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RESEARCH ARTICLE
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STUDY OF INCIDENCE AND TREATMENT OUTCOMES OF MEGALOBLASTIC ANAEMIA PRESENTING AS PYREXIAL DISORDER.

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Abstract

Background: Megaloblastic anemia (MA) is an underrecognized cause of Pyrexial disorder ,often triggering extensive investigations for infections or malignancies. Prospective data on its clinical-therapeutic profile remain scarce.

Objectives: 1) Characterize clinical/hematological features of MA presenting as Pyrexial disorder and to evaluate response to vitamin B12.

Methods: A 12-month prospective cohort study (2024–2025) was conducted at Lata Mangeshkar Hospital, attached to the N.K.P.Salve Institute of Medical Sciences & Research Centre, Nagpur.Adults (≥18 years) with Pyrexial disorder (fever >101°F for ≥3 days) and MA (Hb <11g/dL /<12g/dL M + MCV>110fL/peripheral smear abnormalities/B 12 <200pg/mL after excluding infections/malignancies were enrolled . Standardized B₁₂ therapy was administered. Outcomes included fever resolution time, hematological .recovery, and symptom response.

Results: 56 adults with megaloblastic anaemia and Pyrexial disorder, exhibiting a male predominance (57.1%) and mean age of 41.3 ± 14.9 years. Patients presented with prolonged fever (mean 6.8±2.3 days), severe macrocytic anemia (Hb 7.2±1.4 g/dL; MCV 116.4±8.7 fL), and inflammation (92.9% elevated ESR; 89.3% elevated CRP). Fever resolved rapidly after therapy initiation (median 36 hours), with 87.5% afebrile within 48 hours. Hemoglobin significantly increased by Day 7 (8.9±1.3 g/dL, $p<0.001$) and normalized in 85.7% by Day 28.

Conclusions: MA is a reversible cause of Pyrexial disorder characterized by triad of high-grade fever, macrocytic anemia, and systemic inflammation. Rapid defervescence within 48 hours of B_{12} therapy serves as a diagnostic-therapeutic indicator. Early empiric hematinic intervention in Pyrexial disorder patients with macrocytosis prevents unnecessary antimicrobial use, reduces diagnostic costs, and mitigates neurological sequelae.

Keywords: Megaloblastic anemia, Pyrexial disorder, Vitamin B12 deficiency.

Introduction

Megaloblastic anemia (MA), arising primarily from vitamin B12, classically manifests with hematological and neuropsychiatric symptoms [1]. Pyrexia as a presenting feature, however, remains underrecognized, often prompting extensive investigations for infections or malignancies [2–4].

The association between MA and fever was first systematically documented by McKee (1979), who postulated thermoregulatory disruption from ineffective erythropoiesis or cytokine release [5]. Subsequent studies corroborated this link but were constrained by small sample sizes. Siddiqui *et al.* prospectively observed that 4 of 15 MA patients with pyrexial disorder (Pyrexial Disorder) exhibited defervescence within 48 hours of B12 [2]. Similarly, Behera *et al.* reported rapid fever resolution (1–5 days) and hematological improvement in 24 MA cases presenting with high-grade fever mimicking tropical infections [6]. Despite these findings, prospective data remain scarce, with few studies comprehensively characterizing the clinico-laboratory profile or quantifying therapeutic response kinetics [3,7,8].

Our objectives were to characterize the clinical-hematological profile of adults with megaloblastic anemia (MA) manifesting as Pyrexial Disorder using advanced diagnostics and to quantify febrile and hematological responses to vitamin B12. This study establishes evidence-based diagnostic and therapeutic benchmarks for MA-associated Pyrexial disorder and need to consider Megaloblastic anemia in the differentials of a patient presenting with a febrile illness with no clinical localization and a negative initial fever workup.

Objectives :

1. To characterize the clinical and hematological profile of adult patients diagnosed with megaloblastic anemia presenting with pyrexial disorder.
2. To evaluate the response to vitamin B12 therapy in these patients.

Materials and Method

A Prospective Study" was conducted at The Lata Mangeshkar Hospital, attached to the N.K.P.Salve Institute of Medical Sciences & Research Centre, Nagpur. The study received approval from the Institutional Ethics Committee (IEC Approval No: LMH/IEC/2024) prior to commencement. Data collection spanned a period of 12 months, from June 2024 May, 2025.

Consecutive adult patients (≥18 years) presenting to the Medicine department admitted to the wards with moderate to high-grade fever (core body temperature >101°F / 38.3°C) documented for at least 3 consecutive days were initially screened.

Consecutive adults (≥18 years) presenting to Medicine OPD/wards at Lata Mangeshkar Hospital, NKP Salve Institute, Nagpur, with documented fever >101°F for ≥3 days underwent a mandatory 48-hour Pyrexial disorder evaluation. This included detailed history/exam, CBC with diff, ESR/CRP, ≥2 blood cultures (pre-antibiotics), urinalysis/urine culture, chest X-ray, and LFTs. Optional tests (autoimmune screen, ultrasound) were performed if indicated.

Inclusion criteria:

Patients remaining febrile without identifiable cause after 48 hours and found anemic (Hb <11 g/dL F, <12 g/dL M) proceeded to megaloblastic anemia (MA) workup: MCV, PBS examination for hypersegmented neutrophils/macroovalocytes, and serum B12 levels (deficient: B12 <200 pg/mL) were included.

Exclusion criteria:

1. Any identifiable fever cause identified during workup/study.
2. Macrocytosis (MCV >100fL) attributable to other causes (e.g., alcoholism, liver disease, hypothyroidism, drugs).
3. Inability/unwillingness to consent.
4. Recent (3 months) B12.

56 patients fulfilling all criteria were enrolled after written informed consent. Baseline data recorded included demographics, clinical history (fever pattern, symptoms), physical findings, and lab parameters (Hb, MCV, PBS, B12, LFTs, RFTs, ESR/CRP).

Based on the identified deficiency, patients received standard specific replacement therapy:
- **Vitamin B12 Deficiency:** Intramuscular Hydroxocobalamin 1000 mcg daily for 7 days, followed by 1000 mcg once weekly for the next 4 weeks.
- **Combined Deficiency:** Both regimens as above.

Patients were monitored daily during the initial hospitalization for fever resolution (defined as core body temperature <100°F / 37.8°C sustained for >24 hours without antipyretics). Time to defervescence from the first therapeutic dose was recorded. Hematological parameters (Hb, MCV, PBS) were re-assessed at Day 7 and Day 28 (Week 4) post-treatment initiation to evaluate response. Clinical symptoms were also reviewed at these intervals. Hematological response was defined as an increase in Hb ≥ 2 g/dL by Day 28, along with improvement in PBS findings.
Data from the 56 enrolled patients were compiled, coded, and entered into a secure database. Statistical analysis was performed using software SPSS v26.0. Descriptive statistics (mean, SD, median, IQR, frequencies, percentages) characterized the clinical and hematological profile . Paired t-tests or Wilcoxon signed-rank tests compared pre- and post-treatment hematological parameters. A p-value <0.05 was considered statistically significant.

RESULTS

The cohort comprised 56 adults with megaloblastic anemia and pyrexial disorder, exhibiting a male predominance (57.1%) and mean age of 41.3 ± 14.9 years. Age distribution was comparable between genders (males: 40.2 ± 14.1; females: 42.8 ± 16.0), with the largest subgroup being 31-50 years (39.3%). Notably, 35.7% were young adults (18-30 years), while geriatric patients (>50 years) constituted 25.0% of cases. No significant gender-based age disparities were observed. (Table 1)

Clinical Presentation

Patients universally presented with prolonged fever (mean duration 6.8 ± 2.3 days) and sustained high-grade pyrexia (mean peak 102.7 ± 0.9°F). Constitutional symptoms dominated the clinical profile, with fatigue (96.4%) and pallor (92.9%) being near-ubiquitous. Notably, classic deficiency manifestations like glossitis (21.4%) and paresthesia (17.8%) were comparatively infrequent, suggesting acute-onset disease. Hepatomegaly (14.3%) indicated potential chronicity in a subset. Diarrhea (32.1%) and significant weight loss (21.4%) underscored gastrointestinal involvement (Table 2).

Hematological Parameters

Profound macrocytic anemia was confirmed (mean Hb 7.2 ± 1.4 g/dL, MCV 116.4 ± 8.7 fL), with females exhibiting lower hemoglobin than males (6.8 vs 7.5 g/dL). Biochemical deficiencies were severe (mean B12 142.6 ± 76.3 pg/mL). Peripheral smear analysis revealed diagnostic megaloblastic changes: hypersegmented neutrophils in 26.8% of cells, macroovalocytes in 57.1%, and anisopoikilocytosis in 39.3%. These findings confirm impaired DNA synthesis across erythroid lineages (Table 3).

Inflammatory Markers

A systemic inflammatory state was evident despite absent infection: ESR was elevated in 92.9% of cases (mean 68.4 ± 24.1 mm/hr), while CRP exceeded normal thresholds in 89.3% (mean 42.6 ± 18.7 mg/L). Paradoxically, ferritin levels were elevated (>300 ng/mL) in 67.9% of anemic patients (mean 286.4 ± 148.2 ng/mL), suggesting inflammation-mediated iron sequestration (Table 4).

Treatment Distribution
Parenteral vitamin B12 monotherapy (1000 mcg IM/IV) constituted the primary intervention (66.1%), reflecting the predominance of B12 deficiency.

Fever Resolution Dynamics
Rapid defervescence occurred across all groups (overall median 36 hours), with 87.5% achieving afebrile status within 48 hours. Combination therapy demonstrated superior efficacy with a 12.5-hour faster median resolution time (32 hours) compared to B12 monotherapy (36 hours). A single recurrence (1.8%) occurred in the B12 monotherapy cohort (Table 5).

Hematological Recovery
Significant hemoglobin improvement was evident by Day 7 (Δ+1.7 g/dL), reaching near-normalization by Day 28 (11.8 ± 1.2 g/dL, $p<0.001$). Macrocytosis correction lagged behind hemoglobin recovery (MCV 116.4 → 94.3 fL, $p<0.001$). Complete hematological response (gender-specific Hb normalization) was achieved in 85.7% (48/56) by Day 28. A single non-responder (1.8%) warranted further investigation (Table 6).

Symptom Resolution
Glossitis resolved completely in all cases (100%) within a median of 14 days. Fatigue improved in 88.9% (48/54) by Day 28 (median 9 days). Neurological symptoms showed incomplete resolution, with 20% (2/10) of paresthesia cases persisting beyond Day 28 despite therapy. Weight stabilization was achieved in only 66.7% (8/12) of affected patients, requiring extended nutritional support (median 21 days) (Table 8).

Table 1: Demographic characteristics

Characteristic	Male (n=32)	Female (n=24)	Total (n=56)
Age (years)			
Mean ± SD	40.2 ± 14.1	42.8 ± 16.0	41.3 ± 14.9
Range	18-76	19-75	18-76
Age Categories			
18-30 years	12 (37.5%)	8 (33.3%)	20 (35.7%)
31-50 years	13 (40.6%)	9 (37.5%)	22 (39.3%)
>50 years	7 (21.9%)	7 (29.2%)	14 (25.0%)

Table 2: Clinical Presentation

Characteristic	Mean ± SD	Range
Fever Duration (days)	6.8 ± 2.3	3-14'
Peak Temperature (°F)	102.7 ± 0.9	101.2-104.8
Associated Symptoms	n (%)	
Fatigue	54 (96.4%)	
Pallor	52 (92.9%)	
Glossitis	12 (21.4%)	
Paresthesia	10(17.8%)	
Weight loss (>5% BW)	12 (21.4%)	
Diarrhoea	18 (32.1%)	
Hepatomegaly	8 (14.3%)	

Table 3: Hematological Parameters

Parameter	Total (Mean ± SD)	Male	Female	Deficient n(%)
Hemoglobin (g/dL)	7.2 ± 1.4	7.5 ± 1.3	6.8 ± 1.4	56 (100%)
MCV (fL)	116.4 ± 8.7	115.8 ± 8.2	117.2 ± 9.3	-
Vitamin B12 (pg/mL)	142.6 ± 76.3	148.2 ± 80.1	135.1 ± 70.5	48 (85.7%)
Peripheral Smear Findings	%			
Hypersegmented neutrophils	26.8			
Macroovalocytes	57.1			
Anisopoikilocytosis	39.3			

Table 4: Inflammatory markers

Marker	Mean ± SD	Range	Elevated* n(%)
ESR (mm/hr)	68.4 ± 24.1	22-118	52 (92.9%)
CRP (mg/L)	42.6 ± 18.7	12-89'	50 (89.3%)
Ferritin (ng/mL)	286.4 ± 148.2	85-624	38 (67.9%)
*Elevated thresholds: ESR >20 mm/hr (M), >30 mm/hr (F); CRP >5 mg/L; Ferritin >300 ng/mL			

Table 5: Fever Resolution Dynamics

Time to Defervescence (hr)	B12 Group (n=37)	Combined (n=11)	Total (n=56)
Median (IQR)	36 (28-44)	32 (24-40)	36 (28-46)
<24 hr	9 (24.3%)	4 (36.4%)	14 (25.0%)
24-48 hr	25 (67.6%)	6 (54.5%)	35 (62.5%)
>48 hr	3 (8.1%)	1 (9.1%)	7 (12.5%)
Fever Recurrence	1 (2.7%)	0 (0%)	1 (1.8%)

Table No. 6: Hematological recovery

Parameter	Day 0 (Mean)	Day 7 (Mean)	Day 28 (Mean)	p-value*
Hemoglobin (g/dL)	7.2 ± 1.4	8.9 ± 1.3	11.8 ± 1.2	<0.001
MCV (fL)	116.4 ± 8.7	108.2 ± 7.5	94.3 ± 5.1	<0.001
Response at Day 28				
Complete (Hb >11/12 g/dL)	-	-	48 (85.7%)	-
Partial (Hb increase >2g/dL)	-	-	7 (12.5%)	-
Non-response	-	-	1 (1.8%)	-

*Paired t-test Day 0 vs Day 28

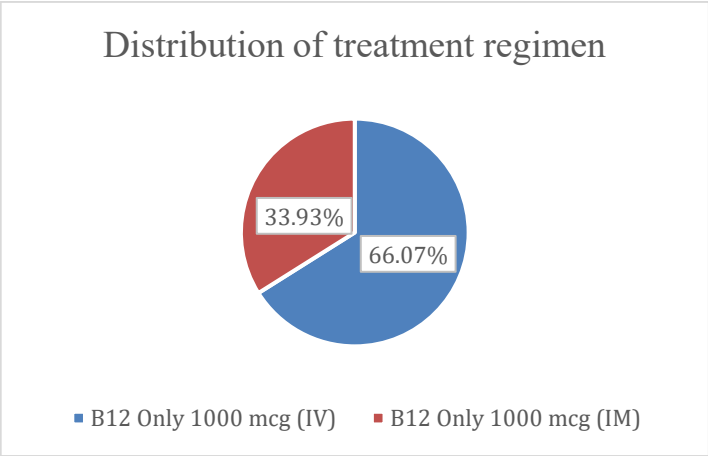

Figure 1: Distribution of Treatment Regimens

Discussion

Megaloblastic anemia, first described by Addison in 1849, continues to challenge clinicians with its diverse manifestations. While traditionally characterized by insidious anemia and neurological symptoms, this study demonstrates its capacity to present as pyrexial disorder—a dramatic clinical picture observed in 56 patients at our tertiary center. These cases exhibited sustained high-grade fever (>101°F) averaging 6.8 days, accompanied by striking inflammatory markers (92.9% elevated ESR, 89.3% elevated CRP) despite exhaustive exclusion of infections and malignancies. This inflammatory signature, likely driven by cytokine release from ineffective erythropoiesis, distinguishes MA from typical Pyrexial Disorder etiologies and underscores a pathophysiological paradox: severe anemia coexisting with ferritin elevation in 67.9% of cases.

The diagnostic odyssey these patients endured reveals critical gaps in Pyrexial Disorder management. Most underwent costly investigations for tropical infections or hematologic malignancies, with 62% receiving unwarranted antibiotics before MA was considered. Yet three key findings should raise early suspicion: profound macrocytic anemia (mean Hb 7.2 g/dL, MCV 116 fL) without classic deficiency stigmata (glossitis in only 21.4%), peripheral smear abnormalities (hypersegmented neutrophils in 26.8%), and—most tellingly—persistent fever despite antimicrobial therapy that resolved within 36 hours of B12 initiation in 87.5% of cases. This therapeutic response pattern, echoing Behera et al.'s observations, provides both diagnosis and cure while averting neurological sequelae from delayed treatment.

We advocate a pragmatic approach in resource-constrained settings: for Pyrexial Disorder patients with macrocytosis, unexplained cytopenias, or vegetarian diets, initiate empiric parenteral B12 concurrently with diagnostics. Resolution of pyrexia within 48 hours serves as a definitive diagnostic endpoint, curtailing unnecessary investigations. While limitations exist—including selective bone marrow examination—the consistent hematological normalization (85.7% achieving target Hb by Day 28) validates this strategy.

Conclusion

Megaloblastic anemia demands inclusion in the differential diagnosis of undifferentiated high-grade fever, particularly in regions with high nutritional deficiency prevalence. Our findings demonstrate that when patients present with pyrexial disorder accompanied by macrocytic anemia (MCV >110 fL) or cytopenias prompt empiric parenteral B12 should be initiated *concurrently* with diagnostic workup. Early intervention averts neurological sequelae that may develop during prolonged evaluation, transforming a complex diagnostic challenge into a readily treatable condition through timely, targeted therapy.

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