Clinico-laboratory Profile and Outcomes of Megaloblastic Anemia presenting as Severe Pyrexial Illness mimicking Tropical Infection

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Received: 22 May 2022; Revised: 07 November 2022; Accepted: 14 December 2022

ABSTRACT

Background: Anemia-causing fever has been described in patients with megaloblastic anemia. Although the exact mechanism of this is unknown, high-grade fever is relatively less reported.

Materials and methods: This prospective observational study included all new cases of megaloblastic anemia presenting with febrile illness (>101°F) during a 3-year period. Patients with existing anemia, comorbidities, and other causes of macrocytosis were excluded. A detailed evaluation for megaloblastic anemia and workup for excluding tropical infections was done. The patients were treated with parenteral vitamin B12, folic acid, and other hematins.

Results: Around 24 cases of megaloblastic anemia presenting with high-grade fever were included, with 14 (58.3%) males, mean duration of fever 7.7 days (4–18 days), and 09 (37.5%) having temperature ≥103°F. The mean hemoglobin (Hb) was 8.15 g/dL (3.7–11.1 g/dL), the mean corpuscular volume (MCV) was 111 ± 7.8 fL, 18 (75%) had unconjugated hyperbilirubinemia, most showed good therapeutic response to B12 or folic acid with defervescence in 1–5 days (mean 2.6 days) and improvement in lab parameters in 1 week. The study population was divided into those with temperature ≥103°F and temperature <103°F it was seen that there was a significant association (p < 0.05) with leucocyte count of ≤3000/cumm, and MCV ≥110 fL, in patients with temperature ≥103°F.

Conclusion: Megaloblastic anemia should be considered in the differentials of a patient presenting with a febrile illness with no clinical localization and a negative initial fever workup. Early identification and prompt therapy of this easily treatable disorder are very essential.

BACKGROUND

Megaloblastic anemia is a common illness known to have protean manifestations involving various organ systems.1–3 There are case reports of megaloblastic anemia presenting as catastrophic acute anemia, and severe pyrexial illness mimicking infections, such as malaria, leptospirosis, dengue, rickettsia, or other bacterial infections.3–8 Low-grade fever is known to occur in megaloblastic anemia but a high-grade pyrexial illness mimicking a tropical infection is anecdotal and not known.9–11 We studied all cases of megaloblastic anemia who initially presented with acute pyrexial illness mimicking a tropical illness, and assessed the clinicopathological profile and outcomes in them.

MATERIALS AND METHODS

Study Design and Population

This was a prospective observational study conducted in a tertiary care hospital in Western India over a period of 3 years. All cases of acute high-grade febrile illness who were detected to have new onset megaloblastic anemia were included in the study.

Inclusion Criteria

The diagnosis of megaloblastic anemia was defined as anemia (Hb < 11 g/dL in females and <12 g/dL in males) with any one of the following:

• Mean corpuscular volume (MCV) > 110 fL
• Peripheral blood smear (PBS) showing hyper-segmented neutrophils, macroovalocytes, or other typical features of megaloblastic anemia.
• Bone marrow picture suggestive of megaloblastic anemia.
• Low serum vitamin B12 or folic acid levels.
• Moderate to high-grade fever (core body temperature >101°F) for at least 3 days.
• Patients ≥ 18 years.

Exclusion Criteria

• Patients who had proven infections, malignancies, or other abnormalities as an underlying cause of fever.
• Patients with preexisting anemia, megaloblastic anemia, or hematological disorders like aplastic anemia or myelodysplastic syndrome.
• Patients with other causes of macrocytosis such as hypothyroidism, drugs, chronic liver disease, and others.12

STUDY PROCEDURE

All cases presenting with high-grade pyrexial illness detected to have megaloblastic anemia, and qualifying the inclusion and exclusion criteria were included in the study. Requisite consent was obtained from all patients. Appropriate clearance was taken from the Institutional Ethics Committee. The clinical and laboratory profile of the cases was studied. Serum vitamin B12, folic acid levels, and bone marrow examination was done.

Detailed evaluation was done in the study population which included complete blood count (leucocyte count, platelet count, and RBC indices) with PBS (including reticulocyte count, anemia typing, and features of hemolysis) and immunochromatographic card test for vivax/falciparum malaria, latex agglutination for enteric fever (Widal test), serum immunoglobulin M (IgM)/immunoglobulin G (IgG) for Leptospira, serum IgM/ IgG/NS1 for dengue, TORCH titers, IgM/IgG for rickettsia, blood and urine culture, microscopy and staining tests of...
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stool, urine and sputum, antinuclear antibody (by immunofluorescence), X-ray chest and ultrasound abdomen were done to evaluate for the causes of fever. If any of these tests were positive, or any other cause of fever was detected, the patients were excluded from the study. No antibiotics, antimalarials, or other antimicrobials were given. In case of antimicrobials were started before presenting to this center, it was stopped.

The study population was treated for megaloblastic anemia with injection of vitamin B12 1000 µg given intravenous/intramuscular every alternate day, oral folate acid 5 mg once daily, and oral B complex once daily. A packed RBC (PRBC) transfusion was given if indicated. Oral or parenteral iron therapy was also added if concomitant iron deficiency was detected. The subsequent therapeutic response was noted in terms of number of days to become afebrile, reticulocyte response, and improvement in other parameters.

Statistical Analysis
Statistical analysis of the data was carried out using appropriate statistical packages (Statistical Package for the Social Sciences version 19). Data was reported as mean ± standard deviation (SD). For purpose of comparison, frequency, percentage, and paired t-tests were used. A p-value of < 0.05 was considered statistically significant. Changes in different parameters between the two fever groups were done using the student’s t-test for paired observations.

Results
Demographic and Clinical Characteristics
A total of 30 cases were presented to this center with high-grade fever and evidence of megaloblastic anemia during the study period. Six cases had evidence of infection or other causes of macrocytosis and hence were excluded. The remaining 24 cases were included in this study as given in Flowchart 1.

The average age of patients was 33.9 years (range 17–69 years), 14 (58.3%) being males and 16 (66.70%) patients were Hindus. A total of 10 (41.6%) patients consumed a strict vegetarian diet. All patients presented with an acute febrile illness ranging from 4 to 18 days (mean duration 7.7 days), with 09 (37.5%) having temperature ≥103°F, and 14 patients (58%) having chills or rigors with fever. All patients had features of anemia like dyspnea, fatigue, or palpitations, as given in Table 1. Clinical evaluation revealed icterus in 12 patients (50%), splenomegaly and/or hepatomegaly in 11 (45.8%), and features of peripheral neuropathy in 4(16.7%), as shown in Table 1. Hyperpigmentation of the tongue, knuckles (Fig. 1), or elbows was a striking finding seen in 11 (45.8%) patients.

Laboratory Findings and Evaluation
Investigations revealed a mean Hb of 8.15 g/dl (range 3.7–11.1 g/dl), leucopenia, and thrombocytopenia in 19 (79.1%) patients. MCV was increased in all patients with the mean ±SD being 111 ± 7.8 fL (maximum 128 fL), as given in Table 2. The peripheral smear was characterized by macrocytosis in 19 (79%), hyper-segmented neutrophils in 20 (83.3%), and other features such as macroovalocytes, Howell Jolly bodies, poikilocytosis, or basophilic stippling. The biochemistry tests revealed unconjugated hyperbilirubinemia in 18 (75% cases), prerenal azotemia, and hypoalbuminemia in 5 (20.8%) cases each. LDH was an important marker being raised in most patients with the mean LDH being 814 ± 24 IU/L. Estimation of serum B12 and folate levels revealed low B12 levels in 9 (37.5%), low serum folic acid levels in 6 (25%), and combined deficiency in 6 (25%), while three patients (12.5%) had normal levels of both. Bone marrow examination showed cellular reactive bone marrow with megaloblastoid changes in all patients.

The infectious disease workup, autoimmune workup, radiological evaluation, and cultures were negative in all patients. Eight (33.4%) of the patients were pure vegetarian (milk only) and etiology could not be ascertained in four (16.5%) patients. Five (20.5%) patients showed gastritis on an upper gastrointestinal endoscopy, as shown in Figure 2. About a quarter of all patients had been given anti-infective agents before the diagnosis of megaloblastic anemia. IntraVenous antibiotics in five (20.8%) and antimalarials in one (4.1%) patient.

Response to Therapy
The patients were treated with parenteral vitamin B12 and oral folate as per the protocol. PRBC support was given to five patients (20.8%) who had features of congestive heart failure or severe anemia (average of 1.6 PRBC units transfused). The response to therapy was closely monitored. The patients showed a satisfactory improvement with defervescence of fever and a sense of well-being occurring within 1–5 days (mean 2.6 days) after initiating therapy. The investigations after one week showed a mean improvement of Hb of 1.42 g/dl after 1 week, a fall in mean MCV by 3 fL, a fall in mean LDH by 180 IU/L, and an appropriate reticulocyte response. A serial follow-up showed gradual normalizing of total leucocyte count (TLC), platelet count, and bilirubin levels. There was no mortality in this study.

Flowchart 1: Consort diagram of the study
Megaloblastic anemia was first described by Addison in 1849 and since then this disease has fascinated physicians due to myriad presentations. Megaloblastic anemia generally presents as insidious onset gradually progressive symptomatic anemia with hepatosplenomegaly, neurological features, gastrointestinal manifestations, hyperpigmentation, pancytopenia, unconjugated hyperbilirubinemia, and other features of ineffective erythropoiesis. The presentation may vary from asymptomatic chronic illness to an acute rapidly progressing disease.

Acute rapidly progressing megaloblastic anemia is rare and has been described in association with inhalational nitrous oxide exposure, high dose trimethoprim, in dialysis patients, alcoholics, and debilitated patients on parenteral nutrition. Agents such as nitrous oxide or trimethoprim cause destruction or severe suppression of methylcobalamin leading to acute megaloblastic anemia.

Fever is known to occur in megaloblastic anemia but it is usually mild with only minimal elevation of temperature (100°F). Studies have shown that fever occurs in about 40% of patients with megaloblastic anemia, caused by a deficiency of either vitamin B₁₂, folic...
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Fig. 2: Etiology of megaloblastic anemia presenting with fever

Table 3: Comparison of hematological and biochemical parameters in megaloblastic anemia with temperature ≥103°F and <103°F (by Chi-squared test, two-tailed p-value given, p-value < 0.05 considered statistically significant)

<table>
<thead>
<tr>
<th>Serial no</th>
<th>Parameter</th>
<th>Temperature ≥103°F</th>
<th>Temperature &lt;103°F</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hb (g/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hb ≤ 8</td>
<td>04 (44.4%)</td>
<td>05 (33.4%)</td>
<td>p = 0.52</td>
</tr>
<tr>
<td></td>
<td>Hb &gt; 8</td>
<td>05 (55.6%)</td>
<td>10 (66.6%)</td>
<td></td>
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<tr>
<td>2</td>
<td>TLC (/cumm)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>TLC ≤ 3000</td>
<td>07 (77.8%)</td>
<td>04 (26.6%)</td>
<td>p = 0.02</td>
</tr>
<tr>
<td></td>
<td>TLC &gt; 3000</td>
<td>02 (22.2%)</td>
<td>11 (73.4%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Plt (/cumm)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Plt ≤ 80,000</td>
<td>06 (66.7%)</td>
<td>06 (40%)</td>
<td>p = 0.22</td>
</tr>
<tr>
<td></td>
<td>Plt &gt; 80,000</td>
<td>03 (33.3%)</td>
<td>09 (60%)</td>
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<tr>
<td>4</td>
<td>MCV (fl)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>MCV ≥ 110</td>
<td>08 (88.9%)</td>
<td>04 (26.4%)</td>
<td>p = 0.01</td>
</tr>
<tr>
<td></td>
<td>MCV &lt; 110</td>
<td>01 (11.1%)</td>
<td>11 (73.4%)</td>
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<tr>
<td>5</td>
<td>LDH (IU/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LDH ≥ 700</td>
<td>05 (55.6%)</td>
<td>07 (46.7%)</td>
<td>p = 0.67</td>
</tr>
<tr>
<td></td>
<td>LDH &lt; 700</td>
<td>04 (44.4%)</td>
<td>08 (53.3%)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Serum bilirubin (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bilirubin ≥ 2</td>
<td>06 (66.7%)</td>
<td>06 (40%)</td>
<td>p = 0.22</td>
</tr>
<tr>
<td></td>
<td>Bilirubin &lt; 2</td>
<td>03 (33.3%)</td>
<td>09 (60%)</td>
<td></td>
</tr>
</tbody>
</table>

Bold values are statistically significant (p < 0.05)

Acid, or both. In a study by Tahlan et al.,21 the incidence of low-grade fever in nutritional megaloblastic anemia varied from 28 to 60%. Persistent low-grade fever has been described in 70% of the females with B12 and/or folate deficiency in a study from North India.22 The exact cause of pyrexia in megaloblastic anemia is not known. It may be due to a defect in oxygenation to the temperature regulatory centers in the brain due to severe anemia, causing hypoxia to these centers, resulting in their stimulation and causing fever.23 However, this hypothesis fails to explain the absence of fever in other etiologies with anemia as the principal manifestation. It is also proposed that megaloblastic anemia leads to hyperplasia of the bone marrow and thus increased activity within the bone marrow leads to systemic pyrexia.20,23 However, the exact cause of fever in megaloblastic anemia is not established.

Megaloblastic anemia presenting as an acute severe illness with high-grade fever is very rare but has also been reported in the literature.3-11 The cause of such a rapid and acute presentation is not understood. It could be due to an acute worsening of an underlying compensated disease, precipitated by a trigger such as an infection, comorbid illness, stress, drugs, and surgery. But in our cases, there was no clinical or laboratory evidence of any of these conditions. Therefore, it is postulated that it could be due to a severe manifestation of the mechanisms causing fever, as discussed above.

Megaloblastic anemia presenting in this fashion can mimic various illnesses especially tropical infections like malaria, leptospirosis, dengue, rickettsial infections; hematological malignancies, hemolytic anemia, or autoimmune conditions.10 Moreover, high fever with leucopenia, can also be due to febrile neutropenia in some cases. This leads to extensive workup and a battery of investigations for the above-mentioned conditions which are costly, and cause patient inconvenience. Moreover, the patients are often empirically given antimicrobial agents like broad-spectrum antibiotics, antimalarials, and antivirals which may be unnecessary. The timely diagnosis of megaloblastic anemia prevents the unnecessary battery of investigations to exclude the above-mentioned conditions, prevents unnecessary fear of conditions like malignancy, can restrict the unnecessary use of antimicrobial agents, and helps in the timely initiation of B12/folate therapy in this easily treatable condition.

A high index of suspicion and early identification of megaloblastic anemia becomes imperative in such a situation especially if there is a history of a purely vegetarian diet, gastrointestinal symptoms, neurological abnormalities, or pigmentation of knuckles or tongue.15 A macrocytic picture, typical PBS findings of hyper-segmented neutrophils and macroovalocytes with leucopenia/thrombocytopenia, MCV ≥ 110 fl, biochemical abnormalities such as raised LDH levels or unconjugated hyperbilirubinemia are strong pointers to the diagnosis of megaloblastic anemia.13,15 The diagnosis is clinched by a therapeutic response of resolution of pyrexia and improvement in patient condition following parenteral B12 and folate supplementation.

The limitations of this study are that there is a rare possibility of this high-grade fever being caused by an unknown self-limiting infection like a mild viral illness or other conditions, which could not be detected by the tests done by us. Secondly, it can be argued that the response to therapy was due to the antimicrobial agents used, in the patients in whom it was used. But as some of these patients persisted to have fever despite antibiotic use till B12/folate replacement was started, and a group of patients who were not given antibiotics also responded well showed that the defervescence is likely due to the use of hematinsics, and not antimicrobials.

It is therefore recommended that megaloblastic anemia be considered as a differential diagnosis of tropical illness with high-grade fever, and clinical indicators as described above and routine investigations like a complete haemogram with PBS, LDH,
and bilirubin be done in all these cases. In case of doubt, a confirmatory evaluation like bone marrow evaluation or serum levels of vitamin B₁₂ or folic acid can be done, and appropriate treatment should be initiated concurrently in all these cases to look for the therapeutic response and avoid unnecessary evaluation and antimicrobial agents.

**Conclusion**

Megaloblastic anemia has protean manifestations and can present with high-grade fever mimicking an infectious etiology. The exact mechanism of this severe presentation is not clear and further research is recommended in terms of larger trials and studies to establish the mechanism of the same. Our study demonstrates that in the Indian context, megaloblastic anemia should be considered in the differentials of a patient presenting with a febrile illness with no clinical localization, a negative initial fever workup, and a hematological profile classical of megaloblastic anemia. Early identification and prompt therapy of this easily treatable disorder are very essential to prevent unnecessary investigations for various tropical disorders and unnecessary usage of antimicrobial agents.

**References**