REVERSIBLE MEGALOBLASTIC HEMATOPOEISIS DUE TO SEVERE VITAMIN B12 DEFICIENCY IN A WELL-LIVED MAN WITH 2 YEARS HISTORY OF TRANSFUSION-DEPENDANT ANEMIA: *- A SILENT TRAGEDY -*

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INTRODUCTION

Patients with transfusion-dependant anemia are often encountered at the emergency rooms across the referral health facilities in Rwanda, where they present for blood top-ups indicated for their severe symptomatic anemia. The mode of work in such busy clinical areas often does not allow taking a focused history aiming at elucidating the diagnosis of the disease behind the recurrent utilization of blood products. In a country where we can only find two hematology clinics for a population size of 13 millions, there is a need for task shifting to encourage the emergency room doctors and residents to recognize and utilize observed trends in etiologies of chronic cytopenias among the Rwandan population, and this would enable them to trigger the testing mechanism to isolate those patients with background disease processes that would be treated otherwise, including the B complex vitamins deficiency.

METHODS

A 55 years old male from Kigali presented to the emergency room for recurrent progressive, effort related fatigue and postural dizziness. His pertinent past medical history consisted of frequent visits at the same hospital for a transfusion dependant anemia that had become worse in terms of frequency and quantity of packed red blood cells being transfused. His medical records showed that he had received a total of 24 units of packed red cells over a 2 years period-time during which he had visited eight times the above mentioned hospital's acute care unit.

His review of systems was positive for Lhermitte's phenomenon and paresthesias in fingers and toes. Otherwise the review was negative for chronic blood loss and constitutional symptoms. He reported isolated episodes of smear positive malaria which had been successfully treated. His dietary history was unremarkable. Prior visits at the hematology clinic in town had been unrevealing, and this had brought about feelings of poisonous misbelieves for which he still resisted to undergo the usual traditional remedies and rituals. His activities of daily living were also gravely affected by the frequent needs to visit the emergency room and he had been obliged to discontinue his job.

His physical exam revealed an apparently healthy man, with severe pallor and glossitis. He had no finger clubbing, petechiae, lymphadenopathy or visceromegaly. The function of the dorsal columns of his spinal cord was assessed normal in terms of joint position and vibration sense. His limbs and spine were normal without any localized swelling or tenderness. The digital rectal exam revealed brown stools with normal consistency. The remainder of examination was essentially unremarkable.
His pertinent laboratory work-up as summarized in the following chart revealed a progressive pancytopenia and reticulocytopenia. He had increased levels of lactate dehydrogenase at a dizzying figure with a negative direct Coomb's test which was interpreted as ineffective erythropoeisis. His total serum iron levels were found decreased and he was started on iron supplementation without a satisfactory effect.

LAB TESTS	JUNE 2013	AUG 2013	2014	ADMISSION	Post-TRANSFUSION
WBC	4.4	4.7	2.8 (L 60%)	1.7 (L 76%)	2.5 (L 31%)
Hb	7	5.6	6.4	5.5	10
MCV fl	85	74	94	88	80
RDW %	26	18	22	13	
PLT	248	203	181	83	14
RETIC % Abs. count/ L			0.1 7000	0	
LDH IU/L		10000	3758		1126
Total BILI mmol/L		4.4		14	
D Coomb's		negative			
Serum Iron mg/L		0.28			

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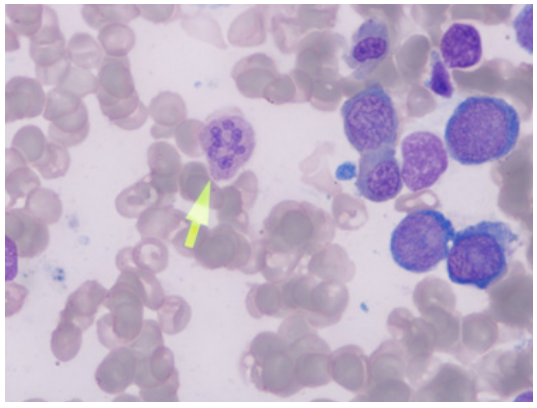
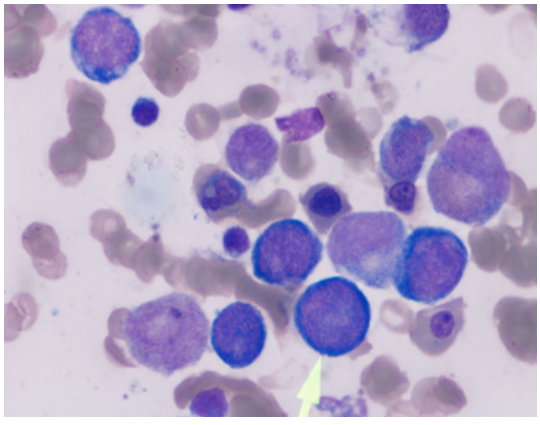
The remainder of the requested chemistry panel (including urea, creatinine and transaminases), viral serology for HIV, Hepatitis B and C were all negative. The abdominal ultrasound and upper GI endoscopy did not reveal any abnormalities.

The following chart shows the summary on findings from serial peripheral blood films that had been requested, which were notable for the presence of "tear drops" red cells, a finding that suggests a disease process involving the bone marrow.

	09/2014	01/2015	09/02/2015
WBC	Toxic granulation No dysplasia	Decreased	Decreased
RBC	Anisocytosis	Tear drops Nucleated RBCs	Dimorphic RBCs
PLT	Adequate	Decreased	Decreased

The smear of the bone marrow aspirate showed a nuclear-cytoplasm asynchrony, erythroid precursors with an open chromatin pattern and an inverted nuclear/cytoplasm ratio. A hyper segmented PMN was also noted. These findings were consistent of dysplastic maturation with features of MDS transforming into erythroleukemia (Di-Guglielmo Syndrome). The other differential diagnosis was thought to be a megaloblastic hematopoesis due to vitamin B12 or folic acid deficiencies.



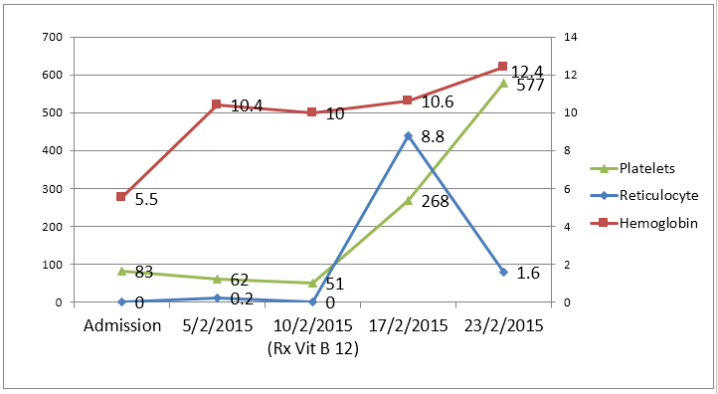


Courtesy of Anatomo-pathology dept. of Kigali University Teaching Hospital, Rwanda

The following chart summarizes the patient's hospital course, which is notable for a brisk boosting of his bone marrow function following injections with vitamin B12. Prior to that supplementation, a sample of his sera that was sent for the measurement of B complex vitamins levels was reported and confirmed the diagnosis of severe vitamin B12 deficiency. His follow-up iron studies also suggested the state of iron overload.

Chronology	Action	Outcome
Day 1	Transfusion with 3 units Packed red blood cells	Clinically improved with Hb 10 g/dL
Day 3	Bone Marrow Aspirate	MDS/AML-M6 vs Megaloblastosis
Day 4	Sera sent for Vit B 12 and folic acid levels Began on parenteral B 12 and oral Folic acid	Persistent depression, lethargy and paresthesias
Day 11	Repeat FBC and reticulocyte count	Stable H/H at 10 g/dL, Reticulocyte count **8.8** % **Vit B12: 53 pg/mL** (200 – 900) Folic acid: 16 ng/mL (2.5 – 20)
Day 13	Discharged home on vit B 12 replacement as per protocol	Improved MS w resolution of depression but persistent paresthesias
Day 18 (OPD)	Gastric juice pH Iron/TIBC/Ferritin LDH	**pH 5.9** --/--/ > **2000 ng/ml** **256**

The following graphic displays the same tremendous improvement as shown on full blood count. Note the brisk reticulocytosis and thrombocytotis following the injections of vitamin B12.



Of today, following a full replacement with vitamin B12 as per protocol, the patient remains free of symptoms, and with a normal full blood count and peripheral blood film. The relevant investigations of value that are still at bench include the antibodies to intrinsic factor and gastric parietal cells that would have been useful in excluding the commonest etiology for vitamin B12, which is pernicious anemia.

DISCUSSION

The diagnosis of vitamin B12 deficiency was somewhat a surprise, especially in a young previously healthy man living in a geographical area where the common etiology for B12 is thought to be a rare problem.

The frequent visits to the emergency room for blood transfusions without triggering the proper diagnostic work-up for the cause of his anemia was seen as an attitude of great concern that is partly explained by our testing capacity that might still be a logistical nightmare at some referral centers across the country. The often busy clinician operating in such settings would find it easier to address the relief of symptoms and let the patient go through the existing channel of outpatient follow-ups for chronic diseases, which is not always possible due to the lengthy and very demanding referral pathway. Most of these patients are both lost in follow-ups or at each visit they end up seeing a different physician who would not be familiar with their case, and hence the latter is unable to activate the needed clinical investigation. It could also be true that this practice is knowledge-problem or simply that the index of suspicion for such disease entities is very low and it might need some sort of awareness campaign across all the referring health facilities.

Since long ago, vitamin B12 deficiency has been cited in several reports across Africa as a potential cause of chronic cytopenias (Abdalla, Corrah, & Mabey, 1986). Among the common etiologies for the deficiency we can cite pernicious anemia as it is worldwide documented as the leading etiology (Toh, van Driel, & Gleeson, 1997). It is worth to be reminded that in settings where basic hygiene and water sanitation is still a domain needing to be improved, infectious causes of vitamin B12 deficiency such as infestation with Giardia Lamblia might still be a public health concern (Cordingley & Crawford, 1986).

Moreover, in the developing world where the consumption of natural sources of this vitamin (animal protein and dairy products) is a scarcity, a nutritional cause for vitamin B12 deficiency has been mentioned as a possible mechanism that should be evaluated further. The increasing number of reports on the unusual presentations of vitamin B12 deficiency i.e. neuro-psychiatric spectrum (Ssonko, Ddungu, & Musisi, 2014) or dermatological changes (Agrawala, Sahoo, Choudhury, Mohanty, & Baliarsinha, 2013), presenting either in combination or as standalone chief complaints, has raised concerns of this health problem being a public health concern that might have reached an epidemic proportion.

CONCLUSION

This case report highlights the need to re-emphasize on initiating the full work up for all patients with recurrent transfusion-dependant anemia. This would lead to the decrease of utilization of our emergency rooms and use of blood products for disease entities that are treated otherwise, and hence alleviate this additional burden from the already overwhelmed healthcare system.

There is a need to design a dedicated study to proper document the burden of B complex vitamins' deficiency in the population at large and avail appropriate policy-impacting recommendations.

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