CASE REPORT

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Treatment of Acute Kidney Injury in Hemolythic Uremic Syndrome (TTP)

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ABSTRACT

Introduction: Plasmapheresis is often used as a therapy in the treatment of thrombotic thrombocytopenic purpura (TTP). TTP is manifested in thrombotic microangiopathy, consumed thrombocytopenia, hemolytic anemia and acute kidney injury with HUS development, neurologic dysfunction, and fever. **Case report**: we will present a case of a patient with acute kidney injury and refractory TTP at the beginning of hospitalization, subsequently manifested in secondary nephrotic syndrome. The patient was a female, 39 years of age, who as an emergency case was referred from the hospital in East Sarajevo to the Clinic of Endocrinology, Diabetes and Metabolism Disorders of the Clinical Center University of Sarajevo with suspected TTP. A few days before hospitalization she had a fever and vomiting, and therefore consulted her physician. She was hospitalized due to severe general condition, generalized edema, visible body hematomas, and diuresis amounting to 600 ml/12 hours. Laboratory results on admission were as follows: Leukocytes 19.5, Erythrocytes 3.23, Hemoglobin 103, Hematocrit 28.8%, Platelets 65.4 with few schistocytes and 2 reticulocytes, Sodium 140 mmol/L,, Potassium 4.5 mmol/L, Calcium 1.90 mmol/L, Glucose 7.9 mmol/L, Urea 37.5 mmol/L, Creatinine 366 umol/L,, Bilirubin 19.0 umol/L, Lactate dehydrogenase 1194 U /L. The patient was communicative, in cardiopulmonary sufficient state. Central venous catheter was placed in the right jugular vein and the first plasmapheresis was performed. During the hospitalization 38 plasmapheresis treatments with frozen plasma were performed, followed by three Rituximab treatment cycles. After the last plasmapheresis treatment a platelet count was 138. Also, parameters of the renal function were in their referent values. At the beginning of the treatment proteinuria was 19.6 g/24 hours urine. We were faced with a dilemma whether renal biopsy should be repeated in the future given that it might be the case of primary and not secondary nephrotic syndrome. Controlled proteinuria was 4.7g after plasmapheresis. The patient used only Prednisolone at a dose of 10 mg daily and although initially diagnosed with acute kidney injury she was not treated with dialysis. **Conclusion**: early diagnosis and early start of plasmapheresis therapy is vital for treatment of patients with acute kidney injury and TTP (HUS). A small number of patients is refractory to plasmapheresis and introducing Rituximab and plasmapheresis treatment is recommended.

Keywords: acute kidney injury, HUS, TTP, plasmapheresis.

1. INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) has been known since 1925, when firstly described by Moschcowitz. TTP as a name was given in 1947 by Singer (1, 2). TTP is manifested in thrombotic microangiopathy, consumption thrombocytopenia, microangiopathic hemolytic anemia and renal insufficiency (with the development of HUS associated with the occurrence of azotemia and hemorrhagic diathesis), nervous breakdown and fever. HUS was first described by Gasser in 1955. For a long time (since the 1960s) plasmapheresis treatment has been used as an adjuvant and "support" therapy in treatment of many diseases. It is a process of removal of the plasma from the blood and its substitution with fresh frozen plasma (FFP) or with other substitute fluids (5% albumin or plasma derivatives–cryosupernatant, crystalloids–0.9% NaCl, Ringer's lactate solution) (1, 2, 3). Plasmapheresis (therapeutic apheresis) treatment is used in rapid reduction in circulating antibody titers (i.e. in anti-GBM glomerulonephritis) or immune complexes (i.e. Lupus nephritis), as an useful addition to chemotherapy for the removal of circulating immunoglobulins or components of immunoglobulin in multiple myeloma and other dysproteinemia, for the removal of other components, not only immunoglobulins (i.e. removal of thrombotic factors as in thrombotic thrombocytopenic purpura (4, 5). Characteristic peripheral blood smear in TTP:

apart from visible red blood cells in peripheral blood smear lack of platelets is evident, with misshapen mature erythrocytes and erythrocyte fragments (6).

Plasmapheresis treatment is used and adjusted to the needs of patients. Plasma (fresh frozen plasma) is the exchange therapy in HUS and TTP (exchange of a deficient plasma factor), when there is a risk of bleeding, as in intensive exchanges.

TTP occurs in three clinical forms (based on the number of clinical manifestation episodes and time intervals): one episode (attack) of the disease with non-recurrent clinical manifestations following the treatment, intermittent form with frequent episodes and clinical manifestations in irregular intervals, chronic form with clinical manifestations in regular intervals. Special approach and clinical course relate to idiopathic thrombocytopenic purpura (acute type in children) and Upshaw-Schulman syndrome (congenital deficit in ADAMTS13). TTP occurs secondary in autoimmune disorders (Postpartum thyroiditis (PPT)) and in infections (*E. Coli, Klebisella pneumoniae, Campilobacter*, etc.). Plasmapheresis treatment with drug therapy (corticosteroids) is often used in the treatment of TTP (6, 7).

2. CASE REPORT

We present a case of a patient with refractory TTP and acute renal injury at the beginning of the treatment, which subsequently manifested in secondary nephrotic syndrome. Thirty-nine years old female patient, with suspected TTP/HUS was urgently referred from the hospital in East Sarajevo to the Clinic of Endocrinology, Diabetes and Metabolism Disorders of the CCUS. A few days prior to her admission to the hospital she had an increase in basal body temperature and vomiting for which she consulted her family physician at the Public Health Center. Due to deterioration of her general condition reflected in weak urination and general swelling, she was hospitalized at the Kasindo hospital. Previously, the patient did not suffer from any diseases or did she undergo any surgeries. She was not allergic to any food or medications. The patient was non-smoker and non-alcoholic, with two normal births, regular menstrual cycle, and no genetic disorders. On admission to the Clinic she was in a severe general condition, with pretibial edema, visible body hematoma, and oliguria (diuresis 600 ml/ 12 hours). Laboratory results at admission, on 15 October 2014, were as follows: Le 19.5, Er 3.23, Hgb 103, Hct 28.8%, Tr 65.4, with rare schistocytes, and 1-2 reticulocytes, Fe 29.7 umol/L, UIBC 10.8 umol/L, TIBC 40.5 umol/L, IZ 73.3 %, Feritin 621 ng/ ml, B12 >128, Na 140 mmol/L, K 4.5 mmol/L, Ca 1.90 mmol/l, Cl 111 mmol/L,, bloog glucose 7.9 mmol/L, Urea 37.5 mmol/L, Creatinine 366 umol/L, D-Dimer 6.77, INR 0.93, APTT 26.7s. Total protein levels were: 52.0 g/L, albumins 26.0 g /L Total bilirubin levels were: 19.0 umol/L, AST 27, ALT 32, CK 50, LDH 1194 U/ L. The patient was without metabolic acidosis. The patient was conscious, communicative, with sufficient respiratory function, TA 130/80 mm HG, and diuresis 1000 ml. Central venous catheter was placed in the right jugular vein and the first therapeutic apheresis was performed. PH test results of gingival biopsy were as follows: morphological findings involve the picture described in TTP. Gingival biopsy showed the presence of hyaline thrombus in arterial and capillaries lumen (biopsy results were obtained later, already at the beginning of the treatment). Color Doppler of the kidneys showed slightly increased resistance in the area of both kidneys, close to the tolerance limits of 0.7 to 0.72. Otherwise, numeric, topographical and morphological aspects of renal arteries, intrarenal branching and perfusion were fully satisfactory. Venous blood flow in normal anatomic and hemodynamic condition with preserved flows in main venous trees on both sides. An MRI of the abdomen and pelvis (without contrast) showed subcutaneous fat tissue edema along the entire scanned area–anasarca. Bilateral pleural effusions, larger on the left side, with condensation of the pulmonary parenchyma. Ascites, edematous liver and kidneys. Small follicular cysts on both ovaries in the small pelvis, one bigger on the right ovary, 20 mm in diameter. Left parametria seems thick, ascites followed to Cavum Douglasi. Analysis of small pelvis lymph nodes was impossible due to ascites. Gynecology report: uterus of normal size and mobility, a thin uterine lining. Adnexa invisible due to large ascites in Cavum Douglasi. Results of proximal endoscopy: no abnormality on the entire esophagus. Blurred hyperemia in the area of pylorus. The presence of bile in the entire stomach. Endoscopic examination of the entire duodenum showed normal results. After 25 plasmapheresis treatments ultrasound guided renal biopsy was performed, followed by regular post-procedure recovery. Laboratory results following the biopsy were as follows: Tr 80.2, Cholesterol 18.3 mmol/l, Triglycerides 3.01 mmol/L, Albumins 18.0 g/L, Creatinine 75 umol/l, diuresis 3000 ml, proteinuria 45 g/d. (Histomorphological characteristics of glomerular component in the analyzed cylinder including also focal necrosis of glomerular capillaries correspond to thrombotic microangiopathy, specifically to microscopic picture as visible in thrombocytopenic purpura and hemolytic-uremic syndrome. Given that there were no specific diagnostic criteria to separate these two entities, the term thrombotic microangiopathy, TTP/HUS, was recommended). Benzidine-negative stool. Serology: Leptospirosis negative (IgG, IgM), Brucella antibody test negative (IgG, IgM), Hantavirus: IgG positive, IgM negative, Hepatitis markers negative, three consecutive urine cultures were performed, Enterococcus faecalis 10-4, follow up urine culture test showed the existence of Klebsiella pneumoniae, 10-4. Thyroid hormones: TSH 0.009, FT4 13.5, FT3, indicating hyperthyreosis, which resulted in an immediate Favistan therapy. Immunologic tests: anti CCP 0.29, CiC 28.85, p ANCA and c ANCA-negative, ANA-ANF negative, Anti-ds DNA-negative, ENA-6 profile: Anti SS negative, Anti SS B negative, Anti Sm/RNP negative, Anti Jo 1–negative, anti Scl. negative. Serum and urine negative for kappa and lambda light chains. After 36 therapeutic apheresis the patient still suffered from thrombocytopenia, with platelet counts 62.0. In an agreement with hematologists monoclonal antibody therapy was introduced, along with 700 mg of Ritux-

imab (Mabhtera) weekly. Two additional plasmapheresis treatments were performed, and the patient received a total of three cycles on a weekly bases.

Laboratory results at time of discharge: Le 8.74, Er 3.62, Hgb 123, Hct 35.2%, TR 138, Na 133 mmol/L, K 4.1mmol/L, Cl 101 mmol/L, Ca 1.98 mmol/L, blood glucose 9.9 mmol/L, urea 11.1 mmol/L, creatinine 60 umol/l, AST 12, ALT 22, CK 24, LDH 248 U /L. D-dimer 0.83.

3. DISCUSSION

During the hospitalization, 38 therapeutic apheresis were performed and the patient also received three cycles of Mabthere. Anticoagulants were not used during the treatment. Plasmapheresis treatment was performed daily with 1800-3700 ml of fresh frozen plasma exchange (blood type B Rh (D) positive). During the entire therapeutic apheresis treatment the patient received corticosteroid therapy (40 mg of SoluMedrol twice a day). Following the last plasmapheresis treatment the platelet count was 138. Majority of TTP treatments with plasmapheresis include daily exchange of plasma over the period of 7-14 days,with monitoring LDH enzyme corrections, bilirubin level and platelets using around 1.5 volume of plasma exchange and fresh frozen plasma as fluid replacement. At the beginning of the treatment levels of protein in urine were 19.6 g/ 24 hours urine. On the day of the renal biopsy proteinuria was 45g /24 hours urine. We were faced with a dilemma whether renal biopsy should be repeated in the future given that it might be the case of primary and not secondary nephrotic syndrome. Following plasmapheresis treatments the follow up proteinuria was 4.7 g (in the nephrotic range). Based on the recommendation of a hematologist the patient used only 10 mg of Nison and was not treated with dialysis although at the beginning of the treatment, during the first ten plasmapheresis, she had increased levels of urea and creatinine, with the symptoms of acute kidney injury. During diagnostic processing the patient was also diagnosed with hyperthyreosis, resulting in the introduction of Favistan therapy. Early diagnosing and immediate start of plasmapheresis treatment is of vital importance in the treatment of patients with acute kidney injury and TTP. More than one third of patients who survive an acute episode of TTP will have relapses (1). Neurologic symptoms are present in 63-70% of patients with TTP, however, the patient in our case did not have neurological manifestations of the disease (2). Plasmapheresis has a significant place in the therapeutic protocols related to treatment of TTP (3).

4. CONCLUSION

A successful treatment requires multidisciplinary approach to this problem, specifically cooperation between hematologist and nephrologist. Small number of patients is refractory to plasmapheresis recurrence. Introducing Rituximab and plasmapheresis twice a day in the therapy is recommended in refractory patients.(8, 9). If the plasmapheresis therapy is not successful, splenectomy is also recommended (4). The therapy could also include vincristine, cyclophosphamide. Eculizumab is recommended for use in the present Shiga toxin, present in patients with HUS (10). Plasmapheresis treatment is significant for the following: exchange of deficient plasma factor with antithrombotic or fibrinolytic activity, removal of circulating toxins causing endothelial dysfunction and/or aggregation of platelets and formation of micro thrombi (5, 11). The basis is in the deficiency of metalloprotease enzyme (ADAMTS 13) which splits von Willebrand factor caused by antibodies. In such patients, exchange of plasma with fresh frozen plasma removes inhibitory antibodies and accumulated von Willebrand factor multimers by enzymes replacement (6, 7, 11). On a molecular level ADAMTS 13 was identified in 2001(8, 11).

- **Author's contribution:** A.C. and H.R. gave substantial contributions to the conception or design of the work in acquisition, analysis, or interpretation of data for the work. Each author had a part in article preparing for drafting or revising it critically for important intellectual content, and all authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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