Гипогликемический синдром при эпителиоидной гемангиоэндотелиоме печени, успешное лечение — трансплантация печени от живого родственного донора

© И.А. Бондарь[1], Л.И. Чесноченко[1], О.Ю. Шабельникова[1,2]*, И.А. Поршенников[1,2]

[1]ФГБУ ВО «Новосибирский государственный медицинский университет» Минздрава России, Новосибирск, Россия;
[2]ГБУЗ НСО «Государственная Новосибирская областная клиническая больница», Новосибирск, Россия

Гипогликемический синдром встречается не только при эндокринных заболеваниях, он может осложнять течение многих соматических болезней и опухолей панкреатической и внепанкреатической локализации. Развитие гипогликемии при опухолях печени связывают с уменьшением объема функционирующей ткани печени, усиленным потреблением и утилизацией опухолевой тканью глюкозы, торможением глюконеогенеза и гликогенолиза, секрецией инсулиноподобных пептидов. Гипогликемия при опухолях печени редко бывает первым симптомом заболевания и обычно возникает при больших размерах опухоли и симптомах опухолевой интоксикации. Эпителиоидная гемангиоэндотелиома печени — первичное злокачественное новообразование из группы мезенхимальных опухолей, занимает менее 1% всех злокачественных новообразований печени. Клиническое течение эпителиоидной гемангиоэндотелиомы печени весьма вариабельно. Встречаются медленно и быстро прогрессирующие варианты. Диагноз основывается на результатах гистологического и иммуногистохимического исследования послеоперационного материала. В литературе отсутствует описание гипогликемии при эпителиоидной гемангиоэндотелиоме. Описан случай тяжелого гипогликемического синдрома, обусловленного большой эпителиоидной гемангиоэндотелиомой печени. Лечение гипогликемии лекарственными препаратами было неэффективно. Массивное билобарное поражение печени опухолью исключало возможность резекции. Гепатэктомия с сохранением нижней полой вены и трансплантация правой половины печени от живого родственного донора позволили сохранить жизнь больному и устранить гипогликемию.

Ключевые слова: гипогликемический синдром, трансплантация печени, эпителиоидная гемангиоэндотелиома печени.

Hypoglycemic syndrome in hepatic epithelioid hemangioendothelioma, successful treatment — liver transplantation from a living related donor

Irina A. Bondar[1], Ludmila I. Chesnochenko[1], Olesia Yu. Shabelnikova[1,2]*, Ivan A. Porshennikov[1,2]

[1]Novosibirsk State Medical University, Novosibirsk, Russia;
[2]Novosibirsk State Regional Clinical Hospital, Novosibirsk, Russia

Hypoglycemic syndrome occurs not only in endocrine diseases but can complicate the course of many somatic diseases and tumors of pancreatic and extra-pancreatic localization. Development of hypoglycemia in liver tumors is associated with a decrease in the volume of functioning liver tissue, increased consumption, and utilization of glucose by the tumor tissue, inhibition of gluconeogenesis and glycogenolysis, and secretion of insulin-like peptides. Hypoglycemia in liver tumors is rarely the first symptom of the disease and usually occurs in patients with large tumor sizes and symptoms of tumor intoxication. Epithelioid hemangiendothelioma of the liver is the primary malignant neoplasm from the group of mesenchymal tumors, it occurs less than in 1% of cases of all malignant neoplasms of the liver. The clinical course of epithelioid hemangiendothelioma of the liver is highly variable. There are slowly and rapidly progressing variants. The diagnosis is based on the results of histological and immunohistochemical examination of the postoperative material. In the literature there is no description of hypoglycemia in epithelioid hemangiendothelioma. We report a patient with severe hypoglycemic syndrome, which was due to an epithelioid hemangioendothelioma of the liver. Pharmacological treatment of hypoglycemia was ineffective. The presence of massive bilobar tumor made it impossible to use a liver resection. Hepatectomy with living related liver transplantation was life-saving procedure and made it possible to eliminate hypoglycemia.

Keywords: hypoglycemic syndrome, liver transplantation, hepatic epithelioid hemangioendothelioma.

Background

Hypoglycaemic syndrome occurs not only in endocrine diseases, but also as a complication of other pancreatic and extrapancreatic diseases. Hypoglycaemia develops in 4% of patients with mesenchymal tumours or hepatocellular liver cancer in North America and in 27% of patients in Hong Kong [1]. Approximately 80% of liver tumours are hepatocellular cancer, and the percentage has increased by 62% in the past 20 years [2]. In liver tumours, hypoglycaemia is associated with a decrease in the volume of functioning liver tissue, increased glucose consumption and disposal by the tumour tissue, inhibition of gluconeogenesis and glycogenolysis, and secretion of insulin-like peptides (ILPs) [3,4]. Hypoglycaemia is rarely the initial symptom of liver cancer. It usually occurs in patients with large tumours and with symptoms of tumour intoxication [5].

Hepatic epithelioid haemangioendothelioma is a primary mesenchymal tumour that accounts for less than 1%

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of all hepatic malignant neoplasms and has an incidence of one case per 100,000 population per year [6, 7]. Even though it is rarely encountered, it is known to have a variable clinical course and either slow or rapid progression. Histological and immunohistochemical evaluation of surgical specimens confirm that epithelioid haemangioendotheliomas are endothelial tumours that express factor VIII-associated antigen (vWF), CD31 and CD34 [8]. In this patient, hypoglycaemia was an early complication of hepatic epithelioid haemangioendothelioma. The patient was successfully treated by orthotopic transplantation of a portion of the liver of a related donor. This appears to be the first report of hypoglycaemia associated with epithelioid haemangioendothelioma.

Case description

a 35-year-old man living in the Novosibirsk Region was treated at the endocrinology and the organ transplantation departments of the State Novosibirsk Regional Clinical Hospital (SNRCH, head physician AV Yudanov). On admission, the patient complained of periodic episodes of weakness, trembling, sweating, fatigue and drowsiness that occurred at night and in the morning. The symptoms resolved, or were prevented, by frequent intake of sweet foods. The patient's history revealed that he was healthy and employed until 29 years of age. Constant, intense headaches and unsteady gait appeared in 2010 after a head injury. At that time, a brain contrast-enhanced MRI examination at the Novosibirsk Research Institute of Traumatology and Orthopaedics (NRITO) found a meningioma in the right parietal region with penetration of the tentorium and large occipital foramen. A giant parasagittal meningioma of the right parietal lobe was partially removed following surgery with decompression trepanation. Histological evaluation confirmed an atypical mixed angiomatous, psammomatous meningioma with signs of growth activity. Repeated surgery 6 months later achieved complete removal of the meningioma. Cranioplasty was performed in 2012 following a course of radiation therapy. Annual follow-up at NRITO included a brain MRI in 2016 that showed no evidence of tumour recurrence. Episodes of weakness, fatigue, sweating and trembling began in February 2016. The patient did not seek medical attention until 2 months later after the occurrence of generalised tonic seizures, which were regarded as symptomatic epilepsy after the treatment of meningioma.

The patient was sent to the endocrinology department of SNRCH after an examination revealed fasting hypoglycaemia of 1.4 mmol/L. Physical examination found a satisfactory general condition, clear consciousness, a normosthenic constitution, body temperature of 36.6°C, weight of 77 kg, height of 180 cm, and a body mass index of 23 kg/m^2. The skin was of physiological colour, moist, clean and with normal turgor and elasticity. Subcutaneous tissue was moderate in extent and evenly distributed. No enlarged lymph nodes were detected and the thyroid gland was not enlarged. The respiratory rate was 19 breaths per minute. Breathing was vesicular and without rales. The pulse was 78 beats per minute with good tension and strength. The blood pressure was 130/90 mmHg with clear heart sounds and a normal rhythm. The tongue was moist and clean. The abdomen was enlarged, soft and painless on palpation. A painless, dense, tuberous 10 cm mass was palpable in the right hypochondrium. The liver had a Kurlov percussion size of 20×16×14 cm and protruded 5 cm below the costal margin. The abdominal murmur was clearly auscultated, and defecation was regular with formed stools. The spleen was not palpable. There was no peripheral oedema. The provisional diagnosis was hypoglycaemic syndrome of unknown origin. It was necessary to clarify whether the hypoglycaemia was fasting or reactive and with or without an increase in insulin levels. Given the history of surgery for meningioma, it was necessary to rule out secondary chronic adrenal insufficiency, insulinoma, tumour or metastasis. Eating foods with a high glycaemic index every 1–2 h was recommended, 4 mg intramuscular dexamethasone at night and 40 ml 40% glucose solution administered 2–3 times during the day in case of episodes of hypoglycaemia were prescribed. Despite treatment, hypoglycaemia occurred up to two times a day. Blood glucose monitoring revealed that glycaemia decreased at night and during the day to 2.0–2.2 mmol/L.

Blood evaluation revealed thrombocytopenia with 133×10^9 cells/L but no other abnormalities in the blood count. Gamma glutamyl transferase (103.3 U/l), alkaline phosphatase (142.2 U/l) and alanine aminotransferase (64 U/l) were increased, but bilirubin (13 μmol/L), total protein (69.5 g/L), urea (2.1 mmol/L), creatinine (59.0 μmol/L), potassium (3.88 mmol/L), sodium (146.2 mmol/l) and glycated haemoglobin (4.7%) were within normal limits. Insulinoma was ruled out because of low insulin (0.7 μIU/ml, normal range 1.9–23.0 μIU/ml) and a C-peptide concentration of < 0.01 ng/ml (normal range 0.9–7.1 ng/ml). Thyroid-stimulating hormone (1.46 μMU/ml, normal range 0.4–4.0 μMU/ml), free thyroxin (15.8 pmol/L, normal range 11.5–22.7 pmol/L) and plasma cortisol (15.2 μg/dl, normal range 5–25 μg/dl) ruled out pituitary gland pathologies. Serum tumour markers were within normal limits, with 0.0 U/ml alpha-fetoprotein (normal range 0.0–14.4 IU/ml) and 1.79 ng/ml carcinoembryonic antigen (normal range 0.0–6.2 ng/ml).

Contrast-enhanced multislice computed tomography (MSCT) revealed multiple rounded structures of various size and 2–3 mm in diameter and larger in the liver parenchyma **(Fig. 1)**. The structures had uneven, clear contours. The largest ones were a 13.2 cm mass in the right lobe and 13 cm mass in the left lobe. They had a cystic–solid appearance with a pronounced uneven accumulation of the contrast agent in the arterial and venous phases that traced a vascular network. Other than the hypervascular lesions in the liver parenchyma, no abnormalities of the abdominal organs or retroperitoneal space were seen. Dynamic magnetic resonance imaging with gadox-

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etic acid contrast enhancement **(Fig. 2)** revealed liver enlargement with vertical dimensions of 24 cm of the right lobe and 18 cm of the left lobe. The horizontal dimension was 21 cm. The contours were clear and even; and with contrast enhancement, the density of the intact parenchyma reached a maximum in the portal and hepatospecific phases. A 12×13 cm spherical pathological mass with uneven macrotuberous contours and heterogeneous appearance was seen in liver segment (Sg)7–8, and a 9×13 cm with a similar appearance was seen in Sg2–3. Both masses intensely and unevenly accumulated contrast agent in the arterial phase. Spherical foci of sizes that varied from 5 to 20 mm in diameter, had clear and even contours, and were homogeneous in structure, were seen in the liver parenchyma. No other changes in the organs of the abdominal cavity and retroperitoneal space were detected. The tomographic signs were consistent with hepatocellular carcinoma with multiple bilobar lesions. MSCT of the chest organs revealed no distant metastases. The clinical diagnosis was hepatocellular cancer in Sg2–3, Sg6–7–8 of the normal liver with multiple intrahepatic T4NxM0, metastases and severe hypoglycaemic syndrome.

Given the young age of the patient, the massive bilobar lesion in the absence of signs of local dissemination or regional metastases, and the absence of liver cirrhosis, liver transplantation was considered as a treatment option. A preoperative puncture biopsy for morphological verification of the diagnosis was not done because of the risks of subsequent implantation metastasis and intraperitoneal bleeding from the hypervascular tumours. As the time needed to obtain an organ from an unrelated donor is not predictable, it was decided to transplant a portion of the

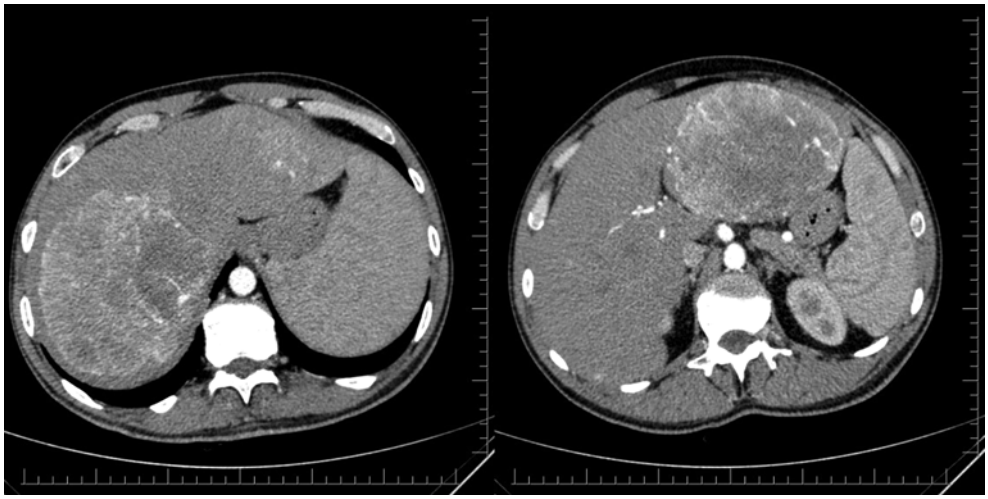

Fig. 1. **MSCT of the abdominal cavity: arterial phase (described in the text).**

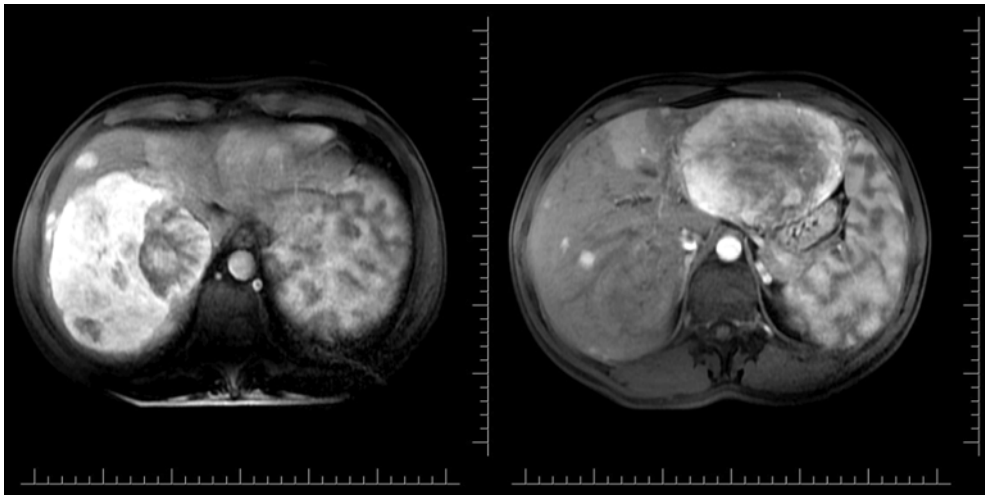

Fig. 2. **MRI: dynamic scanning of the liver in axial projection on the LAVABHAsset pulse sequence using gadoxetic acid (described in the text).**

liver from a related donor. An uncle of the patient was found to be a suitable donor. The surgical procedures were performed in 07 June 2016. The donor tissue was obtained by a right-sided hemihepatectomy without any procedural problems. A Mercedes-Benz type laparotomy was performed in the recipient. The abdominal cavity revision showed no signs of cirrhotic changes in the liver, but it was significantly increased in size. The neoplasms in Sg2–3 and Sg6–7–8 had a soft, elastic consistency and both were approximately 13–14 cm in diameter. There was no tumour invasion of the portal gate, the retrohepatic segment of the inferior vena cava, or the surrounding tissues and organs. There were no signs of paracaval and paraportal lymphadenopathy, carcinomatosis or portal hypertension. The hepatectomy was performed without resection of the retrohepatic segment of the inferior vena cava, and involved a liver that weighed approximately 5 kg (**Fig. 3** and ADDITIONAL INFORMATION). Grafting of the donor liver tissue was completed in 10.5 h and without incident. The surgery in the recipient was performed with continuous intravenous infusion of 10% glucose solution, and intraoperative blood loss of 1100 ml. Immediately after removal of the tumour, the patient's glucose level returned to normal with successive measurements of 5.2, 6.7, 6.3 and 5.9 mmol/L.

Histological examination of resected liver tissue found that the liver tumour nodes included medium-size elongated and round-oval cells with spindle shaped, ovoid or irregularly shaped nuclei. Mitotic activity was low, the tumour tissue was solid with the formation of trabeculae and papillary structures. Cavernous cavities were seen in some visual fields, and tumour cells were present in the lumens of sinusoidal vessels, with reticular and collagen fibrosis and infarctions in some lumens. The histology was consistent with a diagnosis of epithelioid haemangioendothelioma of both lobes of the liver with multifocal growth of two 13 cm nodes and multiple nodes of up to 1 cm in diameter, without signs of tumour growth in the blood vessel margins or distant lymph nodes. Immunohistochemical staining (**Fig. 4** and ADDITIONAL INFORMATION) found that the tumour cells expressed vWF, CD31, CD34 and vimentin, but not smooth muscle actin, chromogranin A or CD117. The immunophenotype of the tumour was consistent with hepatic epithelioid haemangioendothelioma. The final clinical diagnosis was epithelioid haemangioendothelioma, multiple bilobar lesion and severe hypoglycaemic syndrome.

The course of the postoperative period was uneventful. Glycemia varied from 4.2 to 7.6 mmol/l without hypoglycaemia. Immunosuppressive therapy was initiated with de novo everolimus ± tacrolimus. The steroid-free protocol included rapid reduction of steroid doses with complete withdrawal on day 5. After 1 year and 8 months of follow-up, the patient's condition remained satisfactory with no emergence of extrahepatic tumours or signs of disease progression. Everolimus was continued at 5–7 ng/ml, and tacrolimus at 3–5 ng/ml.

Discussion

Yeung et al. described two types of hypoglycaemia in hepatocellular carcinoma patients [5, 9]. Type A hypoglycaemia occurred in patients with low-grade liver tumours. The hypoglycaemia was mild or moderate and appeared 2 weeks before death. Hypoglycaemia occurred because of severe liver damage, low glycogen reserves and inability to satisfy the body's need for glucose. Type B hypoglycaemia occurred in patients with slowly growing tumours, was severe and was accompanied by severe impairment of consciousness, convulsions and coma. It was caused by increased synthesis of tumour tissue ILP-2 and its effect on glucose disposal. Rarely was hypoglycaemia the first manifestation of a liver tumour. Hypoglycaemia occurred in this patient when the tumour had reached a large size and had replaced a significant amount of liver parenchyma. Hypoglycaemia was an early symptom, and the patient did not experience liver failure or tumour intoxication. The clinical course of the hypoglycaemia was short and was initially characterised by episodes of weakness, fatigue, severe sweating, paraesthesia and body tremors that occurred daily. The manifestations were stopped by eating rapidly digested carbohydrates. After 2 months, the hypoglycaemia became severe and was associated with generalised tonic seizures, retardation and abnormal behaviour. After another month, the frequency of seizures increased to 2–4 times a day, which required the intravenous administration of a 40% solution of glucose and glucocorticoids

In contrast to patients with insulinomas, those with extrapancreatic tumours complicated by fasting hypoglycaemia experience decreases in plasma insulin and C-peptide [10, 11]. Insulin and C-peptide levels were low in our patient. Hepatocellular cancer accompanied by hypoglycaemia have been previously reported [12, 13]. The pathogenesis of hypoglycaemia is associated with increased glucose uptake by the tumour and inhibition of gluconeogenesis because of the hepatotoxicity of products secreted by the tumour or activated liver macrophages including cytokines (e.g. interleukin-1, alpha-interferon and tumour necrosis factor-alpha). Increased glucose uptake can be mediated by oncogenes in the tumour cells that increase the activity of glucose transporters. ILP-1 and ILP-2 are increased in 50% of patients with tumours plus hypoglycaemia. Type 3 ILP-binding protein provides access to secreted ILP-2; and in some patients, ILP-2 and type 3 ILP-2-binding protein are present as a binary complex, which dissociates easily in tumour tissue leading to an increase in free ILP. ILP-2 inhibits the secretion of glucagon and somatotropic hormone, which reduces blood glucose. The ILP-1 receptor is similar to the insulin receptor. ILP-1 interacts with the cell receptor like insulin to stimulate the absorption of glucose by muscle and adipose tissue [14, 15]. Hypoglycaemia has been reported in liver cancer, but we have not been able to find any reports of epithelioid haemangioendothelioma in combination with hypoglycaemia.

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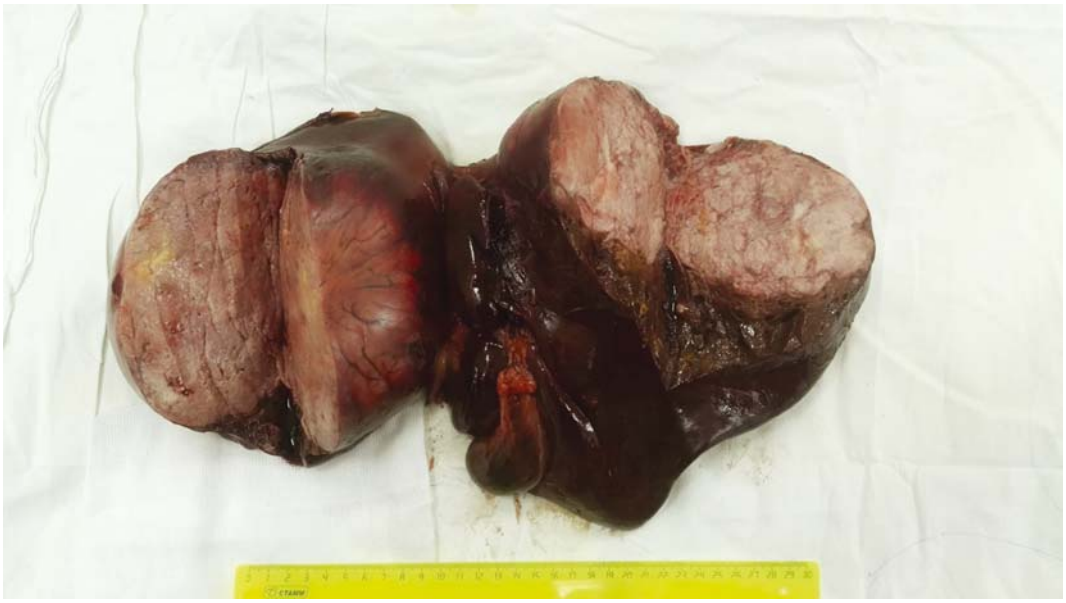

Fig. 3. **Type of liver removed.**

The liver is without signs of cirrhotic changes, significantly increased in size, with soft-elastic neoplasms in Sg2–3 and Sg6–7–8 (diameter 13–14 cm); there is no tumor invasion into the portal gates. The mass of the removed liver is 5 kg.

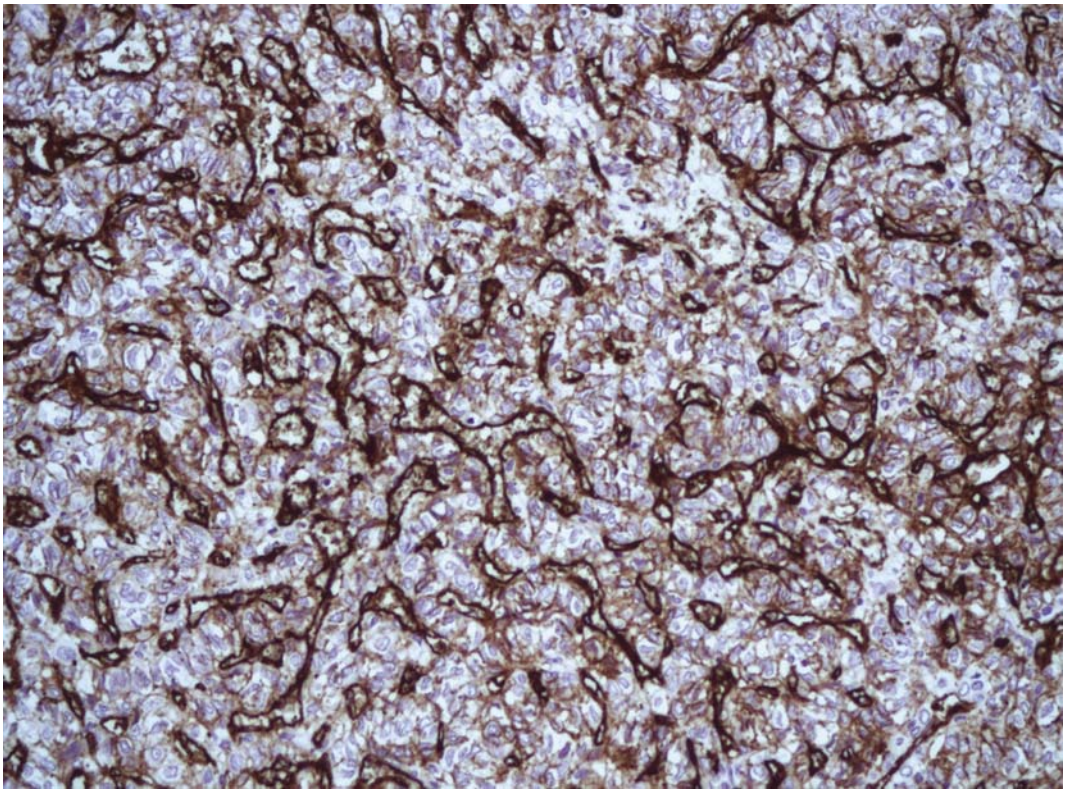

Fig. 4. **Immunohistochemical study.**

Tumor nodes in the liver are represented by proliferating cells of medium size elongated and rounded oval in shape with fusiform, ovoid and irregularly shaped nuclei; mitotic activity is low. Tumor cells grow both solidly and with the formation of trabeculae and papillary structures; in part of the visual fields, cavernous cavities are visible. Tumor cells grow in the lumen of the sinusoidal vessels. The tumor intensively expresses CD34. × 200.

Hypoglycaemic syndrome in patients with tumour is usually treated by eating rapidly digested carbohydrates, which can prevent its further progression. Drug therapy is not effective, but an episode of hypoglycaemia can be arrested for a short time by intravenous administration of 40–60 ml of a 40% glucose solution. Corticosteroids such as dexamethasone 2 mg or prednisolone up to 40 mg per day usually prescribed, but have only a temporary effect on increasing blood glucose, and repeated administration is required [5]. Thipaporn reported that long-acting steroids were more effective than short-acting steroids [16]. Tsai et al. described a case of a 42-year-old woman with severe hypoglycaemia with loss of consciousness and a blood glucose level of 30 mg/dl that was the first manifestation of hepatocellular carcinoma. Computed tomography revealed a 15 cm liver tumour with metastasis. Oral administration of rapidly digested carbohydrates, administration of glucose solution and prednisolone had no effect. Hypoglycaemia episodes decreased to once a month following palliative radiation. Preoperative dexamethasone is not indicated in patients with extrapancreatic tumours accompanied by hypoglycaemia as the drug inhibits the release of insulin from pancreatic beta cells [17]. Administration of growth hormone, or somatostatin, glucagon or adrenaline analogues is not accompanied by a persistent increase in glycemia. The most effective treatment for hypoglycaemia caused by liver tumours is a reduction in tumour volume by surgery, chemotherapy and radiation therapy, or ethanol injection [1,18–20]. Resection is excluded in patients with large tumour volumes.

Conclusion

Hypoglycaemia was arrested or prevented in this patient by frequent meals that included rapidly digested carbohydrates, intravenous administration of 40 ml of a 40% glucose solution, and daily intramuscular administration of 2–4 mg dexamethasone and 30–60 mg prednisolone. Treatment only reduced the frequency and severity of hypoglycaemia. Liver resection was not considered because of the large tumour volume. Liver transplantation was the only life-saving option. The patient was successfully treated by hepatectomy and liver transplantation from a related living donor. The hypoglycaemia completely resolved following the surgical procedure.

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ИНФОРМАЦИЯ ОБ АВТОРАХ
***Шабельникова Олеся Юрьевна**, к.м.н. [Olesia Yu. Shabelnikova, MD, PhD]; адрес: 630087, Россия, Новосибирск, ул. Немировича-Данченко, 130 [address: 130 Nemirovich-Danchenko street, Novosibirsk, Russia 630087]; ORCID: https://orcid.org/0000-0003-3906-4784; eLibrary SPIN: 5941-4815; e-mail: odc@oblmed.nsk.ru
Бондарь Ирина Аркадьевна, д.м.н., проф. [Irina A. Bondar, MD, PhD, Professor]; ORCID: https://orcid.org/0000-0003-4324-2926; eLibrary SPIN: 6633-8947; e-mail: bondaria@oblmed.nsk.ru
Чесноченко Людмила Ивановна, к.м.н. [Ludmila I. Chesnochenko, MD, PhD]; ORCID: https://orcid.org/0000-0001-8806-5906; eLibrary SPIN: 6633-8947; e-mail: z111777@yandex.ru
Поршенников Иван Анатольевич, к.м.н. [Ivan A. Porshennikov, MD, PhD]; ORCID: https://orcid.org/0000-0002-6969-6865; eLibrary SPIN: 7291-7988; e-mail: porshennikov@oblmed.nsk.ru

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