https://doi.org/10.22416/1382-4376-2025-35-5-112-120
UDC 616.34-008.314.4-07

# Case Report: A Patient with Atrial Fibrillation, Functional Class III Heart Failure, and Persistent Diarrhea

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**Aim:** to demonstrate the directions of differential diagnosis of diarrheal syndrome in a polymorbid patient.
**Key points.** Diarrhea is one of the most common syndromes found in the practice of a clinician. Known pathophysiological mechanisms of diarrhea more often cover diseases that are familiar for diagnosis by gastroenterologists and infectious diseases specialists. Severe thyroid dysfunction can manifest itself as diarrhea syndrome. This article presents a clinical case of a 67-year-old male patient with severe amiodarone-induced thyrotoxicosis type 2 (with the development of thyrotoxic protein-losing enteropathy and thyrotoxic heart). The first-line drug of pharmacotherapy for this condition, prednisolone, had a timely positive effect. The patient is currently under the supervision of an endocrinologist and a cardiologist.
**Conclusion.** The presented clinical case shows the need to include thyrotoxicosis in the differential diagnostic search for the causes of diarrhea syndrome in an elderly patient, recalls the need to control the level of thyroid hormones and adjust the dose of amiodarone, considering polymorbidity and possible drug interactions.
**Keywords:** polymorbidity, watery diarrhea, amiodarone, thyrotoxicosis, glucocorticoids
**Conflict of interest:** the authors declare no conflict of interest.

**For citation:** Efremova K.B., Lapshina A.V., Bueverova E.L., Losik E.A., Skhirtladze M.R., Glukhova N.A., Tikhankova A.V., Berezina E.V., Zharkova M.S., Moshenina S.E., Ivashkin V.T. Case Report: A Patient with Atrial Fibrillation, Functional Class III Heart Failure, and Persistent Diarrhea. Russian Journal of Gastroenterology, Hepatology, Coloproctology. 2025;35(5):112–120. https://doi.org/10.22416/1382-4376-2025-35-5-112-120

## Пациент с фибрилляцией предсердий, сердечной недостаточностью III функционального класса и упорной диареей (клиническое наблюдение)

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**Цель:** продемонстрировать направления дифференциальной диагностики синдрома диареи у полиморбидного пациента.
**Основные положения.** Диарея относится к одному из наиболее частых синдромов, встречающихся в практике клинициста. Известные патофизиологические механизмы диареи чаще охватывают заболевания, которые привычны для диагностики гастроэнтерологами, инфекционистами. Синдромом диареи может манифестировать тяжелая дисфункция щитовидной железы. В данной статье представлено клиническое наблюдение пациента 67 лет с тяжелым амиодарон-индуцированным тиреотоксикозом 2-го типа (с развитием тиреотоксической энтеропатии с потерей белка и тиреотоксического сердца). Препарат первой линии фармакотерапии этого состояния, преднизолон, оказал своевременный положительный эффект. Пациент находится под наблюдением эндокринолога и кардиолога.
**Заключение.** Представленное клиническое наблюдение показывает необходимость включения тиреотоксикоза в круг дифференциально-диагностического поиска причин синдрома диареи у пожилого пациента, напоминает о необходимости контроля уровня гормонов щитовидной железы и коррекции дозы амиодарона с учетом полиморбидности и возможного лекарственного взаимодействия.
**Ключевые слова:** полиморбидность, водянистая диарея, амиодарон, тиреотоксикоз, глюкокортикостероиды
**Конфликт интересов:** авторы заявляют об отсутствии конфликта интересов.

**Для цитирования:** Ефремова К.Б., Лапшина А.В., Буеверова Е.Л., Лосик Е.А., Схиртладзе М.Р., Глухова Н.А., Тиханкова А.В., Березина Е.В., Жаркова М.С., Мошенина С.Э., Ивашкин В.Т. Пациент с фибрилляцией предсердий, сердечной недостаточностью III функционального класса и упорной диареей (клиническое наблюдение). Российский журнал гастроэнтерологии, гепатологии, колопроктологии. 2025;35(5):112–120. https://doi.org/10.22416/1382-4376-2025-35-5-112-120

## Clinical case

Patient I., 67-year-old male, was hospitalized in the V.Kh. Vasilenko Clinic of Propaedeutics of Internal Diseases, Gastroenterology, and Hepatology (Sechenovskiy University) with complaints of scanty watery stools without impurities up to 10 times a day, weight loss of 7 kg over 1 month, dyspnea at rest that worsened with minimal physical activity, irregular heartbeats, nausea, and general weakness.

From the patient's medical history, it is known that in 1994, he underwent a laparotomy and multiple blood transfusions due to a gunshot wound to the abdomen. In 1999, hepatitis C virus RNA was detected in a blood test, but no antiviral therapy was administered. In 2014, during a routine health check-up, diabetes mellitus type 2 was diagnosed, and metformin 1000 mg/day was prescribed. In November 2019, the patient first noticed complaints of dyspnea and edema; due to their progression, he was hospitalized in March 2020. During the examination, lower limb edema, ascites, hypoalbuminemia (albumin — 29 g/L), thrombocytopenia (89 × $10^9$/L), an increase in liver transaminases (aspartate aminotransferase — 75 U/L, alanine aminotransferase — 60 U/L), and hyperbilirubinemia (total bilirubin — 46.9 umol/L) were revealed. Esophagogastroduodenoscopy revealed Grade 3 esophageal varices with signs of bleeding from a linear tear in the esophageal mucosa; endoscopic hemostasis with variceal ligation was performed. Portal hypertension was confirmed by computed tomography (CT) of the abdominal cavity. The diagnosis was made: Liver cirrhosis of viral HCV etiology, Class B according to Child — Pugh scale. Portal hypertension: Grade 3 esophageal varices, splenomegaly. The severity of the edematous-ascitic syndrome subsequently decreased with diuretic therapy (furosemide 40 mg, spironolactone 25 mg). In April 2020, the patient was prescribed antiviral therapy (sofosbuvir 400 mg and velpatasvir 100 mg) and sustained virologic response was achieved 12 weeks after the end of treatment. In September 2020, due to progression of previously reported complaints, the patient was hospitalized in the Department of Hepatology. Echocardiography revealed dilated heart chambers, reduced left ventricular ejection fraction to 38 % and an increase in systolic pulmonary artery pressure to 38 mmHg. The patient was therefore transferred to the Department of Cardiology for further evaluation. Echocardiography demonstrated dilated chambers, increased left ventricular trabecularity, left ventricular ejection fraction 33 %, systolic pulmonary artery pressure 50 mmHg; with magnetic resonance imaging of the heart showed dilated chambers, Petersen criterion (ratio of noncompact to compact layer of left ventricular myocardium >2.3 in diastole), and areas of intramyocardial fibrosis; Holter electrocardiogram demonstrated ventricular premature beats with episodes of ventricular rhythm. Based on the test results the following diagnosis was made: Cardiomyopathy due to left ventricular noncompaction. Cardiac arrhythmias: ventricular premature beats with episodes of ventricular rhythm. Therapy was administrated (taking into account the cirrhosis and diabetes mellitus) with a modest positive effect: bisoprolol 1.25 mg, eplerenone 50 mg, furosemide 40 mg, valsartan 25.7 mg + sacubitril 24.3 mg, dapagliflozin 10 mg. In December 2020, the patient was placed on a transplant waiting list due to the decompensation of cirrhosis. In May 2021, as preparation for the transplant, a routine examination was performed: coronary angiography revealed no hemodynamically significant stenosis. Due to frequent ventricular premature beats (with sinus rhythm), amiodarone 200 mg was prescribed. In December 2021, orthotopic liver transplantation was performed, and tacrolimus 5 mg was added. In May 2023, dyspnea and edema progressively worsened. The patient was hospitalized in the Department of Cardiology: paroxysm of atrial fibrillation was registered (against the background of amiodarone therapy), sinus rhythm was subsequently restored spontaneously, and rivaroxaban 20 mg was added to the therapy.

Deterioration of health the patient noted since the end of August 2024, when complaints of watery stools three times per day and general weakness appeared, as a resulted of that he was hospitalized. Anemia (hemoglobin 111 g/L) and an increase in C-reactive protein to 26 mg/L were revealed. Metronidazole 500 mg 3 times per day was administered for 3 days. The patient was discharged with recommendations to continue proton pump inhibitors and antispasmodics.

Due to an increase in diarrhea frequency up to 10 times per day, alongside with general weakness, nausea, and periodic cramping abdominal pain, on September 2, 2024, the patient was admitted to the Infectious Diseases Hospital. The examination showed anemia (hemoglobin 99 g/L) and elevated C-reactive protein (26 mg/L). Fecal occult blood test was negative. Bacterial (*Salmonella, Shigella, Escherichia, Campylobacte*r), viral (*Rotavirus, Norovirus, Astrovirus, Enterovirus*), and parasitic (*Lamblia, Blastocystis*) causes of diarrhea were excluded. The condition was classified as gastroenteritis and colitis of undefined origin. Antidiarrheal, antibacterial, antispasmodic, and enzyme therapy were ineffective. The patient was discharged for outpatient treatment but was subsequently hospitalized due to the severity of his condition on September 10, 2024, to the Intensive Care Unit, and after stabilization was transferred back to the Cardiology Department of the Clinic.

On objective examination: the general condition was severe, the patient was conscious, body temperature — 36.8 °C, body mass index — 28 kg/m$^2$. The skin and visible mucous membranes were pale, moderately moist, and clear. The jugular veins were not distended. The thyroid gland was not palpable. Mild swelling of the lower limbs and feet was present. Peripheral lymph nodes were not palpable. The respiratory rate was 26 breaths per minute; oxygen saturation while breathing room air — 96 %. On auscultation: vesicular breathing, in the lower sections there were soft, moist, fine-bubble rales. The borders of relative heart dullness: right — 2 cm outward from the right edge of the sternum, left — 2 cm outward from the left midclavicular line, upper — at the level of the 2nd rib on the left. Heart sounds were arrhythmic; there was a weakening of the first heart sound at the apex, a systolic murmur at the apex radiating toward the left axillary region, and an accentuation of the second heart sound over the pulmonary artery. The heart rate was 126 beats per minute. A pulse deficit — 16 beats per minute. Arterial blood pressure — 120/70 mmHg. The abdomen was soft and non-tender upon palpation. The liver reached the edge of the costal arch; the spleen was not palpable. Signs of peritoneal irritation were absent. Percussion tenderness (tapping symptom) was negative on both sides. Urination was normal and painless. Stools were up to 10 times per day, small in volume, watery, without pathological impurities. The patient performed a 6-minute walk test with a result of 200 m, which is indicating low exercise tolerance — Functional Class III. Based on complaints, history, and physical examination, the following preliminary diagnosis was formulated: Diarrhea of undefined origin. Cardiomyopathy due to left ventricular noncompaction. Type 2 diabetes mellitus. Cardiac arrhythmia: atrial fibrillation (paroxysm of unknown duration), ventricular premature beats. Class IIB chronic heart failure, Functional Class III according to NYHA (New York Heart Association classification). Orthotopic liver transplantation due to cirrhosis secondary to chronic viral hepatitis C in 2021. Portal hypertension: Grade 3 esophageal varices, endoscopic variceal ligation in 2020, splenomegaly. Antiviral therapy with sustained virologic response.

Taking into account the patient's main complaint of frequent, small-volume, watery stools up to 10 times per day, the differential diagnosis included disorders based on four pathophysiologic mechanisms of diarrhea: secretory (*Clostridioides difficile* (*Cl. difficile*)-associated, cytomegalovirus-associated), hyperkinetic (drug-induced — the patient was receiving tacrolimus and amiodarone), exudative (microscopic colitis), and osmotic (pancreatic insufficiency).

General blood analysis revealed normochromic anemia of mild severity (erythrocytes — 3.32 × 10$^{12}$/L, hemoglobin — 102 g/L, color index — 0.92) and leukopenia (2.52 × 10$^9$/L). Serum biochemical analysis demonstrated hyperglycemia (8.54 mmol/L), hypoproteinemia (total protein — 55 g/L, albumin — 30.3 g/L), hyperuricemia (uric acid — 506.5 μmol/L), slight hyperbilirubinemia (total bilirubin — 24.1 μmol/L, direct bilirubin — 6.5 μmol/L), iron deficiency (iron — 4.2 μmol/L, transferrin — 1.2 g/L), a decrease in amylase (17.3 U/L), and an increase in C-reactive protein (41.9 mg/L) and fibrinogen (4.33 g/L). The glomerular filtration rate is reduced (52 mL/min/1.73 m$^2$, which corresponds to Stage 3 chronic kidney disease). There was also a significant increase in the level of the N-terminal precursor of the brain natriuretic peptide (NT-proBNP 25,738 pg/mL). Troponin T was within normal limits. General urine analysis showed glucosuria (the patient is receiving sodium-glucose cotransporter 2 inhibitor dapagliflozin). Stool analysis revealed liquid consistency with small amounts of mucus and neutral fat. The result of a stool test for toxins A and B of *Cl. difficile* was negative. Fecal pancreas elastase was within normal range. Polymerase chain reaction did not detect cytomegalovirus DNA in blood cells.

According to instrumental studies: Holter-ECG — atrial fibrillation with a ventricular rate ranging from 82 to 173 bpm, 10,514 ventricular premature beats, 6 runs of ventricular tachycardia, no diagnostically significant ST segment deviations; EchoCG — dilation of the chambers, predominantly the atria (left atrium — 117 mL, right atrium — 125 mL), increased trabecularity in the

mid and apical segments of the left ventricular wall, left ventricular ejection fraction — 37 %, systolic pulmonary artery pressure — 50 mmHg, Grade 2 mitral regurgitation, Grade 1 tricuspid regurgitation, and diffuse hypokinesis. Ultrasound and CT scan of the abdominal cavity revealed diffuse abnormalities in the liver consistent with steatosis; atrophy of the pancreas, without focal abnormalities; the intestinal walls were not changed. Endoscopic appearance was without organic pathology, and colonic mucosal biopsy revealed no structural or inflammatory abnormalities. No morphological signs of microscopic colitis were found in the examined material.

The patient had been taking amiodarone at a dose of 200 mg per day for more than 3 years, which, considering the composition of the medication, meant a daily intake of approximately 75 mg of organic iodine and 6 mg of inorganic iodine. This significantly exceeds the average daily requirement for an adult (150 μg of iodine), which prompted an examination of the thyroid gland. Significant serum abnormalities were found, including a reduced thyrotropin (TSH) level (<0.005 μIU/mL), a high free triiodothyronine (T3) level (up to 29.6 pmol/L), and an exceedingly high free thyroxine (T4) level (above 100 pmol/L). Antibodies to the TSH receptor were within normal limits. Ultrasound of the thyroid gland revealed a lesion in the right lobe with destruction of its structure, and color Doppler mapping demonstrated diffusely reduced vascularization.

## Discussion

The presence of signs of systemic inflammatory response syndrome (tachypnea, tachycardia, and leukopenia) and laboratory indicators of systemic inflammation (elevated C-reactive protein, uric acid, and fibrinogen) primarily required the investigation for an infectious cause of diarrhea. Given the available previous diagnostic data, we considered a possible clostridial infection, as the patient had several risk factors: age over 65, the presence of chronic kidney disease, recent hospitalization, and antibiotic use within the last three months. However, this infection was not confirmed, in accordance with the 2023 guidelines [1]. The conduction of a hydrogen breath test to exclude small intestinal bacterial overgrowth was not feasible due to the severity of the patient's condition. Furthermore, considering the lifelong immunosuppression required after liver transplantation with tacrolimus, the patient belongs to a high-risk group for cytomegalovirus reactivation [2]. Cytomegalovirus is known to have tropism for endothelial cells in many organs, including the gastrointestinal tract. However, cytomegalovirus etiology of diarrhea was also excluded. Thus, a secretory mechanism of diarrhea in this patient was ruled out.

The second pathophysiological mechanism of diarrhea syndrome is exudative. Among all possible causes of this type of diarrhea, considering the watery consistency, episodes of cramping pain, weight loss, and the patient's advanced age (despite being male, a group in which this condition is significantly less common than in females), microscopic colitis comes to the upfront. As is well known, it is represented by two main forms: collagenous and lymphocytic. The primary diagnostic criterion is the result of histological examination of colonic mucosal biopsies, even in the presence of a normal endoscopic picture [3]. This diagnosis was also ruled out.

An osmotic mechanism of diarrhea was likewise unlikely. Exocrine pancreatic insufficiency was excluded primarily based on a detailed assessment of the main complaint (the symptoms were not typical for this condition, as hyperosmolar diarrhea is characterized by polyfecalia and steatorrhea) and a normal level of fecal pancreatic elastase, despite CT findings of pancreatic hypotrophy and decreased serum amylase level. In diabetes mellitus, neuropathy of the enteric nervous system may develop, and the most common manifestations are constipation and gastroparesis [4, 5].

Thus, three pathophysiological mechanisms of diarrhea — secretory, exudative, and osmotic — were excluded. Considering the patient's long-term use of the antiarrhythmic drug amiodarone, a hyperkinetic mechanism of diarrhea had to be considered. In addition, we also evaluated the possibility of drug interactions.

The use of calcineurin inhibitors (our patient is receiving tacrolimus) represents a core component of modern immunosuppressive therapy following solid organ transplantation. Tacrolimus is actively metabolized in the liver, primarily by the cytochrome P450 system enzyme CYP3A4, and is also a substrate of the drug transporter P-glycoprotein (Pgp). It is known that these same metabolic pathways are involved in the elimination of 40–60 % of all drugs used in clinical practice, which necessitates a clear understanding of pharmacokinetics and potential drug interactions in managing post-transplant patients [6]. The use of CYP3A or Pgp inhibitors in organ transplant recipients may lead to elevated serum levels of the immunosuppressant, whereas administration of CYP3A inducers may lower the immunosuppressant concentration below the therapeutic threshold and result in organ rejection [7].

Tacrolimus is also extensively metabolized in the intestinal wall. One of the common side effects of this drug, as stated in the prescribing information, is diarrhea. Linking the patient's frequent watery stools to immunosuppressive therapy is challenging, as the duration of tacrolimus use far exceeds the onset of diarrhea. However, it is important to remember that a bidirectional relationship exists between immunosuppressive drugs and the gut microbiota [8]. A 2024 pilot study by A.L. Degraeve et al., involving kidney transplant recipients, demonstrated the influence of tacrolimus pharmacokinetics on gut microbial diversity, contributing to the development of dysbiosis. Conversely, microbial metabolites produced within the altered intestinal landscape may contribute to intraindividual variability in tacrolimus plasma concentrations [9, 10].

Currently, there is not enough data about interactions between tacrolimus and amiodarone, which are both lipophilic agents with potential hepatotropic effects. In our patient, amiodarone (also a CYP3A4 inhibitor) may have contributed to elevated serum concentrations of tacrolimus. The authors of the previously published reports of hepatotoxicity associated with tacrolimus emphasize the need for close monitoring of its serum levels and dose adjustment when co-administered with amiodarone in order to prevent drug-induced liver injury [11, 12].

Amiodarone is an antiarrhythmic agent structurally similar to thyroxine, thyroid gland hormone. Administration of a standard dose of the drug delivers an amount of iodine to the body that exceeds the daily requirement for this micronutrient by more than 100 times. As a result, amiodarone and its metabolites exert a direct, dose-dependent cytotoxic effect on the follicular cells of the thyroid gland, leading to either hypo- or hyperthyroidism. Amiodarone-induced thyrotoxicosis is more common in iodine-deficient regions and occurs more frequently in men than in women. Thyrotoxicosis can develop at any time during amiodarone therapy and even several months after discontinuation.

Two types of the condition are recognized. Type 1 develops as a result of excessive uncontrolled overproduction of thyroid hormones due to excessive iodine intake. This type typically develops in patients with one or more thyroid nodules ≥1.5–2 cm or with latent Graves disease. Type 2 amiodarone-induced thyrotoxicosis is essentially a destructive thyroiditis associated with iodine and/or amiodarone, during which preformed thyroid hormones are released into the bloodstream.

The main test used for differentiating between types 1 and 2 amiodarone-induced thyrotoxicosis is color Doppler mapping, as conventional ultrasound of thyroid gland is not informative in the differential diagnosis of amiodarone-induced thyrotoxicosis [13]. The treatment of thyrotoxicosis should begin immediately after detection. Discontinuation of amiodarone is recommended, except in cases where the drug effectively controls the arrhythmias for which it was prescribed. Type 1 amiodarone-induced thyrotoxicosis is managed with antithyroid medications (e.g., thiamazole), whereas type 2 is treated with glucocorticoids, such as prednisolone. Before initiating amiodarone therapy and every 6 months thereafter, it is necessary to monitor TSH levels [14].

In our patient, the clinical picture is consistent with type 2 amiodarone-induced thyrotoxicosis based on long-term amiodarone use, laboratory findings (suppressed TSH, elevated free T4 and T3 levels, and normal TSH receptor antibody levels), and thyroid ultrasound results (a focus of tissue destruction, absence of hypervascularity in color Doppler mapping). Treatment with prednisolone at a dose of 30 mg/day for 12 weeks is indicated. After normalization of peripheral thyroid hormone levels, the dose should be gradually tapered until complete discontinuation, considering the risk of thyrotoxicosis recurrence. After glucocorticoids withdrawal, type 2 amiodarone-induced thyrotoxicosis may resolve with restoration of euthyroidism; however, hypothyroidism may occasionally develop, necessitating continued TSH monitoring. The patient has been informed about the need for ongoing follow-up with an endocrinologist.

Given the clinical presentation and the results of laboratory and instrumental investigations, the patient was diagnosed with: Combined conditions: 1. Amiodarone-induced thyrotoxicosis type 2. 2. Cardiomyopathy due to left ventricular noncompaction. Complications of the primary condition: Thyrotoxic protein-losing enteropathy. Thyrotoxic heart. Cardiac arrhythmias: atrial fibrillation (tachysystolic form), ventricular extrasystole, nonsustained ventricular tachycardia. Chronic heart failure Stage IIB, NYHA Functional Class III. Chronic kidney disease Stage 3 (glomerular filtration rate — 52 mL/min/1.73 $m^2$). Comorbidities: Type 2 diabetes mellitus. Orthotopic liver transplantation due to cirrhosis secondary to chronic viral hepatitis C in 2021. Portal hypertension: Grade 3 esophageal varices, endoscopic variceal ligation in 2020, splenomegaly. Antiviral therapy (sofosbuvir 400 mg and velpatasvir 100 mg) with achievement of sustained virologic response.

The patient was prescribed hormonal therapy with oral prednisolone 30 mg/day. Concurrent treatment of chronic heart failure, type 3

diabetes mellitus, and arrhythmias was continued (eplerenone 25 mg/day, valsartan 25.7 mg + sacubitril 24.3 mg, dapagliflozin 10 mg, bisoprolol 5 mg). After two weeks of treatment, the significant clinical improvement was observed: stool became mushy in consistency and decreased to 3 times per day; resting dyspnea resolved; exercise tolerance improved (6-minute walk test: 350 m, NYHA Functional Class II); general weakness diminished; serum free T3 and T4 levels decreased (4.8 pmol/L and 33 pmol/L, respectively). One week later, thyroid hormone levels normalized, prompting a gradual tapering of prednisolone. Inflammatory markers, NT-proBNP levels, and hemoglobin improved. ECG showed normosystolic atrial fibrillation with isolated ventricular extrasystoles. Echocardiography demonstrated improvement of left ventricular ejection fraction to 44 % and a reduction of systolic pulmonary artery pressure to 40 mmHg. The patient was discharged in stable condition, he now continues treatment under the supervision of an endocrinologist and cardiologist.

This case is notable for the development of severe amiodarone-induced conditions necessitating rapid resolution of thyrotoxicosis, including thyrotoxic protein-losing enteropathy and thyrotoxic heart (heart failure decompensation, tachysystolic atrial fibrillation, significant ventricular ectopy, and the emergence of a potentially life-threatening arrhythmia — six episodes of non-sustained ventricular tachycardia within 24 hours) in a patient with a complex cardiovascular history (arrhythmias, chamber dilation, myocardial non-compaction, chronic heart failure) and prior liver transplantation for decompensated cirrhosis.

Specific risk factors for type 2 amiodarone-induced thyrotoxicosis remain undefined. A recent systematic review and meta-analysis by F. Rahimi-Bashar et al. (2023) reported a high prevalence of hyperthyroidism (11.61 %; 95 % confidence interval: 7.20–16.02) in patients with chamber dilation and chronic heart failure receiving amiodarone for arrhythmia management [15]. Prednisolone is the first-line treatment for severe type 2 amiodarone-induced thyrotoxicosis due to its ability to suppress cytotoxic reactions, exert anti-inflammatory and membrane-stabilizing effects, and inhibit the peripheral conversion of T4 to T3 by blocking 5'-deiodinase of type 1 activity.

## Conclusion

There are numerous causes of diarrhea. Type 2 amiodarone-induced thyrotoxicosis may manifest with diarrhea. This case highlights the various directions of differential diagnosis for diarrheal syndrome in elderly patients and reminds clinicians of the need to monitor thyroid hormone levels and adjust antiarrhythmic therapy with amiodarone, taking into account comorbidities and potential drug interactions, especially in patients with chamber dilation and chronic heart failure. Timely diagnosis and treatment of severe thyroid dysfunction caused by the cumulative cytotoxic effects of long-term amiodarone use in patients with severe cardiovascular disease is crucial for prognosis.

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Submitted: 26.02.2025 Accepted: 30.05.2025 Published: 31.10.2025
Поступила: 26.02.2025 Принята: 30.05.2025 Опубликована: 31.10.2025