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A Rare Case of Severe Pernicious Anemia with Neuropsychiatric Implications

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Patient: Female, 51-year-old
Final Diagnosis: Pernicious anemia
Symptoms: Weakness
Clinical Procedure: —
Specialty: Hematology • General and Internal Medicine • Psychiatry

Objective: Rare disease

Background: Pernicious anemia (PA) is caused by a deficiency in intrinsic factor (IF), which is necessary for vitamin B12 (cobalamin) absorption, resulting in vitamin B12 deficiency and subsequent megaloblastic anemia. Diagnosis of PA relies on the detection of circulating antibodies to IF. In addition to anemia, patients can develop neuropsychiatric conditions, such as subacute combined degeneration of the spinal cord or psychosis. We present the case of a patient with a history of schizophrenia who exhibited unusually severe manifestations of pernicious anemia, including life-threatening anemia, multiple hypersegmented neutrophils, and significantly elevated methylmalonic acid (MMA) levels.

Case Report: A 51-year-old Hispanic woman with a history of schizophrenia was admitted with severe weakness, shortness of breath, and diarrhea. The hemoglobin (Hb) level was 2.5 g/dL and mean corpuscular volume (MCV) was 133 fL. A diagnosis of pernicious anemia was made by a low vitamin B12 level, high levels of methylmalonic acid (MMA) and homocysteine, and positive IF-blocking antibodies. Her anemia did not improve initially, even after 3 units of blood were transfused. She had no signs of bleeding. It was thought that hemoconcentration due to severe dehydration falsely raised her initial Hb levels, which were corrected by hydration. A peripheral blood smear showed many hypersegmented neutrophils. With parenteral cyanocobalamin therapy, her anemia and schizophrenia symptoms improved. The hypersegmented neutrophils disappeared by 2 weeks.

Conclusions: This is an extreme case of pernicious anemia with life-threatening anemia. The hypersegmented neutrophils disappeared in 2 weeks with vitamin B12 therapy. The symptoms of schizophrenia also improved.

Keywords: Anemia, Pernicious • Vitamin B 12 Deficiency • Neutrophils

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Introduction

Pernicious anemia (PA) is a form of autoimmune gastritis (AIG) resulting from destruction of gastric parietal cells, leading to a deficiency in intrinsic factor (IF), which is necessary for vitamin B12 (cobalamin) absorption by binding ingested vitamin B12. This deficiency results in vitamin B12 deficiency and subsequent megaloblastic anemia [1-4].

Vitamin B12 is necessary for the development and initial myelination of the central nervous system as well as for maintenance of its normal function. In addition to anemia-related symptoms, patients with vitamin B12 deficiency can develop neuropsychiatric conditions, such as subacute combined degeneration of the spinal cord or psychosis [1,2,4]. Less common conditions associated with vitamin B12 deficiency include glossitis, malabsorption, infertility, and thrombosis [2,3].

In the absence of the Schilling test, a definitive diagnosis of pernicious anemia (PA) relies on the detection of circulating antibodies to intrinsic factor (IF) and gastric parietal cells. Cobalamin of <200 ng/L plus the presence of anti-IF antibodies confirm a diagnosis of pernicious anemia [1].

Hypersegmented neutrophils are a characteristic feature of megaloblastic anemia caused by vitamin B12 or folate deficiency, or both [5]. However, neutrophil hypersegmentation does not appear to be a sensitive indicator of mild B12 deficiency. Leukopenia and thrombocytopenia may be present but only rarely cause clinical problems [6]. Although the classical presentation of B12 deficiency is hematological, it is important to note that neuropsychiatric manifestations can be the initial symptoms of a developing B12 deficiency syndrome [7]. Patients with confirmed PA require lifelong vitamin B12 treatment with intramuscular (IM) injections initially followed by high-dose oral supplementation [1-4].

We present the case of a patient with a history of schizophrenia who exhibited unusually severe manifestations of pernicious anemia, including life-threatening anemia, multiple hypersegmented neutrophils, and significantly elevated methylmalonic acid (MMA) levels. We also discuss the neuropsychiatric implications of PA.

Case Report

A 51-year-old woman with a history of schizophrenia was admitted with severe weakness, shortness of breath, and intermittent non-bloody diarrhea. She had been mostly bedridden for the past month. Her medical records showed refills for trazodone, risperidone, and duloxetine for several years. She was homeless, unemployed, and living in a motel. Detailed information about her schizophrenia was not available.

Her vital signs were: blood pressure 84/57 mmHg, pulse 90 beats per minute, temperature 36.4°C, respiratory rate 18 per minute, and oxygen saturation 95% on room air. On examination, she had pale conjunctivae, non-icteric sclera, dry skin and oral mucous membranes, and a scaphoid abdomen with no hepatosplenomegaly. She was drowsy but able to move her extremities. Deep tendon reflex (knee jerk) was absent. Her laboratory

Table 1. Laboratory test results from Day 1 to Day 15 of admission.

	WBC	Hb/MCV	PLT	RET	MMA	HCY	BUN	CR	B12	SF	PRBC
D1	4.3	2.5/133	140	2.7	34,920	198.4	41	1.52	72	11.6	1 unit
D2	3.0	2.5/124	111				36	1.35			1 unit
D3	5.1	2.6/123	102				26	1.23			1 unit
D4											1 unit
D5	26.5	3.1/133	78				16	0.93			1 unit
D6	13.8	4.0/138	94				16	0.95			1 unit
D7	8.8	7.3/107	132	20.7			17	0.84			
D8	6.3	7.9/109	163		1,299		19	0.84	5318	6.1	
D9	7.0	8.1/107	236				22	0.78			
D15	10.4	9.2/102	824				27	0.92	899		

Hb – hemoglobin (g/dL); MCV – mean corpuscular volume (fL); PLT – platelet (10^9/L); RET – reticulocyte (%); MMA – methylmalonic acid (mol/L); HCY – homocysteine (mmol/L); BUN – blood urea nitrogen (mg/dL); CR – creatinine (mg/dL); B12 – vitamin B12 (pg/dL); SF – serum folate (ng/mL); PRBC – packed red blood cells.

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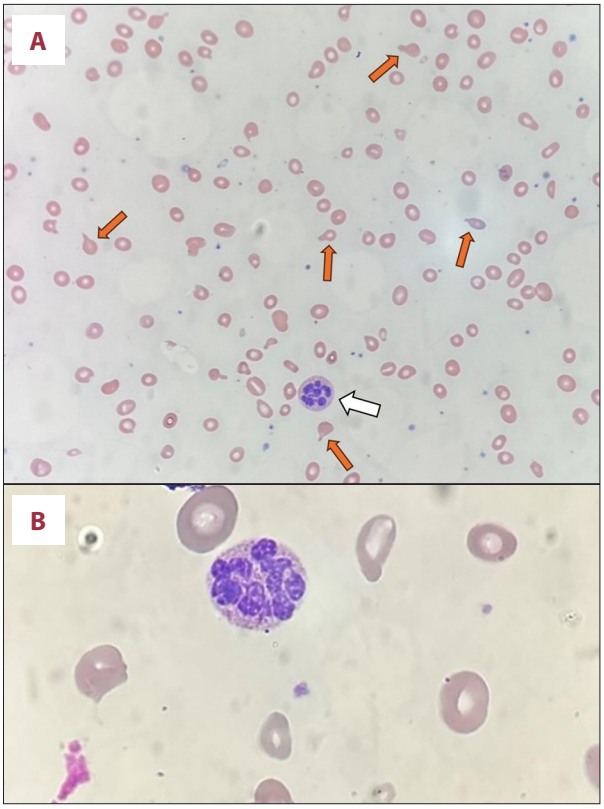

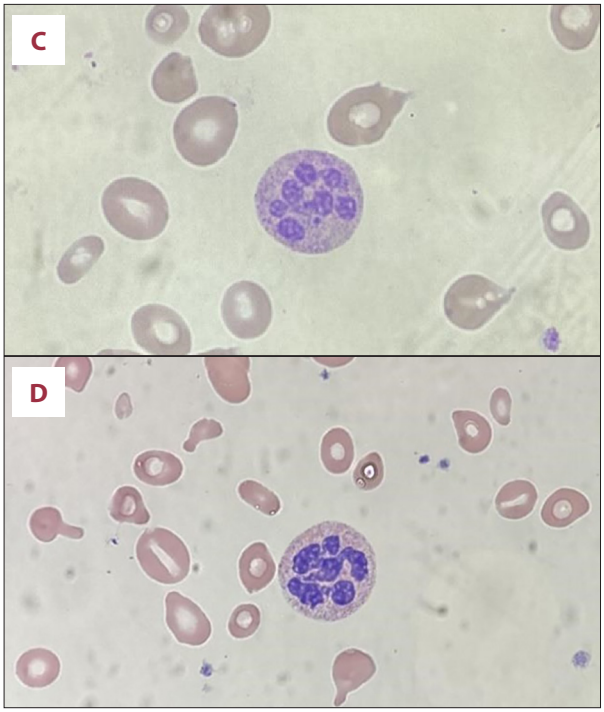

Figure 1. (**A**) Wright-Giemsa stain of the peripheral blood smear (×40) on admission showing a hypersegmented neutrophil (white arrow), poikilocytosis, anisocytosis, hypochromia, and teardrop cells (red arrows). (**B**) A neutrophil with 8-10 nuclear lobes. (**C**) A 7-lobed neutrophil. (**D**) A 6-lobed neutrophil.

test results are summarized in **Table 1**. On the first day (Day 1) of hospitalization, notable results included hemoglobin (Hb) 2.5 g/dL, MCV 133.2, reticulocyte 2.7%, total bilirubin 2.7 mg/dL (direct bilirubin 0.5 mg/dL), LDH 2385 U/L, vitamin B12 level 72 pg/mL, positive intrinsic factor-blocking antibody, and negative anti-parietal cell antibody. The serum MMA was extremely high at 34 920 nmol/L (normal range: 73-475), and homocysteine was elevated at 198 µmol/L (normal range: 5-15).

The peripheral blood smear on Day 1 (**Figure 1A-1D**) revealed frequent hypersegmented neutrophils with 6-8 lobes, as well as poikilocytosis, anisocytosis, hypochromia, and occasional teardrop cells. Hypersegmented neutrophils were seen in 5-10% of the cells.

The patient was treated with daily intramuscular (IM) injections of cyanocobalamin (1000 mcg) and she received packed red blood cell (PRBC) transfusions along with intravenous (IV) fluids. Despite receiving 3 units of PRBCs, her Hb levels did not initially improve. A stool occult blood test was negative, and she had no other clinical signs of bleeding. It was thought that hemoconcentration due to severe dehydration falsely raised her initial Hb levels, which were corrected by IV hydration.

After receiving 4 units of PRBCs, her Hb increased to 3.1 g/dL. Gradually, she regained strength and mental clarity. By Day 7, she was able to walk without any assistance. She said she had mild numbness in both lower extremities. After a total of 6 units of PRBCs and daily IM cobalamin injections, the Hb increased to 8.1 g/dL and reticulocytes to 20.7%. She was discharged on Day 9 with a prescription for oral vitamin B12 (1000 mcg daily). A peripheral blood smear on Day 9 still showed occasional hypersegmented neutrophils, but fewer than before (<5%), with a maximum of 6 nuclear lobes. After discharge, she was placed in a public residential facility and has been monitored by a social worker on a weekly basis.

On Day 15, the patient returned to the hematology clinic with the social worker for a follow-up. She appeared mentally clear and reported feeling well. She denied any symptoms such as paresthesia, ataxia, abdominal pain, nausea, or diarrhea. Her Hb was 9.2 g/dL, and the vitamin B12 level had risen to 988 pg/mL. The total bilirubin level decreased to 1.1 mg/dL. The peripheral smear no longer showed hypersegmented neutrophils.

Two months after discharge, she no longer had anemia. The Hb was 15.1 g/dL and MCV 94.1 fL. The MMA level also normalized at 240 nmol/L. To evaluate for AIG, she was referred to a gastroenterologist for endoscopy. According to her social worker who accompanied the patient, she no longer takes psychiatric medications and shows no signs of mental disorder.

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Discussion

Epidemiological studies estimate that pernicious anemia (PA) affects about 0.1% of the general population, with prevalence increasing to 2-3% among individuals older than 65 years. Although it has traditionally been associated with older women of Northern European ancestry, more recent evidence indicates that PA is also present in a diverse range of ethnic populations, including African, White, and American groups [4]. PA often emerges in the context of autoimmune gastritis (AIG), particularly during its more advanced stages. In this setting, immune-mediated destruction of gastric parietal cells results in a decline in IF and gastric acid production, thereby impairing the release of vitamin B12 from dietary proteins and diminishing IF-mediated absorption of the vitamin in the ileum. Although PA and AIG are closely linked, PA is considered a distinct and later-stage clinical outcome within the AIG continuum [1]. IF, a glycoprotein secreted by parietal cells, is essential for vitamin B12 absorption. The presence of autoantibodies targeting IF can interfere with either the binding of vitamin B12 to IF or the absorption of the IF-B12 complex in the terminal ileum [1,6]. For diagnostic purposes, the "blocking" type of antibody is measured. This antibody is highly specific for PA (with almost 100% specificity) and is present in 70% of PA patients [3,6]. Antibodies to parietal cells are found in 90% of patients with pernicious anemia, but they are less specific, as they can also occur in individuals with simple atrophic gastritis, autoimmune thyroid disease, and in 3-10% of the normal population [1,3,6].

Vitamin B12 deficiency impairs hemopoiesis due to the pivotal role of vitamin B12 in DNA synthesis. Macrocytic anemia (MCV 100-150 fl or more) is the hallmark of PA [6]. Nevertheless, this feature is not always present at diagnosis, as almost 30% of patients do not present macrocytosis, especially in cases of concomitant iron deficiency [4].

Two pathophysiologic processes contribute to the anemia resulting from vitamin B12 deficiency: the ineffective erythropoiesis caused by intramedullary apoptosis of megaloblastic erythroid precursors, and the erythrocytes that are produced have increased rigidity associated with abnormal red cell membrane proteins, leading to shortened red blood cell survival. The resulting hemolysis increases the levels of plasma bilirubin and serum lactic dehydrogenase (LDH) [6], which was observed in our patient.

Measurement of MMA, total homocysteine, or both is useful in making the diagnosis of vitamin B12 deficiency in patients who have not received treatment [1,2]. The levels of both MMA and total homocysteine are markedly elevated in the vast majority (>98%) of patients with clinical B12 deficiency, including those who have only neurologic manifestations of deficiency. Elevated levels of MMA and total homocysteine decrease immediately after treatment, and the levels can be remeasured to document adequate vitamin B12 replacement [2]. Cobalamin of <200 ng/L plus the presence of anti-IF antibodies confirm a diagnosis of pernicious anemia [1]. Bone marrow biopsy and aspiration are not necessary for the diagnosis of PA [2].

Patients with confirmed PA require lifelong vitamin B12 treatment. Initially, IM vitamin B12 is administered daily or on alternate days for 1-2 weeks, then tapered to weekly doses over the next 1-2 months. After this induction period, long-term maintenance can be achieved either with monthly IM injections or with high-dose oral vitamin B12 supplementation (typically for the lifelong maintenance phase) [1-4].

In our patient, the diagnosis of PA was made with typical laboratory findings indicative of severe disease: positive anti-IF antibody, low vitamin B12 level, severe macrocytic anemia, extremely high serum MMA and homocysteine levels, extremely elevated LDH, and indirect bilirubinemia.

Possible future sequelae of PA include increased risk of cancer. A systematic review of PA complications highlighted an overall cumulative incidence of cancer of 2.4% and a gastric cancer incidence of 0.3/100 person-years [8]. The 2021 American Gastroenterological Association clinical practice update recommends endoscopy for patients with atrophic gastritis [9]. Our patient was referred to a gastroenterologist for endoscopy.

This case is unique as our patient not only presented typical clinical and laboratory findings of PA described above but also displayed several unusual features: life-threatening anemia, extreme hypersegmented neutrophils, extremely high MMA level, and schizophrenia possibly associated with PA.

Extreme Anemia with Critically Low Initial Hemoglobin Level (Probably Less Than 2.0 g/dL)

The patient's initial Hb was 2.5 g/dL, and this did not increase initially despite transfusion of 3 units of PRBCs. Upon presentation, she was dehydrated due to poor oral intake and diarrhea, as evidenced by both physical (dry skin) and laboratory findings (BUN 41 mg/dL and creatinine 1.51 mg/dL on Day 1). Apparently, dehydration caused hemoconcentration resulting in falsely high Hb levels initially. With IV hydration, her dehydration and hemoconcentration were corrected, lowering the Hb levels. By Day 5, the BUN had decreased to 16 mg/dL and creatinine to 0.93 mg/dL. Thus, her true initial hemoglobin level must have been lower than 2.5 g/dL, likely less than 2 g/dL. Postoperatively, extreme anemia (Hb <2 g/dL) is often fatal [10,11], although there is a reported case of a patient with megaloblastic anemia due to vitamin B12 deficiency who survived with a Hb level of 1.7 g/dL [10]. It is extremely unusual

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for a patient to develop critical anemia with Hb 2.5 (actual Hb: probably <2.0 g/dL) and survive.

Extreme Hypersegmented Neutrophils with 8-10 Nuclear Lobes

Hypersegmented neutrophils are seen in 98.3% of patients with megaloblastic anemia [2]. The neutrophils in our patient displayed an unusually high number of nuclear lobes. One of the neutrophils (**Figure 1A**) had at least 8 lobes, and depending on the observer, it could be argued that it had as many as 10 lobes, as they could be overlapped in the crowded neutrophil. We reviewed the peripheral blood smears daily during her hospital stay and observed a gradual decrease in the number of hypersegmented neutrophils and their nuclear lobes. On Day 9, hypersegmented neutrophils were still present, but their number was lower, with a maximum of 6 nuclear lobes. By Day 15, no hypersegmented neutrophils were present in the blood smear, consistent with Nath and Lindenbaum's observations that hypersegmented neutrophils disappear by 14 days [12]. They observed no relationship between the severity of anemia and the degree of hypersegmentation [5]. However, we observed the number of nuclear lobes of hypersegmented neutrophils decrease as the Hb levels increase.

Extremely High Serum MMA Levels Which Took a Week to Decrease

The initial serum MMA level of our patient was 34 920 nmol/L (normal: 73-475 nmol/L). Elevated MMA is specific to vitamin B12 deficiency, unlike homocysteine levels, which can also be elevated in folate and pyridoxine deficiencies and hypothyroidism. It was reported that MMA levels tend to remain elevated for several days after vitamin B12 therapy [6]. In our patient, the MMA elevation persisted for over a week, probably due to its extremely high initial level, which took longer to be normalized.

Neuropsychiatric Implications (Peripheral Neuropathy And Possibly Schizophrenia)

After cellular uptake and intracellular release of vitamin B12 in a normal situation, it is metabolized into its active forms, adenosylcobalamin and methylcobalamin, which act as essential cofactors for 2 key enzymatic reactions. A deficiency in vitamin B12 disrupts these pathways, resulting in elevated levels of methylmalonic acid (MMA) and homocysteine in the bloodstream. While increased homocysteine has been linked to neurodegenerative changes such as white matter damage, brain atrophy, and cognitive impairment, the precise impact of elevated MMA remains less well defined [1]. Peripheral neuropathy often is one of the earliest neurologic signs of vitamin B12 deficiency and can progress to subacute combined degeneration (SCD) of the spinal cord if left untreated. This condition usually presents symmetrically, predominantly affecting the lower extremities. On clinical examination, patients can have diminished sensation to vibration, pinprick, and light touch, along with hypoactive or absent deep tendon reflexes, especially at the ankles. Notably, neurologic deficits can occur even in the absence of anemia. Advanced cases of SCD can feature limb weakness, ataxia, and visual disturbances. Timely identification and treatment are essential, as early intervention with B12 replacement offers the best chance for neurological recovery before permanent damage sets in [1,4]. Our patient presented with mild peripheral neuropathy with numbness of both lower legs and absent DTR, which improved with vitamin B12 replacement therapy.

Neuropsychiatric symptoms, including those of schizophrenia, can be an initial manifestation or even the sole symptom of vitamin B12 deficiency [7]. Vitamin B12 levels are often low in hospitalized psychiatric patients with schizophrenia [13]. It is advisable to rule out vitamin B12 deficiency in patients with psychotic symptoms instead of directly diagnosing psychiatric disorders [14]. A recent longitudinal study (3849 patients, aged ≥50 years) revealed the relationship between low blood plasma B12/folate levels and depressive symptoms. Older adults with deficient-low B12 status had a 51% higher likelihood of developing depressive symptoms over 4 years, but no associations of folate status with incident depression were observed. These findings highlight the need to further explore the low-cost benefits of optimizing vitamin B12 status for depression in older adults [15]. In cases of established psychiatric disorders, it is advisable to maintain serum B12 levels within the higher normal range [7].

Although no detailed information about her psychiatry history was available, our patient was reportedly diagnosed with schizophrenia and started taking antipsychotic medications several years ago. As it takes about 10-12 years to clinically develop symptomatic PA, PA can begin with subclinical vitamin B12 deficiency [4]. Therefore, it may be possible that her diagnosis of schizophrenia coincided with the onset of PA several years ago. While it is unclear whether PA directly caused her schizophrenia or exacerbated underlying psychiatric conditions, this case underscores the importance of considering vitamin B12 deficiency in patients with psychiatric symptoms.

Conclusions

We present a severe case of pernicious anemia characterized by life-threatening anemia, unusually abundant hypersegmented neutrophils with many nuclear lobes, extremely high MMA levels, and improvement in schizophrenia symptoms following vitamin B12 replacement therapy. While it remains unclear

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whether the patient's schizophrenia was directly caused by PA or PA exacerbated her underlying mental condition, she improved dramatically after correction of her vitamin B12 deficiency. Further investigation into the relationship between pernicious anemia and schizophrenia is warranted.

Department and Institution Where Work Was Done

Division of Hematology-Oncology, Department of Medicine, Bakersfield, CA, USA.

Patient Consent

The written consent was obtained from the patient.

Ethic Statement

This case report was approved by the IRB at Kern Medical (approval # 24115).

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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