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Case Report

The Use of Liver Support System Devices in Acute Liver Failure as a Consequence of Metastatic Melanoma in the Liver: A Case Report and Review of the Literature

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Keywords
Melanoma · Liver failure · Liver support system devices · BRAF/MEK inhibitors

Abstract
Introduction: Melanoma often metastasizes to the liver, leading to significant morbidity and mortality. Liver injury can also occur due to hepatitis caused by immunotherapy used in the treatment of melanoma. ***Case Presentation:*** This case report presents a 38-year-old male diagnosed with advanced melanoma who experienced acute liver failure (ALF) initially thought to be a side effect of immunotherapy. Despite following aggressive supportive care as per the latest guidelines, the patient's condition deteriorated rapidly. It was discovered that the patient had liver metastases. As the tumor had a positive BRAF mutation, we opted for invasive treatment with therapeutic plasma exchange to restore liver function and create the conditions for initiating treatment with BRAF/MEK inhibitors. After the use of a liver support device, the liver function was resolved, and a BRAF/MEK inhibitor was introduced. After 2 months of targeted therapy, a favorable effect and good melanoma control are observed. ***Conclusion:*** The report underscores the complexity of managing melanoma with liver metastasis and the urgent need for advancements in treatment modalities ALF in oncology patients. We suggest that invasive treatment methods, such as liver support system devices, should be considered in well-selected oncology patients, even in advanced stages of disease.

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Introduction

Cutaneous melanoma is a malignancy arising from melanocytes of the skin. It represents one of the most aggressive types of cancer. Melanoma incidence has been continuously rising in the past 4 decades in the fair-skinned populations, more rapidly than for any other extra-cutaneous cancers [1]. According to GLOBOCAN 2020, the melanoma age-standardized world rate incidence in Europe ranges from 30.8 per 100,000 inhabitants/year in Denmark to 3.8 in Bulgaria [2]. Mortality rates in EU-27 in 2022 are estimated to be an average of 1.5 deaths per 100,000 inhabitants/year (age-standardized world rate). Among the EU-27 countries, there is a threefold variation in mortality between the highest rates in Croatia and the lowest in Spain, with gender-specific differences represented by a 1.34 times higher mortality rate in men compared to women [3]. Malignant melanoma has a high tendency to spread. After the primary tumor is removed, around 30% of patients develop metastases in different organs. The prognosis for patients with metastatic melanoma is poor, with a 5-year survival rate ranging from 5 to 19% which is determined by the location and number of metastases [4, 5]. Visceral metastases, especially in the brain and liver, evolved in most cases to death [6, 7].

Immunotherapy with immune checkpoint inhibitors and molecularly targeted therapy with BRAF inhibitors were pioneered in the treatment of advanced-stage, unresectable melanoma, revolutionizing patient care and significantly improving survival. These therapeutic approaches have also been successfully transitioned into the respectable disease setting, as postoperative (adjuvant) treatments for groups of patients with high-risk melanoma [7]. The potent and durable response has only been limited to a subgroup of patients. Several patients demonstrate a lack of initial response to treatment, and patients with an initial promising response to treatment can develop resistance over time [8]. These treatments, also, can be limited by inflammatory toxicities that can affect any organ system in the body and in some cases can be life-threatening. Considerable progress has been made in understanding the drivers of these toxicities as well as effective management strategies [7, 8].

The liver as one of the largest organs has essential synthetic, excretory, metabolic, and immunogenic functions. Acute or acute-on-chronic liver failure is a devastating condition that can progress to multi-organ failure (MOF) and is associated with very high mortality. The high mortality following liver failure unfortunately has not significantly changed over the last decades. Various extracorporeal liver support (ECLS) system devices have been developed to support patients until the recovery of liver function or the possibility of liver transplantation (LT). In clinical practice, ECLS may be used to support detoxification of liver function in a way to remove albumin-bound toxins as well as water-soluble substances [9–12]. The final goal of all available ECLS is to reduce patient mortality serving as a bridge to liver transplant. Sometimes, ECLS can be used as a method that will temporarily reduce sequelae of liver failure until liver function recovers [11]. The use of ECLS requires the involvement of multiple disciplines such as hepatology, intensive care nephrology, and transfusion medicine specialists. A multidisciplinary team approach in the context of ECLS is required [10–13].

LT is the only curative treatment in patients with acute or acute exacerbation of chronic liver failure associated with a high likelihood of death; however, LT in the context of extended malignant disease is not an option. Here, we report a case of a patient with acute liver failure (ALF) that occurred as a consequence of hyper-progression of malignant melanoma with multiple liver metastases. The ALF in our patient was treated using the combination of therapeutic plasma exchange (TPE) and hemodiafiltration.

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Case Presentation

The 38-year-old male patient, with no significant personal medical history but with a family history of breast cancer on his mother's side, was initially presented at the surgery clinic with a pigmented lesion on his left upper back. A 1.2 cm × 0.8 cm asymmetrical, irregularly bordered, multicolored lesion was observed on physical examination. An excisional biopsy was performed, and the tissue was sent for histopathological examination (Fig. 1). The biopsy revealed a superficial spreading melanoma. The Breslow thickness was measured at 3.6 mm, Clark level III invasion was noted, mitotic rate 6/mm^2, and ulceration. As the side surgical margin was close (1 mm), re-excision with wide surgical excision and sentinel lymph node biopsy were done. Histopathologically, there was no evidence of melanoma in resected tissue and sentinel lymph nodes of the right axilla. Metastases of melanoma were found in lymph nodes of the left axilla, with extracapsular extension. An activating missense mutation in codon 600 of exon 15 (V600E) of the BRAF gene has been identified. Positron emission tomography-computed tomography scan showed multiple hypermetabolic lesions in left axillary lymph nodes, subcutaneously in the location of the scar, and suspicious metastases in the lungs. Lactate dehydrogenase (LD) and S-100 were not elevated. Given the advanced stage and aggressive nature of the disease, without the signs of disease, the patient started on combination immunotherapy with ipilimumab (3 mg/kg every 3 weeks) and nivolumab (1 mg/kg every 3 weeks). Seventeen days after the second cycle of therapy, he presented with fever, abdominal pain, nausea, diarrhea, fatigue, and a nonproductive cough. Physical examination was normal, except for right upper quadrant tenderness without hepatomegaly. Pathological values in laboratory tests included elevated liver transaminases, cholestatic parameters, and inflammatory markers. Stool studies were negative for infectious pathogens. The viral hepatitis panel was negative for hepatitis A, B, and C. Blood and urine cultures were sterile. Abdominal ultrasound showed no biliary obstruction or liver masses, and chest X-ray was normal. He started peroral therapy with an amoxicillin-clavulanic acid 875 mg/125 mg twice daily. Seven days later, the patient complained of pain below the ribs on both sides and had two episodes of diarrhea per day. Liver transaminases and cholestatic enzymes increased further, with a predominance of cholestatic parameters. Four days later, during the next appointment, a chest X-ray was performed due to breathlessness. Pneumonia in the right lobe was revealed. The patient was hospitalized because of pneumonia and due to a more significant increase in liver transaminases (up to 20 times the upper normal limit), with suspicion of grade 1 colitis and grade 3 hepatitis possibly induced by immunotherapy. Ipilimumab and nivolumab were discontinued. Previously induced antibiotic therapy was excluded, and we initiated intravenous methylprednisolone 2 mg/kg/day, meropenem 3 × 2 g, and supportive care. Symptoms of diarrhea improved within 1 week of steroid therapy; however, there was no improvement in the liver tests. During hospitalization, due to further worsening of dyspnea, a CT pulmonary angiography was performed, which described polytopic nodular shadows on the lungs, along with pathological mediastinal, retro pectoral, and axillary lymphadenopathy. Magnetic resonance imaging (MRI) of the abdomen also confirmed the progression of melanoma in the liver, spleen, and thoracic spine. During the corticosteroid therapy, the patient finally developed grade 4 hepatitis, and after receiving mycophenolate mofetil 2 × 500 mg peroral for 6 days, hepatic insufficiency continued progressively. Thus, immune-related adverse events due to immunotherapy were excluded. The follow-up abdominal MRI did not show any improvement in the liver (Fig. 2). There was a failure of the secretory, synthetic, and metabolic liver function. The patients had signs of hepatic encephalopathy grade III according to West Haven classification, with elevated serum bilirubin levels (90 mmol/L), disturbed prothrombin time test (prothrombin time 0.4) and INR (4.7), and marked hypoalbuminemia (serum albumin 22 g/L). Liver enzymes were also increased;

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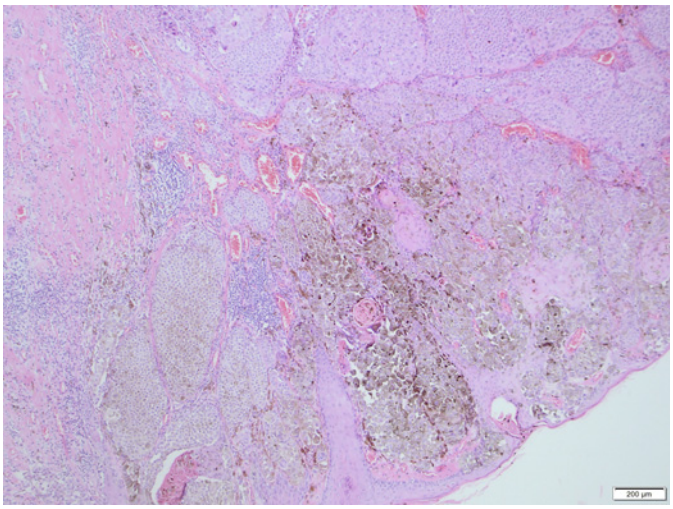

Fig. 1. Histopathological image.

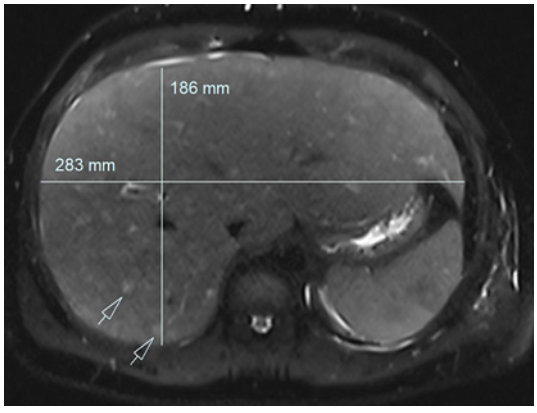

Fig. 2. Axial T2-weighted image with fat saturation shows an enlarged liver with pale innumerable focal lesions (arrows point at two lesions).

aspartate aminotransferase was 121 mmol/L; alanine aminotransferase, 136 mmol/L; alkaline phosphatase, 472 mmol/L; and gamma-glutamyl transferase, 476 mmol/L. Also, LD values and S-100 were extremely high (10,907 U/L and 39,000 μg/dL). Corticosteroids were gradually tapered with close monitoring. Considering the clinical course of the disease, and the bad physical condition of the patient, in agreement with the patient and the patient's family, as a life-saving method, continuous venovenous hemodiafiltration (CVVHDF) and TPE were performed. CVVHDF was performed for 12 h (provisions: dialysate 1,500 mL/h + substitute 1,000 + 1,000 mL/h), ultrafiltration 0 mL/h, applied heparinization – enoxaparin sodium 20 mg every 8 h (with factor Xa monitoring), and flushing the system with a heparin solution before starting CVVHDF. Additionally, after CVVHDF treatment, TPE was performed with the following prescription: 3,500 mL of plasma was exchanged (compensation 2,000 mL albumin 5% + 1,500 mL fresh frozen plasma). After the end of TPE treatment, CVVHDF was performed again for 12 h according to the same prescription. During the next 48 h, the liver function tests showed a significant improvement, as well as the patient's physical condition. There were no more signs of hepatic encephalopathy. There was an improvement in coagulation parameters (PV 0.7 and INR 2.0), as well as in bilirubin (28 mmol/L) and serum albumin (36 g/L) levels. Since liver function has recovered and given the presence of BRAF

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V600E mutation and the urgent need for treatment, 48 h after the treatment with CVVHDF and TPE, BRAF/MEK inhibitors therapy was initiated with dabrafenib 150 mg twice daily and trametinib 2 mg once daily. The first CT and MRI evaluation, 2 months after the beginning of targeted therapy, showed a significant reduction in the size of pulmonary, hepatic, and spleen metastases (Fig. 3). The patient is tolerating the therapy without experiencing any side effects. Two months after the beginning of targeted therapy, liver enzymes were practically within the reference interval suggesting that they were elevated due to multiple liver metastases and also the efficiency of therapy; aspartate aminotransferase 41 mmol/L, alanine aminotransferase 30 mmol/L, alkaline phosphatase 152 mmol/L, gamma-glutamyl transferase 63 mmol/L. Additionally, LD and S-100 values were normalized. Figures 2 and 3 show the first MRI and the MRI of the liver after 2 months. Figure 4 shows the timeline diagram of clinical course.

Discussion

The liver is a common site for metastases, partially because of its unique and diverse cellular and architectural composition, which makes it hospitable to tumor cells. Overall, metastatic disease is known to be responsible for greater than 90% of solid tumor-related mortalities [7]. In our case, the diagnosis of liver metastasis was complicated due to the potential side effects of immunotherapy treatment which is excluded during hospitalization. The deterioration of liver function in our patient was a cause for concern as it was not responding to standard therapy for grade 4 immunotherapy-induced hepatitis. The treatment required intensive monitoring, high doses of corticosteroids, and immunosuppressive therapy. Upon further diagnostics, it became likely that the liver failure was a result of melanoma metastases, highlighting the complexity and severity of the condition. Because of the failure of all liver functions (secretory, synthetic, and metabolic), we could not prescribe BRAF/MEK inhibitors to have a rapid therapeutic effect on our patients at that point. Due to the need for prompt action and impaired liver function, we opted not to proceed with a liver biopsy to confirm the cause of ALF, but instead to attempt to restore liver function. We decided to use CVVHDF treatment followed by TPE for rapid and short-term liver function recovery. This treatment was followed by recovery of all liver functions which enabled us to apply targeted therapy.

Until now, the treatment of liver failure in patients in stage 4 of the malignant disease included only symptomatic measures and most often led to death. Given that our patient is young and, apart from malignant melanoma, healthy, we decided to use an invasive measure of treatment of liver failure so that he could start targeted therapy with BRAF/MEK inhibitors to achieve a rapid therapeutic response. According to our best knowledge, this is the first case of applying some extracorporeal liver support system devices to recover liver function in patients with stage 4 of any kind of malignant disease.

LT is the best treatment option for patients with acute or acute on chronic liver failure. However, LT is contraindicated in patients with stage 4 of malignant disease. Treatment options that will serve as a “bridge” for critically ill patients to LT or methods that will preserve all liver function in a case when LT is either contraindicated or unavailable have been developed in the last decade.

In the context of liver failure, various toxins and various substances accumulate in the blood, consequently aggravating injury of the liver, inhibiting liver functions, and suppressing hepatocyte regeneration as well as causing MOF [12]. Thus, extracorporeal liver support methods are used to reduce the symptoms of liver failure by removing bilirubin, bile acids, ammonia, aromatic amino acids, pro-inflammatory cytokines, nitric oxide, etc., from the body. These substances play a role in the development of hepatic encephalopathy, hepatorenal

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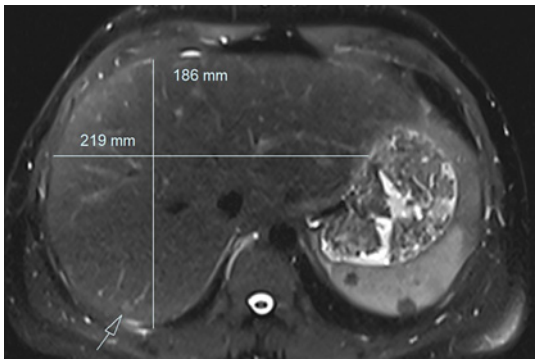

Fig. 3. Axial T2-weighted image with fat saturation shows a decreased liver size with fewer focal lesions (arrow).

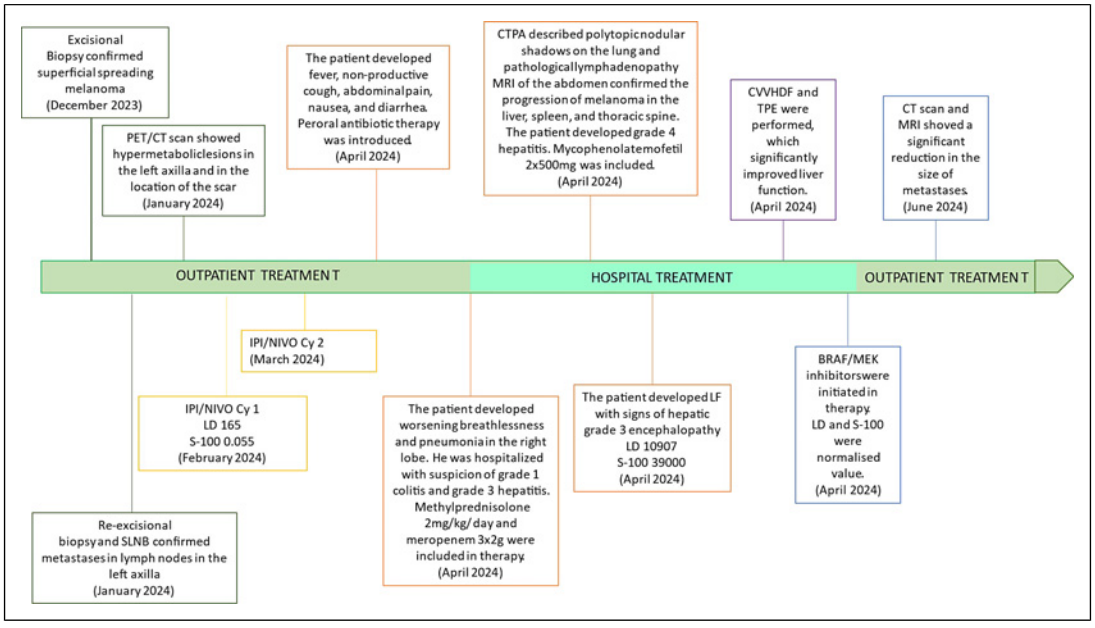

Fig. 4. Timeline diagram.

syndrome, and hyperdynamic circulatory failure [9]. By eliminating them, extracorporeal liver support devices can temporarily stop the progression of liver damage and MOF. The existing literature delineates several indications for the use of extracorporeal methods: acute hepatic failure resulting from alcohol, viruses, drugs, and toxins; post-traumatic hepatic failure; and patient stabilization before and after LT [9].

Generally, blood toxic substances are divided into two groups; water soluble such as creatinine, ammonia, and various interleukins and protein-bound substances such as bilirubin. Conventional methods such as hemofiltration and hemodialysis remove the water-soluble toxins [13]. In 2016, the first randomized controlled trial by Larsen et al. [14] investigating the usefulness of TPE in the context of ALF was published. Nowadays, TPE has been proposed as a beneficial method for patients with liver failure. With the help of this method, we can remove many large compounds from the blood, water-soluble toxins, and albumin-bound substances and replacement with albumin and/or plasma [13]. As it was mentioned earlier, these substances such as ammonia, bilirubin, bile acids, various cytokines and endotoxins, and aromatic amino acids are responsible for the development of MOF in the context of liver failure. Other liver support system devices include extracorporeal albumin dialysis systems such as single-

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pass albumin dialysis, molecular adsorbent recirculation system (MARS), and fractionated plasma separation and adsorption [12–14]. In comparison to TPE, MARS is more costly; however, there are no randomized controlled trials that compare extracorporeal albumin dialysis systems and TPE except for one small study in pediatric patients [12, 13, 15]. In that study, a combination of TPE and hemodialysis was associated with a greater improvement in bilirubin, ammonia, and INR levels in comparison to MARS [15]. One more advantage of TPE in comparison to MARS or some other extracorporeal albumin dialysis systems is the exchange of plasma. Namely, plasma exchange replaces various plasma proteins such as clotting factors, which we know are decreased in acute or acute chronic liver failure due to decreased synthetic liver function [13]. In our case, we used the combination of CVVHDF and TPE, and after the treatment, the coagulation factor was within normal values. To date, there is no consensus on the frequency and duration of TPE treatment. In our case, one treatment session with TPE was associated with improvement in synthetic, excretory, and metabolic liver function, biochemical parameters, and survival of our patient.

In patients with ALF and those with acute or acute-on-chronic liver failure due to other etiologies such as viruses, alcohol, and medications, TPE is the most often used method of liver support. However, there are no data regarding the utilization of liver support system devices in patients experiencing liver failure, whether from liver metastases or immunotherapy side effects. Thus, further studies on this topic need to keep in mind that today, we have some specific cancer therapies that can rapidly and effectively control the disease as was the case with our patient. Nevertheless, potential disadvantages of using these procedures, along with the development of periprocedural complications, may be the prolongation of the patient's suffering in the terminal stage of the disease when the desired therapeutic effect is not achieved.

The use of intensive treatment methods for advanced cancer patients will continue to be a topic of debate in clinical practice. Decisions regarding using intensive methods are based on a personalized approach to each patient. Liver support system devices are generally well tolerated, but it is relatively expensive and requires a multidisciplinary approach. We believe that intensive treatment can greatly benefit certain groups of patients, especially when specific cancer therapies can quickly and effectively control the disease. In the early stages of cancer, liver support system devices could be utilized as a treatment option for immunotherapy-induced hepatitis when conservative treatments are unsuccessful. The authors have completed the CARE Checklist for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000541419).

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. Ethical approval is not required for this case report following local or national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Anamarija Bukovica Petrc, Tihana Salopek, Iva Skočilić, and Ivana Mikolasevic: substantial contributions to the conception or design of the work; the acquisition, analysis, or interpretation of data for the work; drafting the work; reviewing it critically for important intellectual content; final approval of the version to be published. Dag Zahirovic, Lidija Orlic, Ivan Bubic, Zrinka Matana-Kastelan, Sara Francetic, and Karla Lisica: drafting the work or reviewing it critically for important intellectual content; final approval of the version to be published.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the first author.

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