Can thymosin β4 and soluble CD163 be used as biomarkers of the prognosis in acute on chronic liver failure?

To the Editor,

Acute-on-chronic liver failure (ACLF) is a deleterious complication of chronic liver disease characterized by a rapidly progressive course, multi-organ failure and high short-term mortality without liver transplantation. Acute-on-chronic liver failure carries a good prognosis after liver transplantation but has a poor outcome on the waiting list. The window of opportunity for transplantation is narrow, thus, an accurate prediction remains quintessential.

Previous studies have demonstrated that systemic inflammation characterized by strong proinflammatory cytokine response, might be responsible for the sudden deterioration of liver function. Thymosin β4 (Tβ4), an anti-inflammatory factor plays a role in decreasing inflammation, improving healing/hypoxic injury, preventing micro-thrombosis and it was hypothesized to offer protection in terms of survival [1]. Soluble cluster of differentiation 163 (sCD163) is a macrophage activation marker and is correlated with the severity of inflammatory response, thus potentially worse outcomes [2]. Acute-on-chronic liver failure patients are critically ill and have a pre-existing underlying chronic liver disease, which serves as a harbinger for vitamin D deficiency. Low vitamin D levels have been associated with progressive fibrosis, increased risk of infections and higher mortality [3].

Despite the availability of several scoring systems, an accurate prediction remains difficult. We aimed to evaluate if thymosin β4, sCD163 and 25-hydroxy vitamin D [25(OH)D] can be used as biomarkers for the prognosis in ACLF. Apart from their potential predictive role, these biomarkers for ACLF might throw light on the pathogenesis of this condition and suggest strategies for future rational treatments of ACLF.

All consecutive patients with ACLF diagnosed as per Asian Pacific Association for the Study of the Liver criteria, presenting to our institution between December 2017 to March 2019 were included in the study. Exclusion criteria included age <18 and >99 years, pregnancy, hepatocellular carcinoma, portal vein thrombosis, known decompensated cirrhosis prior to acute insult, absence of chronic liver disease or liver transplant. Demographic, clinical and laboratory data was collected. Tβ4, 25(OH)D and sCD163 levels were collected on the day of admission. Primary endpoints of the study were mortality or follow up for 90 days. Fifty patients (mean age 53.82±14.75 years, 86% males) were included in the study. 54% patients died during the course of illness. Etiology of cirrhosis was alcohol in 37/50 patients. Acute insult was caused by alcoholic hepatitis in 23/50 followed by sepsis in 17/50. Laboratory, clinical and prognostic score profile of survivors and non-survivors at the time of admission is shown in Table I. Survivors had a significantly higher Tβ4, 25(OH) D and lower sCD163 levels than non-survivors. Tβ4 at a cut-off of 450 ng/ml predicted 90-day mortality with a sensitivity (Sn) of 88.9%, specificity (Sp) of 95.7%, positive predictive value (PPV) of 96% and negative predictive value (NPV) of 88% and area under receiver operating curve (AUROC) 0.923. sCD163 at a cut-off of 13.06 ng/ml predicted 90-day mortality with Sn, Sp, PPV and NPV of 100%, 91.3%, 93% and 100% respectively with AUROC 0.937. 25(OH)D at a cut-off of 36.05 ng/ml predicted 90-day mortality with Sn, Sp, PPV and NPV of 85.2%, 52.2%, 67.6% and 75% respectively with AUROC 0.676.

Higher sCD163 and lower Tβ4 indicated a higher degree of macrophage activation and a lesser circulation of anti-inflammatory molecules, tissue repair and recovery at the time of admission among non-survivors. Previous studies have reported lower Tβ4 and higher sCD163 among non-survivors in hepatitis B related liver failure [4, 5]. Tβ4 and sCD163 showed excellent discriminatory ability to predict 90-day mortality. The study sheds light on inflammatory and anti-inflammatory molecules as a determinant of outcome and biomarker of prognostication in ACLF. Further studies with larger patient of cohorts, across multiple centers and measurements of dynamic changes in these biomarkers are required to validate their roles as predictive markers.

Table I. Clinical and biochemical profile in survivors and non-survivors patients with ACLF

	Survivors (n=23)	Non-survivors (n=27)	p
Clinical profile			
Organ failures (n,%)			0.001
No organ failure	12 (52.2)	4 (14.8)	
Single organ failure	9 (39.1)	8 (29.6)	
Multi (≥2) organ failure	2 (8.7)	15 (55.5)	
Encephalopathy (n,%)			<0.001
Grade 0	13 (56.5)	0 (0)	
Grade 1	10 (43.5)	7 (25.9)	
Grade 2	0 (0)	16 (59.3)	
Grade 3	0 (0)	4 (14.8)	
Biochemical profile (mean ±S D)			
WBC (cells/µl)	11.385.65 ± 2.632.9	17.860 ± 1.2429.39	0.007
Platelet count (cells/µl)	151,434.78 ± 13,398.867	119,481.48 ± 44,767.236	<0.001
Creatinine	1.04 ± 0.15	2.12 ± 2.06	<0.001
Sodium (mEq/l)	142.09 ± 4.96	133.48 ± 7.78	<0.001
Total bilirubin (mg/dl)	10.73 ± 4.902	15.33 ± 8.56	0.119
ALT (U/L)	238.09 ± 27.27	123.06 ± 62.73	0.019
Albumin (gm/dl)	2.99 ± 0.24	2.64 ± 0.33	<0.001
INR	2.32 ± 0.55	3.30 ± 1.89	0.012
ACLF grade (n,%)			<0.001
0	17 (73.9)	4 (14.8)	
1	4 (17.4)	8 (29.6)	
2	0 (0)	6 (22.2)	
3	2 (8.7)	9 (33.3)	
Scores (mean ± SD)			
MELD	25.3 ± 3.65	33.56 ± 8.04	<0.001
Child-Pugh	11 ± 0.74	12.7 ± 0.95	<0.001
CLIF-SOFA	5.57 ± 2.98	9.96 ± 2.35	<0.001
CLIF-C-ACLF	57.39 ± 7.05	59.44 ± 11.22	0.452
CLIF OF score	9.13 ± 1.52	11.70±2.18	<0.001
Biomarkers (mean ± SD)			
Thymosin β4 (ng/mL)	745.54 ± 228.33	402.318±233.75	<0.001
25(OH)D (ng/mL)	35.63 ± 11.1	29.26±9.72	0.036
sCD163 (ng/mL)	9.24 ± 3.66	17.28±2.35	<0.001

25(OH)D: 25-hydroxy vitamin D; ALT: alanine aminotransferase; dl: deciliter; ACLF: acute on chronic liver failure; CLIF: chronic liver failure; INR: international normalized ratio; mEq: milliequivalents; mg: milligrams; OF: organ failure; SD: standard deviation; µl: microliter; SOFA: sequential organ failure assessment; sCD163: soluble cluster of differentiation 163; U: units; gm: gram.

Sushil Kumar Sharma[1], Rahul Karna[2,3], Dhruv Ahuja[2], Premashis Kar[1]

1) Department of Gastroenterology and Hepatology, Max Super Specialty Hospital, Vaishali, Ghaziabad, India; 2) Department of Medicine, Maulana Azad Medical College, New Delhi, India; 3) Department of Medicine, Allegheny Health Network, Pittsburgh, Pennsylvania, US.

Correspondence: Premashis Kar, premashishkar@gmail.com

Conflicts of interest: None.
DOI: 10.15403/jgld-4161

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Early onset of intrahepatic cholestasis of pregnancy: a case report

To the Editor,

Intrahepatic cholestasis of pregnancy (ICP), also known as cholestasis gravidarum, is a liver disorder characterized by pruritus, which is the most evident clinical symptom that cannot be explained by other causes. Elevated liver function tests (LFTs) and/or elevated serum bile acids (BA) in patients with ICP are characteristic as well [1].

A 31-year-old woman with a dichorionic diamniotic twin pregnancy at 22^{+0} weeks' gestation, was admitted to the hospital complaining of pruritus on her palms, legs, and abdomen, which became worse at night, causing insomnia. The symptoms had begun one week prior and had increased in intensity. LFTs showed alanine aminotransferase (ALT): 643 U/L, aspartate aminotransferase (AST): 425 U/L, alkaline phosphatase (AP): 131 U/L, and total bilirubin: 9.34 µmol/L. A diagnosis of ICP was presumed. Anamnesis revealed that the patient had two previous extrauterine pregnancies, with bilateral tubectomy and the recommendation of *in vitro* fertilization (IVF). She was administered progesterone (according to IVF protocol), which was discontinued after the diagnosis of ICP.

Physical examination upon hospital admission did not reveal any signs of rash or other dermatological problems. She was asked to rate the intensity of her pruritus upon first contact and again following hospital admission, thus revealing an increase in pruritus intensity from 5 to 10 points, based on the visual analogue scale provided. The re-assessment of LFTs reflected the following: BA: 125.7 µmol/L, ALT: 789.7 U/L, AST: 505.2 U/L, total bilirubin: 8.1 µmol/L, AP: 120 U/L, and γ-glutamyl transferase:18 U/L. She was diagnosed with severe ICP. At 22^{+2} weeks gestation, a drastic increase in ALT and AST levels was observed, with ALT levels reaching 1121.5 U/L and AST 657.9 U/L, respectively (Fig. 1).

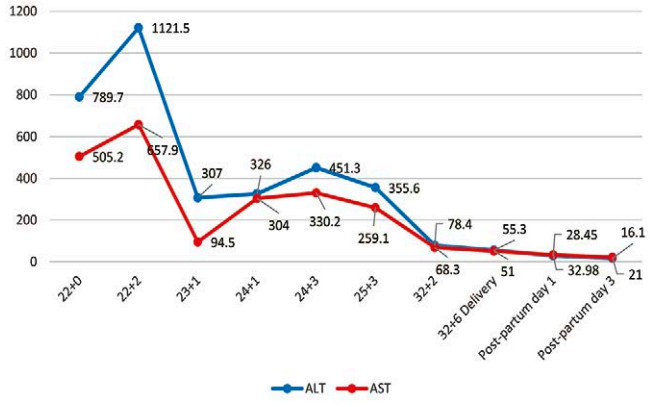

Fig. 1. ALT and AST levels (U/L) by weeks of gestation

Considering the patient's gestational age, symptomatic treatment was initiated, being closely monitored. Clinical management was carried out according to international guidelines. During hospital admission, she was prescribed ursodeoxycholic acid 750 mg/day, divided into twice-daily dosing. Considering the worsening of the clinical symptoms and further elevated LFTs, the ursodeoxycholic acid dose was increased to 900 mg/day, divided into three daily doses. In addition, she received enteroadsorbent polymethylsiloxane polyhydrate and use topical emollients, such as menthol 1% in aqueous cream. At the same time, as a complementary treatment, she received S-adenosyl-l-methionine 500 mg in aqueous solution intravenously and antihistamine medication.

The patient was admitted to the hospital three times throughout the course of pregnancy. She was recommended to have LFTs assessed weekly. However, during weeks 26–31 of pregnancy, the patient did not come in for a consultation; hence, there is a lack of data on LFT levels for this period.

An elective caesarean section was planned to be performed after the patient's gestational age reached 37 weeks. However, a spontaneous premature rupture of membranes occurred at 32^{+6} weeks' gestation, followed by the onset of uterine contractions. Therefore, an emergency caesarean section was performed considering the twin pregnancy. She gave birth to a male fetus weighing 2,158 g and a female fetus weighing 1,369 g. The newborns had Apgar scores of 7/8 and 6/7 points, respectively. LFTs were reassessed 3 days after delivery; ALT and AST levels were 16.1 U/L and 21.0 U/L, respectively. The neonates were admitted to the neonatal intensive care unit, where they spent eight days. In both newborns, diagnosis of congenital pneumonia and neonatal jaundice was established. In addition, the male newborn was diagnosed with necrotizing enterocolitis. The patient was discharged from the hospital on the eighth day after delivery. Her newborn babies required prolonged hospital care and were discharged from the hospital 30 days after birth.

Intrahepatic cholestasis of pregnancy is a severe condition due to its maternal and fetal impact, requiring active management. A careful anamnesis is recommended, as progesterone, recommended according to IVF protocols, might have a possible role in the onset of ICP [2]. Shan et al. [3] analyzed 1,472 twin pregnancies and reported a strong association between adverse maternal and fetal outcomes and ICP in twin patients; also subgroup analyses revealed higher incidences of adverse outcomes in severe and early onset ICP groups [3].

Women should be informed about the risks and possible complications of ICP, such as the inability to predict stillbirth, the high rate of premature birth and respiratory distress that may be exhibited in newborns. Furthermore, despite the fact that ICP usually begins in the third trimester of pregnancy, an early onset of cholestasis gravidarum often manifests as a severe form of the condition. Management of the condition requires cooperation between obstetricians, gastroenterologists, hepatologists, and other specialists as needed, to better ensure the best possible outcomes [4].

Maria Cemortan, Liudmila Stavinskaia, Irina Sagaidac, Olga Cernetchi
Department of Obstetrics and Gynecology, Nicolae Testemitanu State University of Medicine and Pharmacy of the Republic of Moldova, Chisinau, Republic of Moldova.

Correspondence: Maria Cemortan, mariacemortan@yahoo.com

Conflicts of interest: None.
DOI: 10.15403/jgld-4178

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An unusual case of hepatic venous outflow obstruction: sequelae of immune checkpoint inhibitors

To the Editor,

A 69-year-old female with history of stage IV squamous cell carcinoma of lung, receiving a combination of immune checkpoint inhibitors (nivolumab and ipilimumab) therapy for one year, presented with a sudden onset of ascites, which had started one month prior to presentation. She had no prior history of alcoholism, hematologic, hepatic, or cardiac diseases. Laboratory studies revealed normal complete blood count, aspartate aminotransferase 89 U/L, alanine aminotransferase 91 U/L, alkaline phosphatase 499 IU/L, total bilirubin 1.1 mg/dl and international normalized ratio 1.2. Doppler ultrasound showed a heterogeneous liver without cirrhotic morphology or splenomegaly, and appropriate flows in hepatic artery, veins, and portal veins. The Main and right hepatic artery resistive index (RI) were elevated at 0.84 and 0.85, respectively (normal: 0.55-0.8). Chronic liver disease work up was negative. Ascitic fluid analysis revealed serum ascites albumin gradient 2.9 gm/dl, total protein 0.6 gm/dl and no evidence of spontaneous bacterial peritonitis. Computed tomography venogram of abdomen showed patent hepatic, portal, superior mesenteric, inferior mesenteric and splenic veins (Fig. 1 A,B). Transjugular liver catheterization revealed elevated porto-systemic gradient of 13 mm Hg. There was no concern of congestive hepatopathy based on clinical features. Liver biopsy showed lymphocytic inflammation with cholangitis (Fig. 1C, H&E, 100x, black arrow) in portal areas adjacent to congested perivenular sinusoids (Fig. 1C, H&E, 100x, red arrow). A mid-sized sub lobular vein showing a loosely organized thrombus (Fig. 1D, H&E, 100x, black arrow) intermixed with inflammatory cells (Fig. 1D, H&E, 100x, red arrow) with atrophic surrounding hepatocytes was depicted. Cytokeratin-7 immunostaining showed (Fig. 1E,100x) atrophied perivenular hepatocytes with prominent CK-7 positivity indicative of biliary ductular metaplasia. Unfortunately, the patient developed sepsis leading to multi-organ failure and died from the complications.

This case was particularly challenging in terms of diagnosis. Despite new onset ascites and portal hypertension, our patient did not have any clinical or pathological evidence of cirrhosis. Pathology showed a loosely organized thrombus in a sublobular hepatic vein, raising concern of Budd-Chiari syndrome (BCS), but there was no evidence of the BCS on imaging. Some hepatic venules showed mural edema and fibrosis, without obliteration, but the severity of sinusoidal congestion was much less than typically seen with sinusoidal

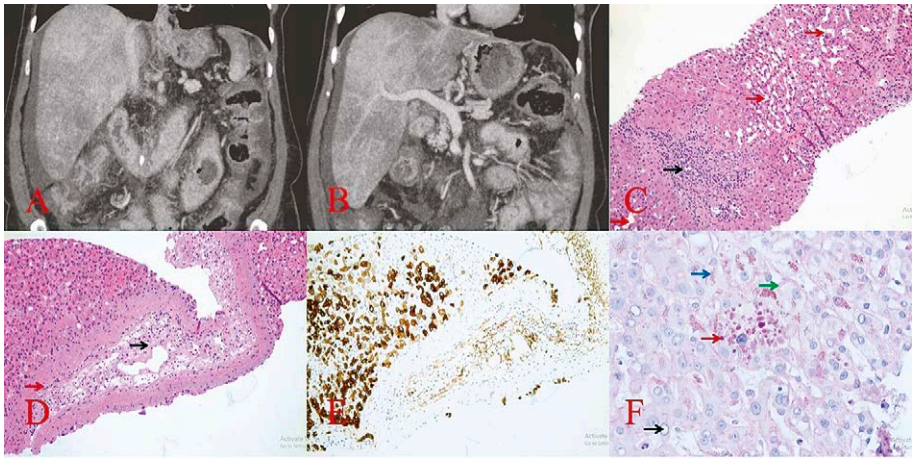

Fig. 1. Computed tomography venogram of abdomen showing (A) patent inferior vena cava and (B) portal vein; (C) H&E stain, 100x: The portal areas show lymphocytic inflammation with cholangitis (black arrow) adjacent to congested perivenular sinusoids (red arrow); (D) H&E stain, 100x: A mid-sized sublobular vein showing a loosely organized thrombus (black arrow) intermixed with inflammatory cells (red arrow). The surrounding hepatocytes are atrophic. (E) CK-7 immunostain, 100x: The atrophied perivenular hepatocytes show prominent CK-7 positivity indicative of biliary ductular metaplasia. (F) PAS immunostain with diastase, 400x showing hepatocellular hyaline globules in perivenular area (red arrow) and perisinusoidal fibrosis (green arrow). The atrophic background hepatocytes showing abundant nuclear glycogenation (black arrow) and yellow lipofuscin pigment (blue arrow).

obstruction syndrome. Marked perivenular hepatocyte atrophy raised the possibility of suboptimal portal vein and/or hepatic artery inflow. Ductular metaplasia of periportal hepatocytes on CK7 raises the possibility of suboptimal biliary drainage. High hepatic artery RI suggested microvascular disease. Immune checkpoint inhibitors are known to cause hepatotoxicity, though rare. Histology most seen with immune checkpoint inhibitors induced liver injury are lobular hepatitis and granulomatous hepatitis including fibrin ring granulomas and central vein endotheliitis [1]. Immune checkpoint inhibitors therapy has been known to predispose to thrombus formation [2-4]. The patient's symptoms were attributed to hepatic venous outflow obstruction in the setting of multifocal phenomenon of thrombogenicity. A high clinical suspicion for hepatic venous outflow obstruction should be considered in patients on immune checkpoint inhibitors that develop sudden onset portal hypertension.

Rahul Karna[1] ,Thayer Nasereddin[2], Harsimran Kaur[1], Cristina Strahotin[2]
1) Department of Medicine, Allegheny Health Network, Pittsburgh, PA; 2) Division of Gastroenterology and Hepatology, Allegheny Health Network, Pittsburgh, PA, USA

Correspondence: Rahul Karna, rahulkarnagovind@gmail.com

Conflicts of interest: None.
DOI: 10.15403/jgld-4204

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Endoscopy capsule in the scrotum

To the Editor,

An 82-year-old man presented with hemorrhagic shock in our emergency room. His medication included anticoagulation and thrombocyte-aggregation inhibition due to a history of atrial fibrillation and coronary artery disease. Physical examination revealed melena in rectal palpation. After hemodynamic stabilization and blood transfusion, neither emergency upper gastrointestinal endoscopy, nor complete colonoscopy the next day were successful in demasking the bleeding site. Video-capsule endoscopy was chosen for examination of the small intestine. A bioresorbable patency capsule can be administered beforehand in patients with suspected stenosis. This patient had no history of bowel disease, but a large scrotal hernia with peristaltic sounds was evidenced at the physical examination. The patency capsule did not pass via naturalis and a radiograph taken after 24 hours (Fig. 1) showed its presence in an intestinal loop within the hernial sac. Further endoscopic or radiological interventions were not necessary as the patient remained symptom free with stable hemoglobin levels after discontinuation of anticoagulation.

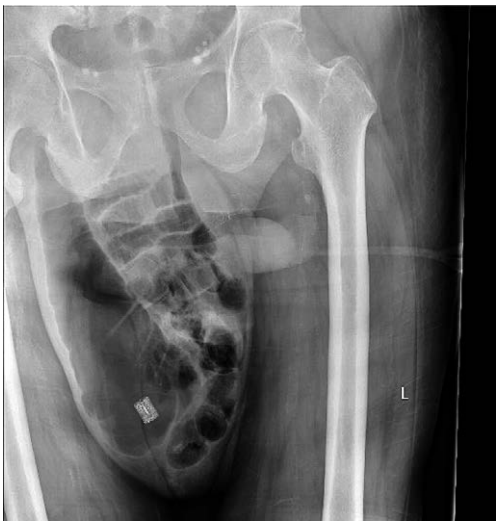

Fig. 1. Radiographic image of the scrotal hernia showing the patency endoscopy capsule within an intestinal loop within the hernia.

Video capsule endoscopy is recommended as the first-line investigation tool in patients with obscure gastrointestinal bleeding [1]. Capsule retention and subsequent obstruction are potential complications. It is reported to occur in approximately 2% of patients undergoing evaluation for bleeding and 4-8% of patients with suspected or manifest chronic inflammatory bowel disease [2]. A patency capsule, computed tomography enterography or magnetic resonance imaging can be used to assess patency, the latter being recommended in Crohn's disease with known or suspected stenosis [1]. A hernia is not generally considered a contraindication for video capsule endoscopy [3] and bowel obstruction due to capsule retention in a hernia has, to the best of our knowledge, not been reported so far. Our image of a capsule in such a large scrotal hernia is an unusual clinical snapshot. Our patient did not experience bowel obstruction, but retention of the patency capsule in the hernia highlights that a patency capsule to probe unobstructed passage is useful before video-capsule administration in such cases of uncertain passage.

Johannes Betge[1,2,3], Maximilian Wekerle[1], Matthias P.A. Ebert[1,3]
1) Department of Medicine II, University Medical Center Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim; 2) Junior Clinical Cooperation Unit Translational Gastrointestinal Oncology and Preclinical Models, German Cancer Research Center (DKFZ), Heidelberg; 3) DKFZ-Hector Cancer Institute at the University Medical Center Mannheim, Mannheim, Germany

Correspondence: Johannes Betge,
johannes.betge@medma.uni-heidelberg.de

Conflicts of interest: None.
DOI: 10.15403/jgld-4208

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First report of successful liver transplant with graft from a JAK-2 positive essential thrombocythemia donor and common hepatic artery thrombosis

To the Editor,

We successfully performed a liver transplantation with a graft from a donor after brainstem death (DBD) with Janus Kinase 2 (JAK-2) positive essential thrombocythemia (ET) and a partially organized thrombus within the common hepatic artery (CHA).

The graft, that we assigned to a 66-year-old patient affected by a 5-cm HCC on decompensated NASH cirrhosis, was from a 57-year-old A+ female DBD who suffered from a JAK-2 positive ET treated with hydroxyurea and aspirin, with no recent evidence of circulating blast cells. Platelet count was 736,000/mm^3. Liver function tests and ultrasound were unremarkable. Computed tomography (CT) was not performed.

At retrieval, the liver was deemed suitable for transplantation and biopsy was not performed. Liver pedicle was unremarkable on palpation and not dissected in situ. Dual perfusion was performed with Celsior. The liver was retrieved with standard en bloc technique.

On bench surgery, a 10 mm-long fully epithelised eccentric thrombus, occupying 2/3 of the lumen of the CHA was found (Fig. 1) and confirmed on histology. The artery, cut beyond the level of the thrombus, was anastomosed with the recipient replaced right hepatic artery from SMA. Post-operative course was unremarkable with patency of the artery on ultrasound. Standard immunosuppression was applied. Aspirin 100 mg was added on day 5 to standard thromboembolic prophylaxis.

Essential thrombocythemia is a Philadelphia-negative myeloproliferative disorder associated with the V617F gain-of-function mutation (50-65% of cases) in a tyrosine kinase enzyme called JAK-2, whose main clinical manifestations are thrombotic events. It has been considered a contraindication

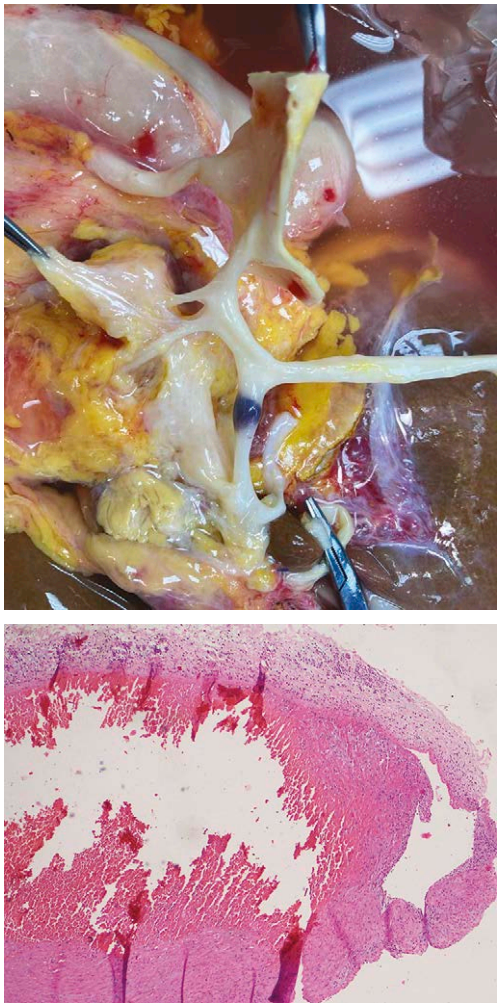

Fig. 1. A) Partially occluding thrombus at the origin of the common hepatic artery, just after the take-off of the splenic artery, identified at bench table preparation of the graft, before implantation. The arterial graft was used after removal of the thrombosed portion. B) Partially organized thrombus with initial recanalization (on the right) and fibroblastic reaction.

for organ donation for the risk of disease transmission. The risk of progression to a malignant condition is rare with an 80% 15-year OS [1].

The use of a donor with JAK2-positive ET raises several issues about disease transmission with risk of increased thrombogenicity and of malignant transformation. Many pathogenetic mechanisms in myeloproliferative disorders also involve the liver and heart [2]. The risk of disease transmission is negligible as it would require the translocation of a donor myeloproliferative cells clone with the graft to the recipient and their implant in the healthy bone marrow. A significant extramedullary haematopoiesis in the donor is also necessary. Essential thrombocythemia carries a low mutation burden [1].

Thrombotic risk within the vascular system of the graft is unknown. Only one case of ET associated with liver cirrhosis, potentially due to intra-hepatic microvascular thrombosis, is described [3]. The presence of a previous medical history of ET in the donor could justify the presence of a thrombus in the CHA. To date, there is no evidence to justify discarding a graft from a donor with ET because of the increased risk of graft

failure due to intrahepatic arterial/venous thrombosis. Donors with JAK-2 ET should undergo a CT scan before retrieval to rule out venous/arterial thrombosis.

To the best of our knowledge, differently from the two previously described cases [4, 5], this is the only case of a successful liver transplant with a graft belonging to a donor affected by JAK2-positive ET and with CHA thrombosis. The origin of the thrombus could not be attributed to other causes (trauma or arterial catheterization). The position of the thrombus, the good quality of the rest of the CHA and normal donor anatomy permitted the use of the graft.

We suggest that organs from ET donors could be used for transplantation after careful evaluation of the donor with CT scan to rule out thrombotic manifestations of the disease and in those scenarios where the benefit of transplant outweighs the risk of ET transmission. Informed consent should be sought before transplantation and close follow-up maintained.

Daniele Ferraro[1], Marcello Di Martino[1], Claudio Napoli[2], Alfonso Galeota Lanza[3], Giovanni Vennarecci[1]

1) UOC Hepato-biliary Surgery and Liver Transplant Centre, AORN Antonio Cardarelli, Naples; 2) UOC Clinical Immunology and Immunohematology, Transfusion Medicine and Transplant Immunology, A.O.U. Università degli Studi della Campania "L. Vanvitelli", Naples; 3) UOC Hepatology, AORN Antonio Cardarelli, Naples, Italy

Correspondence: Daniele Ferraro daniele.ferraro@aocardarelli.it

Conflicts of interest: None.
DOI: 10.15403/jgld-4230

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