Isoniazid Induced Pure Red Cell Aplasia

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Abstract

A case of pure red cell aplasia following antituberculous chemotherapy for pleural effusion is being described in a 51-year male. Patient responded to isoniazid withdrawal and corticosteroid therapy. Retreatment with isoniazid resulted in relapse.

Key words: Pure red cell aplasia, Isoniazid

INTRODUCTION

Pure red cell aplasia (PRCA) is the name given to a group of conditions in which there is a deficiency or virtual absence of nucleated red cell precursors from the bone marrow (erythropoietic hypoplasia), in the absence of abnormalities in the leucopoietic or thrombopoietic system. The marrow is normally cellular but is devoid of erythroblasts. This condition may appear as an acquired defect of either acute or chronic type, and a congenital form (Josephs - Diamond-Blackfan syndrome).1

Acquired form of PRCA is associated with hemolytic disorders, infections, malnutrition, hepatitis, thymoma, various other neoplasms, immunological disorders, drugs and chemical agents etc.1,2

There are only few reports of development of PRCA during antituberculous chemotherapy3-6. The present report is an additional one and also emphasize the need for clinicians to be aware of this rare hematological complication that may arise during antituberculous chemotherapy.

CASE REPORT

A 51-year male smoker, policeman came with complaints of breathlessness, chest pain on right side and decreased appetite for last two months. His initial general physical examination revealed nothing abnormal. Respiratory system showed right-sided moderate pleural effusion on clinico-radiological examination. Other systems were normal. His sputum was negative for acid-fast bacilli but tuberculin test showed an induration of 16 mm.

On thoracocentesis about 800 ml of straw colored fluid was aspirated. Pleural fluid investigations revealed protein 5.3 gm%, sugar 32mg%, cells 1100/mm³ (all lymphocytes), LDH 1250 U/L, ADA level 75U/L and no malignant cells. Other investigations revealed haemoglobin 11 gm%, total leukocyte count 8500/mm³ with normal differential counts and ESR 175 mm in first hour. His blood sugar, liver function tests, renal function tests and urine examination were normal.
Based on above findings, a diagnosis of right-sided tuberculous pleural effusion was made and antituberculous chemotherapy was started with isoniazid, rifampicin, ethambutol and pyrazinamide. Patient improved initially with therapy, however, after 3 weeks he was admitted for weakness, breathlessness and tinnitus. On investigations his haemoglobin was 4.6 gm%, with normal total, differential leukocyte counts, platelet count and bleeding profile. His audiogram was also normal.

Peripheral blood film smear showed marked poikilocytosis, anisocytosis and hypo chromic red blood cells. Few ovalocytes, pear shaped cells and occasional normoblasts were present with no target cells. Reticulocyte count was zero. Bone marrow aspirate from sternum and wedge biopsy from iliac crest revealed hypo cellular marrow with a profound erythroid hypoplasia and a high myeloid / erythroid ratio. The morphology and maturation sequence of the myeloid cells and megakaryocytes was normal. The plasma cells and mononuclear lymphoid cells were also normal.

The marrow picture was consistent with pure red cell aplasia. Other investigations revealed no evidence of haemolysis, Bence Jones protein urea and LE cell phenomenon. Schilling test, direct and indirect Coombs test were also negative. Ultrasonography and radiological examination ruled out any mediastinal miss.

Patient was managed with three units of fresh blood transfusion. In view of our previous experience with PRCA due to isoniazid, we suspected same drug responsible in this case. Isoniazid was withdrawn and rest antituberculosis drugs were continued with oral prednisolone 40 mg/day which was gradually tapered and finally stopped after four weeks. His hemoglobin rose to 9 gm% and reticulocyte count 2.2%.

To confirm the causative role of isoniazid in the present case, challenge with isoniazid showed relapse after two weeks. This time haemoglobin dropped to 6 gm% with reticulocyte count 0.2% with similar marrow picture and normal leukocytes and platelet counts. Withdrawal of isoniazid, re-instituting steroid therapy and two units of blood transfusion resulted in hematological recovery. Patient successfully completed anti tuberculosis chemotherapy without isoniazid and did not show any hematological abnormalities thereafter.

**DISCUSSION**

PRCA in the adults is an uncommon disorder characterized by acquired isolated erythroid hypoplasia and by a frequent association with thymic tumors. The direct demonstration of antibodies which react with nucleated red blood cells in about 50% cases suggest an immunological pathogenesis.  

Drug induced PRCA is further uncommon and accounts for less than 5% cases. Till date only less than 70 cases have been reported and approximately 30 drugs have been implicated. These include amino salicylic acid, glutethimide, aspirin, butabarbital, colchicin, heparin, azathioprine, sulphathiazole, arsphenamine, diphenylhydantoin, carbamazepine, isoniazid, para amino salicylic acid, chenopodium, tolbutamide, chlorpropamide, santonin, calomel, aminopyrine, phenylbutazone. cotrimoxazole, halothane, sulfonamide, quinacrine, amphotericin-B, chloramphenicol, carbimazole and benzene hexa chloride etc. 

In the present case, patient developed PRCA twice on exposure to isoniazid, thus confirming its causative role. Only few reports have been published on development of PRCA during anti tuberculosis chemotherapy and isoniazid was the cause in all of them.

The exact mechanism of drug induced PRCA in most cases is unknown. The possible mechanism suggested includes - (i) toxic interference by drugs with the metabolism of nucleated red Cells, (ii) immunologically mediated reaction with antibodies formation against red cell precursors and (iii) specific inhibitory effect on DNA synthesis probably at the step of deoxyribotide formation.

Drug induced PRCA is usually reversible after discontinuation of the offending drug. The clinician must be aware of these events as failure to recognize and discontinue the responsible drug m time may cause permanent morbidity and mortality due to generalized marrow hypoplasia. With the increasing burden of tuberculosis and frequent use of anti tuberculosis drugs, the adverse reactions during
treatment are more likely to be encountered in future and hence the case has its significance.

REFERENCES


