PREGNANCY RELATED THROMBOTIC MICROANGIOPATHY

DONNA NGO MD, BSN, BSC (HONS)

Background – Thrombotic microangiopathy most commonly presents in pregnancy secondary to pre-eclampsia (PET)/eclampsia and haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome. Less commonly, this can be related to atypical haemolytic ureamia syndrome (aHUS) or thrombotic thrombocytopaenia purpura (TTP). Other serious differentials include acute fatty liver disease of pregnancy (AFLO), systemic lupus erythematosus (SLE) and catastrophic antiphospholid syndrome (CAPS). Urgent diagnostic investigations are required to guide targeted management. Studies exploring diagnostic methods in identifying high risk women and differentiating underlying pathology have included genetic testing for complement gene variants and biochemical markers. An imbalance of anti-angiogenic factors such as soluble endoglin and recept fns-like tyorisine kinase 1 (sFlt1) have been found to be increased in PET.[1] A study by Timmermans et al, has demonstrated that though women who have a variant in complement gene have a component of complement dysregulartion, the risk of developing aHUS cannot be reliably predicted as additional precipitants have a large role and women predisposed to a genetic variant have a high rate of successful, uncomplicated pregnancies.[2]

Case – A 31 year old primip with low antenatal risk delivered via cesarean section after presenting for pre-labour rupture of membranes and failure to progress. Intrapartum, her blood pressure was elevated to 155/96mmHg with a normal PET screen. A repeat screen prior to delivery demonstrated an elevated LDH of 274. Day 1, she received a medical review for a pre-syncopal episode and was found to have normal blood pressure but brisk peripheral reflexes. Pathology demonstrated a severe thrombocytopaenia, acute kidney injury, and deranged liver enzymes. She was transferred to the ICU and commenced on steroids for emperical coverage of TTP. The Haematology and Renal teams were consulted for differential diagnoses of thrombotic microangiopathy (TMA), namely aHUS and TTP.

Pathology at 1301			
Na	138 mmol/L	Hb	104 g/L
K	4.1 mmol/L	WCC	13.1 x10^9/L
Cl	111 mmol/L	Platelets	31 x10^9/L
HCO3	21 mmol/L	RCC	3.4 x10^12/L
Anion gap	10 mmol/L	Hematocrit	0.31 L/L
Urea	9.3 mmol/L	MCV	92 fL
Creatinine	207 umol/L	MCH	31 pg
eGFR	27 ml/min/1.73 m2	MCHC	335 g/L
Total Bilirubin	28 umol/L	RDW	114.5
Total protein	55 g/L	Absolute Neutrophils	9.1 9.1 x10^9/L
Albumin	23 g/L	Absolute Lymphocytes	3.2 x10^9/L
Tot Globulin	32 g/L	Absolute Monocytes	0.7 x10^9/L
ALT	794 U/L	Absolute Eosinophils	0.0 x10^9/L
AST	1514 U/L	Absolute Basophils	0.0 x10^9/L
GGT	33 U/L		
ALP	124 U/L	Blood film	Occasional red cell fragment seen. Occasional bite cells seen. Left shift of granulocytes. Occasional reactive lymphocyte seen. Platelets reduced. No platelet aggregates seen.

Table 1. Patient pathology at 1301

Investigations – CT brain demonstrated a focal hypodensity in the lateral aspect of the right cerebellar hemisphere and a symmetrical hypodensity in the basal ganglia. An MRI demonstrated expected evolutional changes of gliosis secondary to a previous infarction to the right head of caudate and stable appearance of right cerebellar gliosis with resolution to the left. A preliminary ADAMTS13 level was negative ruling out likely TTP.

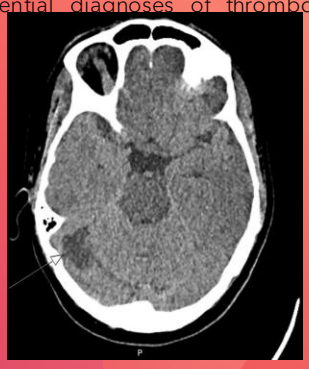

Figure 1. CT brain demonstrating focal hypodensity in lateral aspect of right cebellar hemisphere

Pathology	At 1640	At 1705	
Total bilirubin	25 umol/L	Na	140 mmol/L
Total protein	58 g/L	K	4.4 mmol/L
Albumin	24 g/L	Cl	111 mmol/L
Tot Globulin	34 g/L	HCO3	23 mmol/L
ALT	791U/L	Anion gap	10 mmol/L
AST	1262 U/L	Urea	9 mmol/L
GGT	33 U/L	Creatinine	218 umol/L
ALP	1262 U/L	eGFR	25 ml/min/1.73m2
LDH	1921 U/L	Ca	2.25 mmol/L
Ca corrected	2.57 mmol/L	Magnesium	0.81 mmol/L
Ammonia	48 umol/L	Phosphate	1.47 mmol/L
Haptoglobin	<0.15 g/L	Ammonia	44 umol/L
		Hb	108 g/L
		WCC	12.6 x10^9/L
		Platelets	34 x10^9/L
		Reticulocytes absolute	76 x10^9/L
		Reticulocytes %	2.2%
		PT	12 second(s)
		APTT	27 second(s)
		INR 1.2	

Table 2. Patient pathology at 1640 and 1705

Clinical course – She was commenced on regular labetalol responded well. Given she improved without complement therapy suggested an unlikely underlying aHUS process. She was discharged on day 8 with further outpatient Renal and Neurology review with an overall impression of TMA secondary to PET.

Patient Impact - **From the patient perspective, given the uncertainty of the initial diagnostic stage, early recognition of clinical signs, thorough assessment and clear regular communication held particular emphasis.**

Discussion – This example highlights the importance of the collaborative effort from different medical teams to ensure patient safety and to guide appropriate management for the best patient outcomes. Had the severity not been promptly recognized and treated in a multidiscplinary setting, she could have been facing significant morbidity. This case also demonstrates further confounding factors to recognition and treatment of pregnancy related TMA. Firstly, as demonstrated in the literature, stratifying risk for patients who may develop TMA with biochemical markers or genetic testing still remains beyond the scope of our current capabilities. Even were these tests were available, considering the rarity of the condition, significant consideration regarding the cost-effectiveness of implementation of a screening program would be necessary. As such, predicting which pregnant women will develop a TMA remains difficult, and as such regular assessment and a low index of suspicion is required in preventing poor outcomes of this condition. Furthermore, TMA has many symptoms and biochemical derangements in common with other serious conditions. This case reinforces the need for a broad diagnostic approach and resistance to diagnostic anchoring.

References

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2. Timmermans SAMEG, Werion A, Spaanderman MEA, Reutelingsperger CP, Damoiseaux JGMC, Morelle J, van Paassen P. The natural course of pregnancies in women with primary atypical haemolytic uraemic syndrome and asymptomatic relatives. Br J Haematol. 2020 Aug;190(3):442-449. doi: 10.1111/bjh.16626. Epub 2020 Apr 27. PMID: 32342491; PMCID: PMC7496636.