Literature Review
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Rituximab related non-infectious lung injury complicating treatment of severe TTP in pregnancy – literature review and case-report

Abstract

Background: Thrombotic thrombocytopenic purpura (TTP) in pregnancy is a rare but potentially life-threatening condition. Management of severe, refractory TTP during pregnancy is challenging and includes multidisciplinary approach. The prognosis of cases with a variety of hematological and autoimmune diseases, including TTP has changed profoundly after the rituximab therapy was introduced into clinical practice. However, adverse pregnancy outcomes associated with biological agents should be kept in mind and the decision to treat should be weighed by measurement of potential risks vs benefits.

Case report: We reported the first documented case of noninfectious lung toxicity in pregnancy related to rituximab use for TTP treatment**.** 26 y/o patient at 23 weeks gestation initially presented to ED secondary to numbness, headache, and slurred speech with negative brain imaging. Her laboratory findings revealed severe deficiency of platelets, hemoglobin and ADAMT13 activity. She underwent multiple therapeutic interventions including plasmapheresis, intravenous immunoglobulins (IVIG), prednisone, and eventually required more often hospitalizations. Ultimately, the decision was made to proceed with rituximab therapy. After the third infusion of rituximab, she developed non-infectious lung injury without evidence of SARS-CoV-2 or other infections, pulmonary edema, or pulmonary embolism. The maternal condition worsened acutely resulting in significant desaturation that required intubation and eventual emergent premature delivery at 31-weeks' gestation via C-section.

Conclusion: Rituximab therapy for TTP management in pregnancy may be associated with significant adverse maternal-fetal outcomes. Risks and benefits of treatment should be discussed with each patient and during multidisciplinary communications. Physicians should maintain high index of suspicion for non-infectious lung injury associated with rituximab treatment in order to be able to diagnose this complication early and start treatment to avoid severe mortality and morbidity.

Keywords: case report, thrombotic thrombocytopenic purpura, pregnancy, rituximab, pulmonary edema, non-infectious lung injury

Volume 13 Issue 1 - 2022

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Received: February 01, 2022 | **Published:** February 14, 2022

Introduction

Thrombotic thrombocytopenic purpura (TTP), a potentially incurable clinical syndrome, belongs to a group of rare heterogenous disorders called thrombotic microangiopathies (TMAs), that are characterized by circulating blood clots in arterioles and capillaries resulting in thrombocytopenia, microangiopathic hemolytic anemia and systematic injury of endothelial cells.[1,2] TTP is primarily instigated by autoantibodies cleaving protein ADAMTS13 that is required in the degradation of ultra large von Willebrand multimers secreted from the vascular endothelial cell.[3–6]

Typical TTP cases have severe deficiency of ADAMT13 and subsequently high plasma concentration of ultra large (>20,000 kDa) multimers of von Willebrand factor.[7] Currently, the diagnosis of TTP in patients has been defined by the measurement of ADAMTS13 using both Fluorescence Resonance Energy Transfer (FRET assay) and quantitative immunoblotting (IB assay) methods.[8]

TTP is a very rare complication during pregnancy and ensues in 1 out of 25,000 pregnancies;[9] whereas, the incidence of suspected TTP syndrome in the general / non-pregnant population has been reported as 11 cases per million.[10] Most TTP cases in the general population are acquired and are more prevalent in adults. In contrast, inherited TTP is very rare and mostly occurs in newborns. It is unclear what triggers acquired and inherited TTP; however, the National Heart, Lung and Blood Institute (NIH, USA) defined some factors that may play a role in acquired TTP include, disease conditions (HIV, lupus, infections, pregnancy and cancer), medical procedures (surgery, blood and marrow stem cell transplant), medicines (ticlopidine, cyclosporine, clopidogrel, hormone therapy/estrogens) and health products (quinine/tonic water substances) (https://www.nhlbi.nih.gov). Pregnancy is one of the most common risk factors for acute episodes of TTP.[9] The majority of TTP cases occur in the third trimester or during puerperium; whereas, only 10% occur in the 1st trimester.[9,11]

Currently, therapeutic plasma exchange (TPE) is the mainstay of treatment in pregnancy associated TTP cases; however, different therapeutic drugs (ticlopidine & clopidogrel) and chemotherapeutic drugs (rituximab & eculizumab) are being used in TTP cases.[1] Currently, there is insufficient data on TTP management in obstetric population.[12,13] Untreated TTP during pregnancy is associated with >90% chance of patient mortality.[14] Therefore, pregnancies complicated by TTP are high risk and require a complex multidisciplinary approach. More studies and more experiences are needed in this area to improve maternal-fetal outcomes.

Our case report is the first to describe a non-infectious lung injury from rituximab therapy for TTP in pregnancy. Our case describes a rare case of pregnancy complicated by severe refractory TTP diagnosed in the second trimester of pregnancy, requiring repetitive therapeutic plasmapheresis, intravenous immunoglobulins (IVIG), prednisone and particularly three rituximab infusions, which resulted in non-infectious lung injury, leading to premature delivery via emergent C-section at 31 weeks of pregnancy. Both maternal and fetal outcomes were favorable considering the severity and complex character of pathology.

Case report

Our patient is a 26-year-old G5P3013 who initially presented to the emergency department at 22 weeks and 5 days gestational age with increased bruising, numbness involving her torso and tongue, headache, and slurred speech. Her past medical history is complicated by systemic lupus erythematous, right carpal tunnel syndrome, immune thrombocytopenic purpura, and iron deficiency anemia. For ITP treatment thus far, the patient was receiving IVIG, prednisone 60mg daily and high-dose steroids 1 milligram/kilogram. Upon presentation her hemoglobin was 6.2g/dL and her platelets were 5x10^9/L. She was found to have the following lupus antibodies: Anti Smith, Anti SSA and Anti SSB. ADAMTS13 activity was decreased, confirming the diagnosis of new onset TTP. Due to chronic steroid use, she required steroid-induced diabetes of pregnancy management and Pneumocystis prophylaxis. Ultimately, this patient's TTP, as managed by hematology oncology, was refractory to oral prednisone 60 mg daily, daily plasmapheresis, IVIG 35g, solumedrol 60 mg IV Q8 hours, fresh frozen plasma, platelet transfusions, and cyclosporine 150 mg bid. The multi-disciplinary decision with hematology oncology and maternal fetal medicine was made to proceed with weekly rituximab, which was initiated at 29 weeks of gestation. Five days after her second infusion, she experienced right ear and jaw pain, sore neck, and had a maximum temperature of 38.0 C, for which she received IV vancomycin and cefepime. SARS-COV-2 testing was negative. Blood, streptococcus, and urine cultures were negative. Respiratory viral panel was negative. One week later, she received her third rituximab infusion, during which she experienced shortness of breath, upper abdominal and back pain, tachycardia and tachypnea. The rituximab infusion was slowed to a rate of 50 ml/hr for one hour, then increased to 100 ml/ hr, per consultation with hematology oncology. However, upon restarting at 100 ml/hr, she experienced severe back pain refractory to IV medicines and the infusion was stopped. Twelve hours later, she developed acute respiratory distress, requiring BiPAP and ICU admission, and broad-spectrum IV antibiotics were continued for presumed hospital acquired pneumonia. WBC was normal. BNP 809, lactate 3.5, procalcitonin was 3.44, D-Dimer was 1083k. Her arterial blood gases showed adequate oxygenation but hypercapnia which was concerning for the risk of developing fetal acidemia. Serial chest x-ray demonstrated worsening appearance of the chest with multiple areas of consolidation in the right lung, possibly multilobar pneumonia. She then required intubation due to decreasing oxygen saturation, after which point the fetus developed minimal variability with recurrent variable decelerations requiring emergency primary low transverse cesarean section. This was performed under general anesthesia at 31 weeks and 3 days. Repeat SARS-COV-2 testing was negative. Once stable after delivery, CT angiogram was performed ruling out pulmonary embolism. She met criteria for acute lung injury based on bilateral pulmonary infiltrates and PaO2/FiO2 <300 in the absence of left atrial hypertension. She was extubated POD#2, experienced ICU delirium in her postoperative course, and was discharged POD# 7 in stable condition. She declined contraceptive planning during and after her pregnancy, but ultimately did proceed with IUD placement at her 6-week postpartum visit.

Discussion

This case report is the first to describe the clinical outcomes of a patient with refractory TTP during pregnancy that underwent rituximab therapy resulting in the severe non-infectious lung injury that required emergent delivery at 31 weeks of pregnancy.

The prognosis of cases with a variety of hematological and autoimmune diseases has been changed profoundly after the rituximab therapy was introduced in clinical practices.[15,16] In previous studies, thrombotic thrombocytopenic purpura during pregnancy was associated with 80% of maternal and fetal mortality rate.[17,18] Before the advent plasma therapy, the case-fatality rate reported in clinical series was near 100% until the 1960.[17] In another study, approximately 10-25% of patients with TTP cases are pregnant women, suggesting that pregnancy is an efficient risk factor for precipitating the appearance or presentation of TTP and showing an interrelationship between pregnancy and TTP.[7,19] Furthermore, pregnancy characterizes a hypercoagulable disorder due to an increase of coagulation factors as well as the reduction of fibrinolysis.[5,19]

Rituximab is a chimeric anti-CD20 monoclonal B cell-depleting antibody designated for acute hematologic malignancies and autoimmune diseases treatment.[20] It has additionally been studied in randomized controlled trials, and approved as drug category C by Food and Drug Administration (FDA, USA) classification for treatment of autoimmune diseases, including systemic lupus erythematosus (SLE), idiopathic thrombocytopenia purpura (ITP), thrombotic thrombocytopenia (TTP), and multiple sclerosis (MS).[20] The estimated median terminal elimination half-life of rituximab is 18-22 days. The active drug has been detected in peripheral blood beyond 24 weeks after the last infusion in some patients.[21] Peripheral B-cells remain depleted for 6 months after infusion; however, B-cell reconstitution may not occur after years of followup.[22,23] Except in instances of potentially life-threatening disease occurring during an established pregnancy, all persons of childbearing potential are strongly advised to avoid pregnancy for 12 months after therapy.[20]

Treatment with rituximab could be considered in situations when life-threatening illnesses are diagnosed or relapse during an established pregnancy and when benefits are outweighing potential risks of administration of rituximab. Risks described and associated with rituximab treatment in pregnancy include preterm delivery, chronic medical conditions and rare congenital malformation.[24] Chakravarty et al.,[24] described outcomes from 231 reported pregnancies with maternal or paternal rituximab exposure, in which most pregnancies resulted in uncomplicated live births with preconceptional or antepartum exposure to rituximab.[24] The rate of preterm delivery was found to be higher than in general population (19% vs 10-12%)[25] but may be similar to the rates reported for the women with certain chronical medical conditions.[20,26] Two congenital malformations (2.2%)[24] were reported after rituximab exposure (club foot in an infant from set of twins, and a full term singleton with a ventricular septal defect, patent foramen ovale and patent ductus arteriosus) which is consistent with the rate seen in the general obstetrics population on the official website of Centers for Disease Control and Prevention, Nutritional center on birth defects and developmental disabilities (www.cdc.gov/ncbddd/bd/faq1.htm#chanceofBD). In addition, it is important to keep in mind that underlying pregnancy conditions significantly affect pregnancy outcomes and may make it difficult to interpret consequences of antenatal medical exposure.[20,21,26–29] Literature review of maternal

Citation: Zarudskaya O, Khurshid N, Zoorob D, et al. Rituximab related non-infectious lung injury complicating treatment of severe TTP in pregnancy – literature review and case-report. *Obstet Gynecol Int J.* 2022;13(1):58–63. DOI: 10.15406/ogij.2022.13.00626

complications associated with antepartum rituximab treatment presented in Table 1.

In the product insert, rituximab products can cause severe, including fatal, infusion-related reactions. Severe reactions typically occurred during the first infusion with time to onset of 30–120 minutes. Rituximab product-induced infusion-related reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death (www.pfizerpro.com/product/ruxience). Although, the worldwide reported rate of potential rituximab-induced lung injury is less than 0.01-0.03% in >0.54 million cases.[22,23,29]

Table 1 Maternal complications associated with antepartum Rituximab treatment. Review of literature

Authors, year	Included pregnant	Indications for Rituximab treatment	Comedications	Maternal complications
Azim et al., 2010	n=7	Lymphoma (NHL 6, follicular 1)	Chemotherapy for patient with NHL	NR
Burnette et al., 2014	n=1	Primary CNS lymphoma	Dexamethasone	None
Daver et al., 2013	n=1	DLBCL	Prednisolone, cladribine	None
Decker et al., 2006	n=1	DLBCL	Metoclopramide	None
Kimby et al., 2004	n=1	DLBCL	NR	None
Lee et al., 2014	n=1	DLBCL	Part of R-CHOP regimen	None
Mandal et al., 2014	n=1	DLBCL	Part of R-CHOP regimen	None
Perez et al., 2012	n=1	Primary mediastinal large B cell lymphoma	Part of R-CHOP regimen	None
Rey et al., 2009	n=1	DLBCL	Part of R-CHOP regimen	None
Chakravarty et al., 2011	n=64	Lymphoma, RA, SLE, ITP, MS, TTP, Castleman disease	Cyclophosphamide, vincristine, doxorubicin, methotrexate, corticosteroids, azathioprine, fondaparinux	SAB 11, TAB 15
Abisror et al., 2015	n=1	Lupus, hx of fetal loss	ASA, hydroxychloroquine, prednisone, LMWH, IVIG	Fetal demise 21week, hyperemesis gravidarum
Gall et all., 2010	n=1	ITP	Corticosteroids, IVIG, splenectomy	None
Mariampillai et al., 2016	n=1	TTP	Decadron	None
Martinez-Martinez et al., 2013	n=1	ITP	Methylprednisolone, azathioprine	None
Ojeda-Urbine et al., 2006	n=1	Autoimmune hemolytic anemia	NR	None
Fionan et al.,2020	n=1	ITP	none	None
Puja et al., 2019	n=1	Myositis	Prednisolone	None
Harris et al., 2018	n=1	ANCA associated vasculitis	Methylprednisolone and prednisone	None
Pefanis et al., 2020	n=1	ANCA associated vasculitis	Prednisolone	None
Sica et al., 2019	n=1	NHL		None
Nagata et al., 2020	n=1	APL	IVIG	None
Holden et al., 2020	n=1	Minimal change nephropathy		None
Munger et al., 2019	n=1	Neuromyelitis Optica	Methylprednisolone, plasma exchange	None
Padberg et al., 2017	n=1	DLBCL	R-CHOP	None

NR, non reported; ITP, idiopathic thrombocytopenic purpura; TTP, thrombotic thrombocytopenic purpura; LMWH, low molecular weight heparin; IVIG, intravenous immunoglobulin; ASA, acetylsalicylic acid; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; MS, multiple sclerosis; DLBCL, diffuse large B-cell lymphoma; CNS, central nervous system; NHL, non-Hodgkin lymphoma; SAB, spontaneous abortion; TAB, therapeutic abortion

The outcomes of the present case report are supported by a systematic review that included 121 non-pregnant patients from 21 clinical trials, who developed non-infectious pulmonary toxicity or rituximab-associated interstitial lung diseases.[16] The mean and median number of cycles of rituximab was four. The time of onset from the last rituximab infusion until symptom development or

relevant abnormal radiological changes vary from 0-158 days. Abnormal radiological findings were similar in all patients, with diffuse bilateral lung infiltrates apparent on chest X-ray and/or thoracic CT. Hypoxemia and abnormal functional tests (diffusion capacity deficit and restrictive ventilatory pattern) were seen in all cases. In 18 cases rituximab associated non-infectious lung injury was fatal.[16] Another case-series described rituximab induced interstitial lung disease (R-ILD) that manifested as dyspnea, fever and dry cough without clear evidence of infection during therapy of non-Hodgkin's lymphoma.[30] The median number of cycles to presentation of R-ILD was three infusions. In this case-series, one out of sixteen patients required mechanical ventilation and succumbed to interstitial lung disease.[30]

In a retrospective analysis, interstitial pneumonitis developed in 13 out of 90 cases treated with rituximab+ cyclophosphamide+ hydroxy daunorubicin+ oncovin and prednisolone (R-CHOP); whereas, none occurred in 105 cases treated with CHOP only.[31] Consequently, it is apparent that pulmonary complications have been reported more frequently in rituximab -containing chemotherapy treatments. Furthermore, reported pulmonary complications due to rituximab therapy are hypersensitivity pneumonitis, pulmonary fibrosis, alveolar hemorrhage, acute respiratory distress syndrome (ARDS), interstitial pneumonitis and organizing pneumonia.[22,32]

Our case report is the first to document non-infectious lung injury after rituximab therapy for TTP in pregnancy. More information is needed to understand the frequency of this reaction in pregnant women. We also reported our case to the FDA MAUDE database. In our case report, each rituximab infusion was tolerated progressively less and after the third infusion, our patient developed the non-infectious lung injury with hypoxic hypercapnic respiratory failure necessitating intubation and emergent preterm delivery. Decision for rituximab induction therapy was made secondary to severe disease manifestation refractory to treatment and failure in recovery after first-line therapy with multiple plasmapheresis, IVIG, prednisolone and cyclosporin. In cases of TTP refractory to first line therapies, both hematology and obstetric teams need to be aware of side effects of rituximab. A multidisciplinary discussion should occur regarding the timing of initiation of therapy in relation to drug risks and benefits, particularly aiming to start therapy after fetal viability when possible. If intolerance of the drug is noted in pregnancy, a multidisciplinary discussion should occur to again evaluate risks and benefits of the drug, with careful consideration about continuation of rituximab, as maternal and fetal risks can be severe. The proposed logistic of management of TTP during pregnancy presented in flow diagram (Table 1).[33–45]

Conclusion

Pulmonary complication due to rituximab therapy in TTP management during pregnancy is rare but potentially life threatening for both mother and fetus. Management of severe and refractory TTP during pregnancy is challenging and requires a multidisciplinary approach. Rituximab therapy with potential serious maternal-fetal risks should be carefully chosen during pregnancy when benefits outweigh potential risks. Non-infectious lung injury should be considered among other differential diagnoses in any patient who develops respiratory symptoms or new radiographic changes while receiving this biological agent. As the symptoms are nonspecific at presentation, physicians should maintain a high index of suspicion to diagnose this complication at an early stage and start treatment to avoid severe morbidity and potential mortality (Figure 1) (Figure 2).

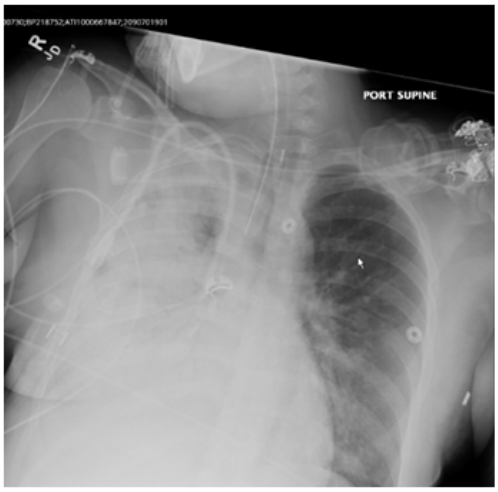

Figure 1 Bedside X-ray demonstrating worsening appearance of the chest with multiple areas of consolidation in the right lung, possibly multilobar pneumonia.

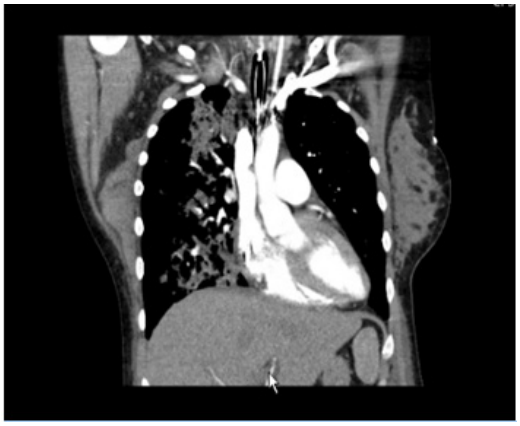

Figure 2 Chest CTA: Multifocal opacities most notably right upper lobe consistent with acute lung injury in the absence of pneumonia and pulmonary embolism. Small pleural effusions, right greater than left.

Acknowledgments

None.

Authors' contributions

OZ literature search and writing manuscript, ML conceive idea, writing and editing manuscript, DZ writing manuscript, NK writing and editing manuscript.

Funding

All listed authors received no funding and have nothing to disclose.

Conflicts of interest

Authors had no conflict of interest.

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