



## D-PENICILLAMINE INDUCED APLASTIC ANEMIA - A CASE REPORT

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### ABSTRACT

Acquired aplastic anemia is characterized by pancytopenia anemia, neutropenia, and thrombocytopenia with a hypocellular bone marrow and no gross evidence of increased peripheral blood cell destruction. In this case the patient has taking D-penicillamine since 1 year in the treatment of Wilson disease, which has been lead to decreased hematopoietic stem cells. Adverse effects of penicillamine include Agranulocytosis, Alopecia, Anorexia, epigastric pain, nausea, vomiting, diarrhea Aplastic anemia. Practitioners should consider the use of D-penicillamine associated with Zinc in the treatment of Wilson's disease is safe.

**KEYWORDS:** Wilson's disease, Aplastic anemia, D-penicillamine.

### INTRODUCTION

Wilson's disease (hepatolenticular degeneration) is an auto- somal recessive defect in cellular transport of copper with prevalence of approximately 1 in 30,000 live births.<sup>[1]</sup> Acquired aplastic anemia is characterized by pancytopenia (anemia, neutropenia, and thrombocytopenia) with a hypocellular bone marrow and no gross evidence of increased peripheral blood cell destruction.<sup>[2]</sup>

The diagnosis of aplastic anemia can be made by the presence of two of the following criteria: a WBC count of 3,500 cells/mm<sup>3</sup> ( $3.5 \times 10^9/L$ ) or less, a platelet count of 55,000 cells/mm<sup>3</sup> ( $55 \times 10^9/L$ ) or less, or a hemoglobin value of 10 g/dL (100 g/L; 6.2 mmol/L) or less with a reticulocyte count of 30,000 cells/mm<sup>3</sup> ( $30 \times 10^9/L$ ) or less.<sup>[3]</sup> Depending on the blood counts, aplastic anemia can be categorized as moderate, severe, and very severe aplastic anemia.<sup>[4-6]</sup>

#### Moderate aplastic anemia (MAA)

Two of the following three criteria; neutrophils less than 1,500 cells/mm<sup>3</sup> ( $1.5 \times 10^9/L$ ), platelets less than 50,000 cells/mm<sup>3</sup> ( $50 \times 10^9/L$ ), and hemo- globin less than 10 g/dL (6.2 mmol/L).

#### Severe aplastic anemia (SAA)

Two of the following three criteria; neutrophils less than 500 cells/mm<sup>3</sup> ( $0.5 \times 10^9/L$ ), platelets less than 20,000 cells/mm<sup>3</sup> ( $20 \times 10^9/L$ ), reticulocytes less than 1%.

#### Very severe aplastic anemia (VSAA)

SAA with a neutrophil count less than 200 cells/mm<sup>3</sup> ( $0.2 \times 10^9/L$ ).

Adverse effects of penicillamine: Agranulocytosis, Alopecia, Anorexia, epigastric pain, nausea, vomiting, diarrhea Aplastic anemia, Blurred vision, Cutaneous macular atrophy, Degenerative changes of the skin (especially of the neck), Initial hypersensitivity: hives, rash, fever, anaphylaxis, lymphadenopathy, Intrahepatic cholestasis, Leukopenia, Lupus-like reaction, Myasthenic syndrome, Nephrotic syndrome, Obliterative bronchitis, Oral ulcerations, Proteinuria, Ptosis, Serous retinitis and Thrombocytopenia.<sup>[7]</sup>

### CASE PRESENTATION

12 yr old male child was admitted in Pediatric Department presented with complaints of fever associated with chills and rigors since 8 days, and history of generalized body pains, cough and cold.

Past medical history: known case of Wilson's disease since 3 years. Past medication history: **Tab. D-Penicillamine 250mg BD.**

On examination: Child was found to be conscious, coherent febrile. On systemic examination pulse rate was 100beats/min, B.P. was 130/90mmHg, all other organ systems were normal. He did not have petechiae, purpura or overt or focal neurological signs. A partial Kayser Fleischer ring was identified.

### Laboratory investigations

General Random Blood Sugar: 98gm/dL (80-120 mg/dL) Blood Urea (BU):11mg % (7- 20mg/dl). Serum creatinine: 0.8mg % (0.6-1.2mg %). Serum electrolytes Sodium- 140mEq/L (135-145), Potassium- 4.1mEq/L (3.5-5.5), Chloride- 102mEq/L(95-105). RBC: 3.9

Cells/ $\mu\text{mm}$  (4.2-5.4) PCV: 33.7% (42-50), MCV: 84.6fL (80-96). MCH: 27.9pg (27.5-33.2), MCHC: 33gm/dL (33.4-35.5), Platelets: 80,000Lakhs/cu mm (1.5-4.0) and Hb: 9g/dL WBC: 1,500 Cells/ $\mu\text{mm}$ , (5000-10,000), Polymorphs: 39% (45-70), Lymphocytes: 38% (20-40), Eosinophils: 01% (1-4), Monocytes: 02% (2-10).

Bone marrow report: Decreased hematopoietic stem cells noted. In this case the patient has taking d-penicillamine since 1 year, so pancytopenia had confirmed by CBP and Bone marrow report.

### Treatment

Inj. Ceftriaxone 1.5g/BD, Inj. Piperacillin - tazobactam 3g IV/TID, Tab. Paracetamol 500mg/QID, Tab. Chloropheniramine 4mg/BD, Tab. Zinc 50mg/TID and Tab. Pyridoxine 25mg/BD.

### DISCUSSION

WD is an autosomal recessive disease associated with defect in the WD gene (ATP7B) located on chromosome 13. Mutation in the WD gene results in retention of copper in the liver as well as in impaired export of copper into bile.<sup>[1]</sup> In WD, serum copper and serum ceruloplasmin are less than normal. The D-Penicillamine was stopped and Zinc tablet 50mg was prescribed on 2<sup>nd</sup> day of admission and he was reviewed after 1 week, when his anemia, leukopenia and thrombocytopenia had improved.<sup>[8]</sup>

D-penicillamine is the mainstay of treatment of WD.<sup>[7]</sup> It is a sulphur containing metabolite of penicillin. It acts as a copper chelating agent. It should be started as small dose because large amount of released copper from liver will deposit in CNS and may worsen the neurological symptoms. It later became standard drug therapy. After treatment, copper is quickly mobilized by tissues and eliminated in urine. But due to its adverse effects, its use is limited.<sup>[11]</sup>

It should be taken 1 hour before meal or 2 hours after meal and atleast one hour apart from that any other drug, food or milk because D-Penicillamine increases the requirement for pyridoxine so pyridoxine tablet had prescribed.

The mechanism by which copper deficiency induces anemia and other cytopenias is unknown. However, copper is an essential cofactor for a number of redox enzymes essential for optimal erythropoiesis, including cytochrome oxidase and ceruloplasminferroxidase and it is hypothesized that decreased activity of these enzymes may lead to anemia

The hematological adverse effects of the chelating agent penicillamine include leukopenia, thrombocytopenia, agranulocytosis and rarely aplastic anaemia. As our patient had anemia, Leukopenia and thrombocytopenia, a bone marrow examination was done to establish the cause of pancytopenia. Copper deficiency can have

protean haematological manifestations with or without neurological manifestations and has been reported to result in anemia, neutropenia and thrombocytopenia. The RBC's were microcytic; Leukocytes and thrombocytes were less than normal.<sup>[8]</sup>

Two of the following three criteria-neutrophils less than 1,500 cells/mm<sup>3</sup> ( $1.5 \times 10^9/L$ ), platelets less than 50,000 cells/mm<sup>3</sup> ( $50 \times 10^9/L$ ), and hemoglobin less than 10 g/dL (6.2 mmol/L) according to this criteria and based on CBP report, it was case of D- Penicillamine induced Moderate aplastic anemia.<sup>[4-6]</sup>

This adverse reaction was assessed by Naranjo's scale and the score was found to be (probable) and Severity was assessed by Hartwig scale and it was a moderate reaction.<sup>[12,13]</sup>

The safety and long term efficacy of zinc as maintenance therapy has been well shown in both adults and children.<sup>[9,10]</sup> The main drawback of zinc therapy is the slow rate at which copper is depleted.

### CONCLUSION

In a patient with WD on treatment who develops pancytopenia, copper deficiency may be considered in the presence of bone marrow dysplasia.

The use of D-penicillamine associated with Zinc in the treatment of Wilson's disease is safe. D-Penicillamine associated to Zinc induces the correction of hepatic and neurological abnormalities of Wilson's disease patients more rapidly, proving a greater therapeutic efficiency than Zinc monotherapy. 24 hour urine copper 4 times per year initially, then at least twice per year, Serum free copper 4 times per year initially, then at least twice per year should be monitored.

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