMA reported with mostly Ibuprofen reported in the literature in 1974, [4-7]. We describe a case of Etoricoxib-induced TTP.

Case Presentation

A 56-year-old man was admitted for a motor vehicle accident and sustained a fracture of left neck of femur and a distal end of right radius. He was a chronic smoker with a background history of hypertension on Felodipine. A total left hip replacement and closed manipulative reduction with percutaneous Kirschner wiring of right radius were done on day 4 of admission uneventful. Post-operation, he was prescribed with epidural pethidine and started on oral etoricoxib 120 mg OD for pain control.

He appeared jaundice 1 day after the operation. His liver function test showed a rise in the total bilirubin level from 31 to 126 μmol/L, alanine transaminase level from 288 U/L to 41 U/L. He also developed acute kidney injury with serum urea and creatinine rose from 5.3 to 22.6 mmol/L and 104 to 343 μmol/L respectively (Table 1). Consistently, his full blood count revealed a significant drop in hemoglobin and platelet levels from 15.6 g/dL to 10.9 g/dL and 348 $\times 10^9$/L to 32 $\times 10^9$/L. Initial assessment was thought to be a pre-renal acute kidney injury due to the dehydration and hypovolemia secondary to intraoperative blood loss with consumptive thrombocytopenia. The rise in the total bilirubin level was thought to be contributed by undiagnosed liver pathology which might be contributing to the low platelet counts. He was then rehydrated with normal saline infusion

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Correspondence:
Lim Kuan Yee, Department of Medicine, University Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif, 56000, Cheras, Kuala Lumpur, Malaysia, Tel: +60176466625; E-mail: limkuanyee@gmail.com

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Table 1: Serial blood investigations.

Admission Day	Full Blood Count			Renal Profile				Treatment
	Hb g/dL	WBC × 10^9/L	Platelet × 10^9/L	Sodium mmol/L	Potassium mmol/L	Urea mmol/L	Creatinine µmol/L	
Day 1	15.6	14.9	348	134	4.1	5.3	104	
Day 5	10.9	14.5	**32**	134	4.2	**22.6**	**343**	Day 1 post op
Day 6	9.6	16.1	**28**	133	3.9	**29**	**510**	Day 2 post op
Day 7	7.6	17.6	**39**	135	4.2	**39.9**	**769**	Day 3 post op
Day 8	9.1	18.9	37	142	3.9	34.5	689	HD + PEx
Day 9	10.5	27.1	44	139	4.1	28.5	627	HD + PEx
Day 10	8.8	27.6	62	139	3.2	17.7	349	HD + PEx
Day 11	10.3	29	48	141	3.3	23.4	462	HD + PEx
Day 12	9.8	30	31	139	3.6	27.1	568	HD + PEx
Day 13	8.7	32.5	85	142	3	23	482	HD + PEx
Day 14	8.4	20.4	98	135	3.3	17.6	369	HD + PEx
Day 15	7	25.6	131	139	5.2	21.8	473	HD + PEx
Day 16	8.9	21.9	200	137	3.2	18.2	385	HD + PEx
Day 49	10.8	14.3	445	135	3.9	21.9	343	Discharge

Hb: Hemoglobin; WBC: White Blood Cell; HD: Hemodialysis; PEx: Plasma Exchange; FFP: Fresh Frozen Plasma

and close fluid monitoring.

On day 2 post operation, he became oliguric with total of 300 ml of urine per day. His repeated blood investigations showed further deterioration of renal profile and further drop in hemoglobin and platelet levels. Etoricoxib was stopped in view of worsening kidney function. An ultrasound abdomen revealed no significant abnormality. His condition further deteriorated on day 3 post-operation with acute delirium. He became confused and restless in the ward and requested for an at-own-risk discharge. An urgent peripheral blood film revealed significant numbers of fragmented red cells with some polychromatic macrocytes consistent with microangiopathic hemolytic anemia suggesting a drug-induced TTP. Since there were no new drugs initiated, the most likely cause of TTP was etoricoxib.

He was commenced on plasma exchange therapy and needed temporary hemodialysis. His platelet counts improved and normalized after 9 sessions of plasma exchange. His renal function was improved, and regular hemodialysis was discontinued after 14 days. However, his hospital stay was further complicated with nosocomial pneumonia, upper gastrointestinal bleeding, and superficial gluteal pressure sore which prolonged his hospitalization for another 1-month duration.

He was discharged after a total 7-week hospitalization with serum urea of 21.9 mmol/L and serum creatinine of 343 µmol/L. A follow-up review after 2 weeks of discharge showed further improvement in the renal profile with serum urea of 7.2 mmol/L and serum creatinine of 203 µmol/L and subsequently remained around 180 µmol/L to 200 µmol/L.

Discussion

TMA was first described in the 1920s is as a diverse term used to describe any condition with arteriolar or capillary thrombosis, leading to microangiopathic hemolytic anemia and thrombocytopenia, with an organ injury particularly the kidney [8]. The classic TMA includes 2 commonly described phenotypes, i.e. TTP and HUS.

Both phenotypes share a common pathological process and characterized by a triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury, with TTP having additional features of fever and neurological symptoms, forming a pentad [9]. However, HUS is commonly described in the pediatric population and associated with *Escherichia coli* infection [9].

Two postulated mechanisms of drug-induced TMA are immune-mediated reactions and toxic reactions [8,10]. Immune-mediated reaction is due to the drug-dependent antibodies acting on different cells to produce a sudden and severe systemic microvascular thrombosis with severe kidney injury. Toxic reaction is due to the direct drug toxicity on the vascular endothelium, leading to TMA. Four principal classes of drugs which are described in toxicity-mediated TMA include chemotherapy drugs such as mitomycin and gemcitabine; immunosuppressive drugs such as cyclosporine and tacrolimus; Vascular Endothelial Growth Factor (VEGF) inhibitors such as bevacizumab and sirolimus; and recreational drugs such as cocaine [8].

There is no clear mechanism explained on how the NSAIDs induce the development of TTP. It is suggested that drug-induced TMA is complement-mediated, involving the alternative pathway of complement due to a complement dysregulation [11]. The alternative complement pathway was found to be activated in acute kidney injury induced by ketoprofen in sheep [12]. This explains a possible correlation of NSAIDs activating the alternative complement pathway, leading to the development of TTP. This correlation is further supported by a case of Diclofenac-induced TTP reported with a concomitant complement dysregulation [7]. Etoricoxib is a selective cyclooxygenase-2 inhibitor which is proven to have a better gastrointestinal tolerability however it is associated with cardiovascular thrombosis [13]. Hypothetically, the probable mechanism of the Etoricoxib-induced TTP in the present case is due to either a microvascular thrombotic event as a direct adverse effect of the drug or a complement dysregulation, or a combination of both, leading to TMA, phenotypically presented as TTP.

A sudden onset of jaundice with a significant drop of hemoglobin and platelet, and acute kidney injury in the gentleman after started on Etoricoxib should trigger the suspect of hemolytic anemia due to TMA. A peripheral blood film sent after that confirmed the diagnosis with

the presence of fragmented red blood cells. The urgent management recommended in the guidelines is to start plasma exchange as soon as possible with FFP [14]. FFP infusion alone can be given instead if there is any delay in giving or unable to provide plasma exchange [14]. The gentleman was given plasma exchange as soon as possible with FFP infusion only when plasma exchange was not available until the normalization of platelet counts and subsequent improvement of renal function. However, his renal function was unable to recover to the baseline with chronic kidney disease as a sequela of the TTP.

Conclusion

Etoricoxib is a better choice of NSAIDs for pain control with a better safety profile. However, physician should be aware on the rare possibility of TTP complication that needs to be considered as it requires urgent treatment.

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