A dramatic recovery in a patient initially expected to die of TTP & its complications

Jennifer Ogilvie and Jaskeerat Singh

ABSTRACT
Thrombotic thrombocytopenic purpura (TTP) has a high fatality rate if not caught early and treated with plasmapheresis. When TTP patients present late in their sequelae with neuro symptoms, an elevated lactate dehydrogenase and systemic symptoms, there is a high mortality rate. This report describes the case of a young female who had no significant medical problems and presented to our hospital after several days of hematuria, new onset blurry vision and dizziness. She was found to have thrombocytopenia and microangiopathic hemolytic anemia consistent with TTP and was thus started on plasmapheresis. Her course was further complicated with seizures and development of bilateral basal ganglia infarcts which lead to the need for mechanical ventilation. This was followed by worsening renal functions which was managed with intermittent hemodialysis. To add to her multi-organ failure, she developed shock liver along with demand ischemia evidenced by significant elevations in liver enzymes and troponin leaks, respectively. However, on Day 4 it was fascinating to see the beginning of her recovery pathway. It began with response to simple commands followed by discontinuing invasive ventilation and gradual improvement in her renal functions evidenced by increasing urine output. Soon her platelets started rising consistently and she did not require plasmapheresis or hemodialysis by the time she was discharged. This case highlights the rapid recovery of a young female with new onset TTP which was complicated by involvement and severe damage of more than five different organs but was followed by complete recovery of each organ system.

KEYWORDS
Thrombotic thrombocytopenic purpura; recovery; plasmapheresis; rituximab; good response; multi organ failure

1. Case presentation
A 44-year-old Caucasian female with no significant past medical history presented to the emergency department for transient blurry vision which resolved on presentation, dizziness and hematuria. For the past week, she had cough, congestion and sneezing. Two days prior to presentation, she went to her primary care physician for hematuria and bruising on her left arm and was diagnosed with urinary tract infection and given nitrofurantoin 100 mg BID. On presentation, she noted that since beginning antibiotics she had nausea, vomiting, anorexia, dizziness and anxiety-related chest pain.

On physical exam, the patient was well appearing, ambulatory and in no acute distress. She had a diffuse petechial rash on her face, extremities and trunk that she reported had begun one day prior and a bruise on her left upper arm. Her cardiovascular and lung exams were within normal limits. On neurologic exam, she had no focal findings.

Some significant lab findings were: platelets as described in Table 1 were lowest at 2000 on Day 2; Hemoglobin of 9.9 g/dL which dropped to 6.5 g/dL on Day 2 requiring transfusion; significant schistocytes and spherocytes noted on peripheral smear; lactic acid of 22.8 mmol/L, troponins peaked at 9.63 ng/mL; creatinine peaked at 8.4 mg/dL without any history of chronic kidney disease (CKD), blood urea nitrogen (BUN) of 38 mg/dL on presentation, peaked at 110 mg/dL; aspartate aminotransferase (AST) peaked at >7000 IU/L; AST peaked at 4117 IU/L; Hyperbilirubinemia of 10.3 mg/dL, primarily indirect. An ADAMST13 was sent to Johns Hopkins lab and results showed decreased levels of the ADAMST13.

CT head on Day 3 of admission showed interval development of areas of diminished densities concerning for bilateral basal ganglia infarcts. These findings were later confirmed with a MRI scan which also suggested on an embolic phenomenon, consistent with thrombotic thrombocytopenic purpura (TTP).

Hospital course/Treatment: She was admitted to the ICU after 4 units of fresh frozen plasma and plasmapher-esis. On admission, her condition began to worsen despite continued plasmapheresis. She had a rapid decline in mentation and a witnessed seizure which required mechanical ventilation for airway protection. She began having multi-organ failure to include anuric renal failure requiring frequent intermittent hemodialysis, NSTEMI, cardiogenic shock and shock liver. Her
prognosis was poor due to the extensive organ involvement of her TTP.

Her treatment regimen primarily was plasmapheresis, high-dose steroids and rituximab infusions. Her organ failure continued to progress and worsen despite continued treatment. Fortunately, on the evening of Day 3 her mental status improved as she started to respond to simple commands. This was followed by gradual improvement in all systems involved thereafter. She received a total of 15 plasmapheresis sessions, an extensive steroid regimen which included a taper and 4 doses of rituximab.

On Day 14 of her hospitalization she was able to stop plasmapheresis after having two days of platelets over 150,000. She required dialysis for several days in the hospital and her kidneys were somewhat slower to recover; however, eventually she regained full renal function evidenced by normal creatinine and BUN levels on discharge.

2. Discussion

New onset TTP in adult patients is most commonly an acquired autoimmune pathology involving the ADAMST13 protein. With a decreased ADAMST13 protein, Von Willenbrand factor cannot be cleaved and therefore microvascular thrombosis occurs [1]. The typical presentation of TTP is thrombocytopenia and microangiopathic hemolytic anemia (MAHA) which most commonly clinically manifests as fever, petechial rash, bruising, fatigue, dyspnea, and/or bleeding. The incidence of acquired TTP in the adult population has been reported to be as low as three cases of TTP per one million adults each year and is most commonly seen in African Americans, females and patients with systemic lupus erythematosus [2].

Our previously healthy patient presented with acute onset of symptoms that were late in the sequelae of TTP. Although neurologically intact and well appearing when she arrived in the ER, her lab work was a key diagnostic tool in the rapid progression of her pathology. When she arrived she already had severe thrombocytopenia, MAHA, acute kidney injury, shock and elevated troponins. Known risk factors for mortality due to TTP are age >60, severe neurological symptoms at presentation, and persistent lactate dehydrogenase (LDH) levels after two plasma exchanges [3].

Our relatively young patient did have some blurry vision on presentation but did not have severe neurological deficits. She did however present with a severely elevated persistent LDH levels despite continued plasma exchange (PEX), which put her at high risk for mortality.

Management with early plasmapheresis, Rituximab and methylprednisolone is the mainstay treatment for TTP. Despite this treatment, our patient continued to decline. There have been very few studies about the clinical course of TTP after initiating PEX and how long it takes to return to a baseline platelet count of 150,000. In our particular patient, a steady decline despite early plasmapheresis, Rituximab and methylprednisolone were all warning signs that our patient may in fact have refractory TTP that was not responding to therapy. Refractory TTP has been defined by some studies as TTP in which the platelet count does not double in a period of four days [4,5].

Due to the unpredictable nature of TTP, the typical course, duration of treatment and recovery are not well defined; however, it is known that it may take several days of PEX to see improvement in platelet counts.

What stood out in this case was the dramatic improvement that our patient made throughout her hospitalization. It was very satisfying to see the steady, rapid rise in her platelets and she began improving in all aspects of her illness. In a patient with such profound organ failure, it was our expectation that her recovery would be slow and steady if there would be any. In many hospitals, ADAMST13 testing is sent out to a tertiary laboratory which can take considerable time to return results. There is a scoring system that recently was developed to help clinically predict whether the patient has an ADAMST13 level of <10%. This PLASMIC score can be useful in predicting the levels

| Test        | 3 December 2017 | 4 December 2017 | 7 December 2017 | 9 December 2017 | 12 December 2017 | 17 December 2017 | 21 December 2017 | 28 December 2017 | 1 January 2018 |
|-------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Hemoglobin  | 9.9            | 6.5            | 6.8            | 7.2            | 7.6            | 7.2            | 7.3            | 7.1            | 10.9           |
| Hematocrit  | 26.9           | 18.0           | 19.4           | 21.5           | 22.7           | 21.2           | 21.7           | 20.9           | 34.3           |
| WBC         | 9.17           | 8.16           | 17.84          | 21.27          | 16.98          | 17.38          | 9.68           | 6.76           | 5.5            |
| RBC         | 3.04           | 2.12           | 2.20           | 2.35           | 2.45           | 2.20           | 2.31           | 2.22           | 3.52           |
| MCV         | 89             | 85             | 88             | 92             | 93             | 96             | 94             | 94             | 97             |
| MCH         | 32.6           | 30.7           | 30.9           | 30.6           | 31             | 32.7           | 31.6           | 32             | 33             |
| Platelets   | 8              | 2              | 42             | 87             | 140            | 152            | 155            | 114            | 256            |
| LDH         | 1131           | 1182           | 861            | 703            | 372            | 220            | 239            | 186            | 204            |
| CK          | 129            | 343            | 116            |                |                |                |                |                |                |
| Total Bilirubin | 2.9   | 7.2        | 3.6  | 3.1        | 1.7  | 0.4        | 0.3  | 0.3        | 0.2            |
| Indirect Bilirubin | 2.3  | 6.1    | 1.3  | 1.1        |                |                |                |                |                |

Table 1. Summary of important labs regarding this patient.
of ADAMST13 to help direct treatment and facilitate early initiation of Rituximab [6]. Our patient received Rituximab on Day 2 of her hospitalization which preceded her drastic improvement. When started within three days of admission for acute onset TTP, Rituximab has been shown to reduce the number of required PEX treatments and time to achieve remission in white females [7]. The recommendation to include Rituximab as the standard treatment for TTP is relatively new. The early initiation of PEX, rituximab and methylprednisolone was a key factor in the drastic turnaround of our patient. This prevented us from having to try other less studied agents for refractory TTP such as cyclophosphamide, Bortezomib, cyclosporine, mycophenolate mofetil, N-acetylcystene and splenectomy [8].

Disclosure statement
No potential conflict of interest was reported by the authors.

References
[1] George JN, Nestor CM. Syndromes of thrombotic microangiopathy — NEJM. Syndromes of Thrombotic Microangiopathy. 2014 Aug 14;371(7):654–666.
[2] Reese JA, Muthurajah DS, Hovinga JAK, et al. Children and adults with thrombotic thrombocytopenic purpura associated with severe, acquired Adamts13 deficiency: comparison of incidence, demographic and clinical features. Pediatr Blood Cancer. 2013 Jan;60(10):1676–1682.
[3] Chaturvedi S, Carcioppolo D, Zhang L, et al. Management and outcomes for patients with TTP: analysis of 100 cases at a single institution. Am J Hematology. U.S. Natl Lib Med. 2013 July;88:560–565. Available from: www.ncbi.nlm.nih.gov/pubmed/23605996
[4] Froissart A, Buffet M, Veyradier A, et al. Efficacy and safety of first-line rituximab in severe, acquired thrombotic thrombocytopenic purpura with a suboptimal response to plasma exchange. Experience of the French thrombotic microangiopathies reference center. Crit Care Med. 2012;40(1):104–111.
[5] Patton JF, Manning KR, Case D, et al. Serum lactate dehydrogenase and platelet count predict survival in thrombotic thrombocytopenic purpura. Am J Hematol. 1994;47(2):94–99.
[6] Bendapudi PK, Hurwitz S, Fry A, et al. Derivation and external validation of the PLASMIC score for rapid assessment of adults with thrombotic microangiopathic: a cohort study. Lancet Haematol. 2017;4(4):e157–e164.
[7] Scully, M., McDonald V, Cavenagh J, et al. A phase 2 study of the safety and efficacy of rituximab with plasma exchange in acute acquired thrombotic thrombocytopenic purpura. Blood. 2011 Feb;118(7):1746–1753.
[8] Veyradier A. Von Willebrand factor – A new target for TTP treatment? New England J Med. 2016 Nov;374(6):583–585.