Clinical Case Reports International

Case Report
Published: 09 Oct, 2023

Severe Low Vitamin B12 Levels with Macrocytosis and Associated Hemolytic Anemia, Mimicking Thrombocytopenic Thrombotic Purpura: A Case Report and Literature Review

Bustos M[1,2]*, Weldt J[1,2], Labarca G[1,2] and Enos D[1,2]

[1]Department of Internal Medicine, University of Concepción, Concepción, Campus Los Angeles, Chile

[2]Center of Undifferentiated Medical Responsibility of Adult Healthcare Dr. Víctor Ríos Ruiz, Chile

Abstract

The typical presentation of cobalamin deficiency is macrocytic anemia with or without neurologic symptoms, and the most frequent cause is Pernicious anemia, an autoimmune disease. We present a case of a 61-year-old man with neurologic symptoms, pancytopenia, and laboratory findings consistent with hemolytic Microangiopathic Anemia (MAHA), like Thrombocytopenic Thrombotic Purpura (TTP). The lack of response to Plasma Exchange (PEX) therapy, concomitant with low plasma levels of cobalamin, low reticulocyte count, macrocytosis and remarkably high Lactic Dehydrogenase (LDH) levels made us suspect a Pseudo-Thrombotic Microangiopathy (Pseudo TMA). The diagnosis was confirmed with a normal serum ADAMPTS13 activity and a rapid clinical and laboratory improvement after cobalamin supplementation. We think the internist must know the wide variety of presentations of cobalamin deficiency, since it is a reversible cause of bone marrow failure and its' misdiagnosis may result in unnecessary costly procedures.

Keywords: Vitamin B12; Pernicious anemia; Pseudo thrombotic microangiopathy; Thrombocytopenic thrombotic purpura

OPEN ACCESS

Correspondence:
Misael Bustos, Center of Undifferentiated Medical Responsibility of Adult Healthcare Dr. Víctor Ríos Ruiz, Av Ricardo Vicuña, 147 Los Angeles, Biobío Province 4400000, Chile, Tel: +56 9 68973576

Received Date: *19 Sep 2023*
Accepted Date: *05 Oct 2023*
Published Date: *09 Oct 2023*

Citation:
Bustos M, Weldt J, Labarca G, Enos D. Severe Low Vitamin B12 Levels with Macrocytosis and Associated Hemolytic Anemia, Mimicking Thrombocytopenic Thrombotic Purpura: A Case Report and Literature Review. Clin Case Rep Int. 2023; 7: 1613.

Background

Vitamin B12 (Cobalamin) participates in cell maturation and its' deficiency can lead to macrocytosis, immature nuclei and hyper segmentation in granulocytes at peripheral blood [1]. The typical hematological finding in cobalamin deficiency is megaloblastic anemia, accompanied or not by neurologic symptoms [1]. The main cause of cobalamin deficiency is Pernicious anemia, an autoimmune disease characterized by the presence of antibodies against parietal cells and intrinsic factor [1,2]. Therefore, there are other clinical pictures related with this vitamin deficiency, which can mimic other clinical entities such as TTP or myelodysplastic syndromes. We report a case of a patient who presented as a very unusual complication: Pseudo-Thrombotic microangiopathy.

Case Presentation

A 61-year-old man, with medical record of self-limited pancytopenia interpreted as transient hypersplenism eight years ago, was admitted at internal medicine ward, derived from primary care presenting a new episode of pancytopenia described as asymptomatic. At arrival, the patient presented slight disorientation in time and space, meanwhile the rest of the neurological exam appeared normal. Fever, jaundice, hemorrhage, and paresthesia were not found. The complete blood count reported macrocytic anemia (hemoglobin 6.32 gr/dL), Medium Corpuscular Volume (MCV) 115 fL, hematocrit 18.5%, white blood cells count 3.470/mm^3 and platelet count 84.000/mm^3 (Table 1). Blood smear showed schistocytes, dacrocytes, and stomatocytes, and negative direct Coombs test. The lactate dehydrogenase was high (4194 IU/L, Normal Value (NV) 150-350). Total bilirubin was 2.54 mg/dl, 55% indirect reacting*, and serum creatinine was normal (Table 1). ADAMTS13 activity and presence of inhibitors were searched. Patient was transferred to intensive care unit for urgent PEX, performing 3 sessions each one daily. However, after second session of PEX, we realized lacking bone marrow compensatory response with low reticulocyte count (1.6%), persistent thrombocytopenia, and lower than expected drop in LDH levels (Figure 1), making megaloblastic anemia confirmed by low plasmatic levels of cobalamin (140 pg/mL, NV 187 pg/mL - 883 pg/mL)

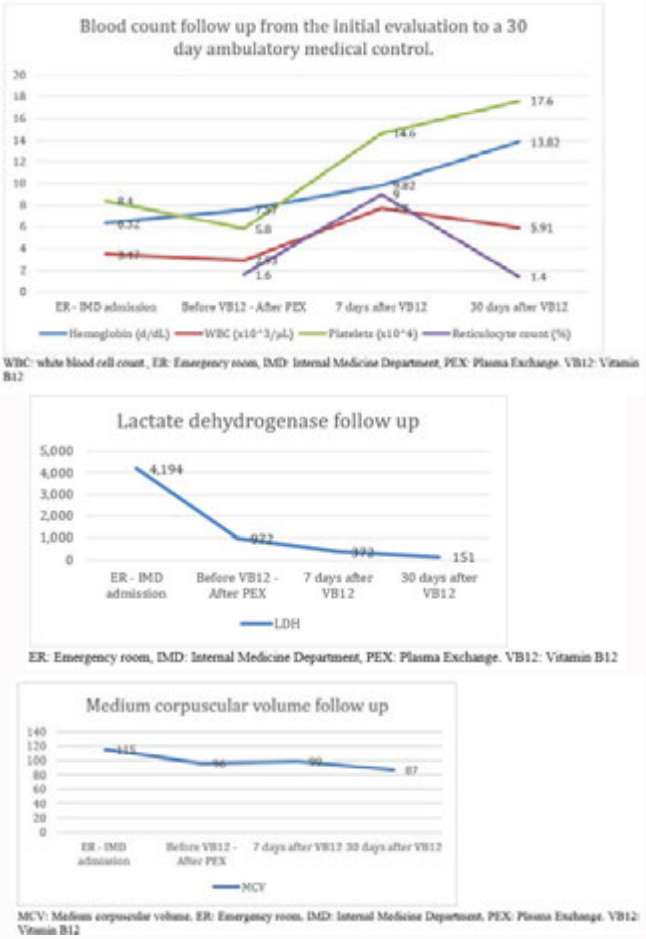

Figure 1: Laboratory tests follow-up.

(Table 1). Thus, we suspected Pseudo-TMA and began cobalamin supplementation.

Differential diagnosis if relevant

Pseudo-TMA due to cobalamin deficiency, in contrast to TTP, should be suspected when there is a deficient medullary response after acute hemolysis or PEX, demonstrated by a low reticulocyte count and low intramedullary cell counts, without renal involvement [1,3,4,5]. In TTP, there is a high reticulocyte count since it affects a normal bone marrow [5]. Other features have been described to suggest Pseudo-TMA, such as higher lactate dehydrogenase levels, higher mean platelet counts, and lower mean neutrophil count [3,4]. In differential diagnostic workup, the finding of elevated homocysteine, methylmalonic acid, presence of hyper segmented neutrophils and megaloblasts in the peripheral blood smears are also useful to guide the diagnose of cobalamin deficiency [1].

In addition, bone marrow study (myelogram and bone biopsy) may find 3 series dysplasia, making any myelodysplastic syndrome another differential diagnosis of cobalamin deficiency [1] (Figure 2).

Treatment

We performed 3 PEX sessions since we suspected TTP diagnosis, but after finding low medullary response and low levels of vitamin B12, PEX was withdrawn and we decided to use intramuscular vitamin B complex (3 doses of 10,000 units), with excellent response. One week after vitamin B12 supplementation there was improvement

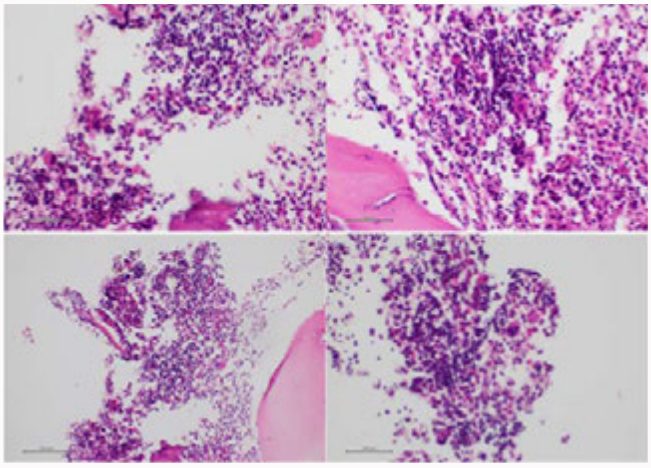

Figure 2: Bone marrow biopsy.
Bone marrow biopsy seen by optical microscopy, showing diffuse hyperplasia, megaloblasts and some scarce elements of myelodysplastic changes

in symptoms and laboratory tests, both in blood (Table 1, follow up tests) and bone marrow samples (myelogram and bone biopsy). The diagnostic study was negative for TTP, and the upper gastrointestinal endoscopy was consistent with Pernicious Anemia (Table 1).

Outcome and follow-up

The patient underwent a rapid, clinically significant improvement in his neurological condition and laboratory findings. Thus, one week after the initiation of vitamin B complex, a reticulocyte peak was evident. Afterward, within two weeks of hospitalization and after ten days of cobalamin supplementation, the patient was discharged without any neurological symptom, mild normocytic anemia, and normalization of the other blood cell counts, with the indication of prolonged treatment with vitamin B12. Two weeks after discharge, with an almost normal blood count, ADAMTS13 activity resulted normal, reflecting the absence of metalloprotease inhibitors. In the current context of contingency due to SARS-CoV-2, a most comprehensive study of probable pernicious anemia could not be performed.

Discussion

One common cause of cobalamin deficiency is pernicious anemia, an autoimmune disease with plasmatic autoantibodies against the intrinsic factor [1,2]. In our case, the gastric tissue biopsy result was consistent with pernicious anemia, but the antibodies could not be studied yet.

This cobalamin deficiency presentation, with clinical and laboratory findings consistent with TTP (neurological involvement and suggestive findings of MAHA: Anemia, schistocytes in peripheral blood, thrombocytopenia, high levels of lactate dehydrogenase and indirect-reacting bilirubin [6]), is called Pseudo-Thrombotic Microangiopathy [2-5,7]. Few case reports have described similar cases, postulating laboratory findings due to ineffective erythropoiesis. Other authors think there is a raise in homocysteine's blood levels, provoking endothelial dysfunction, fragmentation, and destruction of erythrocytes appearing schistocytes in the blood smear [2]. The LDH levels appear to be higher in Pseudo TMA than in TTP because of peripheral and intramedullary destruction of red blood cells; the presence of lower neutrophil mean count and less severe thrombocytopenia should help in differential diagnostic workup

Table 1: Laboratory analysis.

Variable	Reference Range	Results on ER admission and IMD*	Results after PEX and Before Vitamin B12**	Outcome results (7 days // 30 days after first dose of Vitamin B12**)
WBC, × 10^3/μL	4.4–11.30	3.47	2.93	7.70 // 5.91
Neutrophils, %	40–75	57.02	59.2	71.76 // 60.95
Lymphocytes, %	25–40	31.32	31.68	12.33 // 25.93
Monocytes, %	2–8	6.01	6.29	9.30 // 7.59
Band neutrophils, %	0–5	0	0	0
Metamyelocytes, %	0	0	0	0
Promyelocytes, %	0	0	0	0
Myelocytes, %	0	0	0	0
Eosinophils, %	2–4	4.51	1.7	4.66 // 3.70
Basophils, %	0–1	1.12	1.12	1.194 // 1.82
Hemoglobin, g/dL	13–17.5	6.32	7.57	9.82 // 13.82
Hematocrit, %	40–52	18.51	21.34	30.48 // 42.59
Reticulocyte count, %	0.5–1.5		1.6	9 // 1.4
Platelet count, × 10^3/μL	140-400	84	58	146 // 176
MCV, fL	80–96	115	96	99 // 87
Total Bilirubin, mg/dL	0.2–1.2	2.54	2.68	0.96 // 0.3
Indirect Bilirubin, mg/dL	0–1.0	1.4	1.9	0.5 // 0.2
LDH, UI/L	125–243	4,194	972	372 // 151
ESR, mm/h	0-20	1		
Crea, mg/dL	0.72–1.25	0.9	0.7	0.7
Blood smear:	-	Anisocytosis, Macrocytosis, Schistocytes, Dacrocytes, Stomatocytes	-	Anisochromia ***
Myelogram				Hypercellularity, erythroid hyperplasia, scarce blasts, dysplasia of the three blood cell lineages. (•)
ADAMPTS 13 Activity, %	41–180	92		
Presence of ADAMPTS 13 inhibitors	No inhibitors present			
Upper GI endoscopy	Atrophic pangastritis, intestinal metaplasia. Urease test: negative.			

WBC: White Blood Cell count; MCV: Medium Corpuscular Volume; AST: Aspartate Transaminase; ALT: Alanine Transaminase; AP: Alkaline Phosphatase; Crea: Serum Creatinine; ESR: Erythrocyte Sedimentation Rate; ER: Emergency Room; IMD: Internal Medicine Department; PEX: Plasma Exchange; GI: Gastrointestinal

(*): Initial laboratory findings.

(**): After initiating Vitamin B Complex administration.

(***): Blood smear after one week of treatment with Vitamin B Complex didn't inform any abnormalities in the red blood cells or the platelets' morphology.

(•): one week after VB12

too [3,4]. Other features that guide us to cobalamin deficiency is the presence of low reticulocyte count in Pseudo-TMA due to bone marrow failure, in contrast of being always elevated in TTP [1,3,4,5]. Also, elevated homocysteine, methylmalonic acid, hyper segmented neutrophils, and megaloblasts in peripheric blood smears, and the absence of acute kidney injury in Pseudo TMA, opposite to TTP [1,5]. In addition, the response to cobalamin supplementation also suggested the etiology of hemolytic anemia due to specific vitamin deficiency.

Pathophysiology of TTP consists in a quantitative or functional decrease of the protease ADAMPTS13, whose task is cleaving von Willebrand factor (vWf) from a macromolecule with a high capacity to recruit and activate platelets, into lower molecular weight segments with less activity [5]. Consequently, a decrease in ADAMPTS13 activity promotes platelets activation and thrombus formation through every organ microcirculation [5].

In our case, diagnosis was made after significant medullary response after vitamin B12 supplementation. Some elements of myelodysplastic syndromes were shown in the biopsy, but this data was not given importance since all cellular series responded to vitamin B12 administration, including reticulocyte count peak.

Unlike TTP, a hematologic emergency that implies the urgent need of PEX, the Pseudo TMA does not need that therapy [1,3,4,5]. Due to the similarity of both, our opinion is that PEX was an initially appropriate indication.

The differential diagnosis between pseudo-TMA and TTP could be very subtle and requires a quickly deep analysis for correct diagnosis. Our opinion is that it is of utmost importance for internists to know the wide variety of presentations of cobalamin deficiency, since it is a reversible cause of bone marrow failure and misdiagnosis may lead to unnecessary costly procedures.

Learning Points/Take Home Messages

- Pseudo TMA and TTP are very similar in their clinical features
- TTP is a hematologic emergency that needs a quick PEX. Pseudo TMA does not.
- The presence of schistocytes in blood smear do not differentiate Pseudo TMA and TTP
- Clues to think in Pseudo TMA are a medullar response to hemolysis, finding low levels of reticulocytes and serum Vitamin B12, and normal levels of ADAMTS-13 activity without inhibitors.

References

1. Stabler SP. Vitamin B12 Deficiency. N Engl J Med. 2013;368:149-60.
2. Saroj K, Nibash B, Shanta P, Bikash B, Aam B, Ramesh P, et al. Pseudo-thrombotic thrombocytopenic purpura presenting as multi-organ dysfunction syndrome: A rare complication of pernicious anemia. SAGE Open Med Case Rep. 2017;5.
3. Tuten N, Bennett C, Babcock W. Thrombotic thrombocytopenic purpura or cobalamin deficiency? A case report and review. Clin Case Rep Rev. 2015.
4. Podder S, Cervates J, Dey BR. Association of acquired thrombotic thrombocytopenic purpura in a patient with pernicious anemia. Podder S, et al. BMJ Case Rep. 2015;2015:bcr2015211989.
5. George JN. Thrombotic Thrombocytopenic Purpura. N Engl J Med. 2006;354:1927-35.
6. Moscoso F, Polanco E. Myelodysplastic syndrome clinically presenting with the "Classic TTP Pentad". Case Rep Hematol. 2017;2017:4619406.
7. Bailey M, Maestas T, Betancourt R, Mikhael D, Babiker HM. A rare cause of Thrombotic Thrombocytopenia Purpura-(TTP-) Like syndrome, vitamin B12 Deficiency: Interpretation of significant pathological findings. Case Rep Hematol. 2019;2019:1529306.