Post-transplant primary liver lymphoma: always to remember

To the Editor,

Primary hepatic lymphoma (PHL) is a lymphoproliferative disease originating from intrahepatic lymphatic and residual hematopoietic tissues and is characterized by the absence of extrahepatic infiltration. It is a rare disease, accounting for 0.1% of all liver malignancies, 0.4% of extranodal non-Hodgkin lymphomas (NHL) and 0.016% of all NHL [1].

A retrospective analysis of all patients diagnosed with PHL between January 2010 and December 2019 was performed. Patients were selected from a computerized database with every histopathological examination performed and relevant information was extracted from electronic medical records. Those with evidence of systemic involvement were excluded.

Three patients with PHL were identified (Table I). Their mean age was 61 years old (range 45-75) and 2/3 were male. Histological subtype was diffuse large B-cell lymphoma (DLBCL) in all of them. Clinical manifestations at presentation were reported in 2/3 patients: one patient reported fever and the other abdominal discomfort and jaundice. The remaining patient was asymptomatic. Lymphoproliferative disease occurred in the setting of immunosuppression in 2/3 patients, both as a result of previous liver transplantation. Laboratory abnormalities were variable: normal liver tests were found in one patient whereas the other 2/3 presented marked cholestasis with gamma-glutamyl transferase levels elevated more than 10x the upper limit of normal (ULN) and alkaline phosphatase 2-4x ULN and mild cytolysis with levels of aspartate aminotransferase and alanine aminotransferase elevated 1-2x ULN; one additionally presented direct hyperbilirubinemia (total bilirubin: 3.1 mg/dL; direct bilirubin: 1.73 mg/dL) correlating with clinical jaundice. Computed tomography (CT) scan was performed in 2/3 patients and the disease had uninodular presentation in one as a single hypodense nodule with 67 mm diameter located at the left lobe and multinodular in the other as three nodules, the largest with 40 mm diameter, dispersed through both right and left lobes. Both patients had simultaneous imaging evidence of hepato- and splenomegaly and one also had bilateral pleural effusion. Chemotherapy was started in 2/3 patients with complete response in one and absence of response in the other. One patient had rapid unfavorable evolution and it was not possible to start treatment. The patient with complete response died after 48 months from septic shock in the setting of bacterial cholangitis whereas the patient that did not respond died after 8 months from disease progression.

Primary hepatic lymphoma usually develops in association with previous liver disease: association with viral infection

Table I. Patients' characteristics

Case	Gender	Age	Histological subtype	Immune suppression	Clinical manifestations	Laboratory abnormalities	Imaging findings	Treatment	Outcome
# 1	Female	75	DLBCL	No	Fever	Anemia, elevated LDH, normal liver tests	N/A	None	Death after 1 month
# 2	Male	63	DLBCL	Liver transplant	Abdominal discomfort, jaundice	Anemia, leukopenia, thrombocytopenia, cytolysis, cholestasis, hyperbilirubinemia	Single nodule	Chemotherapy (complete response)	Death after 48 months (cholangitis)
# 3	Male	45	DLBCL	Liver transplant	Asymptomatic	Anemia, leukopenia, cytolysis, cholestasis, elevated LDH, elevated CA19.9	Multiple nodules	Chemotherapy (absence of response)	Death after 8 months

(Hepatitis B virus, Hepatitis C virus, Epstein-Barr virus), autoimmune diseases, immunosuppression or liver cirrhosis were described. Overall, the most common histological subtype is DLBCL. Clinical manifestations are non-specific and most commonly include abdominal discomfort due to liver distension and constitutional symptoms (fever, night sweats, weight loss, asthenia), although patients may be asymptomatic. Biochemical analysis often reveals altered liver tests, particularly cholestasis due to liver infiltration. On CT scan, most cases of PHL presents as nodular solid lesions, either single (60%) or multiple (40%) [2].

Remarkably, we report two cases of DLBCL presenting as PHL after orthotopic liver transplantation. In fact, post-transplant lymphoproliferative disease is one of the most common forms of transplant-associated malignancies and DLBCL is the most common subtype of NHL in the post-transplant setting. The highest incidence of lymphoma occurs during the first year. Hepatic involvement typically occurs as part of the extra nodal involvement and may also rarely present as localized hepatic lymphoma [3]. Primary hepatic lymphoma has been reported after other solid organ transplantation, including lung [4] or kidney [5]. However, to the best of our knowledge, these are the first cases occurring in an allograft following liver transplantation.

In conclusion, PHL is a rare disease that presents with variable and non-specific clinical manifestations and imaging findings. This diagnosis should be particularly considered in nodular hepatic lesions in the setting of post-transplant immunosuppression. Its diagnosis requires high clinical suspicion and is established histologically.

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Complementary medicine in the management of functional and inflammatory gastrointestinal disorders: a survey among Italian gastroenterologists

To the Editor,

The use of complementary medicine (CM) is increasing because of patients' dissatisfaction with conventional treatments and/or fear of their side-effects [1]. However, most of the physicians are not familiar with CM [2], therefore often cannot prescribe it judiciously and, more importantly, are unaware of its possible side-effects and interactions.

We tested by means of a questionnaire distributed to 113 Italian gastroenterologists attending specialty meetings their knowledge of and interest in CM, how frequently they prescribed it in functional and inflammatory gastrointestinal disorders (FGIDs and IBDs respectively) and how frequently their patients asked for it or used it in order to define the need for formal education on this issue.

Knowledge of CM was null in 42.27% and poor in 26.37% of the respondents; 60% of them would have liked to learn more about it. Half of the respondents (56.36%) thought that CM is useful in FGIDs, mostly in the irritable bowel syndrome (IBS) (91.94% of them).

Half of the respondents never prescribed CM to patients with FGIDs mainly because of insufficient knowledge (64.29%). Those who prescribed it did so mainly in the IBS (92.31%). The patients with FGIDs reported CM use rarely (41.82%) or occasionally (28.18%) and asked for it never (32.73%) or rarely (35.45%).

Regarding IBDs, 34.55% of the respondents thought that CM was not useful in this setting and 34.55% did not have an opinion. Complementary medicine was prescribed rarely (16.36%) or never (69.09%) in this setting because of insufficient knowledge (46.32%) or no indication deemed (37.89%). Most of the IBDs patients (81.82%) did not use or rarely used CM and asked for it rarely (23.64%) or never (60%).

Our results show that insufficient/null knowledge of CM was common in the participating physicians, but 60% of them would like to know more about it. Complementary medicine is prescribed more frequently for FGIDs than IBDs patients, perhaps because unconventional treatment modalities might seem inappropriate in organic disorders.

Our data is in agreement with previous reports as regards both little physicians' knowledge of CM and their desire to gain a better knowledge of it [3].

Regarding the patients' attitude toward CM, in the field of FGIDs it was used and asked for by a sizeable minority of them and in a remarkably lower percentage in the IBDs. These results are at variance with previous studies reporting on average greater interest for CM in patients with these disorders [4]. This may be due to the way the data has been collected, since patients might have been reluctant to admit to their physicians the use of a self-prescribed and unconventional treatment, as suggested by the high prevalence of CM use reported in online surveys [4]. Moreover, fear of physicians' disapproval is one

of the main reasons for non-disclosure of CM use to medical providers [5].

Complementary medicine should be included in the education and training of physicians in general and gastroenterologists in particular in order to solve the discrepancy between physicians' knowledge and patients' interest in this matter, thus ensuring an adequate knowledge of the side-effects and compatibility of this treatment modality.

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Safety and efficacy of budesonide during pregnancy in women with autoimmune hepatitis

To the Editor,

Standard treatment for autoimmune hepatitis (AIH) involves steroids alongside alternative immunosuppressive agents, which have proved to successfully improve liver function, increase survival time and ameliorate symptoms. Although the disease mostly affects women, only few reports exist on AIH during pregnancy and risks involved in fertility, foetus development and other pregnancy-related complications [1, 2].

Novel medications, in vitro fertilization, and improved knowledge about the pathology allow for a diminished risk and a secure pregnancy in these days [1]. Still, there is a need for further studies to clarify the impact of AIH in pregnant women. Several smaller cohort studies suggested that treatment with prednisolone and /or azathioprine was generally safe [3]. With an increasing use of budesonide, its safety in pregnant patients with AIH is yet to be evaluated. To further support a recent case series by Rahim et al. [4] we hereby add an additional case with an excellent maternal and foetal outcome.

In July 2017, a 33-year-old female patient was diagnosed with AIH type I. Being initially on prednisolone, the patient herself stopped the treatment. Subsequently, rapidly increasing transaminases [alanine aminotransferase (ALT)=160 IU/L, aspartate aminotransferase (AST) 72 IU/L) were treated with budesonide 9 mg/d and within two months, the lab result improved significantly (ALT 78 IU/L, AST 34 IU/L), which indicated the efficacy of budesonide. After an attempt to reduce budesonide to 6 mg/d ALT and AST increased again to 108 IU/L and 56 IU/L, respectively. Azathioprine was refused by the patient. Approximately 6 months later the patient became pregnant, which was unknown for us throughout the first trimester, the most sensitive period for foetal harm. Upon acknowledging the pregnancy after 5 months at the occasion of the next routine appointment, budesonide was tapered and eventually terminated after 6 months. Meanwhile, ALT and AST levels remained low and even continued decreasing to 9 IU/L and 8 IU/L, respectively. At this stage, AIH disease seemed stable and in remission. Three months later our patient gave birth to a perfectly healthy child. Although the ALT and AST levels rose slightly after birth, the mother also did not suffer any major complications or flairs. More than one year after birth the child still does not suffer from any adverse events and has passed mandatory check-up screenings without any abnormalities.

Thus, our case furthermore supports the view that treatment with budesonide in patients with AIH may also be safe during pregnancy. In consequence, with an increasing number of drugs at hand, we would like to reassure patients

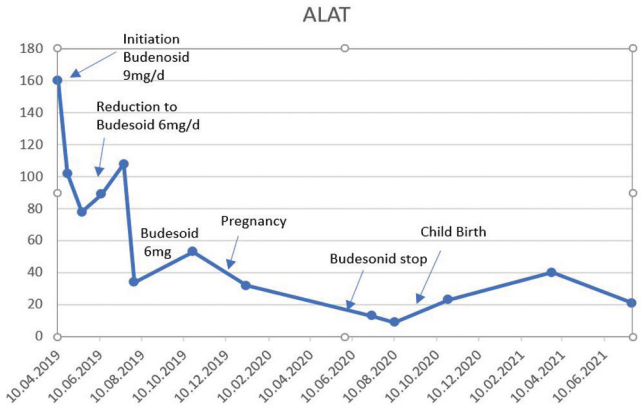

Fig. 1. Alanine aminotrasferase (ALT) values and treatment.

with AIH that it may be very well possible to become pregnant without putting their health and /or child at risk.

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Primary amyloidosis presenting with acute intestinal obstruction. An unusual case

To the Editor,

We read with great interest the article published by Luigetti et al. [1] and the letter to the editor published by Patel et al. [2], dealing with amyloidosis of the gastrointestinal (GI) tract.

Luigetti et al. [1], presented a cohort of 39 patients with hereditary transthyretin (ATTR) amyloidosis, where the prevalence of GI symptoms was 82%, the most frequent complain being weight loss and diarrhoea. Patel et al. [2] referred to a case with severe GI primary amyloidosis, with a history of nausea, diarrhoea, abdominal pain, and weight loss. The patient's course was complicated by GI bleeding and pulmonary embolism. Both publications show the most frequent digestive symptoms of the disease, regardless of amyloidosis type [3], which usually occur after 5 years of disease onset.

However, GI symptoms may also be the presenting form of systemic amyloidosis. We report a rare case of primary amyloidosis in a patient who initially presented subacute small bowel obstruction (SBO), mimicking a midgut volvulus, which required surgery for the final diagnosis.

A 73-year-old man with medical history of hypertension, well controlled type 2 diabetes mellitus and chronic kidney disease presented at the Emergency Department with abdominal pain, nausea, and constipation. Physical examination revealed non-painful and distended abdomen, without abdominal mass or ventral nor groin hernias. Laboratory tests confirmed stable chronic kidney disease; abdominal X-ray showed small bowel dilatation (Fig. 1A). Contrast-enhanced computed tomography (CT) showed dilation of a jejunal loop with engorgement of mesenteric vessels, suspecting a midgut volvulus (Fig. 1B). These findings were compatible with SBO. Initially, non-operative management was undertaken. The patient responded favourably to fluids, nasogastric (NG) tube and after gastrografin administration through the NG tube, the patient recovered bowel function, showed radiological and clinical improvement, and was discharged. However, the patient was readmitted again due to SBO symptoms and the cycle kept repeating itself. After 3 weeks, a surgical intervention was proposed, a exploratory laparotomy being performed. During the surgery, a midgut volvulus was not observed; the findings were non-specific intestinal dilation and non-acute confined hematoma of the mesentery; however, there were no macroscopical signs of inflammatory bowel diseases (IBD). Therefore, given these nonspecific findings, intestinal resection

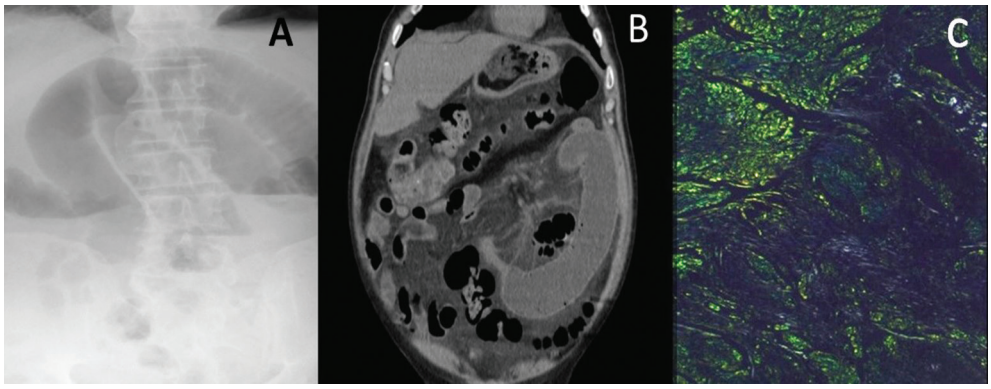

Fig. 1. Abdominal radiograph disclosed dilatation of small bowel (A) and abdominal computed tomography showed a dilatation of jejunal loop with engorgement of mesenteric vessels (B). Deposits of material with apple-green birefringence on the Congo red stain (C).

was not performed. Subsequently, the patient presented a long-lasting postoperative ileus, treated with prokinetic drugs and before hospital discharge, a CT scan was performed showing no pathological issues and the resolution of initial radiological findings. Due to poor clinical evolution with recurring episodes of SBO without an identified etiology, the patient underwent another laparotomy, which evidenced multiple adhesions, and an inflamed and dilated jejunal loop of 70 cm. Macroscopical findings were not characteristic of IBD, but IBD was one of the differential diagnoses considered. So, intestinal resection and manual latero-lateral anastomosis were performed. Patient presented postoperative ileus, but progressively recovered adequate oral tolerance and bowel function, and was finally discharged on the 15th postoperative day.

The histological analysis reported extensive deposits of amorphous material with apple-green birefringence on the Congo red stain, consistent with amyloidosis (Fig. 1C). Serum electrophoresis test disclosed an amyloid light-chain amyloidosis. Following the diagnosis, the patient received chemotherapy (daratumumab, cyclophosphamide, bortezomib and dexamethasone). Unfortunately, the patient did not respond to treatment, and died after 4 months.

As the previously cited publications referred, amyloidosis may present with non-specific upper and lower GI symptoms. Although any part of the digestive tract could be affected, small bowel is the most frequently affected [4]. Intestinal obstruction, which is not usually reported in case of amyloidosis, carries a grave prognosis. Clinical manifestations and radiological findings may show mechanical complete or non-complete SBO, suggesting the need for surgical treatment. Although in our patient bowel resection allowed us to make the diagnosis, it is critical to consider this disease within differential diagnosis to avoid laparotomy, which may not benefit the patient, delaying chemotherapy administration [5].

In conclusion, due to its non-specific symptomatology, intestinal amyloidosis can be confused with other digestive disorders, being misdiagnosed, and delaying effective treatment. Therefore, it is important that clinicians and surgeons include amyloidosis in their diagnostic workup.

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Immune checkpoint inhibitors in hepatocellular cancer patient with congenital haemophilia A

To the Editor,

Congenital haemophilia A (HA) (factor VIII deficiency) and B (factor IX deficiency) are X-linked bleeding disorders [1]. The principal hallmark of congenital HA is hemorrhage, particularly hemarthrosis [1]. Lyophilized plasma FVIII concentrates revolutionized treatment of HA patients in the 1970s, with an increase in their life expectancy [2]. However, replacement therapy was complicated during the 1980s and early 1990s on account of the human immunodeficiency virus (HIV) and hepatitis C virus (HCV) accidental infections from contaminated blood products [1]. Nowadays, the main risk of replacement therapy is associated with an inhibitor development (which occur in 30% of patients) that negatively influences bleeding prevention and life expectancy [1]. Chronic hepatitis C is a major cause of advanced hepatic fibrosis and cirrhosis, with significantly increased risk for the development of hepatocellular carcinoma (HCC). Focus on surveillance and early HCC diagnosis is mandatory as underlined by Marrero et al. [3]. The treatment of advanced HCC includes in the first-line tyrosine-kinase inhibitors (sorafenib, lenvantinib) and, recently, the combination of atezolizumab plus bevacizumab [4]. Sorafenib, lenvantinib and bevacizumab are contraindicated in HA patients for an increased risk of bleeding.

The concomitant presence of HA and HCC is a very challenging situation in clinical practice. We would like to share our experience in the treatment of a 71-year-old man affected by congenital haemophilia A who was diagnosed of HCV-related metastatic HCC, with well-preserved liver function (Child-Pugh A) and good clinical conditions (ECOG PS 0). Based on the result of the CheckMate 459 trial [5], first-line line Nivolumab treatment was proposed, using a dosage schedule of 240 mg IV Q2W. Nonetheless, despite a good profile of tolerability, one of the risks of immune checkpoint inhibitors (ICI) introduction is the emergence of a new and broad spectrum of immune-related adverse events, including serious hematological events such as acquired haemophilia (AH) [1]. One of the predominant

pathogenetic traits is the synthesis of IgG directed against the VIII factor and neutralizing its coagulation function. Contrary to the congenital form, AH frequently occurs with mucosal, subcutaneous or deep soft tissue haemorrhages. Our patient accepted the risk of the possible collateral effects of the therapy and, after approval by the local Ethics Committee, the treatment was started. The patient continued the concomitant plasma-derived VIII factor therapy by haematologists during the whole time of immunotherapy, monitoring the functional activity of the VIII factor as well as its inhibitor. In total, six cycles of Nivolumab were administered without any significant delay. Levels of VIII factor functional activity remained stable (Fig. 1A) and the dose of VIII factor inhibitor was around zero during the whole treatment (Fig. 1B).

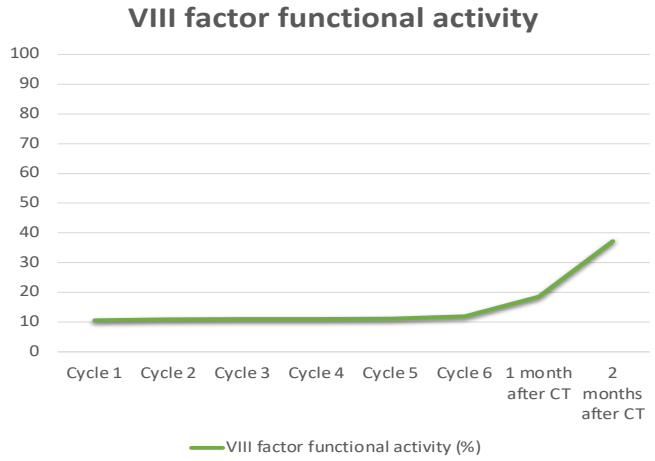

Fig. 1A. Levels of factor VIII functional activity during immunotherapy

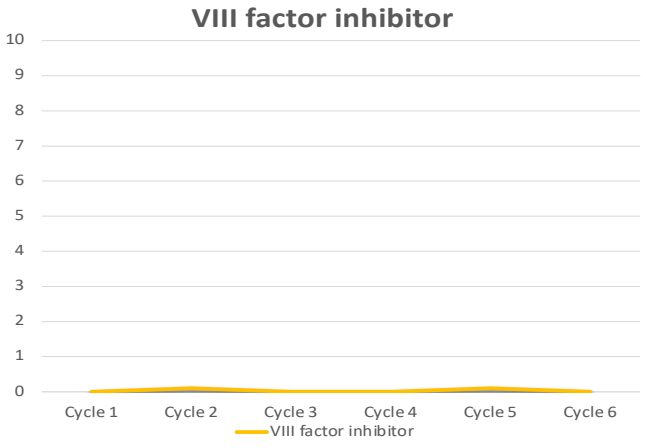

Fig. 1B. Levels of factor VIII inhibitor during immunotherapy

Nivolumab was overall well tolerated by the patient, excepting for a single episode of grade 2 diarrhoea. No signs of bleeding were registered. The only haematological adverse event detected was grade 2 thrombocytopenia, which was ascribed to the presence of platelet pools in the sample thus revealing a subsequent underestimation of the real platelet count. Nevertheless, alfa-fetoprotein values progressively increased, and a CT scan showed intrahepatic progression with worsening of the thrombotic neoplastic component after two months of Nivolumab treatment. Interestingly, levels of the VIII factor functional activity progressively increased after the interruption of immunotherapy. Subsequent lines of anticancer therapies were not indicated, and the patient continued with best supportive care.

As far as we are aware, this is the first description of an advanced HCC patient with concomitant congenital HA treated with an anti-PD-1 inhibitor. Nivolumab was well tolerated, and factor VIII functional activity remain stable. Interesting was the finding of the increase in factor VIII functional activity after discontinuation of immunotherapy. Further studies are required to assess the safety of immunotherapy in cancer patients affected by congenital haemophilia A in order to avoid undertreatments.

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