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BUDD–CHIARI SYNDROME IN A PATIENT WITH SMALL CELL LUNG CANCER: A CASE REPORT

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Budd–Chiari syndrome (BCS) is a rare disease caused by hepatic venous outflow tract obstruction which can occur anywhere along the path from the hepatic venules to the inferior vena cava inflow into the right ventricle. Liver congestion results in hypoxic damage of hepatocytes. Etiologic factors related to BCS are hematologic and malignant disease. Budd–Chiari syndrome is a rare condition in lung cancer patients. Only a few cases have been reported during the last decades. We present a very rare case of acute BCS syndrome in a patient with primary small cell lung cancer caused by tumor thrombus of the inferior vena cava. The diagnosis was made based on ultrasound findings. Thereafter treatment with anticoagulant therapy was started. Due to the poor performance status and significant liver damage, specific oncological treatment with chemotherapy was not started. The patient was discharged from the hospital and advised to continue symptomatic therapy. Pulmonologists should be aware that BCS syndrome could be a presenting feature of an unrecognized lung cancer.

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Key words: *Budd–Chiari syndrome, lung cancer*

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Introduction

Budd–Chiari syndrome (BCS) is a rare disease caused by impaired venous outflow which can occur anywhere along the path from the hepatic venules to the inferior vena cava inflow into the right ventricle. It is quite often defined as congestive hepatopathy (1-5). British internist George Budd described in 1845 a triad of symptoms characteristic of disease, hepatomegaly, ascites and abdominal pain (6). After more than half a decade Austrian pathologist Hans Chiary described its pathohystology (7). Etiologic factors related to BCS are hematologic and malignant disease. Malignancies are an etiologic factor in 10% of patients with BCS, predominantly in the liver and kidney. Budd–Chiari syndrome is a very rare condition in lung cancer patients. The incidence of BCS differs between Western and Eastern countries. It is estimated that BSC occurs in 1/100000 of the general population worldwide (8). BSC is classified according to etiologic factors into primary (caused by primary hematological disorders or hypercoagulable conditions) and secondary (invasion or compression of inferior vena cava or hepatic veins with their thrombosis) (9). Two major hepatic veins must be blocked for clinically manifest disease. Blockage of hepatic veins increases the sinusoidal pressure and reduces sinusoidal blood flow. Asymptomatic BCS syndrome accounts for 15–20% of cases and is associated with the existence of collateral veins (4). Liver congestion results in hypoxic damage of hepatocytes. According to the course, it can be fulminant, chronic, or asymptomatic (3). The clinical picture is characterized by a triad in the form of pain in the right upper quadrant of the abdomen, ascites, and hepatomegaly. Leg swelling and jaundice are also common (10). The diagnosis is established by using non-invasive imaging techniques (ultrasound, computed tomography, magnetic resonance) (11). Doppler ultrasonography, with a sensitivity and specificity of 85%, is the imaging technique of choice for initial investigation when BCS is suspected. Laboratory analyses are also important. The recommended therapeutic approach to BCS consists of medical treatment (anticoagulation

therapy), endovascular treatment to restore vessel patency, and liver transplantation as a rescue treatment. The prognosis depends on etiology and the presence of risk factors. Survival rates range from 42% to 100% (12). We present a case of acute BCS syndrome in a patient with primary small cell lung cancer.

Case report

A male patient aged 51 years was referred to our clinic due to a non-productive irritating cough. A month before admission he had a productive bloody cough, after which only a dry irritating cough remained. Among associated diseases, he had a rapid heart rate. He had a 30 pack-year history of smoking. The performance status of the patient was 0 on the Eastern Cooperative Oncology Group scale. Lung auscultation revealed weakened right basal breath without accompanying murmurs. In routine laboratory analyses, hematocrit: 0.393 (0.410–0.560) L/L, thrombocytes: 435 (120–380) x 10^9/L, glucose: 7.2 (3.9–6.1) mmol/L, C reactive protein: 69.2 (0.0–5.0) mg/L, and other laboratory findings were within the reference values. On the chest X-ray in the middle and lower lung fields, a homogeneous soft-tissue shadow was found, masking the right hemidiaphragm and costophrenic sinus with clearly delineating cranial boundaries (Figure 1). This shadow may correspond to atelectasis or superimposed pleural effusion. On the right side, close to hilus lightening zones were described with a partially present bronchial pattern. On the same day, diagnostic and therapeutic thoracocentesis of the right pleural space was performed and 850 ml of serohemorrhagic content was evacuated. Pleural fluid was sent for biochemical, microbiological, and cytological analysis. According to the biochemical characteristics and Light's criteria, the pleural effusion corresponded to exudate (lactate dehydrogenase (LDH) punctate (p)/serum (s) ratio: 0.84, total proteins p/s ratio 0.65, and LDH in the punctate: 320). No pathogenic bacteria or fungi were isolated from the pleural punctate. The results of the cytological examination described a mixed type of pleural effusion, probably of inflammatory etiology. In addition, computed tomography (CT) of the chest and upper abdomen was performed. CT described a massive right - sided pleural effusion with a thickness of 94 mm and compressive atelectasis. Enlarged lymph nodes were described, with the largest in the lower mediastinum measuring 74 x 82 x 59 mm including the lower mediastinum and right hilus. The organs of the upper abdomen, as well as the bone structures, were free of secondary deposits (Figure 2). Furthermore, a bronchological examination was conducted. An enlarged carina for the upper right lobe of the lung was seen in the right bronchial tree. The confluence, as well as the initial part of the bronchus for the lower lobe, were stenosed and infiltrated. The mucous membrane was rough, with strongly accentuated folds of the mucosa from longitudinal striae. Endobronchial biopsies were taken for pathohistological verification. The pathohistological findings showed that it was small-cell cancer of the lung T4N2M1a stage IV A. The patient was presented to the Board for malignant lung and pleural diseases in April 2023. The board decided to start the treatment with the first line of chemotherapy according to the Etoposide/Cisplatin regimen for 4 cycles. Until the start of specific oncological treatment, the patient was discharged from the hospital in good general condition. Specific oncological treatment was not started due to complaints in the form of dizziness, pallor, nausea, urge to vomit, swelling of the lower legs, as well as pronounced weakness and malaise. Therefore, the patient was hospitalized again for symptomatic treatment. Lung auscultation revealed weak to inaudible breath sounds without accompanying murmurs on the right. He had retromalleolar and pretibial leg oedema. Blood pressure was 84/55 mmHg. In laboratory analyses, leukocytes: 19.8 (4.0-9.0) x 10^9/L, neutrophils: 13.53 (2.10-7.50) x 10^9/L, glucose: 11.6 (3.9-6.1) mmol/L, urea: 9.1 (2.5-7.5) mmol/L, creatinine: 151.8 (53.0-115.0) µmol/L, uric acid: 523 (208-428) µmol/L, direct bilirubin: 9.3 (0.0-3.4) µmol/L, CRP: 35.8 (0.0-5.0) mg/L, albumin: 28 (35-52) g/L, cholesterol: 2.05 (3.90-5.20) mmol/L, K: 5.5 (3.5-5.5) mmol/L, chlorides: 96 (98-108) mmol/L, Ca: 2.16 (2.20-2.65) mmol/L, aspartate aminotransferase (AST): 58 (10-37) U/L, alkaline phosphatase (ALP): 154 (30-120) U/L, gama glutamil transpeptidase (GGT): 339 (0.0-55) U/L, lactate dehydrogenase (LDH): 623 (220-450) U/L, prothrombin time (PT): 19 (9-15) sec, activated partial thromboplastin time (APTT): 23.9 (24-35) sec, D-Dimer: 1200 (0.0-250) ng/ml, INR: 1.69, hs Troponin I: 0.001 (0.000-0.040). In gas analyses, pH: 7.36 (7.35-7.45), pCO_2: 24 (35-45) mmHg, bicarbonate (HCO3): 13.6 (22-26) mmol/L, lactates: 9.2 (0.00-1.80) mmol/L, base excess extracellular fluid (BEecf): -11.8 (-2.3-+2.3) mmol/L, pO2: 76 (70-100) mmHg, SpO2: 94%. On the chest X-ray, a homogeneous soft-tissue shadow was seen on the right in the middle and lower radiological field, overshadowing the right hemidiaphragm and the right costophrenic sinus (Figure 3). Control laboratory analyses on the second day of hospitalization were urea: 16.0 (2.5-7.5) mmol/L, creatinine: 251.2 (53.0-115) µmol/L, sodium: 133 (135-148) mmol/L, potassium 6.0 (3.5-5.5) mmol/L, chlorides: 94 (98-108) mmol/L, calcium: 1.71 (2.20-2.65) mmol/L, AST: 13411 (10-37) U/L, ALT: 4650 (10–42) U/L, GGT: 277 (0.0–55) U/L, LDH: 33129 (220–450) U/L, PT: 45 (9-15) sec, APTT: 37.7 (24-35) sec D-Dimer: 10451 (0.0-250) ng/ml, INR: 4.05. In control gas analyses, metabolic acidosis was registered pH: 7.27 (7.35-7.45), pCO2: 21 (35-45) mmHg, Lac: 13.4 (0.00-1.80), and HCO3: 9.6 (22-26) mmol/L. BEecf: -17.3 (-

2.3-+2.3) mmol/L; pO2: 76 (70-100) mmHg; Spo2: 93%. A gastroenterologist was consulted due to the sudden extreme increase of transaminases and LDH values, as well as marked hypotension. On physical examination, the abdomen was symmetrical, distended and flatulent in the upper parts, soft on palpation, and not sensitive to superficial and deep palpation. The liver and spleen were not palpable. The kidney lodges were free. An abdominal ultrasound was performed, which described an enlarged liver with an oval hyperechoic shadow with a diameter of 3.33 cm in the basin of the hepatic veins, which extends into the vena cava and gives the impression that it obliterates it (Figure 4a). A moderate amount of ascites was found in the abdomen (Figure 4b), and a small right-sided pleural effusion was also observed (Figure 4c). Ultrasonographic findings of gallbladder, pancreas, spleen and kidneys were normal. The gastroenterologist prescribed symptomatic therapy and recommended further examination by a vascular surgeon. The vascular surgeon confirmed thrombosis of the inferior vena cava and prescribed therapeutic doses of low-molecular-weight heparin. Due to hypotension and deterioration of renal function, a nephrologist was consulted. He prescribed symptomatic therapy. On the control abdominal ultrasonography after 7 days of therapy, the previously described thrombosis of the vena cava was partly resolved. In the control blood count, a decrease in platelets Tr 52 (120–380) x 10^9/L was registered. The hematologist suggested the introduction of therapeutic doses of fondaparinux. After 7 days of therapy, laboratory results were repeated: Le 13.8 (4.0-9.0) x 10^9/L, HCT 0.403 (0.410-0.560) L/L, glucose 7.0 (3.9-6.1) mmol/L, urea: 10.5 (2.5-7.5) mmol/L. L, uric acid: 186 (208-428) µmol/L, total bilirubin 54.8 (5.0-21.0) µmol/L, direct bilirubin 23.6 (0.0-3.4) µmol/L, total proteins: 51 (62-81) g/L, CRP 8.1 (0.0-5.0) mg/L, albumin: 26 (35-51) g/L, cholesterol: 3.21 (3.90-5.20) mmol/L, Na 130 (135-148) mmol/L, chlorides: 93 (98-108) mmol/L, Ca 1.94 (2.20-2.65) mmol/L AST 52 (10-37) U/L, ALT 147 (10-42) U/L, LDH 673 (220-450) U/L After the control laboratory analyses the patient was discharged from the hospital. Symptomatic treatment was recommended.

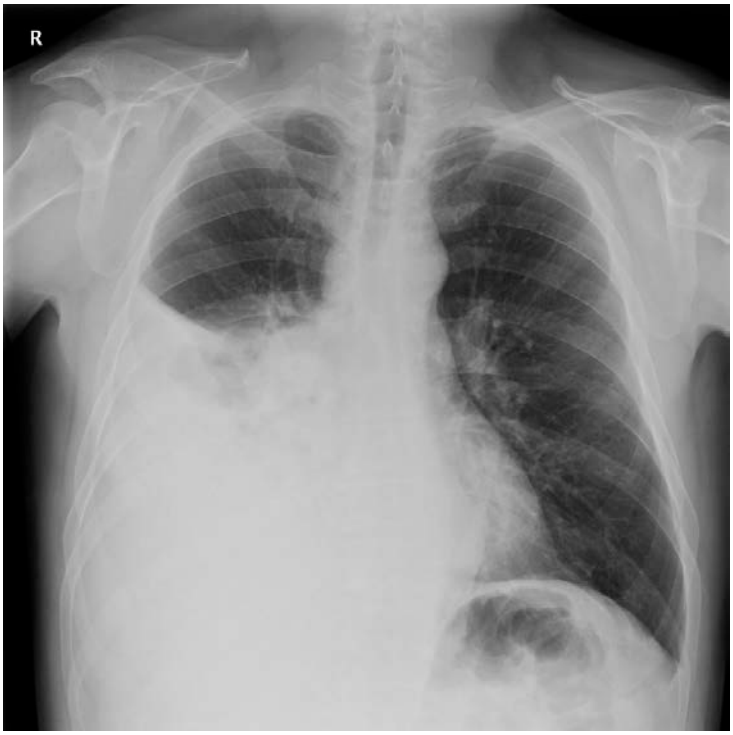

Figure 1. Initial chest radiography

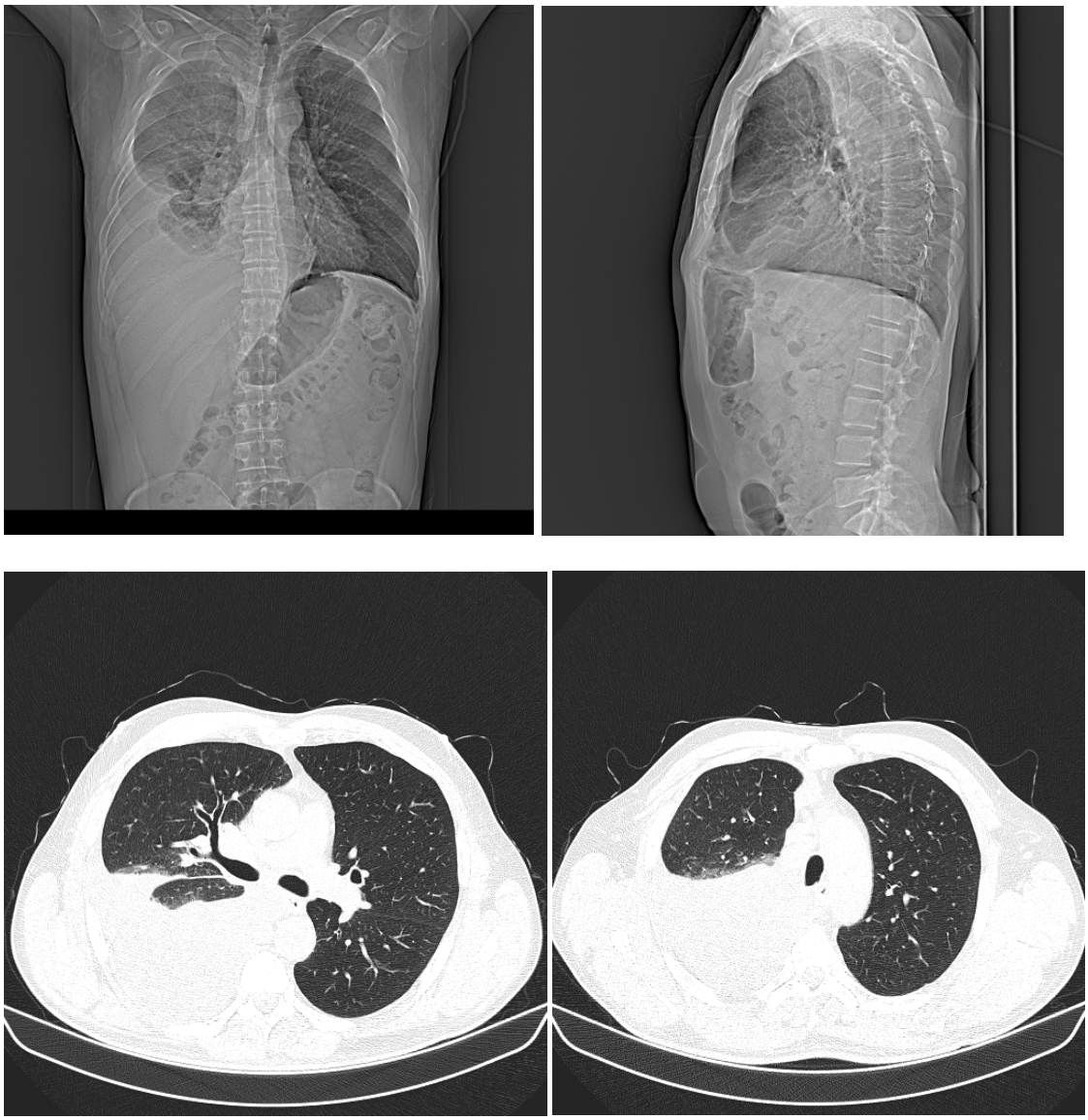

Figure 2. Computed tomography of the chest

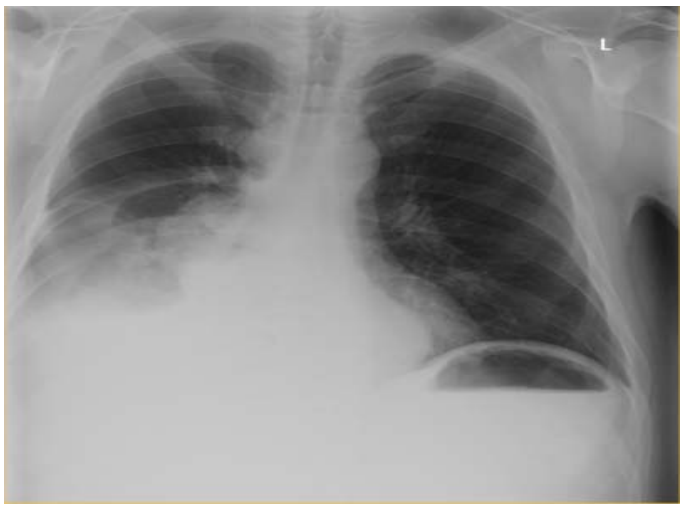

Figure 3. Control chest radiography

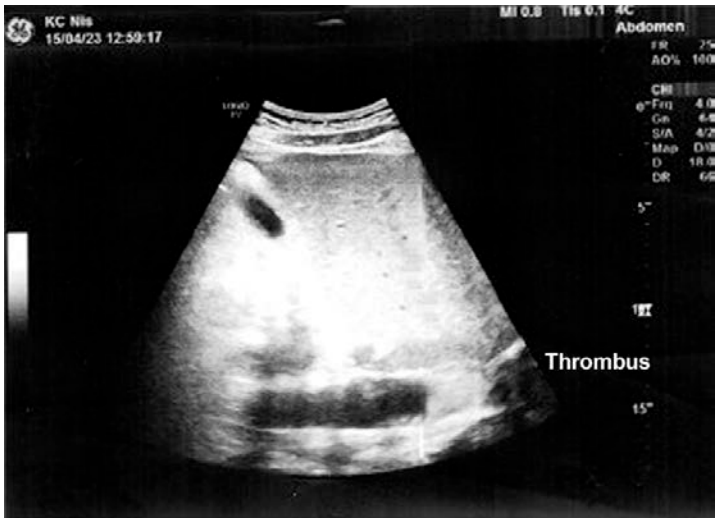

Figure 4a. Abdominal ultrasonography – visible thrombus in vena cava inferior

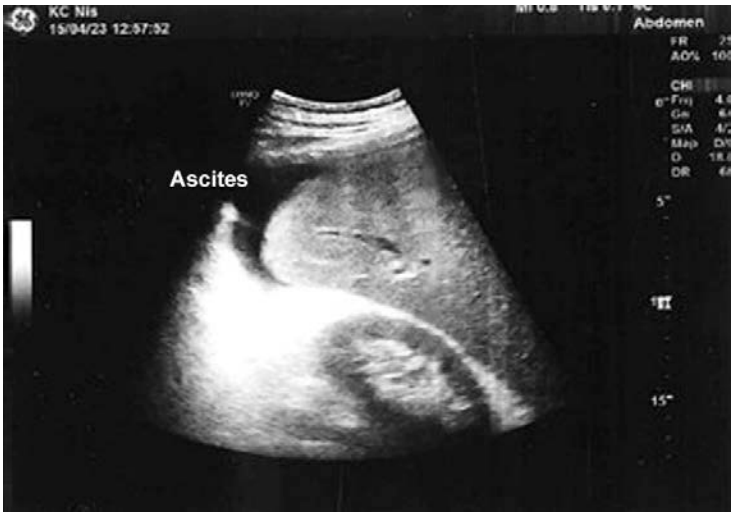

Figure 4b. Abdominal ultrasonography – ascites

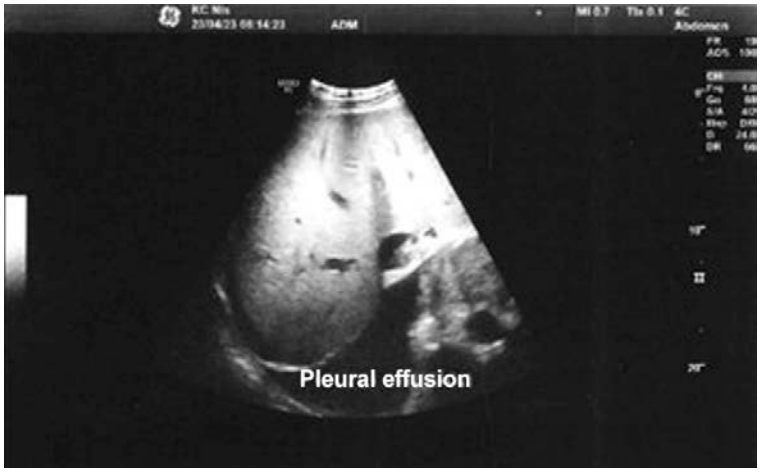

Figure 4c. Abdominal ultrasonography – pleural effusion

Discussion

We present a very rare case of BCS syndrome associated with small-cell lung cancer. According to etiology, this is the primary BCS caused by tumor thrombus of the inferior vena cava. According to the course, the described case represents a fulminant form of BCS syndrome. The symptoms are most often manifested in the form of a triad of pain in the upper part of the abdomen, ascites, and hepatomegaly. In general, patients with BCS syndrome have serious liver damage at the time of diagnosis. Doppler ultrasonography, CT or MR are non-invasive imaging techniques of choice for initial investigation when BCS is suspected (9). The prognosis depends on the degree of obstruction. Patients with complete obstruction of the inferior vena cava die within 3 years of liver failure, while in patients with incomplete obstruction, the course of the disease differs. In half of the patients, etiologic factors cannot be detected. The most common cause of BCS syndrome is diseases that cause blood hypercoagulability, such as polycythemia rubra vera and myeloproliferative diseases. Malignancies are the cause of BCS in about 10% of cases (13). The most common tumors that cause thrombus formation are liver and kidney tumors, rarely pancreas, and stomach tumors.

Although lung cancer is the leading cause of cancer death worldwide, (14) it is very rarely the cause of BCS syndrome. To date, only a few cases of BCS associated with lung cancer have been described. Patients had non-small lung cancer predominantly and rarely small cell lung cancer. (15) So, our case would be a very rare case in a patient with SCLC. Similarly, Japanese authors described a case of small cell cancer causing BCS syndrome by tumor thrombus of the inferior vena cava (16) Barbosa-Martins et al. (17) described metastatic lung cancer with multiorgan thrombosis and BCS syndrome. A rare case of BCS syndrome caused by tumor thrombus in the inferior vena cava secondary to lung cancer was reported by Dhali et al. (18). Huang et al. (19) reported a case of a patient with small cell lung cancer with an unusual initial presentation of both acute pancreatitis and acute BCS syndrome.

Clinicians rarely think about BCS syndrome. Therefore, the diagnosis is established late after severe liver damages occur. In our case, the diagnosis was made on time and treatment with low-molecular-weight heparin in therapeutic doses was started. However, significant liver damage developed early in the course of BCS syndrome in our case. Consequently, chemotherapy was not indicated.

Conclusion

We presented a very rare case of primary BCS syndrome in a patient with small cell lung cancer caused by tumor thrombus of the inferior vena cava. The diagnosis was made using Doppler ultrasound after which treatment with anticoagulant therapy was started. Due to the poor performance status and significant liver damage specific oncological treatment according to the Etoposide/Cisplatin regimen, which is the only choice of treatment in our country for patients with small cell lung cancer at this stage of disease, was not started. The patient was discharged from the hospital and advised to continue symptomatic therapy. Clinicians should be aware that acute BCS syndrome could be a feature of an undiagnosed lung cancer.

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BAD–KJARIJEV SINDROM KOD BOLESNIKA SA SITNOĆELIJSKIM KANCEROM PLUĆA: PRIKAZ SLUČAJA

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Bad–Kjarijev sindrom (*Budd–Chiari Syndrome* – BCS) predstavlja retku bolest uzrokovanu opstrukcijom hepatičnih vena koja se može javiti bilo gde na putu od hepatičnih venula do mesta gde se donja šuplja vena uliva u desnu komoru. Kongestija jetre dovodi do hipoksičnog oštećenja hepatocita. Hematološke i maligne bolesti predstavljaju etiološke faktore povezane sa Bad–Kjarijevijem sindromom. Pomenuti sindrom je retko stanje kod osoba sa kancerom pluća; poslednjih decenija opisano je samo nekoliko takvih slučajeva. U ovom radu prikazan je veoma redak slučaj akutnog Bad–Kjarijevog sindroma kod bolesnika sa primarnim sitnoćelijskim kancerom pluća izazvanim tumorskim trombom donje šuplje vene. Nakon što je dijagnoza postavljena na osnovu nalaza ultrazvuka, započeto je lečenje antikoagulantnom terapijom. Specifično onkološko lečenje nije započeto zbog lošeg opšteg stanja bolesnika i zbog značajnog oštećenja njegove jetre. Bolesnik je otpušten iz bolnice uz preporuku da nastavi simptomatsko lečenje. Valjalo bi da kliničari imaju na umu da akutni Bad–Kjarijev sindrom može biti obeležje kancera pluća koji nije prepoznat.

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***Ključne reči**: Bad–Kjarijev sindrom, kancer pluća*