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CAROLI'S DISEASE: A DISEASE THAT RARELY COMES TO MIND: A CASE REPORT

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Caroli's disease is a rare disease characterized by dilatation of large intrahepatic bile ducts. It occurs in the classic form presented by repeated episodes of cholangitis (Caroli's disease), as well as in the form of syndrome with the development of fibrosis and cirrhosis of the liver (Caroli's syndrome). The disease can occur throughout entire life, but mostly before the age of 30. The incidence of this disease is estimated at about 1 in 1,000,000 cases for Caroli's disease and 1 in 100,000 for Caroli's syndrome. The main symptoms are: fever, jaundice, itchy skin, pain under the right costal arch, nausea and vomiting. Possible complications are the development of liver fibrosis and cirrhosis and cholangiocellular carcinoma. Diagnosis is made by clinical and ultrasound examination, computed tomography, more often by magnetic resonance cholangiopancreatography and liver biopsy. We present a clinical case of an elderly patient who has been suffering from Caroli's disease for a few years now. Diagnostic challenges and applied therapy are presented. *Acta Medica Medianae 2023;62(2): 77-82.*

Key words: *Caroli's disease, Caroli's syndrome, cholangitis, cholangiocarcinoma*

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Introduction

Caroli's disease is a rare disease characterized by dilatation of large intrahepatic bile ducts (1). The modern classification includes two forms of the disease: classical Caroli's disease and Caroli's syndrome. The classic form is isolated involvement of the bile ducts, while Caroli's syndrome is characterized by the development of periportal fibrosis and portal hypertension. The disease appears in more common diffuse form presented in both lobes of the liver, and significantly much less often in one, usually the left lobe (2).

The exact incidence of this rare disease is not accurately known, but it is estimated that classic Caroli's disease occurs in 1 in 1,000,000 cases, while Caroli's syndrome affects 1 in 100,000 people. It is difficult to identify all cases of Caroli's syndrome, because its characteristics can look like many similar conditions (3). It is estimated to affect men and women equally, with a slightly higher incidence of the Asian and the younger population (1, 4).

The disease is inherited in an autosomal recessive pattern. A mutation in the gene for polycystic kidney and liver disease (PKHD1) has been identified on the short arm of chromosome 6. This results in a defect in the fibrocystin protein that exists in bile duct cells, liver, pancreas, and renal tubular cells (4). Its role is in the proper development of the liver and kidneys through controlled cell proliferation (5, 6). The disease is often asymptomatic, and when there are symptoms, they are most often presented with episodes of acute cholangitis, jaundice, fever, high body temperature and abdominal pain below the right costal arch. An increase in bile acids in blood causes itchy skin. These symptoms disappear with aging and the development of liver cirrhosis and portal hypertension. Caroli's disease increases the risk of cholangiocellular liver cancer (4).

The Caroli's disease is diagnosed by taking anamnesis, through clinical examination and non-invasive and invasive diagnostic procedures. Laboratory examination mainly shows elevated levels of leukocytes, alkaline phosphatase and direct (conjugated) bilirubin (7). Abdominal ultrasound is the first diagnostic method that determines sacral enlargements of the intrahepatic bile ducts. Final diagnostics include computed tomography of the liver and biliary tract, invasive methods such as endoscopic retrograde

cholangiopancreatography (ERCP) and magnetic retrograde cholangiopancreatography (MRCP), which confirm the diagnosis of the disease. Due to the connection between cystic changes and liver fibrosis, it is possible to perform a liver biopsy (8, 9).

Case report

We present the case of a 67-year-old male patient who first contacted a gastroenterologist 5 years ago due to pain in the upper half of the abdomen, nausea, vomiting of yellowish contents and fever up to 37.5ºC. The patient felt exhausted and noticed a yellow discoloration of the skin and scleras, and lighter stool color. He denied losing weight, but his appetite was weakened. He also drank alcohol until a couple of years ago. The gastroenterologist indicated hospital treatment when the further diagnosis was made. Laboratory results of the patient at the start of hospitalisation showed elevated values of parameters: CRP 337.9 mg/L, creatinine 801.6 µmol/L, gGT 200 U/L, LDH 254 U/L, ALP 425 U/L, T.Bil 95, 8 µmol/L, D.Bil 64.2 µmol/L. Abdominal ultrasound determined enlarged liver with rounded edges, inhomogeneous parenchyma with numerous transonic changes up to 14 mm in diameter predominantly in the left lobe of the liver, while intrahepatic bile ducts were dilated with the presence of aerobilia. The spleen was enlarged up to 144 mm in interpolar diameter (Figure 1). This raised suspicion of Caroli's disease. In order to confirm the diagnosis, the computed tomography of the abdomen was performed and it verified the enlargement of the right lobe of the liver up to 179 mm, as well as dilated intrahepatic bile ducts filled with multiple calculi up to 1 cm in diameter, predominantly in the right liver lobe - "pearl" sign. The ductus choledochus was dilated in its proximal segment up to 11.5 mm and filled with air, while the diameter of the Wirsung duct was 4.5 mm (Figure 2). This confirmed the Caroli's disease. On several occasions, the patient was examined by a surgeon who did not indicate surgical treatment and due to altered values of acid-base status (pH 7.309, HCO_3 11.3 mmol/L, BE -14.9 mmol/L, Lac 2.15 mmol/L), the patient was treated by a nephrologist. In the next couple of years, the patient regularly visited a gastroenterologist, where he was regularly examined due to similar problems, and on a couple of occasions he was hospitalized again. Proximal endoscopy was performed in order to monitor the disease and it showed polycolor gastric mucosa, mosaic appearance, sometimes with submucosal hemorrhages, without macroscopic changes, while the finding on the esophagus was normal, without dilated esophageal veins (Figure 3). This indicated the possible occurrence of portal hypertension, which is common in patients with Caroli's disease. Physical examination revealed no signs of manifest cirrhosis of the liver. Control computed tomography of the abdomen did not show a significantly different finding on the liver and bile ducts, except for a small amount of free fluid in the abdomen and bilateral effusion in the lungs. The patient was prescribed antibiotic, gastroprotective and hepatoprotective therapy to improve liver function. After a detailed diagnosis, the patient was regularly visiting the clinic for check-ups, but since he stopped coming in 2021, the clinic has not kept a record of him .

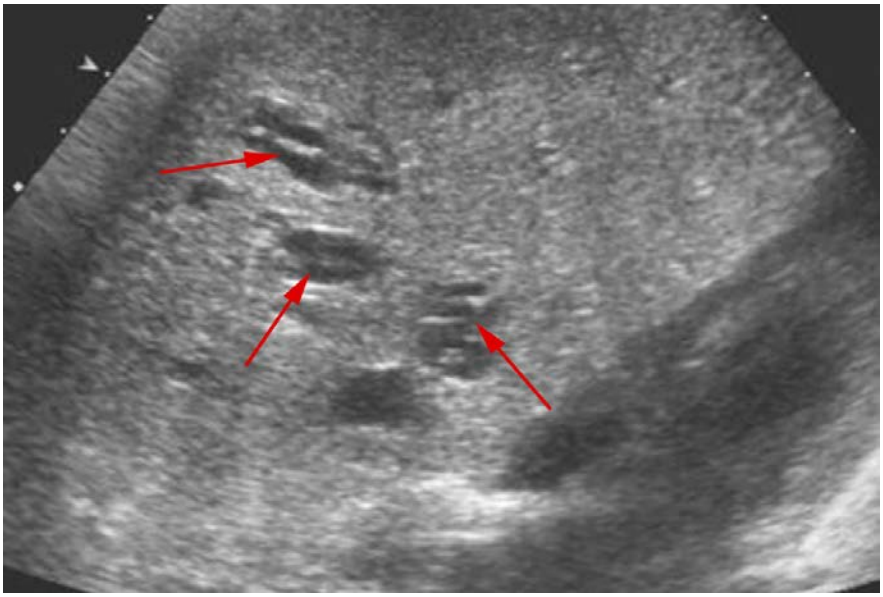

Figure 1. Dilated intrahepatic bile ducts with calculi and aerobilia

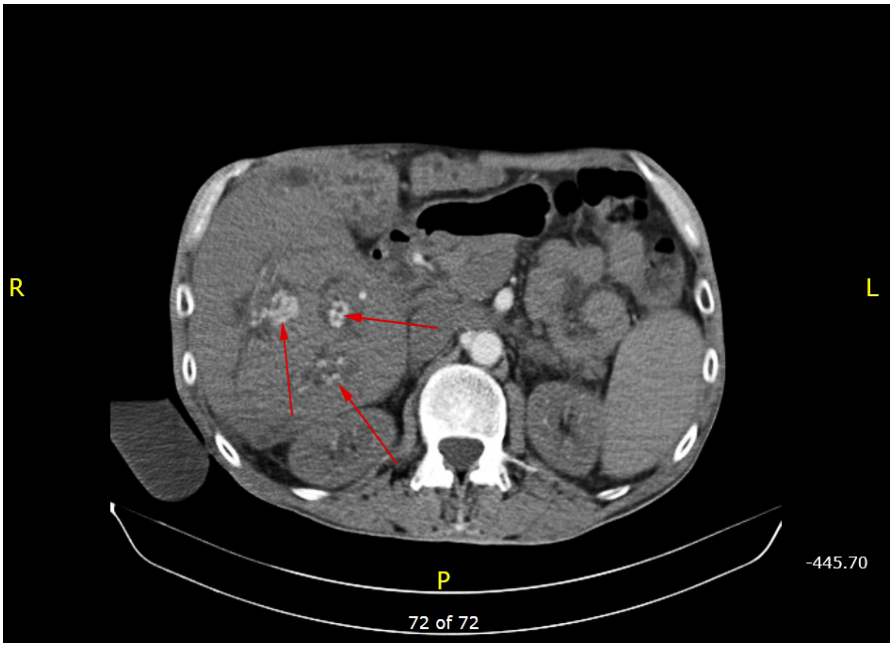

Figure 2. Computed tomography of the abdomen - dilated intrahepatic bile ducts filled with multiple calculi - a sign of "pearls"

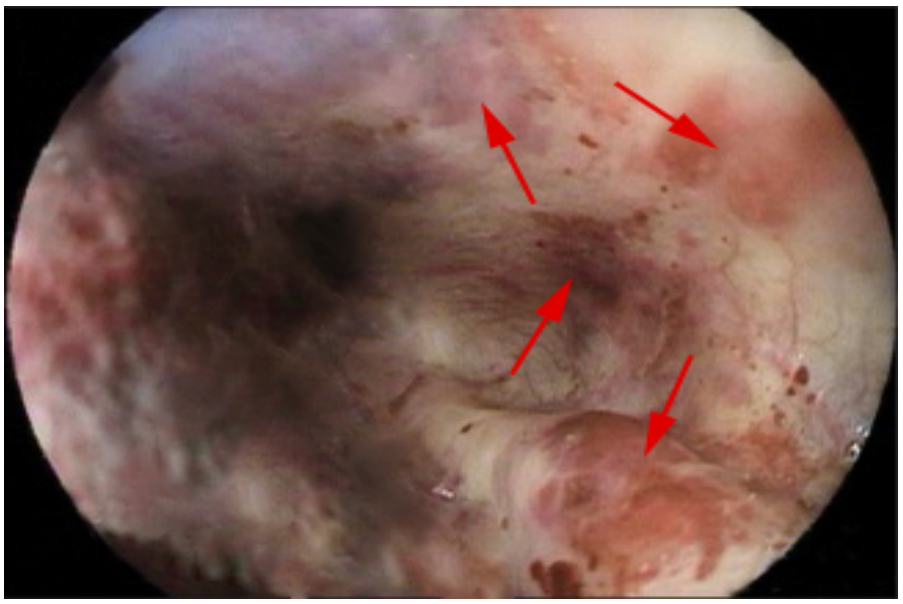

Figure 3. Proximal endoscopy - Polychlorine, mosaic appearance of gastric mucosa with numerous submucosal hemorrhages

Discussion

Caroli's disease is a rare disease of the intrahepatic bile ducts which exact cause is still poorly known (10). It was first described in 1906 by Vachell and Stephens, then in 1958, Caroli J and co-workers gave the disease its final name and defined it as a congenital, cystic liver disorder with dilated intrahepatic bile ducts. Tonadi and co-workers classify Caroli's disease as the fifth type of congenital cysts of the bile ducts (2, 11). These disorders of embryogenesis are often associated with hepatobiliary and renal malformations (11). The most common mutated gene is PKHD1 (gene for polycystic kidney and liver disease) on chromosome 6p12, which participates in the cell differentiation of the liver, kidneys, lungs and pancreas (12). This results in a defect in fibrocystin, which is a part of the cilia of cholangiocytes and represents an important receptor through which chemical, mechanical and

osmotic stimuli trigger intracellular mechanisms that change the composition of bile (13). It also plays an important role in liver and bile proliferation, which explains cystic defects in Caroli's disease (4, 13). Parada and co-workers also found an unbalanced translocation between chromosomes 3 and 8 (loss of 3p and an increase in 8q) in the liver tissue of those patients. It has been suggested that this could be the cause of cholangiocarcinoma development after many years of Caroli's disease (14). In a number of cases, autosomal dominant inheritance has been described together with polycystic kidney disease (15). The disease is usually diagnosed in childhood or adolescence, but also in elderly patients (16). Patients may be asymptomatic for a long time or may occasionally have milder symptoms of the disease (17). The most common symptoms are abdominal pain, fever and repeated attacks of cholangitis, and with disease progression, signs of portal hypertension such as haematemesis and melena may occur (18). The fact that there is no exact age when the disease develops was confirmed by a study by Bisvas and co-workers who showed that the most common period of illness is from 2 to 16 years of age, with an average age of 10 years. These younger patients developed a serious clinical picture in the form of fever and jaundice, while ultrasound examination revealed numerous bile calculi in the dilated bile ducts, which is the case in our elderly patients (19). Bile stasis and chronic cholangitis are predispositions for the development of biliary tract dysplasia and cholangiocarcinoma, which occurs in 7% (according to some studies from 5 to 33%) of patients with Caroli's disease and is the most severe complication of this disease (20, 21). Cases of hepatocellular and gallbladder cancer have been reported, although this is significantly less common (20, 22). The risk of developing cholangiocellular carcinoma in Caroli's disease and Caroli's syndrome is about 100 times higher compared to healthy individuals. This development of cancer was first described in the literature in 1968, but the etiology is still not completely clear (23). However, there are a couple of theories: long-term bile stasis followed by bacterial infection, irritation of the calculi and release of carcinogenic substances may participate in the development of cholangiocarcinoma. It is assumed that older age and long duration of the disease contribute to its development (23, 4). A study by Ghadir Mohammad and co-workers shows cases of two elderly patients in England who developed cirrhosis of the liver after numerous years, and one of these two patients also developed hepatocellular carcinoma. Although this review reveals an elderly patient with initial signs of portal hypertension, numerous other studies show that these complications are also possible in significantly younger patients (25).

Beside the clinical examination, the diagnosis is made by ultrasound examination, which shows accuracy in only 27.3% of cases, so it is much more often recommended to use computed tomography of the abdomen to verify changes in the bile ducts with an accuracy of 71.4%. This method verifies the “central point” sign which is representing the fibrovascular bundles containing the portal vein and artery around the dilated bile ducts (26). Today, the traditional method of diagnosis by ERPC (endoscopic retrograde cholangiopancreatography) is increasingly being replaced by MRCP (magnetic resonance cholangiopancreatography) and is becoming the method of choice for diagnosing Caroli's disease (30). Its non-invasive nature is detecting malignancy make it the most effective method. The MRCP method has a sensitivity and specificity of 97 to 99% (26, 27). This method is effective in the differentiation of Caroli's disease from similar conditions such as benign biliary cysts, choledochus cysts and polycystic kidney disease (26).

Treatment of Caroli's disease includes the use of antibiotics (in the case of cholangitis) and ursodeoxycholic acid in the case of severe lithiasis. Surgical resection is useful in patients with segmental or monolobar disease in the absence of recurrent cholangitis, advanced fibrosis, or cirrhosis (28). The most commonly used surgical methods are endoscopic sphincterotomy, cholecystectomy and resection of the affected liver lobe - lobectomy, segmentectomy (29). In the case of advanced disease, development of fibrosis, liver cirrhosis and portal hypertension, the most effective method of treatment is liver transplantation (30).

Conclusion

Caroli's disease is a rare disease of the biliary tract. The exact incidence of this disease is not known because a large number of cases are asymptomatic, so the disease is rarely diagnosed. This disease can occur throughout life, but most often in adolescence and in elderly patients. In order to discover the disease in the early stage it is necessary to conduct right diagnosis and to hospitalize the patient with the appearance of the first symptoms of the disease. Although there is no reliable therapy for liver fibrosis and cirrhosis, the use of hepatoprotective drugs and changes in lifestyle habits could at least slow down the further progression of the disease. In case of complications of developed portal hypertension, rapid endoscopic interventions would increase survival in later stages. Regular monitoring of these patients could reduce the risk of complications and increase the survival of this rare disease.

References

1. Ilić S. Tumori i ciste jetre. U: Interna medicina, Prosveta, Niš, 2004, 357.
2. Sweeney WE, Avner ED, Adam MP, Mirzaa GM, Pagon RA, Wallace SP et al. Polycystic Kidney Disease, Autosomal Recessive. In: GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2022. [PubMed]
3. Yonem O, Bayraktar Y. Clinical characteristics of Caroli's disease. World J Gastroenterol 2007; 13(13): 1930-1933. [CrossRef] [PubMed]
4. Alhaddad M, Elsabaawy M, Elshaarawy O, Ehsan NA, Maher D, Elazab D et al. Congenital hepatic fibrosis (CHF): a report of two cases and an overview. Ann Clin Lab Res 2017; 5: 1. [CrossRef]
5. Correia PC, Morgado B. Caroli's disease as a cause of chronic epigastric abdominal pain: Two case reports and a brief review of the literature. Cureus 2017; 9(9): e1701. [CrossRef] [PubMed]
6. Mamone G, Cortis K, Sarah A, Caruso S, Miraglia R. Hepatic morphology abnormalities: beyond cirrhosis. Abdom Radiol 2018; 43(7): 1612-1626. [CrossRef] [PubMed]
7. Soares C, Goldstein SD, Ghaseb MA, Kamel I, Hackam DJ, Pawlik TM. Pediatric choledochal cysts: diagnosis and current management. Pediatr Surg Int 2017; 33(6): 637-650. [CrossRef] [PubMed]
8. Blechacz B. Cholangiocarcinoma: Current knowledge and new developments. Gut Liver 2017; 11(1): 13-26. [CrossRef] [PubMed]
9. Moslim A, Gunasekaran G, Vogt D, Cruise M, Morris-Stiff G. Surgical management of Caroli's disease: Single center experience and review of the literature. J Gastrointest Surg 2015; 19(11): 2019-27. [CrossRef] [PubMed]
10. Hao X, Liu S, Dong Q, Zhang H, Zhao J, Su L. Whole exome sequencing identifies recessive PKHD1 mutations in a Chinese twin family with Caroli disease. PLoS One 2014; 9: 0. [CrossRef] [PubMed]
11. Bettini G, Mandrioli L, Morini M. Bile duct dysplasia and congenital hepatic fibrosis associated with polycystic kidney (Caroli syndrome) in a rat. Vet Pathol 2003; 40: 693–694. [CrossRef] [PubMed]
12. Sgro M, Rossetti S, Barozzino T, Toi A, Langer J, Harris PC et al. Caroli' s disease: prenatal diagnosis, postnatal outcome and genetic analysis. Ultrasound Obstet Gynecol 2004; 23: 73–76. [CrossRef] [PubMed]
13. Yang XY, Zhu LP, Liu XQ, Zhang CY, Yao Y, Wu Y. Genetic diagnosis of Caroli syndrome with autosomal recessive polycystic kidney disease: a case report and literature review. Beijing Da Xue Xue Bao Yi Xue Ban 2018; 50(2): 335-339. [PubMed]
14. Parada L, Hallen M, Hagerstrand I, Tranberg K, Johansson B. Clonal chromosomal abnormalities in congenital bile duct dilatation (Caroli's disease). Gut 1999; 45: 780–782. [CrossRef] [PubMed]
15. Torra R, Badenas C, Darnell A, Brú C, Escorsell A, Estivill X. Autosomal dominant polycystic kidney disease with anticipation and Caroli's disease associated with a PKD1 mutation. Rapid communication. Kidney Int 1997; 52(1): 33-38. [CrossRef] [PubMed]
16. Desmet VJ. Pathogenesis of ductal plate abnormalities. Mayo Clin Proc 1998; 73: 80–89. [CrossRef] [PubMed]
17. Madjov R, Chervenkov P, Madjova V, Balev B. Caroli's disease. Report of 5 cases and review of literature. Hepatogastroent 2005; 52: 606–609. [PubMed]
18. Hadžić N, Strazzabosco M. Fibropolycystic liver diseases and congenital biliary abnormalities. Sherlock's diseases of the liver and biliary system 2018; 13: 313–317. [CrossRef]
19. Biswas NK, Raju U, Sodhi K. Caroli's disease. Med J Armed Forces India 2007; 63(4): 388–389. [CrossRef] [PubMed]
20. Dayton MT, Longmire WP Jr, Tompkins RK. Caroli's disease: a premalignant condition? Am J Surg 1983, 145: 41–48. [CrossRef] [PubMed]
21. Moslim MA, Gunasekaran G, Vogt D, Cruise M, Morris-Stiff G. Surgical Management of Caroli's Disease: Single Center Experience and Review of the Literature. J Gastrointest Surg 2015; 19: 2019-2027. [CrossRef] [PubMed]
22. Abdalla EK, Forsmark CE, Lauwers GY, Vauthey JN. Monolobar Caroli's Disease and cholangiocarcinoma. HPB Surg 1999; 11: 271–276. [CrossRef] [PubMed]
23. Schiewe R, Baudisch E, Ehrhardt G. Congenital intrahepatic bile duct cysts with calcinosis and malignant degenerations. Bruns Beitr Klin Chir 1968; 216: 264-271. [PubMed]
24. Preston D, Flanigan DP. Biliary carcinoma associated with biliary cysts. Cancer 1977; 40: 880-883. [CrossRef] [PubMed]
25. Ghadir MR, Bagheri M, Ghanooni AH. Congenital hepatic fibrosis leading to cirrhosis and hepatocellular carcinoma: a case report. J Med Case Reports 2011; 5: 160. [CrossRef] [PubMed]
26. Kassahun WT, Kahn T, Wittekind C, Mossner J, Caca K, Hauss J et al. Caroli's disease: liver resection and liver transplantation. Experience in 33 patients. Surgery 2005; 138: 888–898. [CrossRef] [PubMed]
27. Jarufe N, Figueroa E, Muñoz C, Moisan F, Varas J, Valbuena JR et al. Anatomic hepatectomy as a definitive treatment for hepatolithiasis: a cohort study. HPB (Oxford) 2012; 14: 604-610. [CrossRef] [PubMed]
28. Ananthakrishnan AN, Saeian K. Caroli's disease: Identification and treatment strategy. Curr Gastroenterol Rep 2007; 9(2): 151-155. [CrossRef] [PubMed]
29. Yamaguchi T, Cristaudi A, Kokudo T, Uldry E, Demartines N, Halkic N. Surgical treatment for monolobular Caroli's disease – Report of a 30-year single center case series. Biosci Trends 2018; 12(4): 426-431. [CrossRef] [PubMed]
30. Fahrner R, Dennler SGC, Dondorf F, Ardelt M, Rauchfuss F, Settmacher U. Liver resection and transplantation in Caroli disease and syndrome. J Visc Surg 2019; 156(2): 91-95. [CrossRef] [PubMed]

Prikaz bolesnika

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KAROLIJEVA BOLEST – BOLEST O KOJOJ SE MALO RAZMIŠLJA: PRIKAZ BOLESNIKA

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Karolijeva bolest je retko oboljenje, koje karakteriše dilatacija velikih intrahepatičnih žučnih kanala. Javlja se u retkoj izolovanoj formi, koju odlikuju ponovljene epizode holangitisa i periportalna fibroza (tip I). Znatno češća varijanta povezana je sa kongenitalnom fibrozom jetre (tip II). Iako se bolest može javiti tokom čitavog života, najčešće se javlja pre tridesete godine. Incidencija i prevalencija ove bolesti nisu poznate, ali je procena da se javlja jednom u 10.000 do 20.000 slučajeva. Glavni simptomi su povišena telesna temperatura, bol ispod desnog rebarnog luka, napadi žutice, svrab po koži, mučnina i povraćanje. Dijagnostika se vrši kliničkim pregledom, ultrazvučnim pregledom, kompjuterizovanom tomografijom abdomena, a u cilju definitivne dijagnostike primenjuju se endoskopska retrogradna holangiopankreatografija i biopsija jetre. U slučaju razvoja ciroze jetre i portne hipertenzije radi se proksimalna endoskopija. Prikazujemo klinički slučaj čoveka starijeg životnog doba, koji nekoliko godina unazad boluje od Karolijeve bolesti. Prikazani su dijagnostički izazovi i primenjena terapija. *Acta Medica Medianae 2023;62(2):77-82.*

Ključne reči: *Karolijeva bolest, holangitis, fibroza jetre, ciroza jetre*