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## ABSTRACT

# PECULIARITIES OF THE CLINICAL COURSE AND DIAGNOSIS OF VITAMIN B12 AND FOLATE DEFICIENCY ANEMIA IN PATIENTS WITH DIABETES MELLITUS

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**Introduction.** A typical manifestation of anemia is a decrease in the blood's hemoglobin content, which, in combination with the changes in the color index and other indicators of the blood, allows us to assume its nature. Deficiency of vitamin B12 and folic acid in patients with diabetes mellitus requires the attention of clinicians because it can be accompanied by usual clinical manifestations, but it may also disguise itself as other diseases and be pathogenetically related to them. It is extremely important to detect anemia caused by a deficiency of vitamin B12 and folic acid in time. Therefore, clinicians need to pay attention to the problem of comprehensive assessment of the condition of patients with diabetes mellitus and to the use of reliable diagnostic methods aimed at studying the status of vitamin B12 and folic acid.

**The aim of the study** was to demonstrate the peculiarities of the clinical course and the patient's own experience in the diagnosis of vitamin B12 and folate deficiency anemia in a patient with diabetes mellitus.

**Materials and methods.** A 77-year-old woman with diabetes mellitus was under our observation; at the time of hospitalization, she complained of dizziness, general weakness, episodes of loss of consciousness, yellowing of the skin and sclera, nausea, dry mouth, discomfort in the right hypochondrium, and weight loss over the last month. To establish the diagnosis, a thorough anamnesis was collected, a complex of laboratory and instrumental studies was

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performed, and related specialists consulted the patient. For the diagnosis of anemia, in addition to the usual complete blood count, the content of vitamin B12 and folic acid in the blood, as well as the concentration of methylmalonic acid in the urine and the content of homocysteine in the blood were determined.

**Results and discussion.** During the thorough examination, hyperchromic anemia, increased blood content of vitamin B12, folic acid, and homocysteine, and an increase in the concentration of methylmalonic acid in the urine were revealed. The patient had no damage to the nervous system, and damage to the gastrointestinal tract was manifested by gastric hyperplastic polyps. The patient's clinical diagnosis was verified, and treatment was prescribed, considering vitamin B12 and folate deficiency as well as the underlying pathology. A reticulocyte crisis was noted as a result of correct tactics. As a result of the treatment, her condition improved, and she was discharged from the hospital with a recommendation to continue treatment at home.

**Conclusions.** A comprehensive approach, taking into account the peculiarities of the clinical course, the determination of vitamin B12, folic acid, as well as methylmalonic acid and homocysteine are decisive for the differentiation and diagnosis of vitamin B12 and folate deficiency anemia in patients with diabetes mellitus.

**KEYWORDS:** anemia, vitamin B12 deficiency, folate deficiency, diabetes mellitus, polymorbid pathology.

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### ОСОБЛИВОСТІ КЛІНІЧНОГО ПЕРЕБІГУ ТА ДІАГНОСТИКИ В12-ФОЛІЄВОДЕФІЦИТНОЇ АНЕМІЇ У ХВОРИХ, ЯКІ СТРАЖДАЮТЬ НА ЦУКРОВИЙ ДІАБЕТ

**Вступ.** Типовим проявом анемії є зменшення вмісту гемоглобіну в крові, що в поєднанні зі змінами колірного показника та інших показників крові дозволяють припустити її характер. Дефіцит вітаміну В12 і фолієвої кислоти у хворих на цукровий діабет може супроводжуватись не лише звичними клінічними проявами, але й маскуватися під інші хвороби, а також бути патогенетично пов'язаний із ними. Вкрай важливо вчасно виявити анемію, спричинену дефіцитом вітаміну В12 і фолієвої кислоти. Відсутність своєчасної діагностики та відповідного лікування можуть мати негативні наслідки для пацієнта і навіть призвести до летального результату. Тому є потреба у приверненні уваги клініцистів до проблеми комплексної оцінки стану хворого на цукровий діабет та використання надійних методів діагностики, передбачених для вивчення статусу вітаміну В12 і фолієвої кислоти.

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**Мета дослідження.** Продемонструвати особливості перебігу та власний досвід діагностики вітамін В12-фолієводефіцитної анемії у пацієнтки, хворої на цукровий діабет.

**Матеріали і методи.** Під нашим спостереженням знаходилась жінка, 77 років, хвора на цукровий діабет, яка на момент ушпиталення скаржилася на запаморочення, загальну слабкість, епізоди втрати свідомості, пожовтіння шкіри та склер, нудоту, сухість у роті, дискомфорт у правому підребер'ї, втрату ваги, які виникли впродовж останнього місяця. Для встановлення діагнозу було ретельно зібрано анамнез, проведено комплекс лабораторно-інструментальних досліджень, а також пацієнтка консультована суміжними спеціалістами. Для діагностики анемії, окрім звичного загального аналізу крові досліджували вміст вітаміну В12 і фолієвої кислоти в крові, а також концентрацію метилмалонової кислоти в сечі та вміст гомоцистеїну в крові.

**Результати та їх обговорення.** Під час обстеження хворої виявлено гіперхромну анемію, збільшення вмісту вітаміну В12, фолієвої кислоти і гомоцистеїну в крові, та збільшення концентрації метилмалонової кислоти в сечі. У пацієнтки було відсутнє ураження нервової системи, а ураження шлунково-кишкового проявлялося гіперпластичними поліпами шлунка. Хворій верифіковано клінічний діагноз і призначено лікування з урахуванням дефіциту вітаміну В12 і фолієвої кислоти та основної патології. Було відзначено ретикулоцитарний криз як результат вірної лікувальної тактики. Стан хворої покращився і вона виписана додому з рекомендацією продовжити лікування за місцем проживання.

**Висновки.** Комплексний підхід з урахуванням особливостей клінічного перебігу, визначення вітаміну В12, фолієвої кислоти, а також метилмалонової кислоти і гомоцистеїну є визначальними для диференціації та діагностики вітамін В12-фолієводефіцитної анемії у хворих на цукровий діабет.

**КЛЮЧОВІ СЛОВА:** анемія, дефіцит вітаміну В12, дефіцит фолієвої кислоти, цукровий діабет, поліморбідна патологія.

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**ABBREVIATIONS**
N – normal range
CBC – complete blood count

## INTRODUCTION

Deficiency of vitamin B12 and folic acid in patients with diabetes mellitus is often disguised as other diseases and can have a cause-and-effect relationship with them. The high prevalence of megaloblastic anemias and the lack of timely diagnosis and appropriate treatment can have negative consequences for the patient and even be fatal. It is crucial to detect anemia caused by vitamin B12 and folic acid deficiency in time. Using reliable diagnostic methods and a comprehensive patient management approach that considers any additional health issues are necessary to prevent complications and enhance the quality of healthcare services.

**CASE REPORT.** An elderly woman who is 77 years old was taken by ambulance to the admission department of the Municipal Non-Profit Enterprise of the Lviv Regional Council "Lviv Regional Clinical Hospital". She complained of dizziness, general weakness, episodes of loss of consciousness, yellowing of the skin and sclera, nausea, dry mouth, discomfort in the right hypochondrium, and weight loss over the last month. Her blood pressure was observed to have increased to 170/100 mm Hg.

A detailed medical history revealed that the patient had been suffering from type 2 diabetes mellitus for about six years and was being treated with glucose-lowering tablets, particularly metformin. However, her blood glucose concentration was not well controlled. The patient also has been dealing with hypertension for many years.

The patient's blood test revealed an increase in total bilirubin level (54.6 (normal range (N) 4.3-20.5) μmol/L) and hyperglycemia (glucose was 22.0 (N 4.6-6.4) mmol/L). As a result, it was decided to admit the patient to the gastroenterology department for further treatment.

During the physical examination, the patient's general condition was found to be moderately severe. The patient was conscious and in an active bed position. The body structure appeared to be correct, with an asthenic constitution and a weight of 55 kg. The visible mucous membranes were icteric, and the skin had a yellowish tint. Auscultation revealed vesicular breathing over the lungs, while the heart tones were clear and rhythmic, with a heart rate of 80 beats per minute and a blood pressure of 145/85 mm Hg. The tongue was moist and clear. The right hypochondrium was sensitive, while the liver was located along the edge of the costal arch, and the spleen was not palpable. There were no peripheral edemas.

The patient underwent a comprehensive laboratory and instrumental examination. A complete blood count (CBC) revealed severe hyperchromic anemia (erythropenia (1.45 (N 3.5-4.5) × $10^{12}$/L)), reduced hemoglobin (61.0 (N 120.0-140.0) g/L), increased color index (1.26 (N 0.9-1.1)) and thrombocytopenia (33.0 (N 180.0-320.0) ×$10^{9}$/L).

As hyperglycemia was noted on admission, the patient underwent a glucose tolerance test, which showed that her capillary blood glucose level was 17.7 mmol/L fasting, 21.6 mmol/l on the second dose, and 6.5 mmol/L on the third dose (N 3.3-5.5 mmol/L).

During the laboratory blood tests, the patient was found to have hyperbilirubinemia (total bilirubin – 29.4 μmol/L; direct bilirubin – 11.7 (N<3.4) μmol/L); hypoproteinemia (total protein – 57.7 (N 64.0-83.0) g/L), hyperglycemia (11.5 mmol/L), and increase in hematocrit (0.25 (N 0.35–0.45) l/L). However, the blood transaminases, creatinine, alkaline phosphatase, amylase, and β-lipoproteins were within the normal range. Glycated hemoglobin was 7.09 (N 4.5-5.6) %. Markers of viral hepatitis B and C (antiHCV, HBcore, HBeAg, HBsAg) were negative.

On the ECG, a sinus rhythm with a normal heart rate, a horizontal position of the electrical axis of the heart, and probable left atrial hypertrophy were recorded.

An echocardiographic examination revealed signs of a hypertensive heart, mild mitral insufficiency, and fibrous sealing of the aortic valve leaflets with minimal stenosis. The total contractility of the left ventricle is preserved (ejection fraction – 60%). Diastolic dysfunction of the left ventricle of type I is present. There is no pulmonary hypertension.

During the ultrasound examination of the aortic arch branches, signs of deviations and fibromuscular dysplasia were found in both internal carotid arteries, along with initial manifestations of atherosclerotic lesions. An ultrasound of the abdominal and pelvic organs revealed severe intestinal distension and signs of uterine fibroids.

To rule out the main possible causes of anemia, the patient underwent additional studies. Barium X-ray examination showed no narrowing or filling defects. After 24 hours, the large intestine fills up until the splenic flexure, causing flatulence and slowing down intestinal permeability.

During the fibroesophagogastroduodenoscopy, gastric polyps and a hemangioma measuring approximately 0.5 cm were observed in the corner of the stomach. One of the polyps, measuring about 0.4 cm, was slightly eroded and had a thin stalk; it was located in the middle third of the stomach body along the front wall, closer to the greater curvature. The other polyp, approximately 1.0 cm in size, was not eroded and had a wide stalk; it was situated in the pylorus on the lesser curvature. A biopsy was taken from the polyps, and the histological analysis concluded that the polyps were hyperplastic. To exclude acute surgical pathology, including gastrointestinal

bleeding, which could be the cause of anemia, the patient was consulted by a surgeon, who denied this diagnosis.

Since the patient had hyperglycemia, she was consulted by an endocrinologist. Transferring the patient to insulin replacement therapy was suggested for better glucose control. Once the glucose level is maintained at an appropriate level, the patient can be returned to tablet forms of hypoglycemic drugs such as Metformin and Gliclazide.

Taking into account information from the patient's history, the results of instrumental studies, and the presence of diabetes mellitus, one of the manifestations of which is damage to the cardiovascular system, the patient underwent consultations with a cardiologist and an ophthalmologist. The cardiologist diagnosed arterial hypertension of the II degree, stage 2, in connection with which he added a fixed combination of Perindopril and Indapamide to the medical complex. The ophthalmologist diagnosed open-angle glaucoma in both eyes and prescribed Travatan eye drops, a fixed combination of Brinzolamide and Timolol eye drops, and oral Acetazolamide.

Since the patient had hyperchromic anemia, she was consulted by a neurologist to exclude damage to the nervous system, but the doctor denied this.

A consultation with a gynecologist was also scheduled, who ruled out a pathology that could cause anemia and diagnosed a posterior vaginal wall prolapse. A swab was taken from the cervical canal for cytology.

The patient's CBC showed severe anemia along with an unusual clinical presentation. Therefore, it was decided to evaluate several indicators whose changes would help make a differential diagnosis and determine the type of anemia. Among them, serum iron content (37.3 (N 7.6-26.8) μmol/L), ferritin (115.0 (N 5-148) ng/ml), vitamin B12 (153 (N 187-883) pg/ml), and folic acid (3.37 (N>5.38) ng/ml).

Furthermore, the homocysteine level in the blood (18.4 (N 3.7-11.0) μmol/L) and methylmalonic acid concentration in the urine (9.4 (N <4) mg/g creatinine) were measured. They are used to differentiate between vitamin B12 deficiency and folate deficiency anemia. The results conclusively confirmed that the patient's anemia was caused by a simultaneous deficiency of vitamin B12 and folic acid, so treatment included a daily dose of 1 mg of vitamin B12 intramuscularly and 5 mg of folic acid orally.

So, after a comprehensive evaluation that included the patient's complaints, medical history, laboratory and instrumental study results, as well as consultations with relevant specialists, the final clinical diagnosis was made: decompensated type 2 diabetes mellitus; severe anemia due to vitamin B12 and folate deficiency; gastric hyperplastic polyps; gastric hemangioma; arterial hypertension II degree, stage 2; atherosclerosis with predominant damage to the carotid arteries; open-angle glaucoma of both eyes; rectocele; and uterine fibroid.

After a comprehensive pathogenetic treatment, which included recommendations from related specialists, the patient's condition improved. A CBC was performed again on the seventh day of the hospital stay. The patient's medical results indicate a slight improvement; however, erythropenia ($1.88\times10^{12}$/L), decreased hemoglobin (67.0 g/L), and thrombocytopenia ($63.0\times10^{9}$/L) persist. In addition, the patient was found to have significant reticulocytosis (75 (N 5-15) ‰), along with hypersegmentation of neutrophil nuclei, anisocytosis, and poikilocytosis. The hematologist also noted a reticulocyte crisis.

On the twelfth day, the patient's erythrocyte count in the blood increased to $2.65\times10^{12}$/L; the hemoglobin content increased to 84.0 g/L, and the color index and the number of platelets normalized (color index – 0.95; platelets – $212\times10^{9}$/L). The reticulocyte count decreased to 30 ‰. The glucose tolerance test indicated that the glucose level in capillary blood on an empty stomach was 10.2 mmol/L, at the second withdrawal – 10.6 mmol/L, and at the third withdrawal – 6.0 mmol/L. Serum glucose was 12.0 mmol/L. The total bilirubin content in the blood returned to normal (19.2 μmol/L).

As a result, the patient was discharged from the hospital and advised to continue treatment at home.

**DISCUSSION**

Our clinical case shows that diagnosing vitamin B12 and folate deficiency anemia in patients with diabetes mellitus is not always simple and may require a special differentiated approach. The most critical role of the clinician in this scenario is to identify the pathogenetic links, which have a decisive impact on the comprehensive approach to diagnosis and, as a result, treating the underlying pathology.

Our patient had type 2 diabetes mellitus and was taking metformin for about six years. It has been found that diabetics taking metformin are more likely to be deficient in vitamin B12 than those not taking the drug [3, 15]. Vitamin B12 deficiency often depends on the dose and duration of metformin treatment [9, 10, 14, 20]. Studies show that long-term use of metformin inhibits vitamin B12 absorption, which can cause peripheral neuropathy and other complications [4, 9, 20]. There may also be an increased risk of gastroparesis, which makes it even more difficult to absorb nutrients [2]. Folic acid deficiency in diabetes also increases the risk of anemia, particularly through malabsorption and metabolic changes associated with hyperglycemia [2, 8].

The patient had jaundice and hyperbilirubinemia, which are signs of hemolytic anemia [1, 18], but the CBC indicated hyperchromic anemia, which is atypical in this

case. These findings led to a thorough diagnostic search.

Damage to the gastrointestinal tract is a characteristic sign of vitamin B12 deficiency [17]. However, in our patient, it was atypical and was manifested by gastric polyps. The presence of gastric polyps can affect the metabolism of vitamin B12, but this is mostly related to the general condition of the gastric mucosa. Polyps themselves are not a direct cause of vitamin B12 deficiency, but they often occur against the background of atrophic gastritis or other stomach pathologies that can interfere with the absorption of vitamin B12 [11].

Atrophy of the mucous membrane of the stomach (especially in atrophic gastritis) leads to a decrease in the production of the internal factor Castle, a protein necessary for the absorption of vitamin B12 in the small intestine [5]. If this process is disturbed, B12 deficiency anemia manifests. Stomach polyps can indicate similar changes in the mucous membrane, so their presence can be an indirect indicator of problems with vitamin B12 metabolism. Therefore, patients with gastric polyps and atrophic changes are recommended to check the level of vitamin B12 and, if necessary, correct its deficiency [17].

Funicular myelosis occurs much more often in vitamin B12 deficiency anemia than in folate deficiency anemia [16]. Our patient had no signs of damage to the nervous system; that is, the clinical picture of anemia is atypical. This is what makes the presented clinical case interesting.

During the examination of a patient with hyperchromic anemia, vitamin B12, and folic acid levels are usually examined. In our patient, both of these indicators were reduced. However, vitamin B12 levels can change several times a day, and the change in the content of vitamin B12 in the blood does not reflect either excess or deficiency but simply shows how much of this vitamin is floating in the plasma at the moment [19]. Thus, there is a need to utilize reliable pathogenetic markers, which can help more clearly differentiate and establish the nature of anemia. Such markers could be methylmalonic acid and homocysteine.

With the help of vitamin B12, methylmalonyl-CoA is converted to succinyl-coenzyme A, and with the participation of folic acid, homocysteine is converted to methionine. An increase in the level of methylmalonic acid in the blood or urine occurs when the level of vitamin B12 begins to decline. Measuring elevated methylmalonic acid in the blood or urine is an early indicator of vitamin B12 deficiency [12]. Additionally, analyzing methylmalonic acid in urine is a non-invasive method for detecting vitamin B12 deficiency [6, 7]. Folate deficiency anemia is indicated by an increase in blood homocysteine, provided that methylmalonic acid is within the normal range. Our patient's urinary methylmalonic acid concentration and blood homocysteine level were simultaneously elevated. Combined with changes in the CBC and a decrease in vitamin B12 and folic acid levels, this finally confirmed the diagnosis of vitamin B12 and folate deficiency anemia.

Treatment for vitamin B12 deficiency anemia typically results in a significant increase in reticulocyte count, known as a "reticulocyte crisis". This reaction indicates a positive response to the therapy. As erythropoiesis stabilizes and vitamin B12 and folic acid deficiencies are corrected, the body's demand for new red blood cells decreases. Consequently, the count of reticulocytes gradually returns to the normal range. In our clinical case, the situation was similar. As a result of the treatment, the count of reticulocytes increased sharply and then gradually began to decrease, which indicates a correctly chosen strategy.

Summarising, the results of the research obtained by using reliable methods of diagnosing vitamin B12 and folic acid deficiency, as well as a comprehensive assessment of the patient's condition, allowed us to correctly establish a detailed clinical diagnosis and prescribe a comprehensive pathogenetic treatment, which resulted in an improvement in the patient's condition and life quality.

## CONCLUSIONS

Consideration of peculiarities of clinical course and determination of vitamin B12, folic acid, methylmalonic acid, and homocysteine will make it possible to differentiate and diagnose vitamin B12 and folate deficiency anemia in patients with diabetes mellitus.

## AUTHOR CONTRIBUTIONS

All authors substantively contributed to the drafting of the initial and revised versions of this paper. They take full responsibility for the integrity of all aspects of the work.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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