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A challenging diagnosis of hereditary microspherocytosis (Minkowski-Chauffard disease) in a child (a case report)

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Hereditary microspherocytosis (HM) is an inherited hemolytic anemia associated with erythrocyte membrane abnormalities which should be suspected in patients with a triad of symptoms: anemia, jaundice, and splenomegaly. The distinct clinical manifestations may not appear until a certain age, resulting in many undiagnosed mild-to-moderate forms of HM. Although modern technology allows to detect genetic mutations for HM confirmation, many issues remain largely unresolved and need to be addressed.

The aim: to analyze a complex clinical case of HM in a child with a long-term diagnostic stage to raise awareness among physicians about this pathology.

The **clinical case** of a 17-year-old boy with a clinical diagnosis of «Hereditary microspherocytosis, crisis course, complicated by secondary chronic calculous cholecystitis» was discussed. Clinical and paraclinical findings were analyzed. The medical case describes HM in the boy who presented with the first symptoms of anemia at the age of 3 years, and manifestations of jaundice syndrome with hyperbilirubinemia, hepatomegaly debuted only at the age of 12 years. Such features of the disease course have translated to diagnostic delay of HM and the development of calculous cholecystitis as a complication.

Conclusions. Currently, mild forms of hereditary microspherocytosis are underdiagnosed. Mild and moderately severe course of hereditary microspherocytosis, apart from jaundice and moderate splenomegaly, can be manifested by cutoff hemoglobin values, making it difficult to timely diagnose primary disease and its complications. Since the most common complication of hereditary microspherocytosis is gallstone disease, regular ultrasound examinations of the gallbladder and monitoring of the hepatobiliary system are the best imaging modalities for patients even in the absence of overt hemolysis. In case of conservative therapy ineffectiveness, it is necessary to consider the issue of performing a complete or partial splenectomy, and in the presence of a complication in the form of calculous cholecystitis, it should be combined with cholecystectomy. The analyzed clinical case is a demonstrative example of underdiagnosed mild hereditary microspherocytosis complicated by secondary chronic calculous cholecystitis.

The research was carried out in accordance with the principles of the Declaration of Helsinki. The informed consent of the patients was obtained for the study.

The authors have no conflicts of interest to declare.

Keywords: hereditary microspherocytosis, Minkowski-Chauffard disease, jaundice, children.

Складний випадок спадкового мікросфероцитозу Мінковського-Шоффара в дитини (клінічне спостереження)

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Спадковий мікросфероцитоз – спадкова гемолітична анемія, пов'язана з порушенням мембрани еритроцитів, яку слід запідозрити в пацієнтів із тріадою симптомів: анемією, жовтяницею та спленомегалією. Відсутність виражених клінічних симптомів до певного віку призводить до великої кількості недіагностованих легких/середніх форм спадкового мікросфероцитозу. Хоча сучасні технології дають змогу виявляти генетичні мутації, які підтверджують спадковий мікросфероцитоз, проте багато питань залишаються невирішеними та досліджуються.

Мета: проаналізувати складний клінічний випадок спадкового мікросфероцитозу в дитини з довготривалим діагностичним етапом для покращення обізнаності лікарів про цю патологію.

Розглянуто **клінічний випадок** хлопчика 17 років із клінічним діагнозом «Спадковий мікросфероцитоз, кризовий перебіг, ускладнений вторинним хронічним калькульозним холециститом». Проведений аналіз клінічного та параклінічного обстеження. Перші симптоми анемії в хлопчика з'явились у віці трьох років, а прояви жовтяничного синдрому з гіпербілірубінемією, гепатомегалією дебютували лише у віці 12 років. Такі особливості перебігу захворювання призвели до відтермінування своєчасної діагностики спадкового мікросфероцитозу та розвитку ускладнень як калькульозного холециститу.

Висновки. На теперішній час має місце гіподіагностика нетяжких форм перебігу спадкового мікросфероцитозу. Легкий та середньотяжкий перебіг спадкового мікросфероцитозу, окрім жовтяниці, помірної спленомегалії, може проявлятися пограничним значенням рівня гемоглобіну, що утруднює своєчасну діагностику основного захворювання та його ускладнень. Оскільки найпоширенішим ускладненням спадкового мікросфероцитозу є жовчнокам'яна хвороба, пацієнти навіть за відсутності важкого гемолізу потребують регулярного проведення ультразвукового дослідження жовчного міхура, моніторингу стану гепатобіліарної системи. У разі неефективності консервативної терапії необхідно розглянути питання про проведення повної або часткової спленектомії, а за наявності ускладнення як калькульозного холециститу – поєднати її з холецистектомією. Проаналізований клінічний випадок спадкового мікросфероцитозу є яскравим прикладом гіподіагностики легкого перебігу спадкового мікросфероцитозу, ускладненого вторинним хронічним калькульозним холециститом.

Дослідження виконано відповідно до принципів Гельсінської декларації. На проведення дослідження отримано інформовану згоду.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: спадковий мікросфероцитоз Мінковського-Шоффара, жовтяниця, діти.

Introduction

Hereditary microspherocytosis (HM) is the most common non-immune hemolytic anemia with an incidence of 1:2000–5000 in the Caucasian population. However, the prevalence may be higher due to undiagnosed mild-to-moderate forms. HM is a heterogeneous group of hereditary anemias with a wide spectrum of clinical severity, ranging from asymptomatic to severe transfusion-dependent forms, which can occur even within the same family [1,5,6].

HM is caused by mutations in the genes encoding erythrocyte membrane proteins and is mainly inherited in an autosomal dominant manner [11], but in 25% of cases, it is inherited in a non-dominant (autosomal recessive) pattern [10]. There are 5 genes associated with HM, including α-spectrin (SPTA1), β-spectrin (SPTB), ankyrin (ANK1), band3 (SLC4A1), and protein 4.2 (EPB42), which are involved in the interaction between the erythrocyte membrane and the lipid bilayer. Mutations in one or more HM-associated genes can cause a membrane protein deficiency, resulting in HM [3,8].

Variable disease severity is a characteristic feature of HM and at the same time brings about difficulties in the diagnosis [12]. A study in Turkey was conducted and enrolled 65 children aged between 15 days and 17 years, among whom 20% were diagnosed with mild HM, 55.4% – with moderate HM, and 24.6% – with severe HM; 13.8% showed aplastic crisis, none of the children developed megaloblastic crisis, and cholelithiasis was diagnosed in 30.8% of patients [7]. Jaundice, which is one of the principal clinical manifestations, may be the only symptom of the disease for a long time, and physicians have to come an arduous way to make a correct final diagnosis by ruling out other hereditary or acquired chronic diseases [13].

The aim of the study is to analyze a complex clinical case of hereditary microspherocytosis in a child with a long-term diagnostic stage to raise awareness among physicians about this pathology.

Clinical case

The medical case of a 17-year-old *boy Ya.*, who was on examinations and treatment at the Community Enterprise «Regional Medical Center for Family Health», DRC» (RMCFH) with a clinical diagnosis: «HM, crisis course; complication: secondary chronic calculous cholecystitis; concurrent diagnosis: gallbladder polyp» was discussed. Clinical and paraclinical findings were analyzed.

The study was performed following the principles of the Declaration of Helsinki. The study protocol was approved by the Local Medical Ethics Commission of RMCFH. The informed consent to participate in the study was obtained from the child and his parents.

The child presented to the hospital with complaints of right-sided abdominal pain, weakness, fatigue, jaundice of the skin and mucous membranes.

Past medical history revealed that he was born at a gestational age of 39 weeks by normal spontaneous vaginal delivery with a birth weight of 3100 g, a birth height of 51 cm from gravida 1 para 1 mother diagnosed with mild anemia during pregnancy. The child got about 4 episodes of acute respiratory diseases per year and was age-appropriately vaccinated according to the National Immunization Schedule. The mother provided information about a positive family history including a father who was anemic since childhood. However, a more detailed history-taking was impossible as the father lived away from them. The boy had a personal history of allergic reactions to ascorutin and heparin occurred as dermatological manifestations.

According to the present medical history, the child debuted with mild normochromic anemia and abdominal pain at the age of 3 years. A preliminary diagnosis was made at that time «Functional disease of the gastrointestinal tract», and symptomatic treatment was prescribed. A week later, the boy was admitted to a City Hospital with a diagnosis of acute respiratory infection and mild iron deficiency anemia. Because of the clinical manifestations, the child was prescribed symptomatic treatment for acute respiratory infection and iron-chelating agents for anemia. Following this, his condition improved, and his hemoglobin (Hb) level was normalized. Later on, at the age of 5 years, the boy was hospitalized with a diagnosis of right-sided focal community-acquired pneumonia. A complete blood count (CBC) showed severe anemia (HB – 65 g/l), and an iron preparation was prescribed for treatment, which the child continued to receive after discharge for 14 days with a total duration of 1 month. Outpatient CBC was monitored periodically, Hb levels were within normal ranges (129–144 g/l). Overall, the boy's condition was relatively satisfactory until the age of 12 years.

At 12 years of age, the child complained of a bitter taste in the mouth, periodic abdominal pain that occurred on an empty stomach and subsided after eating; flatulence, loose stools; pruritus, and jaundice.

Table 1

Dynamics of the complete blood count parameters

Parameter	Reference values	Age of the child					
		3 years	3 years and 2 months	5 years	12 years	17.5 years	17 years and 11 months
Erythrocytes, T/l	3.5–4.7	**3.1**	**3**	**2.6**	4.1	4.68	4.1
Hemoglobin, g/l	110–145	**92**	**96**	**65**	129	144	128
CI	1.05–0.85	0.89	0.9	0.85	0.98	0.9	0.96
Platelets, G/l	150–410	254	247	226	299	302	251
Leukocytes, G/l	4.5–10.5	6.7	9.4	7.8	6.8	7.8	**29**
Myelocytes, %	0–1	0	0	0	0	0	0
Metamyelocytes, %	0–1	0	0	0	0	0	0
Band neutrophils, %	1–5	3	1	3	0	1,3	**20**
Segmented neutrophils, %	35–65	47	**66**	31	68	62.7	77
Lymphocytes, %	20–54	37	27	58	28	24	**2**
Monocytes, %	2–10	10	5	6	3	6,4	1
Eosinophils, %	1–5	3	1	2	1	**5,6**	0
Basophils, %	0–1	0	0	0	0	0	0
ESR**, mm/h	4–12	6	**14**	**15**	7	2	4

Notes: CI – Color Index; ESR – Erythrocyte Sedimentation Rate; values in bold indicate abnormal findings.

For further examination, he was referred to the State Institution «Institute of Gastroenterology of the National Academy of Medical Sciences of Ukraine» in Dnipro. Following laboratory and instrumental examinations and based on a persistent increase in transaminases, a high antinuclear antibody (ANA) titer, and the presence of hyperbilirubinemia, a clinical diagnosis was made «Type I autoimmune hepatitis with moderate inflammatory activity without extrahepatic manifestations; concurrent diagnoses: «Catarrhal proctosigmoiditis, internal hemorrhoids, combined crystalluria (urate, oxalate, phosphate). Complications: chronic calculous cholecystitis, gallbladder polyps. A consultation with a pediatric hematologist was requested, and hemolytic anemia was ruled out at the time of examinations.

Since the established diagnoses and the child condition dynamics were not adequate to satisfy physicians, the diagnostic workup continued. For further examinations and a more accurate diagnosis, the boy was referred to the State Institution «Institute of Pediatrics, Obstetrics and Gynecology named after Academician O.M. Lukyanova of the National Academy of Medical Sciences of Ukraine» (Kyiv). Hereditary diseases manifesting as hyperbilirubinemia, hepatomegaly, jaundice, abdominal pain, and anemia were considered as differential diagnoses of the child. In the Center for Orphan Diseases of the National Children's Specialized Hospital «ОНМАТДУТ» (Kyiv), genetic testing was performed to distinguish between thalassemia, glucose-6-phosphate dehydrogenase (G6PD) deficiency, alpha-1-antitrypsin deficiency, Gilbert's syndrome, Wilson's disease, Gaucher's disease, and HM. The final result of testing for Minkowski–Chauffard hemolytic anemia was positive, and other diseases were ruled out.

Thus, after the complex and meticulous diagnostic workup, the final clinical diagnosis was established: «HM, crisis course; complication: secondary chronic calculous cholecystitis; concurrent diagnosis: gallbladder polyp». Treatments were prescribed: dairy-free diet; ursodeoxycholic acid 300 mg/day (at a dosage of 10 mg/kg body mass) for 2 months; Omega-3 fatty acids for 2 months. Thereafter, the boy was followed up until the age of 17 by a hematologist at the Oncohematology Center of RMCFH. CBC was regularly monitored, and symptomatic treatments were provided. However, during the crises, which were documented twice, at 17 years and 6 months and again at the age of 17 years and 11 months, the child's condition deteriorated severely due to intoxication and jaundice syndromes, while anemic syndrome was not marked. During the first documented crisis, the boy complained of weakness, fatigue, loss of appetite, abdominal pain. The laboratory examination data of the child in dynamics from 3 to 17 years are presented in Tables 1 and 2.

The recent exacerbation of hemolytic anemia was in May 2023. The condition severity was influenced by intoxication, jaundice, and pain syndromes,

Table 2

Dynamics of the biochemical blood parameters

Parameter	Reference values	Age of the child				
		12 years	13 years	16 years	17,5 years	17 years and 11 months
ALT, U/L	<39	**147**	25	**123**	**105**	39
AST, U/L	<47	**58.1**	31	38	42	17
Total bilirubin, µmol/L	3.4–21.5	**55.7**	**54**	**56.4**	**38.3**	16
Direct bilirubin, µmol/L	<3.4	19.5	-	11.3	8.5	-
Indirect bilirubin, µmol/L	<19	**36.2**	**54**	**45.1**	**29.8**	-
Iron, µmol/L	9–21.5	17.2	-	-	-	-
Ferritin, ng/L	7–140	199.1	-	-	-	-
Total protein, g/L	52–78	70	64.5	72	56	71
Albumin, g/L	35–54	31	-	49	39	44
Urea, mmolL	1.8–6.4	3.3	-	4.9	3.9	**7.3**
Creatinine, µmol/L	45–105	68.9	-	73	68	70
Glucose, mmol/l	3.8–6.1	4.4	-	-	-	4.6
Amylase, U/l	<120	38	-	280	282	47
Blood urea nitrogen, mmol/l	1.2–3.9	-	-	2.3	1.9	3.6
C-reactive protein, mg/ml	<6	-	-	<6	<6	**24**
Sodium, mmol/l	135–148	-	-	142	-	138
Potassium, mmol/l	3.5–5.3	-	-	4.3	-	4.8
Chloride, mmol/l	98–107	-	-	109	-	106

Notes: ALT – alanine aminotransferase; AST – aspartate aminotransferase; values in bold indicate abnormal findings.

there was no anemia. The child was admitted to RMCFH for treatment and addressing issues on further tactics.

Physical examination revealed the boy with a body height of 175 cm and a body weight of 70 kg (body mass index of 22.9 kg/m^2); temperature – 36°C, respiratory rate (RR) 20/min, heart rate (HR), 78 beats/min; clear consciousness, negative meningeal signs, and no focal neurological symptoms. His skin and visible mucous membranes were normal but with scleral icterus. Cardiovascular and pulmonary examinations were unremarkable. The abdominal wall was painful on palpation in the right hypochondrial region. The liver was enlarged and palpable at 2 cm below the right costal and the spleen – at 3 cm below the left costal.

Laboratory examinations at admission revealed neutrophilic leukocytosis with a leukocyte formula left shift and elevated erythrocyte sedimentation rate (ESR). Biochemical blood tests showed hyperbilirubinemia due to the indirect bilirubin and the serum iron level was within the normal range. Myelogram demonstrated abnormalities in the form of hypercellularity, expanded erythroid lineage cells, accelerated hematopoiesis, suppressed leukocyte lineage and normoblastic type.

Abdominal ultrasound (US) examinations revealed the following changes. The right liver lobe was enlarged with clear regular contours and smooth edges, an inhomogeneous parenchymal pattern and a fine-granular hyperechoic structure. There were no bile duct ectasia or scarring. The gallbladder was 94×40 mm in size, pear-shaped with unchanged walls but folded in the corpus and neck regions. Multiple easily displaced hyperechoic stones with acoustic shadowing ranging in size from 2 to 6 mm (the largest – 12 mm) were visualized in the gallbladder lumen coupled with inspissated bile and biliary sludge at the posterior wall. The spleen was seen crescent-shaped with smooth clear contours, homogeneous parenchyma, granular structure, normal echogenicity and splenic dimensions were increased (155×54 mm).

After consulting a surgeon and establishing the diagnosis «HM, crisis course, complicated by secondary chronic calculous cholecystitis; concurrent diagnosis: gallbladder polyp», a decision was made to perform concomitant splenectomy and cholecystectomy.

After the surgery, the child showed significant improvements with positive dynamics due to eliminated pain, intoxication, jaundice and hemolysis

syndromes. Laboratory parameters were stabilized: serum total, direct and indirect bilirubin were decreased (total bilirubin – 15.4 μmol/l, direct bilirubin – 4.5 μmol/l, indirect bilirubin – 10.9 μmol/l). The boy was discharged in a satisfactory condition to outpatient treatment with recommendations for further follow-up by a general practitioner, gastroenterologist, hematologist, and surgeon in local health facilities. The patient was advised to continue pharmacological therapy with ursodeoxycholic acid for a long period with further monitoring of biochemical blood parameters and abdominal ultrasound after 3 months. Regular vaccination according to the National Immunization Schedule was recommended to be administered no earlier than 2 months after the surgery.

Discussion

Patients with the symptom triad, consisting of anemia, jaundice, and splenomegaly, should first be suspected of HM, although a family history could be ambiguous [7]. The child presented with a mild course of the disease clinically manifested by jaundice persistent for such a long time, and that was the reason for a rather late diagnosis.

Jaundice is one of the main clinical manifestations and it can be the only presenting symptom of the disease for a long time. The degree of jaundice depends on the one hand, on the hemolysis severity, and on the other hand, on the hepatocyte conjugating ability to form bilirubin conjugates with glucuronic acid [14].

The variable clinical severity of HM is its distinctive characteristic that at the same time presents significant diagnostic challenges [13]. The course of HM is usually classified as mild, moderate, moderate-to-severe, and severe based on Hb and reticulocyte count. Mild HM, which occurs in 20% of patients, presents with fully compensated hemolytic anemia with near-normal Hb levels, minimal spherocytes in peripheral blood smears, slight reticulocytosis (<6%), and mild splenomegaly. In fact, many of these individuals are not diagnosed until adulthood, when they develop complications related to chronic hemolysis, such as gallstones. The largest group of HM patients, representing about 60% of cases, suffers moderate disease with Hb levels in the range of 8 to 11 g/dL and reticulocytes >8%. Splenomegaly occurs in approximately 50% of children and 75 to 95% of adults. A smaller group of patients (about 10%) presents with moderate-to-severe HM with Hb values in the range of 6–8 g/dL and reticulocytosis >15% and need occasional red blood cell transfusions to manage anemia. Around 3–5% of HM patients show severe life-threatening anemia requiring regular blood transfusion therapy, and the inheritance pattern is recessive in most of these cases [10]. In the reported case, the child was diagnosed with mild HM.

Indeed, HM is characterized by the development of cholelithiasis in addition to the clinical triad of anemia, jaundice, and splenomegaly [8]. However, the above clinical manifestations and cholelithiasis as the common complication, can also be seen in patients with conditions such as thalassemia and autoimmune hemolytic anemia. Therefore, HM is difficult to differentiate between other types of anemia [15], especially since most patients are asymptomatic [9]. In the considered case, no clinical manifestations of gallstone formation were present in the boy.

The child, however, was misdiagnosed as having autoimmune hepatitis, since he presented with long-lasting jaundice as the main clinical manifestation. The literature describes a case of a male patient with jaundice but without symptoms of anemia who was misdiagnosed with autoimmune hepatitis quite similarly to the clinical case presented, while his 5-month-old son with manifest symptoms of anemia and jaundice was misdiagnosed with autoimmune hemolytic anemia. But in the final result, they both were diagnosed with HM [4].

H.X. Zhong et al. have reported four cases of patients with HM who were treated for varying degrees of anemia and jaundice in a lot of hospitals, but nevertheless, they were misdiagnosed or reported as having an uncertain diagnosis for a long time [17].

In some cases, HM patients may experience hematologic crises – hemolytic, aplastic, or megaloblastic. Among these crises, hemolytic is the most common and is clinically manifested by fever, which can be provoked by viral infections or occur spontaneously. Hemolytic crisis in HM due to suddenly accelerated hemolysis is characterized by more marked jaundice than that in a stable state. Aplastic crisis is typically more severe than hemolytic one and can even cause acute heart failure and is correlated with parvovirus B19 infection. Children commonly develop chills and fever, abdominal pain, myalgia, and a generalized maculopapular rash. The typical clinical onset of aplastic crisis is

characterized by a decrease in Hb and reticulocyte levels, followed by a decrease in bone marrow erythroblasts and serum bilirubin. During recovery, an increase in neutrophils and platelets comes first, followed by reticulocytosis and a gradual increase in Hb levels. Megaloblastic crises are rare and usually caused by folic acid deficiency [16]. In the clinical case presented, the child experienced hemolytic crises.

Reticulocytosis (from 6–10% to 35% in severe cases), a raised mean corpuscular Hb concentration (MCHC) >34.5 g/dl, an increased red cell distribution width (RDW >14), and a normal or slightly reduced mean corpuscular volume (MCV) are considered by researchers to be the major laboratory diagnostic criteria for HM. In most patients, anemia is mild (Hb >110 g/l) to moderate (Hb 80–110 g/l), resulted from chronic compensated hemolysis [1].

The diagnosis of HM is based, in addition to clinical manifestations, on positive family history and a peripheral blood smear, which may show a variable percentage of spherocytes (related to the degree of anemia), poikilocytosis, acanthocytosis, and ovalostomatocytosis.

The diagnostic guidelines for HM from the British Committee for Standards in Hematology do not recommend any additional screening tests for patients with classic clinical manifestations and laboratory findings [2].

However, indirect tests can be performed if necessary. These include the eosin-5-maleimide (EMA) binding test, which demonstrates high sensitivity (92–93%) and specificity (almost 99%), although it can be positive in patients with similar diseases, in particular, congenital dyserythropoietic anemia type II [1].

To sum up, here are the diagnostic criteria for HM recommended by the 2021 updated protocol [15].

1. Clinical manifestations: characteristic symptoms are anemia, jaundice, and splenomegaly, a common complication is gallstone disease.

2. Routine laboratory tests: Hb level may be normal or decreased (forms of the trait: normal; mild 110–150 g/L; moderate 80–120 g/L; severe 60–80 g/L); reticulocyte level may be normal or increased (forms of the trait: <3%; mild 3–6%; moderate >6%; severe >10%); MCHC index is normal or increased; mean reticulocyte volume (MRV) is decreased (cutoff value: ⩽95.77 fL); mean spherical corpuscular volume, which includes erythrocytes and reticulocytes (MSCV) < MCV; the number of spherocytes may be increased; serum total bilirubin is elevated, mainly due to unconjugated bilirubin.

3. Family history: patients mostly present with the autosomal dominant inheritance pattern and show the same test results and clinical manifestations as one of their parents or other family members.

4. Genetic testing and other screening tests: genetic testing combined with erythrocyte osmotic fragility test, EMA binding test, flow cytometry, acidified glycerol lysis test (AGLT), Coombs test, and G6PDH level determination for patients in whom the diagnosis of HM is challenging, are required.

In the case of ineffective symptomatic conservative therapy, surgical treatment for HM is required. Currently, surgical strategies consist mainly of total or partial splenectomy, which can be performed by open laparotomy or laparoscopically [14]. According to a study that enrolled 65 children in Turkey, 20% of patients at the mean age of 8.3 years underwent splenectomy. The most commonly reported post-splenectomy complications that may occur are sepsis or thrombosis [7]. The postoperative period in the case presented was uneventful.

Conclusions

Currently, mild forms of hereditary microspherocytosis are underdiagnosed.

Mild and moderately severe course of hereditary microspherocytosis, apart from jaundice and moderate splenomegaly, can be manifested by cutoff Hb values, making it difficult to timely diagnose primary disease and its complications.

Since the most common complication of hereditary microspherocytosis is gallstone disease, regular ultrasound examinations of the gallbladder and monitoring of the hepatobiliary system are the best imaging modalities for patients even in the absence of overt hemolysis.

In case of conservative therapy ineffectiveness, it is necessary to consider the issue of performing a complete or partial splenectomy, and in the presence of a complication in the form of calculous cholecystitis, it should be combined with cholecystectomy.

The analyzed clinical case is a demonstrative example of underdiagnosed mild hereditary microspherocytosis complicated by secondary chronic calculous cholecystitis.

The authors declare no conflict of interest.

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