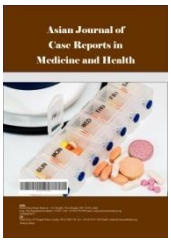

Asian Journal of Case Reports in Medicine and Health

6(2): 14-18, 2021; Article no.AJCRMH.74730

A Case of Megaloblastic Anaemia Complicated with Extra-Pulmonary Tuberculosis

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Authors' contributions

This work was carried out in collaboration among all authors. All the authors contributed in patient management. Authors GACG and CSM were involved in manuscript writing. All authors read and approved the final manuscript.

Article Information

Editor(s):
(1) Dr. Hab. Mariusz Cycon, Medical University of Silesia, Poland.
Reviewers:
(1) Indranil Sen, West Bengal University of Health Sciences, India.
(2) Rajharsh D. Hanmante, MUHS, India.
Complete Peer review History: https://www.sdiarticle4.com/review-history/74730

Case Report

Received 20 July 2021
Accepted 30 September 2021
Published 07 October 2021

ABSTRACT

Megaloblastic anaemia is known to cause elevated lactate dehydrogenase (LDH) levels due to increased cell turn over with ineffective erythropoiesis in the bone marrow, a laboratory parameter which can help in the diagnosis and monitoring the response to treatment with vitamin B12 and folate as well. Serum LDH level can get significantly elevated in many other non- neoplastic and neoplastic conditions as well, such as metastatic cancers, infections, haematological malignancies including lymphomas and conditions with haemolysis. Elevated LDH is considered as an independent predictor of mortality and a marker of major complications in hospitalized patients [1].
This case is about a young man, a vegan who presented with features of megaloblastic anaemia,generalized lymphadenopathy, constitutional symptoms and a very high LDH level mimicking a diagnostic possibility of a high grade lymphoma, ultimately confirmed to have megaloblastic anaemia and tuberculous lymphadenitis, the latter was an unexpected finding of the lymph node biopsy done to exclude a lymphoma.

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His significantly high LDH level at diagnosis which declined dramatically in response to vitamin B12 replacement therapy, can be used as a supportive diagnostic tool and also to monitor the response to therapy in megaloblastic anaemia.

Keywords: Megaloblastic anaemia; lactate dehydrogenase (LDH); tuberculosis.

1. INTRODUCTION

Megaloblastic anaemia (MA) encompasses a heterogeneous group of macrocytic anaemias characterized by the presence of large erythroblasts (megaloblasts) in the bone marrow with characteristic asynchrony in maturation of nucleus and cytoplasm, where the nuclear maturation is delayed than that of the cytoplasm. It is caused by defective DNA synthesis in the erythroblasts in vitamin B12 or folate deficiency and less commonly with defects in the metabolism of these vitamins [2].

Deficiencies of vitamin B12 and folic acid are the leading causes of megaloblastic anaemia especially among vegans. It can also arise from inherited or acquired metabolic defects of vitamin B12 and folate or defects in DNA synthesis as well. There is a failure of converting deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP), as the coenzyme 5,10-methylene tetrahydrofolate polyglutamate is reduced in both vitamin B12 and folate deficiency. Late-replicating DNA is particularly affected by this and there is developmental arrest of some cells and cell death occurs with apoptosis. This nuclear cytoplasmic asynchrony in the developing cells leads formation of megaloblasts. Intramedullary destruction of cells with ineffective erythropoiesis leads to raised serum indirect bilirubin, LDH, urine urobilinogen, serum iron with reduced serum haptoglobins and presence of urine haemosiderin. Thrombocytopenia occurs with ineffective megakaryopoiesis and there can be a weakly positive direct antiglobulin test (DAT) due to complements. Most cases are detected on routine full blood count analysis by increased mean corpuscular volume (MCV). More severe cases present with clinical features like symptomatic anaemia, anorexia, loss of weight, diarrhoea mild fever, mild icterus, reversible melanin pigmentation, neurological features, leucopenia and thrombocytopenia. The characteristic peripheral blood smear findings are oval macrocytes with significant anisopoikilocytosis with high MCV usually more than 100fL and hypersegmented neutrophils, both features together strongly suggest megaloblastic haematopoiesis. The MCV will be lower than this in cases with concurrent iron deficiency, thalassaemia trait or where there is excessive red cell fragmentation. Occasionally a leucoerythroblastic blood film is seen. The characteristic bone marrow findings are erythroid hyperplasia with megaloblasts, giant and abnormally shaped metamyelocytes and enlarged hypersegmented megakaryocytes [3].

The diagnosis can be made with complete blood count, blood picture and serum cobalamin assay. Treatment is done with parenteral or oral vitamin B12 preparations and oral folic acid.

2. CASE PRESENTATION

A previously healthy 31 year old male, presented with dizziness, lethargy, exertional dyspnoea and loss of appetite over a period of one month. He had a significant weight loss of 15 kg over one year and a chronic dry cough over months. He had been a pure vegan for the past 4 years and a non smoker.

On examination he was moderately pale with a tinge of icterus. Further examination revealed bilateral cervical and axillary lymph node enlargement size ranged from 2cm to 4cm in diameter and a just palpable, non tender spleen. Rest of the examination was unremarkable.

Investigations revealed severe macrocytic anaemia with (Hb- 4g/dL, MCV-96fL), mild leucopenia with mild neutropenia and mild thrombocytopenia. Direct Coomb's test was negative. Blood picture showed mixed population of cells, oval macrocytes, hypochromic microcytic red cells, tear drop poikilocytes, few nucleated red cells, moderate polychromasia, rouleaux formation and few hypersegmented neutrophils with no abnormal cells confirming mixed deficiency anaemia predominantly due to vitamin B12 and folate deficiency. Erythrocyte sedimentation rate (ESR) was 80 mm 1st hour and C-reactive protein (CRP) was normal. He had indirect hyperbilirubinaemia and a significantly elevated LDH level of 5200/IU. His serum iron studies were marginally low. Ultrasound scan of the abdomen revealed mild

splenomegaly (13 cm). Chest X ray was unremarkable. While awaiting CECT and lymph node biopsy, he was managed with 3 units of packed red cell transfusions for the symptomatic anaemia. Bone marrow examination was performed and confirmed the diagnosis of megaloblastic anaemia with no evidence of lymphoma or granulomata formation in the trephine biopsy. His sputum for acid fast bacilli (AFB) was thrice negative, tuberculin skin test was positive (13cm) and the CECT revealed a cavitating lung lesion in the apical posterior segment of left upper zone compatible with an old tuberculous lesion. The axillary lymph node biopsy revealed multiple discrete, confluent epithelioid granulomas with central caseous necrosis, compatible with chronic granulomatous tuberculous lymphadenitis and he was started with antituberculosis drug (ATD) therapy.

He was treated with intramuscular injections of vitamin B12 1000 micrograms every other day for 6 days, folic acid 1mg daily and iron therapy with Ferrous sulphate 200mg twice daily.

Bone marrow aspiration (Fig.3) and bone marrow trephine biopsy (Fig. 4) showed giant metamyelocytes, megakaryocytes with hypersegmented nucleus and erythroid hyperplasia.Few megaloblasts were seen as the bone marrow aspirate was performed 24 hours after the first dose of parenteral vitamin B12.

His clinical symptoms markedly improved following the first dose of vitamin B12 injection with dramatic reduction in serum LDH level to normal over few days. His blood counts and MCV were gradually normalized. He showed further clinical improvement 4 – 6 weeks later with ATD therapy [4].

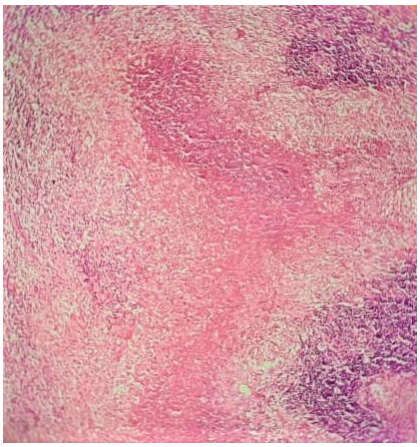

Fig. 1

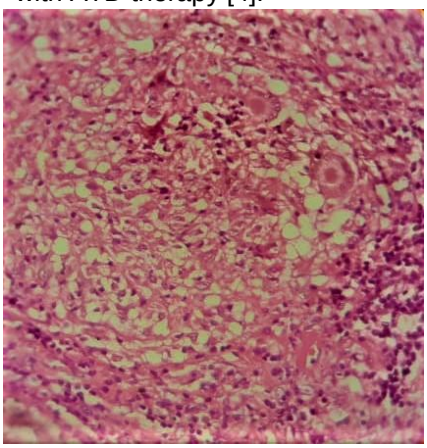

Fig. 2

Figs. 1 and 2. Axillary lymph node histology showing caseous necrosis and granulomas

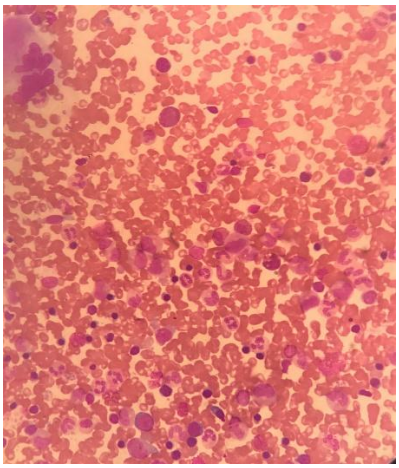

Fig. 3

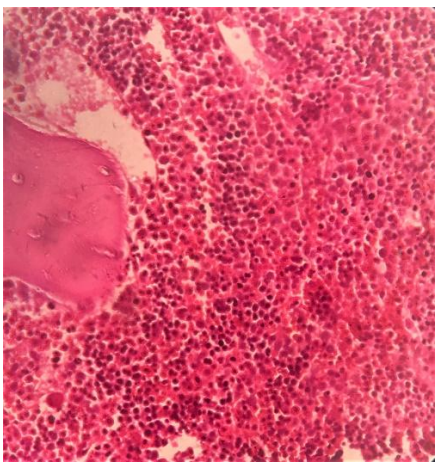

Fig. 4

Figs. 3 and 4. Bone marrow aspiration and bone marrow trephine biopsy

3. DISCUSSION

Most cases of megaloblastic anaemia show macrocytic anaemia with oval macrocytes, hypersegmented neutrophils, and elevated serum lactate dehydrogenase (LDH) level as a result of increased cell turn over [1]. Several studies have been done on patients with megaloblastic anaemia to evaluate serum LDH levels, some of them emphasizing its utility as a screening tool and assessing the response to therapy as well [5,6,7]. Minor megaloblastic changes were not usually associated with elevated LDH [5].

A prospective cross sectional study done in India, on patients with megaloblastic and non-megaloblastic anaemias (iron deficiency, haemolytic) based on bone marrow findings has shown 19 fold rise in megaloblastic anaemia, 4 fold rise in haemolytic anaemia with statistical significance in LDH levels of megaloblastic anaemias vs haemolytic and iron deficient anaemias [8].

Another study done on children aged 6 months to 14 years with clinically suspected megaloblastic anaemia, has shown a very high LDH levels(>3000 IU/L) and significant fall in LDH levels post treatment with vitamin B12. This has identified that the serum LDH level helps in diagnosis as well as assessing response to therapy in megaloblastic anaemia [6].

With very high LDH along with constitutional symptoms and lymphadenopathy and mild splenomegaly, this case got complicated with additional diagnostic possibility of lymphoma. (12) Interestingly the high LDH level of > 5000 IU/Ml, started to reduce by 1000 IU/mL, with each dose of vitamin B12 and folate replacement, which showed that the rise in LDH is solely due to megaloblastic anaemia and its value in response assessment as well.

Sri Lanka, being a middle burden country with Tuberculosis with 8500-9500 new cases every year, it can coexist with another disease diagnosed, making diagnostic dilemmas and diagnostic difficulties [6], such as in a lymphoma where the patients present with constitutional symptoms and lymphadenopathy. Therefore, excluding tuberculosis is mandatory in such patients [9].

When considering our case, ileocaecal tuberculosis could be a possibility, which can cause megaloblastic anaemia.It is associated with the clinical triad of prolonged fever, knuckle pigmentation and right lower quadrant abdominal tenderness in endemic areas [10]. But being a vegan for 4 years explained the reason for megaloblastic anaemia in our patient and the lower gastrointestinal endoscopy with biopsy excluded the ileoceacal tuberculosis, which only revealed a small ulcer with nonspecific colitis in histology.

4. CONCLUSION

Megaloblastic anaemias can present with significantly elevated LDH, which can be used as a diagnostic and response monitoring tool. Considering the moderate prevalence of tuberculosis in this region, it is always necessary to exclude the possibility of tuberculosis in patients presenting with signs and symptoms suggestive of lymphoma.

CONSENT

As per international standard or university standard, patient's consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle4.com/review-history/74730