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CASE REPORT

Multifaceted Clinical Spectrum of Vitamin B12 Deficiency - a Case Report and Literature Review

Ewa Pustelnik[1,*], Katarzyna Pikora[1,*], Magdalena Zofia Hartman[2], Marta Kurzeja[3], Joanna Czuwara[3], Paweł Łaguna[1]

[1]Department of Oncology, Pediatric Hematology, Clinical Transplantology and Pediatrics, Medical University of Warsaw, Warsaw, Poland; [2]Laboratory of Cytohematology, Department of Oncology, Pediatric Hematology, Clinical Transplantology and Pediatrics, Medical University of Warsaw, Warsaw, Poland; [3]Department of Dermatology, Medical University of Warsaw, Warsaw, Poland

*These authors contributed equally to this work

Correspondence: Ewa Pustelnik, Department of Oncology, Pediatric Hematology, Clinical Transplantology and Pediatrics, Medical University of Warsaw, Żwirki i Wigury 63a street, Warsaw, 02-091, Poland, Tel +48 22 317 96 16, Email ewa.pustelnik@wum.edu.pl

Background: Vitamin B12 (cobalamin) deficiency is a well-known cause of hematologic and neurological disorders; however, its presentation can be highly variable, leading to diagnostic challenges. The etiology is diverse: while the most common cause is dietary insufficiency, other potential causes include malabsorption syndromes, autoimmune gastritis, gastrointestinal disorders, chronic infections, and genetic defects. Clinical presentation varies significantly, ranging from clinically silent macrocytosis to life-threatening anemia or pancytopenia. Neurological and psychiatric manifestations may include vision and gait impairment, depression, and cognitive dysfunction. Given this complexity, vitamin B12 deficiency can mimic other conditions, often leading to a delay in diagnosis.

Case Presentation: A 15-year-old male was admitted in critical condition with severe anemia, thrombocytopenia, jaundice, progressive weight loss, fatigue, gait disturbances, and vision impairment. Initially, Evan's syndrome was suspected, but further laboratory investigations, including a peripheral blood smear and elevated mean corpuscular volume (MCV), led to the diagnosis of profound vitamin B12 deficiency. Additional workup revealed chronic atrophic gastritis as the underlying cause. The patient was treated with vitamin B12 injections, leading to significant hematologic and neurological improvement, weight gain, and resolution of psychiatric symptoms. However, optic nerve atrophy was detected as a late complication.

Conclusion: This case emphasizes the need to consider vitamin B12 deficiency in pediatric patients with unexplained hematologic, neurological, and psychiatric symptoms, particularly when associated with chronic atrophic gastritis. Early recognition and intervention are crucial to preventing irreversible complications, such as optic neuropathy. Given the multidisciplinary nature of its presentation, this case serves as an important reminder for pediatricians, hematologists, gastroenterologists, and neurologists to maintain a high index of suspicion for vitamin B12 deficiency in complex clinical scenarios.

Keywords: cobalamin, hemolytic anemia, thrombocytopenia, atrophic gastritis

Background

Vitamin B12 (cobalamin) is an essential nutrient that plays a key role in maintaining nervous system function, proper blood cell production, and DNA synthesis. Vitamin B12 deficiency is a common condition, typically presenting as mild to moderate macrocytic anemia. However, in cases of chronic, severe deficiency, it can lead to pancytopenia, hemolytic anemia, and serious neurological (such as coordination disorders and paresthesias) or psychiatric conditions, including depression, mania, or memory impairment. The most common cause of vitamin B12 deficiency is inadequate dietary intake. Less frequently, it results from conditions that impair cobalamin absorption, such as pernicious anemia, gastritis, a history of gastrectomy, or prolonged use of proton pump inhibitors. This issue affects both children and adults, with significant geographic and demographic variability. In adults, the global prevalence is estimated at around 6% in individuals under 60 years and up to 20% in those over 60, with rates as high as 70–80% reported in low-income

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Table 1 Average Daily Recommended Amounts of Vitamin B12 Intake for Different Ages Given in Micrograms

Age	Recommended Amount
0-6 months	0.4 mcg
7-12 months	0.5 mcg
1-3 years	0.9 mcg
4-8 years	1.2 mcg
9-13 years	1.8 mcg
14-18 years	2.4 mcg
>19 years	2.4 mcg
Pregnancy	2.6 mcg
Lactation	2.8 mcg

regions such as India and parts of Africa due to low intake of animal-based foods. In high-income countries like the United States and the UK, deficiency is less common but still affects 6–20% of adults, particularly the elderly. Among children, approximately 12.5% globally are affected, with prevalence rising to 21–45% in low- and middle-income countries. Infants of vegan or vegetarian mothers are particularly vulnerable due to maternal deficiency and exclusive breastfeeding. These disparities highlight the influence of diet, age, socioeconomic status, and regional health infrastructure on B12 status worldwide.[1–3] Table 1 presents the recommended intake of vitamin B12 according to age and during pregnancy and lactation. Here, we present a rare case of a boy with severe vitamin B12 deficiency secondary to gastritis. This case highlights the importance of assessing cobalamin levels in patients with hemolytic anemia or unexplained neurological or psychiatric symptoms.

Case Report

We present the case of a 15-year-old patient who was admitted to the Department of Oncology, Pediatric Hematology, Clinical Transplantology and Pediatrics in severe condition with complaints of increasing fatigue, weakness, jaundice and anorexia. He noted a gradual weight loss for about a year, he had not been losing weight intentionally. The boy also reported non-specific walking abnormalities with periodic balance disorders, and vision problems - difficulty in reading information from a distance despite normal visual acuity on ophthalmologic examination. Physical examination revealed significant low body mass, protruding bones, absent of subcutaneous fat, muscle wasting. Facial changes included extremely prominent cheekbones, hollow and sunken eyes. On admission to the clinic, the boy weighed 38 kg with a height of 164 cm (BMI 14,12 kg/m^2), which equals the zero percentile of body weight and BMI for age (Figures 1 and 2). The skin of the entire body was pale and jaundiced, and on the chest and lower torso were numerous, scattered, red, ring-shaped skin lesions 1–4 cm in diameter (Figures 3 and 4). The left testicle was enlarged - ultrasound showed swelling and thickening of the epididymal and scrotal tissues, increased fluid in the scrotum. In addition, the patient had persistent massive, pitting edema of the lower extremities, primarily the feet. Laboratory tests performed before admission (Table 2) showed life-threatening anemia (hemoglobin: 4.4 g/dl), red blood cell macrocytosis (MCV 111.8 fl) and significant thrombocytopenia (PLT 24,000/ul). The boy received an immediate transfusion of red blood cell concentrate and platelet cells. Additional laboratory tests demonstrated high markers of hemolysis and deep vitamin B12 deficiency. A microscopic smear of peripheral blood revealed marked anisocytosis of red blood cells, macrocytes, single megalocytes and granulocytes with nuclear hypersegmentation (Figure 5). Continuing diagnostics, viral infections: Epstein-Barr virus (EBV), cytomegalovirus (CMV), human immunodeficiency virus (HIV), hepatitis A, B, C; parasitic infections, tuberculosis and Wilson's disease were excluded. Treatment included a subcutaneous formula of vitamin B12, folic acid, and additional treatment with albumin, diuretics and

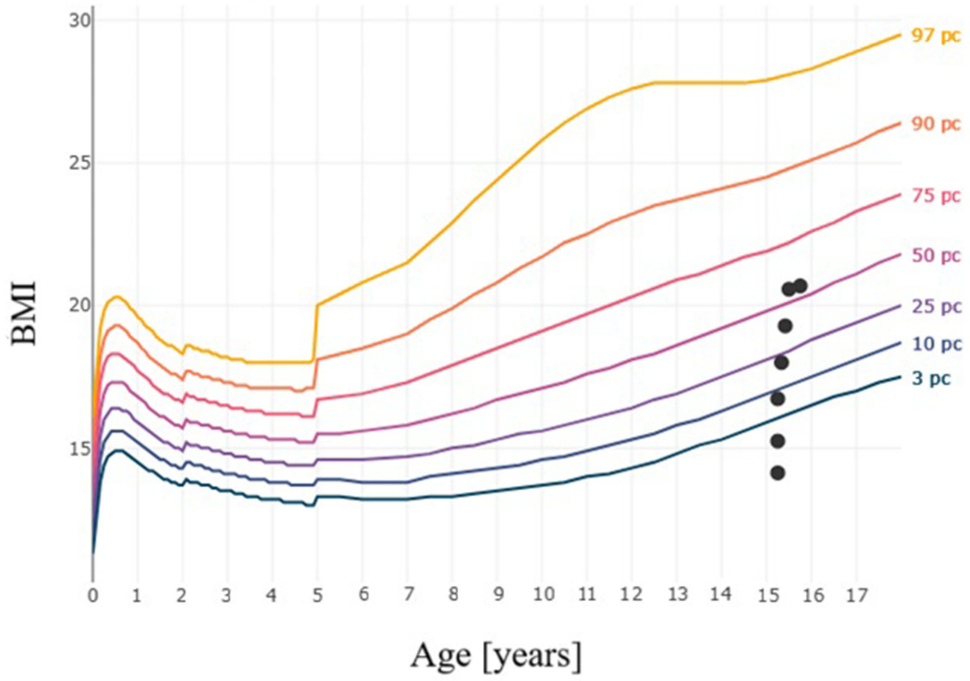

Figure 1 The percentile charts illustrate the boy's Body Mass Index (BMI) over time during his observation period at the Clinic. Based on the Polish 2010 growth references of school-aged children and adolescents.

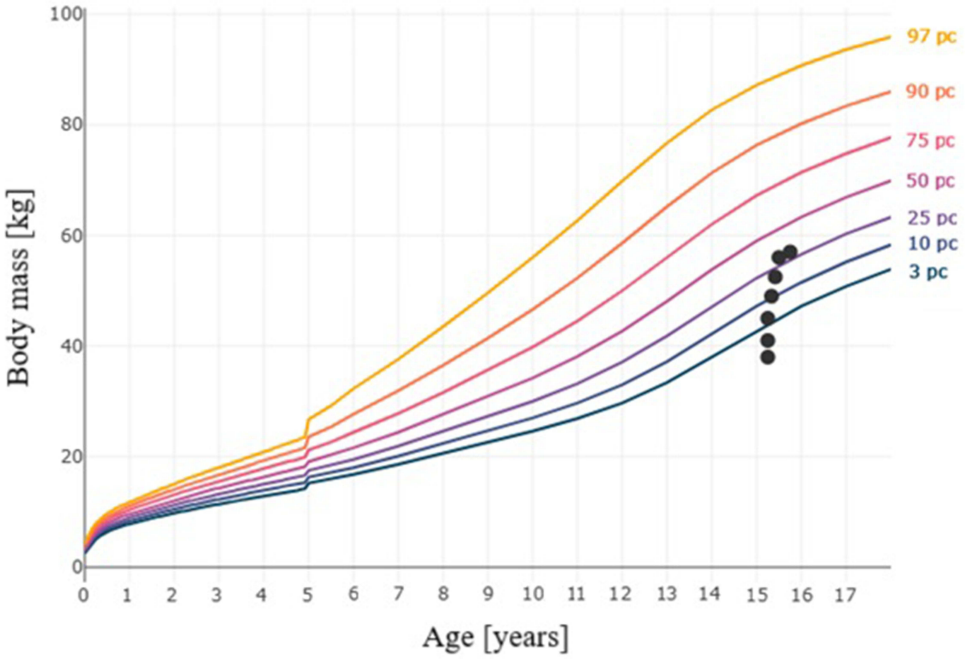

Figure 2 The percentile charts illustrate the boy's Body Mass over time during his observation period at the Clinic. Based on the Polish 2010 growth references of school-aged children and adolescents.

fluconazole due to the suspected fungal etiology of the skin lesions. Searching for the cause of the vitamin B12 deficiency during the diagnostic process, celiac disease, inflammatory bowel disease, Helicobacter Pylori infection were excluded, and tests for Addison-Biermer anemia were taken. We conducted a psychiatric consultation to verify the eating disorder, it was

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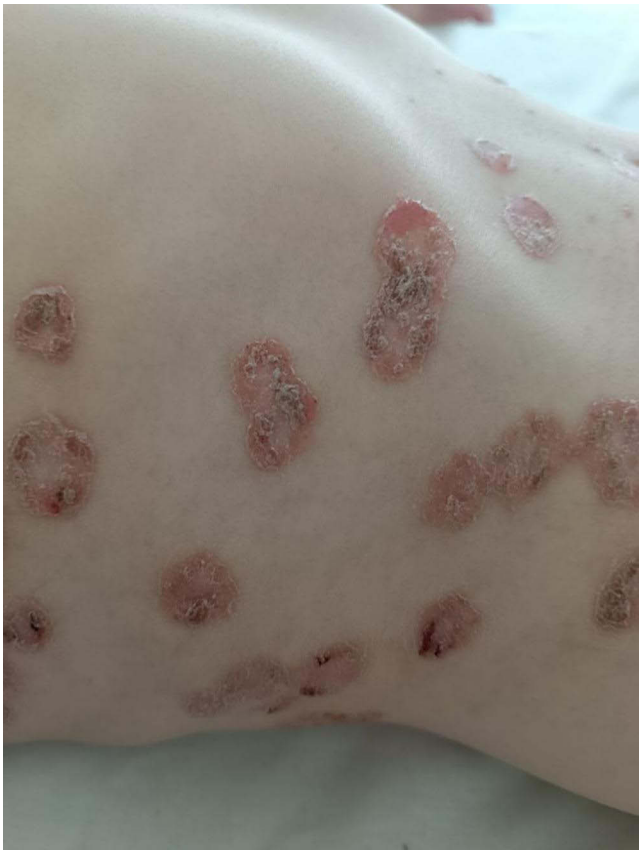

Figure 3 Diffuse, scaly, ring-shaped skin lesions covering most of the trunk. Status on admission to the Department.

found that the malnutrition and anorexia had been caused by the underlying disease. During the hospitalization the boy reported improved mental status, greater appetite for food, and his weight increased by 3 kg. In the following days, the patient's general condition improved greatly, weakness and eating disorder subsided, peripheral edema withdrew, and laboratory parameters improved (Table 2). Due to the persistence of skin lesions on the trunk and the lack of improvement after antifungal treatment after dermatological consultation, we took the scrapings from the lesions for mycological examination and we performed a skin biopsy. After nine days of hospitalization, we decided to discharge the boy from the hospital and continue follow-up care, deepening diagnosis and treatment in the outpatient clinic.

He returned for a follow-up visit seven days later. Physical examination revealed a weight gain of 4 kg and severe pitting edema in the lower extremities. Multiple annular lesions were still present but without scaling (Figures 6 and 7). A loud systolic murmur (3/6 on Levine's Scale) was heard across the precordium. Due to the recurrence of lower limb edema and the emergence of a new cardiac murmur, we decided to perform an urgent echocardiogram, which revealed no abnormalities. We added spironolactone to the treatment, as recommended by the cardiology consultant.

Complete blood count (CBC) showed moderate leukocytosis (WBC 13.42 × 10^3/μL) with a neutrophilic predominance (neutrophils 9.68 × 10^3/μL), thrombocytosis (platelet count 731,000/μL), and anemia (hemoglobin 10.3 g/dL). Biochemical investigations revealed elevated transaminase activity but no other signs of hemolysis; ionogram, coagulogram, renal parameters, and urinalysis remained normal (Table 3). The boy received a single dose of intramuscular vitamin B12.

Histopathological examination of the skin showed uneven epidermal hyperplasia, with clusters of neutrophils observed in the upper layers, leading to the formation of spongiotic pustules. The granular layer was absent, replaced by stratified parakeratotic masses abundantly filled with neutrophils. The papillary dermis exhibited edema and a mixed

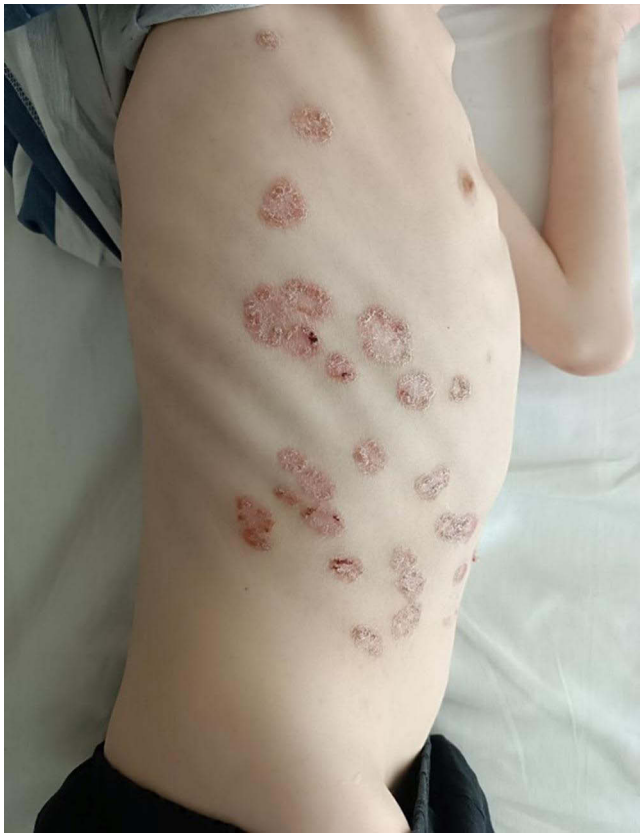

Figure 4 Extensive annular, scaly dermatoses involving the majority of the trunk. Condition upon admission to the Department.

cellular inflammatory infiltrate, consisting of lymphocytes and a considerable number of neutrophils. Additionally, a mixed inflammatory reaction with numerous eosinophils was observed around the superficial vascular plexus (Figures 8 and 9).

Table 2 Laboratory Tests Conducted on the Patient Upon Admission to the Department and Upon Discharge From the Hospital

Parameters	Values on Admission	Values on Discarge	Normal Value
Total leukocyte count (x 10^3/uL)	5.24	9.36	4.00–10.00
Differential leukocyte count			
Neutrophils (x 10^3/uL)	2.43	5.67	2.0–7.0
Lymphocytes (x 10^3/uL)	2.66	2.52	0.8–4.0
Eosinophils (x 10^3/uL)	0.04	0.26	0.02–5.0
Monocytes (x 10^3/uL)	0.11	0.79	0.12–1.2
Basophils (x 10^3/uL)	0.00	0.01	0-0.1
Hemoglobin (g/dl)	4.4	9.0	13.00–18.00
Red blood cells (x 10^6 /uL)	1.13	3.07	4.50–6.50

(*Continued*)

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Table 2 (Continued).

Parameters	Values on Admission	Values on Discarge	Normal Value
Hematocrit (%)	12.6	29.3	40.00–54.00
Mean corpuscular volume (fl)	111.8	95.4	83.00–103.00
Mean corpuscular hemoglobin (pg)	38.7	29.3	27.5–32.00
Mean Corpuscular Hemoglobin Concentration (g/dl)	34.7	30.7	32.00–36.00
Platelet count (x 10^3/uL)	24	381	150-400
Mean platelet volume (fl)	12.3	11.2	6.5–12.0
Aspartate aminotransferase (IU/L)	44	61	<46
Alanine aminotransferase (IU/L)	32	39	<47
Total bilirubin (mg/dL)	3,44	0.45	0.15–1.00
Direct bilirubin (mg/dL)	0.53	0.17	0.00–0.20
Lactate dehydrogenase (U/L)	1723	1501	135-225
Vitamin B12 (pg/mL)	97.0	492.0	138.0–652.0
Folic Acid (nmol/l)	21,7	40,00	4,76–32,39

The microscopic findings were challenging to interpret definitively, as they could correspond to psoriasis rupioides or allergic contact dermatitis with pustular eczema features. We prescribed oral amoxicillin (1 g every 8 hours for 14 days) and topical betamethasone with fusidic acid, as recommended by the dermatology consultant.

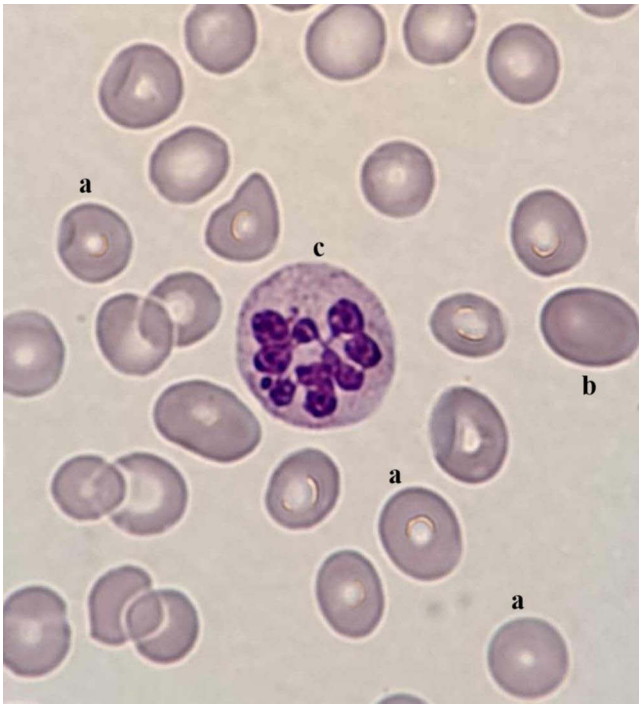

Figure 5 Peripheral blood smear (Wright-Giemsa, × 1, 000). Distinct anisocytosis of red blood cells. Macrocytes (**a**) and single megalocytes (**b**) present. Granulocytes with hypersegmented nuclei present (**c**). The white blood cell percentage pattern showed: myelocytes 1, segments 53, eosinophils 1, lymphocytes 40, stimulated lymphocytes 2, macrophages 2, plasmacells 1.

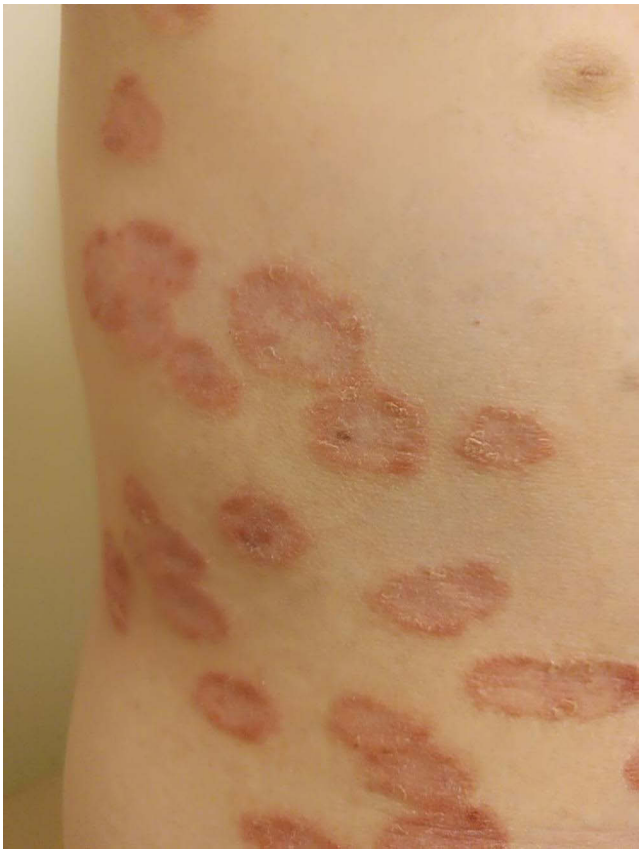

Figure 6 Multiple annular, bright red lesions without scaling, elevated above skin level. The lesions were primarily located on the skin of the chest, back, and abdomen, with single lesions appearing on the forehead, neck, and scrotum.

After two weeks, the boy returned for a follow-up visit. He had gained 4 kg, and no edema was noted on physical examination. The skin lesions had decreased in size and flattened, leaving only pink patches at skin level (Figure 10). The systolic murmur had resolved. Laboratory markers normalized, with a hemoglobin concentration of 13.2 g/dL (Table 2).

He received a single dose of intramuscular vitamin B12. The fourteen-day course of amoxicillin was completed. We recommended continued treatment of the skin lesions with topical betamethasone and fusidic acid. Further diagnostics, including gastroscopy, were planned, along with a follow-up visit in five weeks.

The boy was seen after five weeks in good general condition. He had gained 3 kg. The skin lesions had changed, becoming smoother and even paler (Figures 11 and 12). No edema was noted on physical examination, and no other abnormalities were detected. Laboratory tests revealed no significant abnormalities (Table 3).

Esophagogastroduodenoscopy was performed under general anesthesia and revealed mild gastritis (Figure 13). Additionally, the gastric walls were elastic and responsive to both insufflation and suction. The esophageal inversion and lateral walls appeared normal. The Z-line was regular and correctly positioned at the end of the gastric folds. No abnormalities were observed in the duodenal mucosa or esophagus. The urease test was negative.

Histopathological examination revealed a moderate lymphoid infiltrate in the superficial mucosal layer of the gastric antrum, consistent with chronic inactive mucositis of moderate severity. Two non-invasive tests for *Helicobacter pylori* infection were conducted, both of which returned negative results.

Given the negative outcomes of both the urease test and the non-invasive tests—and considering that amoxicillin had already been administered for dermatological lesions—we decided not to continue antibiotic treatment for gastritis. However, based on the recommendation of the gastroenterology consultant, we initiated a six-week course of proton pump inhibitors.

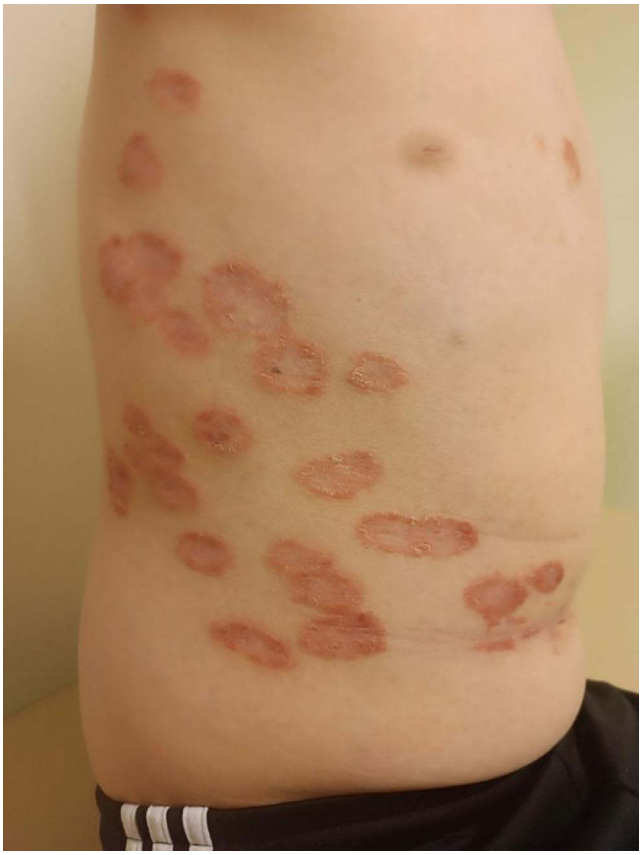

Figure 7 Numerous erythematous, annular plaques lacking desquamation, raised above the surrounding skin. They are mainly distributed over the thoracic, dorsal, and abdominal integument.

We repeated tests for anti-gastric parietal cell antibodies and antibodies against Castle's intrinsic factor, but the results remained negative.

A follow-up visit was conducted four weeks later. On physical examination, apart from slight skin discoloration (Figure 14), no abnormalities were observed. Laboratory tests also showed no pathological findings.

Table 3 The Values of Complete Blood Count and Biochemical Tests During Follow-up Visits Conducted After the Patient Has Been Discharged From the Department

Parameters	**Time Points After Discharge from the Hospital:**				**Normal Value**
	1 Week	**3 Weeks**	**8 Weeks**	**12 Weeks**	
Total leukocyte count (× 10^3/uL)	13,42	11,92	9,18	9,67	4.00–10.00
Differential leukocyte count					
Neutrophils (× 10^3/uL)	9,68	6,08	3,58	4,59	2.0–7.0
Lymphocytes (× 10^3/uL)	2,36	3,95	4,4	3,96	0.8–4.0
Eosinophils (× 10^3/uL)	0,14	0,56	0,33	0,2	0.02–5.0

(*Continued*)

Table 3 (Continued).

Parameters	Time Points After Discharge from the Hospital:				Normal Value
	1 Week	3 Weeks	8 Weeks	12 Weeks	
Monocytes (× 10^3/uL)	0,99	1,14	0,78	0,82	0.12–1.2
Basophils (× 10^3/uL)	0,2	0,16	0,08	0,08	0-0.1
Hemoglobin (g/dl)	10,3	13,2	13,9	14,9	13.00–18.00
Red blood cells (× 10^6 /uL)	3,36	4,41	4,93	5,47	4.50–6.50
Hematocrit (%)	32,5	40,4	41,1	44,2	40.00–54.00
Mean corpuscular volume (fl)	96,7	91,6	84	80,8	83.00–103.00
Mean corpuscular hemoglobin (pg)	30,7	29,2	28,2	27,2	27.5–32.00
Mean Corpuscular Hemoglobin Concentration (g/dl)	31,7	32,7	33,6	33,7	32.00–36.00
Platelet count (× 10^3/uL)	731	548	425	459	150-400
Mean platelet volume (fl)	9,9	10,1	9,6	9,4	6.5–12.0
Aspartate aminotransferase (IU/L)	175	45	22	20	<46
Alanine aminotransferase (IU/L)	192	86	15	13	<47
Total bilirubin (mg/dL)	0,37	0,31	0,26	0,26	0.15–1.00
Direct bilirubin (mg/dL)	0,22	0,19	0,11	0,15	0.00–0.20
Lactate dehydrogenase (U/L)	372	250	206	205	135-225
Vitamin B12 (pg/mL)	695	648	411	481	138.0–652.0
Folic Acid (nmol/l)	31,4	22,9	10,6	9,1	4,76–32,39

Ultimately, we diagnosed gastritis leading to severe vitamin B12 deficiency, which resulted in progressive malnutrition, neurological disorders (including visual disturbances, gait abnormalities, depressive symptoms, and anorexia), as well as profound hemolytic anemia and thrombocytopenia.

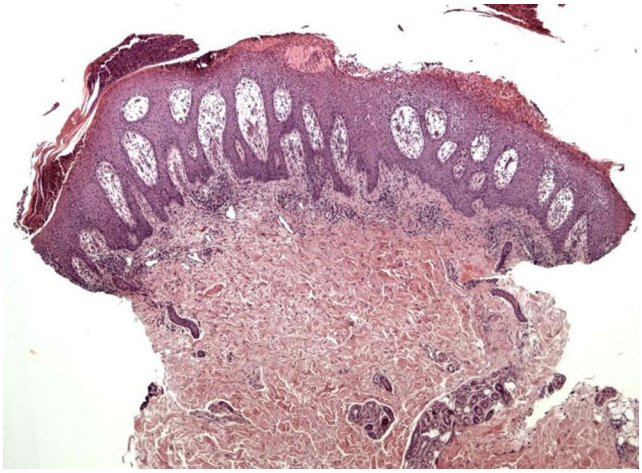

Figure 8 Histopathology of skin lesions. The hematoxylin and eosin stain.

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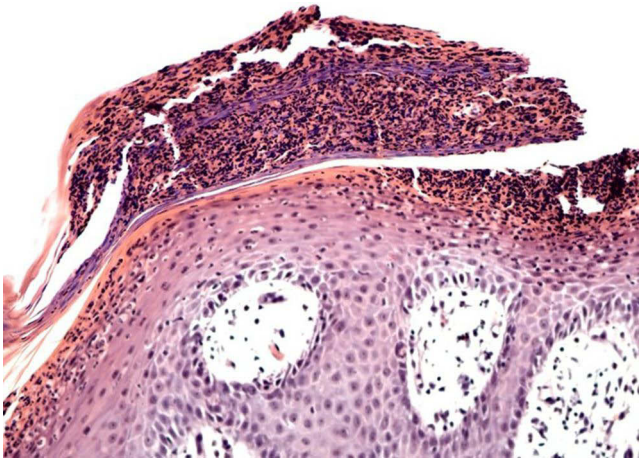

Figure 9 Histological evaluation of cutaneous lesions using hematoxylin and eosin staining.

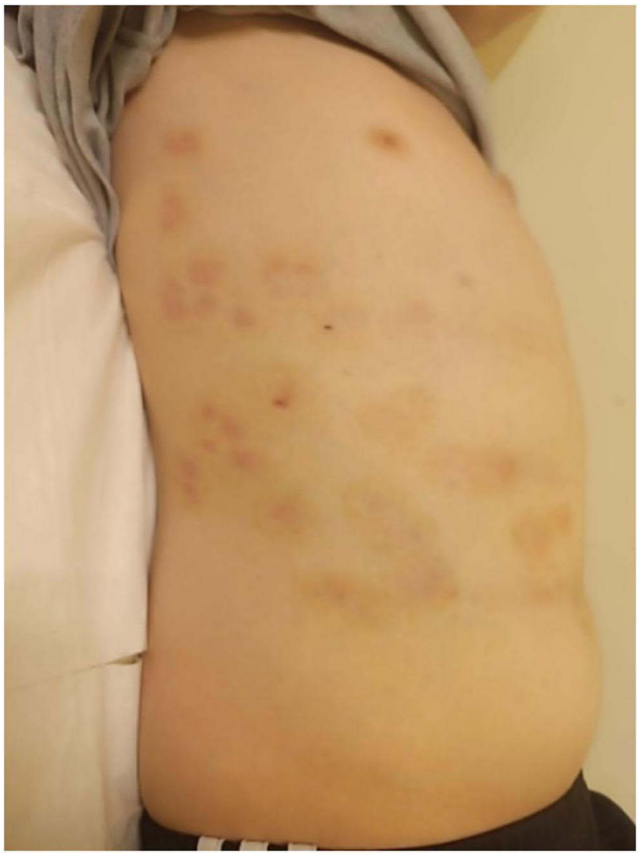

Figure 10 Multiple round, pale patches at skin level. Mostly located in the skin of the chest, back, abdomen; single macules were located in the skin of the forehead and neck.

Six months after the initial hospitalization, the boy's general condition remains excellent. He has gained nearly 25 kg over this period. No skin lesions are present, and his neurological and psychiatric symptoms have fully resolved. His complete blood count and other biochemical tests remain within normal ranges.

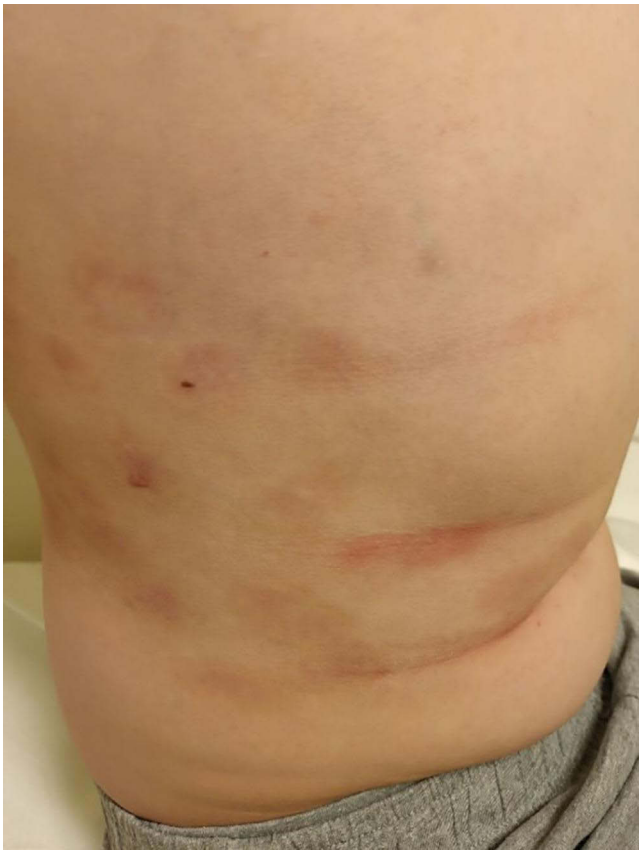

Figure 1 Multiple macules at skin level, located in the skin of the chest, back and abdomen.

However, the results of the Optical Coherence Tomography (OCT) scan revealed optic nerve disc atrophy, leading to impaired vision in the right eye.

Discussion and Conclusions

Characteristics of Vitamin B12

Vitamin B12 (cobalamin) is an essential, water-soluble micronutrient characterized by a corrin ring that chelates a central cobalt ion. Unlike most eukaryotes, animals are incapable of de novo synthesis of this vitamin; instead, its production is restricted to certain prokaryotes—primarily anaerobic bacteria and archaea. Consequently, cobalamin must be obtained exogenously, predominantly through the consumption of animal-derived foods.[4,5]

Cobalamin absorption and metabolism involve a highly regulated, multi-step process. In the gastric phase, dietary cobalamin is bound to animal-derived proteins and must be liberated by the proteolytic action of pepsin and the acidic environment maintained by gastric parietal cells. Once released, cobalamin binds to haptocorrin (R-protein), a glycoprotein secreted in saliva and gastric fluids, which stabilizes it in the harsh acidic environment of the stomach. Upon entering the duodenum, pancreatic proteases degrade haptocorrin, enabling cobalamin bind to intrinsic factor (IF), a glycoprotein secreted exclusively by gastric parietal cells. The B12-IF complex remains intact until it reaches the terminal ileum, where it is specifically recognized by the cubam receptor complex, composed of cubilin and amnionless, on the apical brush border of enterocytes. Receptor-mediated endocytosis facilitates the internalization of the complex, followed by lysosomal degradation of IF and subsequent intracellular release of free B12. Once liberated, cobalamin is exported via an ATP-dependent transporter, and binds to transcobalamin II (TCII) in the circulation, forming holotranscobalamin, the only biologically active fraction of B12 available for cellular uptake. Within cells, cobalamin is converted into its two active coenzyme forms: methylcobalamin and adenosylcobalamin.[5–7]

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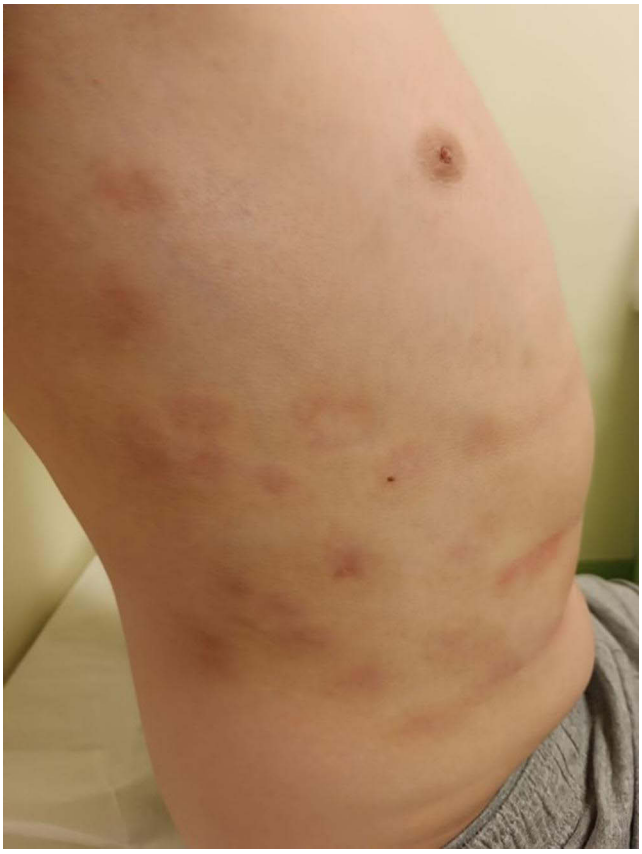

Figure 12 Numerous flat macular lesions distributed across the thoracic, dorsal, and abdominal skin.

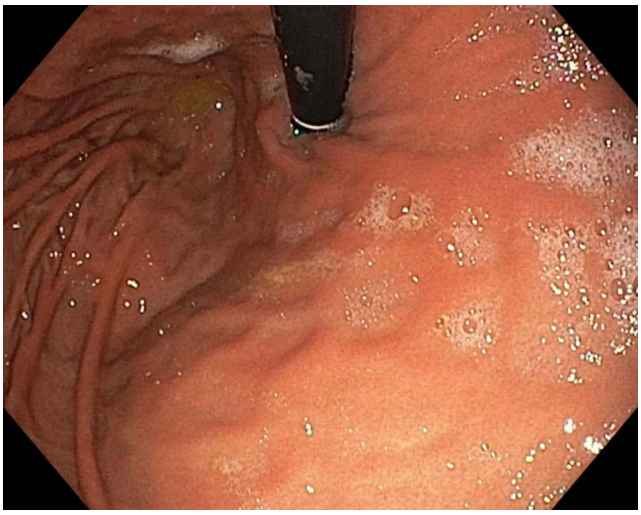

Figure 13 Gastric mucosa slightly reddened at the pylorus, with slight reddening at the peaks of the folds.

Metabolically, vitamin B12 functions as a critical cofactor in enzymatic reactions central to cellular metabolism. Its two biologically active forms serve distinct biochemical roles: methylcobalamin sustain the metabolism critical for nucleic acid synthesis and methylation reactions. Adenosylcobalamin plays a crucial role in the catabolism of odd-chain fatty acids and certain amino acids. The absorption of vitamin B12 is uniquely mediated by its binding to intrinsic factor,

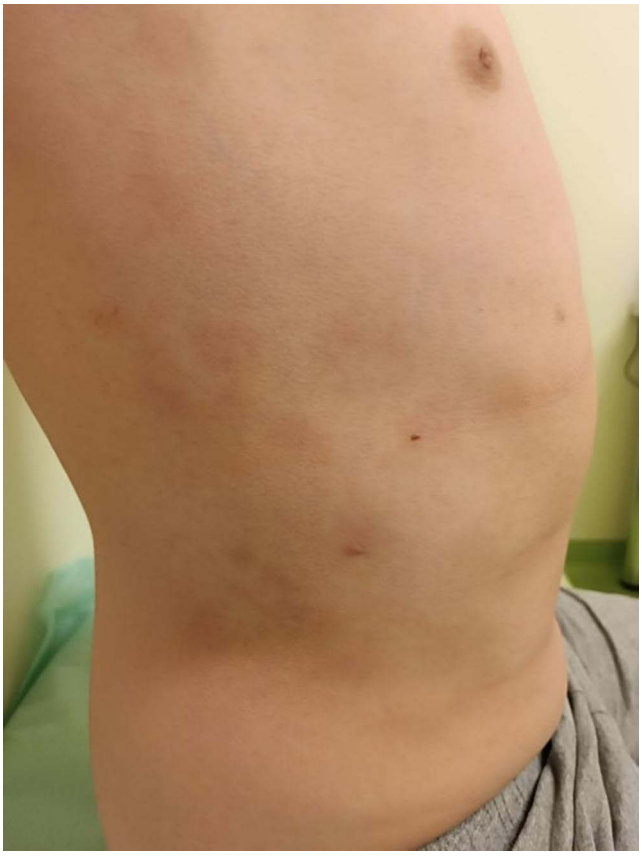

Figure 14 Discrete skin discoloration in areas of previous skin lesions.

a glycoprotein secreted by gastric parietal cells, which ensures its uptake in the terminal ileum via receptor-mediated endocytosis. Cobalamin also contributes to the formation and maintenance of the myelin sheath, which is crucial for proper nervous system function.[8,9]

Vitamin B12 is primarily found in animal-based foods, which are the most reliable sources of this essential nutrient. Liver from ruminant animals, particularly beef liver, contains the highest levels of vitamin B12, providing up to 110 µg per 100 g. Other meats, including beef, lamb, veal, and chicken, also offer significant amounts, though their vitamin B12 content varies from 0.4 to 5.2 µg per 100 g. Although raw meats are rich in vitamin B12, cooking can result in notable losses, with up to 33% of vitamin B12 being diminished through various cooking methods such as boiling and frying.[10,11] Dairy products like milk, although lower in vitamin B12 (0.3–0.4 µg per 100 g), but they contribute significantly to overall intake due to their widespread consumption. However, milk processing, including pasteurization and light exposure, can degrade vitamin B12, leading to losses of 5% to 50%.[12] Eggs, another common source, provide moderate amounts (0.9–1.4 µg per 100 g), though their bioavailability is lower compared to other animal products. Shellfish, such as oysters and mussels, also contain high concentrations of vitamin B12, sometimes exceeding 10 µg per 100 g. Fatty fish, including salmon and tuna, are also excellent sources, with vitamin B12 levels ranging from 3.0 to 8.9 µg per 100 g, and they exhibit minimal losses during cooking.[13] On the other hand, plant-based sources of vitamin B12 are either absent or contain biologically inactive forms. For example, edible algae like *Spirulina* contain pseudovitamin B12, which is not bioavailable to humans. Therefore, while animal foods are the most effective and reliable sources of vitamin B12, the bioavailability is influenced by cooking methods, food processing, and storage conditions.[6,14]

Symptoms and Differential Diagnosis

Vitamin B12 deficiency can lead to a wide range of hematological, gastrointestinal, psychiatric, and neurological disorders (Table 4). Hematological manifestations are the most common and include macrocytic anemia (MCV > 100

Table 4 Clinical Manifestation of Vitamin B12 Deficiency

Hematological Symptoms
Macrocytic anemia
Thrombocytopenia
Leukopenia
Pancytopenia
Hepatosplenomegaly
Hemolysis
Pseudo-thrombotic microangiopathy
Neurological Symptoms
Myelopathy
Peripheral neuropathy
Paresthesia
Optic nerve atrophy
Subacute combined degeneration (SCD)
Psychiatric Symptoms
Apathy
Anorexia
Memory changes
Confusion
Delirium
Hallucinations
Depression
Acute paranoid states
Catatonia
Mucocutaneous / Non-Specific Symptoms
Atrophic glossitis
Oral ulcers
Xerostomia
Recurrent aphthous stomatitis
Angular cheilitis
Dermatological Symptoms
Hyperpigmentation
Brittle hair
Dull hair texture

fL) as the primary clinical presentation.[15] As a differential diagnosis of macrocytosis, we checked the level of folic acid, which was within the norm. Symptoms associated with anemia include pallor, dyspnea, weakness, headaches, palpitations, and chest pain. A peripheral blood smear may reveal macrocytic erythrocytes, anisocytosis (variation in cell size), poikilocytosis (variation in cell morphology), and, in severe cases (eg, hematocrit < 20%), megaloblasts. Other findings may include schistocytes, Howell-Jolly bodies, and nucleated red blood cells.[16,17] Due to the numerous hematological manifestations of vitamin B12 deficiency, it can present similarly to myelodysplastic syndrome or acute leukemia. The presence of pancytopenia and hepatosplenomegaly may suggest these conditions, and a bone marrow biopsy is required for a definitive diagnosis. The bone marrow typically shows hypercellularity, with erythroid hyperplasia and a decreased myeloid-to-erythroid ratio. The presence of megaloblasts is notable, some of which may exhibit Howell-Jolly bodies and chromatin stippling. Additional features of dyserythropoiesis, such as nuclear budding, irregular nuclear membranes, and nuclear fragments, may also be observed.[15]

In vitamin B12 deficiency, ineffective erythropoiesis can lead to intramedullary hemolysis. Surviving red blood cells may have membrane abnormalities, making them susceptible to premature destruction in the spleen or circulation. This process results in hemolysis, marked by elevated lactate dehydrogenase (LDH), increased indirect (unconjugated)

bilirubin, and undetectable haptoglobin levels.[18] The secondary mechanism of hemolysis is associated with elevated levels of homocysteine. Vitamin B12 plays an essential role as a cofactor in the conversion of homocysteine to methionine and 5-methyl tetrahydrofolate to tetrahydrofolate. In the absence of sufficient vitamin B12, the body is incapable of converting homocysteine, which consequently results in elevated levels of this amino acid. Elevated homocysteine levels have been demonstrated to result in low levels of tetrahydrofolate, a crucial component of DNA synthesis. This imbalance has been shown to contribute to oxidative damage to cell membranes, including red blood cells.[19] Therefore, vitamin B12 deficiency may be misdiagnosed as other types of hemolytic anemia.

Vitamin B12 deficiency affects all blood cell types. Hypersegmented neutrophils with more than five lobes are often observed and can serve as an early indicator of megaloblastic anemia, as they are rarely seen in other conditions.[16] Thrombocytopenia and leukopenia may also be present, though they are typically not severe. In our patient, hemoglobin and platelet levels were critically low upon admission, and the patient also exhibited jaundice. As a result, Evans syndrome (a combination of autoimmune hemolytic anemia and immune thrombocytopenic purpura) was suspected. However, the anti-human globulin test was negative, and after one platelet infusion, the platelet count stabilized.

Pseudo-thrombotic microangiopathy (pseudo-TMA) is another manifestation of vitamin B12 deficiency. It is characterized by hemolytic anemia with thrombocytopenia and is similar to thrombotic thrombocytopenic purpura (TTP), which is caused by a deficiency of ADAMTS13, a metalloprotease that cleaves von Willebrand factor. The loss of ADAMTS13 leads to microthrombi and tissue ischemia, and untreated TTP has a 90% fatality rate. Pseudo-TMA involves intramedullary hemolysis, and laboratory tests show elevated LDH, low haptoglobin, thrombocytopenia, and schistocytes in the peripheral blood smear. Pseudo-TMA is rare, accounting for only 0.6% to 2.5% of vitamin B12 deficiency cases.[20,21] In our patient, both pseudo-TMA and TTP were considered; however, schistocytes were not detected, and ADAMTS13 levels remained normal. Other potential causes of jaundice, such as hepatitis A, B, C, CMV, EBV were excluded. We proceeded with the diagnosis of Wilson's disease, and subsequently, we conducted a thorough evaluation of the patient's copper and ceruloplasmin levels. These levels were found to be within the standard range. An ophthalmological examination was conducted, excluding the presence of Kayser-Fleischer rings. It was not possible to perform a 24-hour urine copper test or to measure copper levels in liver tissue. However, the boy's condition improved significantly and jaundice resolved after three doses of vitamin B12 were administered, which led to the rejection of the hypothesis that Wilson's disease was present.

Vitamin B12 deficiency can also cause a variety of neurological manifestations, including myelopathy, peripheral neuropathy, paresthesia, and optic nerve atrophy. This is due to vitamin B12's role in myelin synthesis and the incorporation of abnormal fatty acids into neuronal lipids, affecting both the central and peripheral nervous systems.[22,23] A distinctive form of demyelination caused by vitamin B12 deficiency is subacute combined degeneration (SCD), which affects the posterior and lateral columns of the spinal cord. Involvement of the brain and peripheral nerves may also occur, with severe consequences if untreated. Clinical manifestations of SCD include vibratory loss, paresthesia, ataxia, cognitive impairment, muscle weakness, and spastic paraparesis or tetraparesis.[24] Another complication of vitamin B12 deficiency is optic neuropathy, characterized by progressive, bilateral, painless vision loss associated with abnormal color vision and central or centrocecal scotomas, as well as optic nerve head changes on optical coherence tomography (OCT). This rare condition is reported in less than 1% of vitamin B12-deficient patients, and the underlying mechanism remains unclear.[25] In our patient, non-specific gait abnormalities, balance issues, and vision problems—including difficulty reading from a distance—were present for one year. The patient consulted with several specialists, including ophthalmologists and neurologists, and underwent brain MRI, which showed no significant findings. Only after one year did the OCT reveal optic nerve disc atrophy, leading to impaired vision in the right eye.

Psychiatric symptoms of vitamin B12 deficiency include apathy, anorexia, memory changes, confusion, delirium, hallucinations, delusions, depression, acute paranoid states, and even catatonia.[26,27] Depression is particularly associated with B12 deficiency.[28] Up to 28% of patients with vitamin B12 deficiency experience neuropsychiatric abnormalities even without hematological signs. Our patient experienced a 10 kg weight loss over one year, which was challenging to attribute solely to B12 deficiency. However, the patient expressed willingness to eat, and psychiatric examination revealed no signs of anorexia nervosa or other eating disorders. After receiving parenteral vitamin B12, the patient's appetite improved, and he gained 3 kg by the time of discharge. We hypothesize that weight loss was a symptom of

vitamin B12 deficiency rather than an independent cause. It is regrettable that neither the previous specialists nor the primary care physician noticed the patient's weight loss of approximately 10 kg.

Another common non-specific manifestation of vitamin B12 deficiency is atrophic glossitis, which presents as a smooth, swollen, erythematous tongue.[15] It is characterized by the partial or complete loss of primarily filiform papillae, with minor loss of fungiform papillae on the tongue's dorsal surface. Patients with glossitis often report a burning sensation, numbness, pain, and loss of taste.[29] The prevalence of vitamin B12 deficiency in patients with atrophic glossitis ranges from 5.3% to 70%.[29,30]

Dermatological manifestations of vitamin B12 deficiency can be diverse, with hyperpigmentation being a common feature. This condition primarily affects the dorsal surfaces of the hands and feet, especially areas subject to pressure, such as the terminal phalanges, knees, and elbows. In some cases, it may extend to the oral cavity. Hyperpigmentation can serve as an early indicator of vitamin B12 deficiency and is often bilaterally symmetrical. Other dermatological findings include brittle hair, dull hair texture, and oral lesions such as ulcers, xerostomia, recurrent aphthous stomatitis, and angular cheilitis. Skin pigmentation changes, hair changes, and oral or perioral lesions may occur with or without hematological and neurological symptoms.[31–33] Although a variety of cutaneous lesions have been associated with vitamin B12 deficiency, a review of the literature did not identify any similar case reports. Therefore, we hypothesize that the observed skin lesions were a consequence of a bacterial superinfection precipitated by malnutrition and dehydration.

Causes of Vitamin B12 Deficiency

Inadequate Dietary Intake

Suboptimal nutrient consumption is a well-recognized and the most common cause of vitamin B12 deficiency, particularly among individuals following vegetarian or vegan diets. Medical research consistently shows that since vitamin B12 is naturally found almost exclusively in animal-derived foods - such as meat, dairy, and eggs - those who exclude these products without incorporating fortified alternatives or supplements face a significantly higher risk of developing a deficiency. Studies indicate that insufficient consumption of B12-rich foods leads to decreased serum levels of the vitamin.[3,8,34] Furthermore, research highlights that certain populations, including older adults and individuals with limited access to nutritional education or resources, may be particullary vulnerable to inadequate B12 consumption. This underscores the need for targeted dietary interventions and supplementation strategies to prevent deficiency.[35] Inadequate dietary intake is also a major concern among individuals with psychiatric disorders, as these conditions often disrupt normal eating behaviors and compromise overall nutritional status. Patients with disorders such as major depressive disorder, schizophrenia, or bipolar disorder frequently experience appetite disturbances, diminished motivation, and cognitive impairments that hinder their ability to procure, prepare, or consume balanced meals. These challenges may lead to suboptimal intake of essential nutrients, including vitamin B12. Emerging research indicates that vitamin B12 deficiency in psychiatric populations is not merely a consequence of poor dietary habits but may also exacerbate neuropsychiatric symptoms - such as cognitive deficits, mood instability, and psychosis - potentially creating a vicious cycle.[36,37]

Malabsorption of Vitamin B12

Pernicious anemia is an autoimmune disorder characterized by impaired absorption of vitamin B12 due to intrinsic factor (IF) deficiency. Its pathophysiology typically involves the production of autoantibodies against intrinsic factor and parietal cells, leading to chronic atrophic gastritis and a decrease in gastric acid secretion. This decline in gastric acid impairs the release of vitamin B12 from dietary proteins, further contributing to malabsorption. Additionally, autoimmune destruction of parietal cells decreases intrinsic factor production, a glycoprotein essential for vitamin B12 absorption in the terminal ileum. Without sufficient intrinsic factor, vitamin B12 cannot be effectively absorbed, leading to systemic deficiency. In contrast, congenital pernicious anemia, often caused by mutations in the GIF gene, which encodes intrinsic factor, manifests in infancy or early childhood with profound vitamin B12 malabsorption, leading to severe megaloblastic anemia and developmental delays.[38–40]

Atrophic gastritis leads to vitamin B12 deficiency primarily due to the loss of gastric acid secretion and intrinsic factor production, both essential for cobalamin absorption. The progressive destruction of gastric parietal cells results in significantly reduced or absent gastric acid levels, a condition known as hypochlorhydria or achlorhydria. Gastric acid

plays a crucial role in releasing vitamin B12 from dietary proteins, allowing it to bind with haptocorrin - a transport protein that protects B12 as it moves through the stomach. However, in atrophic gastritis, the lack of gastric acid prevents the initial release of vitamin B12 from food, leading to malabsorption even before intrinsic factor becomes involved. Additionally, an alkaline gastric environment promotes bacterial overgrowth in the small intestine, which can further deplete vitamin B12 by increasing microbial competition for available cobalamin.[41–44]

Inflammatory bowel diseases, particularly Crohn's disease, contribute to vitamin B12 deficiency through several interconnected mechanisms. One of the more aggravating treatment methods for the disease is surgical removal of the terminal ileum, which is crucial for cobalamin absorption. Additionally, chronic inflammation inherent to IBD disrupts the mucosal architecture and impair the function of intrinsic factor receptors necessary for B12 uptake. Inflammation-induced mucosal damage and ulceration reduce the absorptive surface area, leading to malabsorption even in the absence of surgical intervention. Moreover, the altered gut environment in IBD, characterized by dysbiosis and bacterial overgrowth, may further exacerbate vitamin B12 deficiency, as some bacterial species can compete for or deplete cobalamin in the gastrointestinal tract. Additional factors include the effects of prolonged corticosteroid or immunosuppressive therapy, which may indirectly impair nutrient absorption by altering gut permeability and immune function.[45,46]

Helicobacter pylori infection has been implicated in the development of vitamin B12 deficiency through multiple mechanisms. Chronic gastritis induced by H. pylori can lead to atrophic changes in the gastric mucosa, resulting in decreased secretion of hydrochloric acid and intrinsic factor, both essential for vitamin B12 absorption. A study by Kadhim et al found that 64% of patients with H. pylori infection exhibited vitamin B12 deficiency, highlighting the bacterium's role in impairing cobalamin absorption.[47] Similarly, a meta-analysis conducted by Cai et al demonstrated that H. pylori-induced atrophic gastritis disrupts stomach acidification and secretion, negatively affecting serum vitamin B12 levels.[48] Eradication of H. pylori has been shown to improve vitamin B12 levels and resolve anemia in affected individuals, emphasizing the need to consider this infection in patients with unexplained vitamin B12 deficiency.[49]

Zollinger-Ellison syndrome (ZES) is characterized by gastrin-secreting tumors that cause excessive gastric acid production. This hyperacidity may impair vitamin B12 absorption, as the elevated acid levels can damage the gastric mucosa and affect the intrinsic factor function, a protein essential for vitamin B12 uptake. Additionally, the chronic use of proton pump inhibitors (PPIs) to manage acid hypersecretion in ZES patients may further contribute to vitamin B12 deficiency. A study involving 175 ZES patients undergoing long-term acid-suppressive therapy found that 21% developed vitamin B12 deficiency, with a significant correlation between elevated gastric pH levels due to PPI use and reduced vitamin B12 levels.[43,50]

Imerslund-Gräsbeck syndrome (IGS) is a rare autosomal recessive disorder characterized by selective malabsorption of vitamin B12 in the terminal ileum, leading to systemic cobalamin deficiency. This condition results from mutations in genes encoding components of the cubam receptor complex -specifically cubilin and amnionless - which are essential for the uptake of the intrinsic factor-vitamin B12 complex. The defective receptor impairs endocytosis of this complex, causing decreased vitamin B12 absorption despite normal dietary intake. Clinically, IGS typically presents in childhood with megaloblastic anemia and is frequently associated with mild proteinuria, although renal function remains largely unaffected. As detailed in a study by Kingma et al, early recognition through genetic testing and prompt initiation of parenteral vitamin B12 supplementation are crucial to prevent irreversible neurological damage and correct hematologic abnormalities. This underscores the essential role of the cubam receptor in maintaining vitamin B12 homeostasis and highlights the importance of considering IGS in the differential diagnosis of unexplained cobalamin deficiency.[51,52]

Parasitic infections, particularly those involving fish tapeworms such as *Diphyllobothrium latum*, are a well-recognized cause of vitamin B12 deficiency. This parasite, acquired through the consumption of raw or undercooked fish, competes for dietary cobalamin within the host's gastrointestinal tract. *D. latum* has a high affinity for vitamin B12, effectively sequestering it and preventing its absorption in the terminal ileum, ultimately leading to systemic cobalamin depletion. Studies have documented significantly lower serum vitamin B12 levels in patients infected with *D. latum*, with resolution of deficiency observed following appropriate anthelmintic therapy and vitamin B12 supplementation.[53]

Giardia lamblia, a flagellated protozoan responsible for giardiasis, has been implicated in vitamin B12 deficiency due to its disruptive effects on the small intestinal mucosa. The parasite adheres to and damages the epithelial lining, leading to microvillus blunting and an inflammatory response that compromises the gut's absorptive capacity. This mucosal injury not only reduces the efficiency of vitamin B12 uptake in the terminal ileum but also interferes with the proteolytic

processes required to liberate cobalamin from dietary proteins. Clinical studies, such as those conducted by Gutierrez et al, have reported that patients with chronic giardiasis may exhibit reduced serum vitamin B12 levels, resulting in hematological and neurological manifestations.[54]

Metabolic Disorders

Transcobalamin II deficiency is a rare autosomal recessive disorder resulting from mutations in *TCN2*, the gene encoding the essential plasma transport protein responsible for delivering vitamin B12 to target tissues. Under normal conditions, TCII binds cobalamin in circulation and facilitates its receptor-mediated uptake into cells, where it is converted into its active coenzyme forms. As detailed by Kose et al, even with adequate dietary intake, vitamin B12 remains unbound and is subsequently excreted, leading to a functional intracellular deficiency. This impairment triggers a cascade of metabolic disturbances, including the accumulation of methylmalonic acid and homocysteine, which contribute to the development of megaloblastic anemia.[55] Watkins and Rosenblatt further emphasize that early diagnosis through genetic testing and biochemical screening (eg, measuring holo-transcobalamin levels) is crucial, as prompt parenteral vitamin B12 supplementation can correct hematologic abnormalities and help prevent irreversible neurological damage.[56]

Inborn errors of cobalamin metabolism disrupt the synthesis of its active coenzymes, methylcobalamin and adenosylcobalamin, leading to functional vitamin B12 deficiency. These disorders are categorized into distinct complementation groups, each associated with specific genetic mutations affecting different steps in cobalamin processing. For instance, the cblC defect, the most prevalent among these disorders, is caused by a MMACHC mutation and impairs the conversion of dietary cobalamin into both coenzyme forms. This leads to the accumulation of methylmalonic acid and homocysteine, as well as decreased methionine synthesis. Clinically, this manifests as a spectrum of typical cobalamin deficiency symptoms. Clinical features of the early-onset form include a multisystemic disease affecting hematologic, neurological, ocular, renal, gastrointestinal, pulmonary, and cardiac systems. Common manifestations include epilepsy, hypotonia, nystagmus, and hemolytic uremic syndrome. The late-onset form is less common than the early-onset form. Patients may present at any time from childhood to adulthood and are often misdiagnosed. In addition to milder or absent hematological abnormalities, the clinical course is marked by behavioral and psychiatric symptoms, including rapid mental deterioration, disorientation, confusion, dementia, delirium, and psychosis. Early diagnosis through genetic testing and metabolic screening is crucial, as prompt treatment with parenteral hydroxocobalamin, often combined with other adjunct therapies, can mitigate disease progression and improve outcomes.[57–59] The causes of vitamin B12 deficiency are summarized in Table 5.

Table 5 Causes of Vitamin B12 Deficiency

Inadequate Dietary Intake
Vegeterian diet
Vegan diet
Limited access to food resources or disrupted eating behaviors
Malabsorption of Vitamin B12
Pernicious Anemia
Atrophic Gastritis
Inflammatory Bowel Disease (eg, Crohn's Disease)
Helicobacter pylori Infection
Chronic PPI use
Zollinger-Ellison Syndrome
Imerslund-Gräsbeck Syndrome
Parasitic Infections
Diphyllobothrium latum
Giardia lamblia
Metabolic Causes
Transcobalamin II Deficiency
Inborn Errors of Cobalamin Metabolism (eg mutation in MMACHC gene)

In conclusion, we present a case study of a 15-year-old male patient with hemolytic anemia, thrombocytopenia, emaciation, and a prolonged history of impaired vision and gait resulting from vitamin B12 deficiency. While food restrictions are the most common cause of vitamin B12 deficiency in children, this case highlights the rarity of chronic atrophic gastritis as an underlying condition. The article emphasizes the importance of performing a complete blood count and understanding the diverse symptoms triggered by cobalamin deficiency, including hematological, neurological, gastrointestinal, and psychiatric manifestations. Clinicians must recognize that neuropsychiatric symptoms may precede hematological manifestations, underscoring the need for comprehensive evaluation and treatment. Vitamin B12 treatment is straightforward and can effectively address all of these symptoms, often leading to significant improvement in the patient's condition.

Abbreviations

MCV, Mean Corpuscular Volume; CBC, Complete Blood Count; WBC, White Blood Cells; PLT, Platelets; BMI, Body Mass Index, EBV, Epstein-Barr Virus; CMV, Cytomegalovirus; HIV, Human Immunodeficiency Virus; LDH, Lactate Dehydrogenase; IF, Intrinsic Factor; TCII, Transcobalamin II, SCD, Subacute Combined Degeneration; Pseudo-TMA, Pseudo-Thrombotic Microangiopathy; TTP, Thrombotic Thrombocytopenic Purpura; ZES, Zollinger-Ellison Syndrome; IGS, Imerslund-Gräsbeck Syndrome; OCT, Optical Coherence Tomography; MRI, Magnetic Resonance Imaging; PPIs, Proton Pump Inhibitors; GIF, Gastric Intrinsic Factor.

Consent for Publication

Written informed consent was obtained from the patient's parents for publication the case details including the images and further using them for educational purposes.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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