CASE REPORT: PSEUDO-THROMBOTIC THROMBOCYTOPENIC PURPRA AND COBALAMINE DEFICIENCY.

Housam Almadani, Ziyad T. Mirza and Banan Alsaied.
Department of pediatrics, Hematology Oncology, King Fahd Armed Forces Hospital, Jeddah, Saudi Arabia.

Abstract
Pseudothrombotic microangiopathy is thrombocytopenia, anemia and schistocytosis caused by Cobalamine deficiency. It could be easily misdiagnosed as microangiopathic hemolytic anemia.
Evaluation of lactate dehydrogenase, reticulocyte count, peripheral blood smear, platelet count, cobalamin and homocysteine level are crucial for differentiating pseudothrombotic microangiopathy from a true microangiopathic hemolytic anemia.
A case of pseudothrombotic microangiopathy due to severe vitamin B12 deficiency is presented.

Introduction:-
Thrombotic Thrombocytopenic Purpura (TTP) is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and neurologic symptoms or renal injury with the disease process driven by a severe deficiency of ADAMTS13, metalloprotease and disintegrin that cleaves Ultra Large Von Willebrand Factor multimers (ULVWF). ¹ ² ³
Vitamin B12 deficiency can present with microangiopathy and can be mistaken for TTP⁴.
Inadequate consumption of animal foods is considered the most common cause of severe vitamin B12 deficiency worldwide in pediatric age group ⁵. Most of the Cobalamine deficient cases have only mild haematological findings, in approximately 10% of patients presents with severe anemia, pancytopenia and hemolytic anemia⁶.

Case report:-
A 2 years old boy was admitted to hospital with decreased oral intake, decreased appetite, fever and vomiting once. On examination the patient looked pale, apathy, weak; weight and height below 5th centile; and his sclerae were icteric. Laboratory investigations revealed macrocytic anemia (hemoglobin 6.6g/dl; leukopenia (neutrophil1300);and thrombocytopenia (58000). Reticulocyte count was 0.039. Lactate dehydrogenase (LDH) was 3707u/l. Direct Coombs and glucose-6-phosphate dehydrogenase deficiency tests were all negative. Alkaline phosphatase was high 991.7u/l. Plasma homocysteine level was elevated 27.6. A peripheral blood smear showed schistocytes and hypersegmented neutrophils .B12 level was 77.12pg/ml. folate serum was normal. Vitamin D was low and serum Iron was normal. ADAMTS13 was normal. Bone marrow aspiration study demonstrated megaloblastic erythropoiesis and ruled out leukemia. Intramuscular cyanocobalamin was started and patient respond very well.

Corresponding Author:- Housam Almadani.
Address:- Department of pediatrics, Hematology Oncology, King Fahd Armed Forces Hospital, Jeddah, Saudi Arabia.
Discussion:
Inadequate consumption due to dietary restriction or unavailable access to animal sourced food is the most common cause of Vitamin B12 deficiency in infants and children. In our patient, he was on exclusive breastfeeding. His four year-old sister presented 8 months later with decreased activity and appetite, and vomiting with evidence of hemolytic anemia and pancytopenia. Her lab consisted with elevated LDH (6310 U/L) and Schistocytes in peripheral blood smear, and low vitamin D.

Cobalamine deficiency is relatively common in the general population, with prevalence estimates ranging from 4-15%, it should be considered in the differential diagnosis of patients with microangiopathic hemolytic anemia.² ⁷

In vitamin B12 Deficiency pseudothrombotic microangiopathy is related to ineffective erythropoiesis & intramedullary destruction of erythrocytes.⁸

In addition to intramedullary haemolysis, homocysteine accumulation due to vitamin B12 deficiency was found to increase haemolysis in vitro.⁹ ¹⁰ pseudothrombotic microangiopathy presents in 2.5% of patients exhibited In one study of 201 patients with vitamin B12 deficiency.⁷

Its association with Vitamin B12 deficiency has been reported most frequently in adults with pernicious anaemia rather than in those with dietary insufficiency. ⁷ ¹¹

Cobalam is essential co-factor for DNA synthesis and haematopoiesis, and its severe deficiency causes Neutropenia, thrombocytopaenia, & megaloblastic anaemia, as the case in our patient.¹² ¹³ ¹⁴ (table1)

Our patient had severe pancytopenia and findings of haemolysis (fragmented Red blood cells & polychromasia) in the peripheral smear mimicking microangiopathic haemolytic anaemia, low reticulocytes in relation to anemia and marked increase in Alkaline phosphatase & LDH.

Many authors reported a decreased absolute reticulocyte count, and a markedly elevated LDH favor the diagnosis of vitamin B12 deficiency (Psuedo-thrombotic Microangiopathy) over TTP.² ⁷ ¹¹

An LDH value exceeding 3000 U/L strongly favors pernicious anemia.²

Furthermore there was dietary and family history of low vitamin D which rises a high suspicion of Nutritional B12 deficiency.

Plasma exchange has no rule in the treatment of B12 deficiency-induced pseudo-TTP.¹⁵

B12 deficiency, responds dramatically to oral or parenteral vitamin B12.¹¹

Reticulocyte counts reportedly respond to Vitamin B12 administration usually by day five, and the available data suggests that administration of vitamin replacement therapy in such cases is enough without any further intervention. ⁷ ¹⁶

We achieved a reticulocytes response in our patient together with alkaline phosphatase & hemoglobin & decrease in LDH after five days of administration of parenteral Vitamin B12.

However platelet improved by day nine, and we noted a response in absolute Neutrophil Count by day fifteen.

Conclusion:
Pseudo- TTP secondary to B12 deficiency should be in the differential diagnosis of patient presenting with microangiopathic hemolytic anaemia in childhood.

We highly recommend performing B12 level, homocysteine level, LDH, reticulocyte count & reviewing peripheral blood smear in suspected TTP cases.
### Acknowledgment:
The authors declare no conflict of interest.

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<tr>
<th>Age</th>
<th>Gender</th>
<th>Clinical Presentation</th>
<th>Lab</th>
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<tbody>
<tr>
<td>31 years</td>
<td>Male</td>
<td>SOB, Fatigue and tingling sensation, inability to cooperate to complete Neurological Exam.</td>
<td>Hb: 4.4g/dL  MCV:100.6fL  PLT:87K/cmm  Total Bilirubin: 2.7mg/dL  Ind. Bilirubin: 1.9mg/dL  LDH &gt;665 U/L  Haptoglobin: &lt;7.8mg/dL  Normal Coagulation profile  Peripheral Blood Smear: Schistocytes  Cbl: 68 pg/mL</td>
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<tr>
<td>12 months</td>
<td>Male</td>
<td>Fatigue, bruise &amp; pallor</td>
<td>Hb:7g/dL  Hct:20.2%  WBC:11.000/mm³  MCV:92.5fL  Peripheral Blood Smear: RBC Macrocytic, Hypersegmented Neutrophils.  Cbl: 93pg/mL  BMA: Megaloblastic changes</td>
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<td>16 months</td>
<td>Female</td>
<td>Fatigue, Bruise &amp; pallor. Received PRBC transfusion from another center due to Low amount of RBC.</td>
<td>Hb:14.2g/dL  Hct:44.6%  (after transfusion)  WBC:6.800/mm³  MCV:92.6 fL  Peripheral blood smear: Macrocytic RBC, Hypersegmented Neutrophils  BMA: Megaloblastic changes</td>
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<td>14 years</td>
<td>Female</td>
<td>Chronic Abdominal Pain, vomiting and pallor</td>
<td>Hb: 6.5g/dL  WBC: 2.200/µl  ANC: 968/µl  PLT:62.000/µl  Peripheral Blood Smear: Normal White Cells, No atypical lymphocytes, blasts or hypersegmented Neutrophils.  BUN: 16mg/dl  Creatinine: 0.7mg/dl  Total Bilirubin: 2.7 mg/dl  Direct Bilirubin: 0.8mg/dL  LDH: 3454 U/L  Uric Acid: 3.8 mg/dL  DCT:Negative  BMA: Normoblastic trilineage Hematopoisis  Cbl: 75 pg/ml</td>
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<tr>
<td>8 months</td>
<td>Female</td>
<td>Pallor, Vomiting, Diarrhea &amp; Failure to thrive</td>
<td>Hb: 6.5g/dL  WBC: 5.3x10³/µL  ANC:0.42x10⁴ MCV:96.2 fL  PLT: 147x10³/µL  Peripheral Blood Smear: Macroovalocyte, Microcytes, Basophilic stippling and rare hypersegmented Neutrophils.  BMA: hypercellular with absolute erythoid Hyperplasia, Megaloblastic Erythroid and myeloid maturation, dyserythropoiesis and dysgranulopoiesis.  Cbl: &lt;30 pg/ml</td>
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<td>42 years</td>
<td>Female</td>
<td>Fatigue, weakness</td>
<td>Hb:2.4g/dL  Retic:4%  WBC: 5.5x10³/µL  PLT:42x10³/µL  LDH: &gt;2500 U/L  Haptoglobin: &lt;10 mg/dL  TIBC: 263 µg/dL  Iron saturation:60%  Cbl: 46pg/mL</td>
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<td>42 years</td>
<td>Male</td>
<td>Weight loss 6-8 pounds over 2 months, fatigue, presyncope, pale mucous membrane &amp; Diabetic Ketoacidosis.</td>
<td>Hb:8.1g/dL  WBC: 4100cells/mm³  MCV: 107.1 µm³  PLT: 39,000cells/mm³  RDW:19 Ind. Bilirubin: 1.6mg/dL  Peripheral blood smear: Macrocyte, 3+ Schistocytes, hypersegmented Neutrophils and very few Platelets.</td>
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<tr>
<td>Age</td>
<td>Gender</td>
<td>Symptoms</td>
<td>Hematological Parameters</td>
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<td>77</td>
<td>Female</td>
<td>Altered mental status, nausea, vomiting, bowel incontinence and bloody diarrhea</td>
<td>Serum Iron: 174µg/dL  TIBC: 199µg/dL  iron Saturation: 87.4%  Cbl: 159 pg/mL</td>
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<tr>
<td>31</td>
<td>Female</td>
<td>Fatigue, Paresthesia, Scleral icterus and pallor</td>
<td>Hb: 5.7 g/dL  MCV:120 fL  WBC:5.9x10⁹/L  PLT:40x10⁹/L  Peripheral blood smear: Anisocytosis, Poikilocytosis &amp; multiple schistocytes. Creatinine: 300µmol/L  LDH:3981 IU/L  DCT: negative  Cbl: undetectable</td>
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<tr>
<td>86</td>
<td>Female</td>
<td>Altered mental status, intubated in ER due to respiratory distress</td>
<td>Hb: 3.2g/dL  Hct: 9.6%  MCV: 127 fL  Retic: 7.5%  WBC: 6.5x10⁹/µL  PLT: 59x10⁹/µL  LDH: 7077 IU/L  Haptoglobin: 14mg/dL  BUN: 34mg/dL  Creatinine: 1.9mg/dL  Peripheral blood smear: large RBC, Hypersegmented Neutrophils, 1% schistocytes, Poikilocytes, &amp; Anisocytes. Cbl: 38 pg/mL  MMA: 753nmol/L  Homocysteine:99.3µmol/L</td>
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<tr>
<td>36</td>
<td>Male</td>
<td>Fatigue, poor exercise tolerance.</td>
<td>Hb: 7.9g/dL  MCV: 104.4 fL  Retic: 1.6%  WBC: 3300/mL  PLT: 157,000/µL  Bilirubin: 1.2 mg/dL  DCT: Negative  Peripheral blood smear: Red cell fragmentation, schistocytes, prominent anisopoikilocytosis with teardrop cells, macroovalocytes, &amp; rare hypersegmented Neutrophils  LDH: 3988 U/L  Haptoglobin: &lt;30mg/dL  BMA: Macrocytic Anemia, mild hypercellularity with trilineage dysplasia &amp; a shift towards immaturity. Cbl: 111pg/mL  MMA: 19.69mM/L  Homocysteine:181.3µM/L</td>
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<tr>
<td>35</td>
<td>Male</td>
<td>Progressive pallor, headache, fever &amp; red colored urine. On physical examination: pale, jaundice and there was patechia on the extremities and trunk</td>
<td>Hb: 5 g/dL  Retics: 30%  WBC: 4.4x10⁹/L  PLT: 12x10⁹/L  Peripheral blood smear: Polychromasia, oval &amp; crenated cells &amp; many fragmented cells. DCT: Negative  G6PD: Deficient  LDH: 2250 U/L  Liver and renal function: Normal  BMA: Erythroid hyperplasia.</td>
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<td>15</td>
<td>Female</td>
<td>Status Epilepticus, Loss of consciousness, unable to control urination. CT abdomen: slight swelling of the liver with edema around portal vein.</td>
<td>Hb: 2.5g/dL  MCV: 128.8 fL  Retic: 8.7%  WBC: 11600/mm³  PLT: 53000/mm³  Peripheral blood smear: hypersegmented Neutrophils, red cell Microcytes, Schistocytes, teardrop cells &amp; macrocytes. LDH: 1903 U/L</td>
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<tr>
<td>Age</td>
<td>Gender</td>
<td>Symptoms</td>
<td>Laboratory Findings</td>
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<tr>
<td>15 years</td>
<td>Male</td>
<td>Vegetarian boy with easy fatigue, breathlessness, pain on the legs on walking. Paleness and icterus in the sclera. Abdominal U/S: Splenomegaly: 130 mm in length</td>
<td>Hb: 5.1 g/dL  MCV: 116 fL  Retic: 0.8%  WBC: 2540/µL  ANC: 1230/µL  PLT: 107,000/mm³  LDH: 5565 U/L  Peripheral blood smear: Anisocytosis, Poikilocytosis with macrocytes and small fragmented red cells.</td>
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<tr>
<td>33 years</td>
<td>Female</td>
<td>Woman in 2nd pregnancy with Gestational Age of 37 weeks and 3 days.</td>
<td>Hb: 7.2 g/dL  Hct:22.2%  MCV: 103fL  WBC:9500/µL  PLT: 42000/µL  Peripheral blood smear: Slight hypochromia with Macrocytosis</td>
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References:


19. Volodymyr Shponka, MD; Maria Proytcheva, MD. Megaloblastic anemia caused by severe B12 deficiency in a breastfed infant. 2017


