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CASE REPORT

When B12 therapy fails: two case reports of intravenous vitamin B12 resistance in pernicious anemia

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ABSTRACT

BACKGROUND: Pernicious anemia is an autoimmune disorder causing vitamin B12 deficiency resulting from impaired absorption caused by intrinsic factor absence. Positive parietal cell and intrinsic factor antibodies confirm the diagnosis. Intravenous vitamin B12 effectively treats Pernicious anemia. Severe cytopenias (anemia, thrombocytopenia, neutropenia) may result, sometimes requiring emergency care and hospitalization.

CASE PRESENTATION: Case A: A 54-year-old male presented with six months of generalized fatigue and dyspnea on exertion. Laboratory tests revealed severe macrocytic anemia (Hb: 4.7 g/dL, MCV: 120 fL), with a peripheral blood smear showing hyper-segmented neutrophils and macro-ovalocytes, suggestive of megaloblastic anemia. Bone marrow biopsy demonstrated decreased cellularity with megaloblastic changes. Despite six-weeks of intravenous vitamin B12 therapy, there was no improvement in hematological parameters. Endoscopy revealed atrophic gastritis, and biopsy showed anti-parietal cell antibodies. Following a trial of immunosuppressive therapy with cyclosporine, no significant response was observed. Bone marrow transplantation was recommended.

Case B: A 62-year-old male presented with epigastric pain, dyspepsia, fatigue, and a three-month history of anorexia. He was diagnosed with macrocytic anemia (Hb: 6.7 g/dL, MCV: 100 fL), and peripheral blood smear indicated megaloblastic changes. Bone marrow biopsy confirmed decreased cellularity and megaloblastic anemia. Despite standard intravenous vitamin B12 therapy, the patient showed no hematological improvement. Endoscopic findings revealed atrophic gastritis. Immunosuppressive therapy with cyclosporine also failed, leading to the recommendation of bone marrow transplantation.

CONCLUSION: Continued efforts in understanding the pathophysiology of Pernicious anemia and autoimmune-mediated bone marrow failure syndromes may pave the way for innovative therapeutic approaches in the future.

KEYWORDS: Anemia (MeSH); Pernicious Anemia (MeSH); Megaloblastic Anemia (MeSH); Vitamin B 12 (MeSH); B-12 Therapy (Non-MeSH); Autoimmune Diseases (MeSH); Autoimmune disorder (Non-MeSH); Intrinsic Factor (MeSH); Cytopenia (MeSH).

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INTRODUCTION

Pernicious anemia is a type of megaloblastic anemia caused by the deficiency of vitamin B12, typically due to impaired absorption resulting from the autoimmune destruction of gastric parietal cells.[1] Although prompt administration of IV vitamin B12 supplementation is the standard treatment as it bypasses the gastrointestinal tract,[2] a subset of patients may fail to respond adequately, necessitating further investigation and alternative treatment options.[3]

CASE PRESENTATION

Case A: A 54-year-old male patient reported experiencing generalized fatigue, increasing over the past six months. He also described dyspnea on exertion, limiting his physical activities. Initial laboratory investigations demonstrated severe macrocytic anemia, with a hemoglobin level of 4.7g/dL (reference range: 13.5-17.5 g/dL), MCV at presentation was 120fL after blood transfusion of 1-pint RCC MCV was 112fL and lowered to 98fL in week 3 and 4 of admission (reference range MCV: 80-100fL). All other investigations are mentioned in Table I. Peripheral blood smear examination revealed hyper-segmented neutrophils and macro-ovalocytes, consistent with megaloblastic changes. Bone marrow biopsy done revealed decreased cellularity in all hematopoietic lineages along with megaloblastic changes.

Case B: A 62-year-old male presented to the gastroenterology clinic with complaints of severe epigastric burning pain, dyspepsia, loss of appetite, and fatigue for three months. He reported experiencing significant discomfort after meals, which further contributed

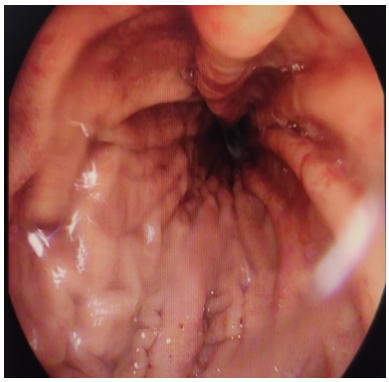

Figure 1: Case A: The stomach on endoscopy shows decrease mucosal folds with mucosal erythema and erosions throughout the stomach

to his decreased appetite.

Routine blood tests revealed a low hemoglobin level of 6.7g/dL (reference range: 13.5-17.5 g/dL) and MCV 100fL at presentation, after transfusion with 1-pint RCC MCV was 96.1fL (reference range MCV: 80-100fL). Other laboratory parameters as mentioned in Table II.

Peripheral blood smear examination revealed hyper-segmented neutrophils and macro-ovalocytes, supporting the diagnosis of megaloblastic anemia. Due to minimal response to intravenous Vit B12 therapy, bone marrow biopsy was advised which revealed decreased cellularity in all hematopoietic lineages along with megaloblastic changes consistent with MDS.

Diagnosis and treatment: Both patients were admitted for intravenous (IV) vitamin B12 therapy due to suspected pernicious anemia. Intravenous (IV) vitamin B12 therapy was initiated following the standard treatment protocol. [4,5] In both patients 1000μg IV once daily for 7 days. After that 1000μg IV was administered once weekly for 5 weeks during their hospital stay. Serum potassium levels of both patients were measured during and after administration which were within normal limits. No hypersensitivity reactions were observed in either of the patients.

However on follow up, despite six weeks of regular treatment, there was no improvement in the patient's hematological parameters. Despite the ongoing treatment and close monitoring of complete blood counts (CBC), both patients failed to respond adequately. Table I and II show lab parameters of case A and B done throughout their hospital stay. Endoscopic examinations revealed atrophic gastritis in both cases. Figure 2 shows anti-parietal cell antibodies seen on endoscopic biopsy from the stomach in case A, associated with type A atrophic gastritis. The bone marrow biopsies of both patients revealed hypocellularity, with reduced cellularity in all hematopoietic lineages. Megaloblastic changes were evident, characterized by dysplastic features in erythroid and myeloid precursors. Importantly, no lymphocyte or plasma cell infiltrates were observed, ruling out lymphoproliferative disorders as a cause of hypocellularity. The lack of response to vitamin B12 therapy and positive serological tests, a trial of immunosuppressive therapy was given. The patients were administered cyclosporine at a dose of 5 mg/kg/day for 4 weeks. [6] However, there was no significant improvement in the hematological parameters.

Considering the failure of conventional therapies, a multidisciplinary team discussion recommended the patients for bone marrow transplantation. The patients are planned to undergo extensive evaluation for eligibility, including tissue typing, cardiopulmonary assessment, and

Table I: Case A summary of laboratory results from admission till discharge

Blood Counts	Week 1	Post Transfusion	Week 2	Week 3	Reference Values
TLC (10^9/L)	3.8	5.2	5.2	5.3	4-10
Hb (g/dl)	4.7	6.4	7.9	8.6	13.5-17.5
HCT (%)	15.1	18	25.1	24.5	40-52
MCV (fl)	120	112	98	98.4	80-100
Platelets (10^9/L)	17	38	21	16	150-400
Serum Folate (ng/ml)	3.55				3-12
Vitmain B-12 (pmol/L)	>1476				138-652
Retic Count (%)	3.45			0.3	0.5-1.5

TLC: Total leukocyte count; Hb: Hemoglobin; HCT: Hematocrit ; MCV: Mean corpuscular volume

Table II: Case B summary of laboratory results from admission till discharge

Blood Counts	Week 1	Post Transfusion	Week 2	Week 3	Reference Values
TLC (10^9/L)	2.1	3	3.3	3.6	4-10
Hb (g/dl)	6.7	9.7	9.2	8.1	13.5-17.5
HCT (%)	20.1	29.7	24.4	24.7	40-52
MCV (fl)	100	96.1	97	97.2	80-100
Platelets (10^9/L)	18	33	14	10	150-400
Serum Folate (ng/ml)	2.37				3-12
Vitmain B-12 (pmol/L)	111.9				138-652
Retic Count (%)	1.03			0.4	0.5-1.5

TLC: Total leukocyte count; Hb: Hemoglobin; HCT: Hematocrit ; MCV: Mean corpuscular volume

Figure 2: Case A: Anti-parietal cell antibodies of PCA (LKS) pattern seen on endoscopic biopsy from the stomach, associated with Type-A Atrophic Gastritis.

infectious disease screening.

DISCUSSION

Pernicious anemia, a condition characterized by the inability to absorb vitamin B12 due to intrinsic factor deficiency, is a common cause of vitamin B12 deficiency. The standard treatment for pernicious anemia is intravenous (IV) vitamin B12 therapy, which typically results in significant improvement of symptoms and hematological parameters.[7] However, in rare cases, pernicious anemia may coexist with other underlying hematological disorders, complicating the diagnostic and therapeutic approach.[8]

In these cases, the patient presented with classic symptoms of pernicious anemia, including fatigue, weakness, and paresthesia. Laboratory investigations confirmed the diagnosis, with findings of macrocytic anemia, and low serum vitamin B12 levels. The patient was initiated on IV B12 therapy, following the standard dosing regimen. However, despite several weeks of treatment, there was no improvement in symptoms, and the patient's hemoglobin levels remained persistently low.

The bone marrow biopsy revealed decreased cellularity in all hematopoietic lineages along with megaloblastic changes, consistent with myelodysplastic syndrome (MDS).[9] Myelodysplastic syndromes are a heterogeneous group of hematological disorders characterized by ineffective hematopoiesis, leading to cytopenia's and an increased risk of progression to acute myeloid leukemia.[8,9] The coexistence of pernicious anemia and MDS explained the refractory anemia and the lack of response to vitamin B12 replacement therapy. It is important to note that MDS can present with macrocytic anemia, mimicking the clinical features of pernicious anemia. Therefore, in patients with pernicious anemia who do not respond to treatment, a bone marrow biopsy should be considered to identify potential concurrent hematological disorders, such as MDS. [9] At present mainstay of treatment for myelodysplastic syndromes includes:

• Supportive care: Many patients require frequent blood transfusions due to persistently low blood counts and for symptoms of anemia such as shortness of breath and fatigue. Erythropoiesis stimulating agents may be given to increase the number of mature red blood cells in the body and reduce symptoms of anemia.

• Drug therapy: This can include immunosuppressive drugs to weaken the immune system which reduces the need for blood transfusions. Other drugs like lenalidomide, azacitidine and decitabine may be used

• Stem cell transplantation: Hematopoietic stem cell transplantation (HSCT) offers the potential for cure, but timing of the procedure may be important and a limiting factor. Most patients with MDS are elderly and only a few young patients will have a matched donor, the use of bone marrow transplantation is limited.

CONCLUSION

We presented two cases of pernicious anemia where patients did not respond to IV vitamin B12 therapy and showed hypocellularity on bone marrow examination. Despite 6 weeks of IV B12 and 4 weeks of cyclosporine immunosuppressive therapy, their hematological parameters remained unchanged. Bone marrow biopsies revealed myelodysplastic syndrome, prompting consideration of HSCT. These cases highlight the complexity and challenges in managing pernicious anemia when standard treatment approaches fail.

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AUTHORS' CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

Ze & SAS: Identification and management of the case, drafting the manuscript, approval of the final version to be published.

ANK & SOA: Identification and management of the case, critical review, approval of the final version to be published.

SKA: Diagnosis of the case, drafting the manuscript, critical review, approval of the final version to be published.

RA: Management of the case, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

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