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Do lymphomas have an autoimmune background and how can we increase the sensitivity of the diagnosis of primary pancreatic lymphoma with relatively small samples ?

To the Editor,

We read with great interest the paper by Anderloni et al. [1], in which the authors describe the case of a primary pancreatic non-Hodgkin's lymphoma (NHL) that mimicked an autoimmune pancreatitis. Primary pancreatic lymphoma is a very rare disease but as evidenced by the case report, it should be considered as a differential diagnosis when a patient presents with a pancreatic mass. Most of the primary pancreatic lymphomas are B cell NHL; however, studies have reported T cell malignancies as well. Other types of lymphoma that occur in the pancreas include anaplastic large cell lymphomas and Hodgkin's lymphoma (HL) [2]. In this particular case, an endoscopic ultrasound guided FNA or biopsy was not necessary as the patient was found to have a duodenal mass. However, in cases where the mass is confined to the pancreas, it has been noted that flow cytometry in addition to cytology examination increases the sensitivity of diagnosing this disorder [3, 4]. Flow cytometry is a very sensitive tool which can easily distinguish lymphomas especially B cell lymphomas from nonmalignant causes such as autoimmune pancreatitis. An onsite look at the FNA sample aids in establishing the diagnosis and helps with decisions on what further investigations to request. If the predominant cells noted on the sample are lymphocytes, extra passes are requested in order to perform flow cytometry. In B cell NHL involving the pancreas the distinction between an autoimmune process versus a B cell NHL is fairly easy as a lambda or kappa clone is seen in the latter case with B cell markers such as CD20 and CD19. Thus, the morphology on the cytology in addition to the markers expressed on flow cytometry (B cell markers and a clone) in most cases is sufficient to make the diagnosis and obviates the need for histology diagnosis in cases where the sample available is limited.

Sometimes, a lymphoma is diagnosed in association with an autoimmune disease [5, 6]. The experience of our Cancer Centers confirms this hypothesis, when a lymphoma is diagnosed and treated. In some cases, we observed that when the lymphoma is considered cured, a second autoimmune disease is often diagnosed. The autoimmune diseases are considered to be second diagnoses, associated with the malignancy, but it is of key importance to consider that a NHL often appears after a chronic alteration of the immune system and years after a diagnosis of a hemophagocytic syndrome (HS), also of autoimmune origin. We should thus take into consideration that the NHLs may actually not be necessarily isolated diseases, but a malignancy associated with various autoimmune diseases. By using chemotherapy followed often by radiation oncology, physicians only have a symptomatic approach and take care of just one syndrome, in this case the lymphoma. Current protocols used by physicians take into account just one syndrome. But, as we do not interfere with the principal disease, it is to be expected that a patient may come back to the hospital with other complaints, whether they are gastrointestinal, neurological or rheumatologic. Italian physicians report the problem of the differential diagnosis between pancreatitis and pancreatic lymphomas; however, it is of equal importance to stress the association of NHL with gastrointestinal diseases. Therapy may be urgent and the overall survival is completely different between the two lymphoma-associated conditions, but this observation may show that lymphoproliferative disorders are associated with autoimmunity, of key importance in understanding their genesis and thus in developing new, more patient-tailored therapies.

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Conflicts of interest: No potential conflicts of interest are reported.

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Cytoreductive surgery (CR) followed by hyperthermic intraperitoneal chemotherapy (HIPEC): a chance of survival for patients with advanced colorectal cancer

To the Editor,

About 7% of the patients with colorectal cancer have already peritoneal carcinomatosis at diagnosis, leading to a 0% 5-year survival rate [1]. Furthermore, the recurrence of peritoneal diseases was reported in up to 56 % of the patients who had received radical colorectal resection [1, 2]. With systemic chemotherapy alone, the median survival rate does not exceed 15 months [2].

Cytoreductive surgery (CR) followed by hyperthermic intraperitoneal chemotherapy (HIPEC) may lead to an increased median survival of up to 33 months, and a 5-year survival rate of 17-51% [2]. Complete cytoreduction, obtained by multivisceral resections and extensive peritonectomy, is the only treatment able to provide these results, the completeness of the cytoreduction score (CC) being the main prognostic factor [3]. The intraoperative chemotherapy plan requires administration of systemic 5FU and folinic acid [4], followed by intraperitoneal continuous lavage with oxaliplatin or mitomycin for 30-90 minutes, at a constant temperature of 41-43°C. In terms of survival, recurrence or morbidity, studies have shown the superiority of hyperthermia (HIPEC) when compared with early postoperative intraperitoneal chemotherapy (EPIC) or sequential postoperative intraperitoneal chemotherapy (SPIC), procedures based on normothermic lavage [5, 6].

Despite these favorable results, highlighted in one randomized trial [7], two multicenter trials [8, 9], several phase II and III studies and numerous other reports [10], CR and HIPEC are not considered as standard of care, except in a few tertiary surgical centers in the US and Europe. The associated perioperative mortality is up to 5.8%, and the incidence of Clavien-Dindo's grade III-IV complications is 12-52 % [2].

Since January 2015, patients with peritoneal malignancies may benefit from CR followed by HIPEC also in our hospital. By July 2015, we applied this technique in six cases: five patients with adenocarcinoma of the colon and one with malignant peritoneal pseudomyxoma caused by a mucinous adenocarcinoma of the appendix. The peritoneal carcinomatosis index (PCI) of these patients was between 10 and 18. The surgical intervention lasted 360 to 720 minutes and the blood loss did not exceed 1500 ml, all this in terms of obtaining a CC0 score in all cases. We resected the primary colorectal tumor, then we performed extensive peritonectomy (including from the diaphragm and the urinary bladder) and by resection of all organs involved (enteral and colonic resections, omentectomy, hysterectomy) (Figs. 1, 2). There were no postoperative deaths. Five patients developed minor complications: wound infections and transient leukopenia. One patient had grade IV complications: severe leukopenia, acute liver failure and peripheral neuropathy, with full

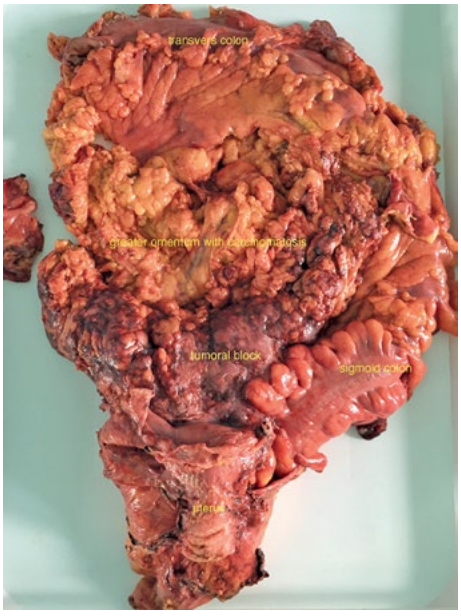

Fig. 1. "En bloc" resection of rectum, sigmoid, transverse and descendent colon, greater omentum and uterus, involved by the primary tumor and peritoneal carcinomatosis.

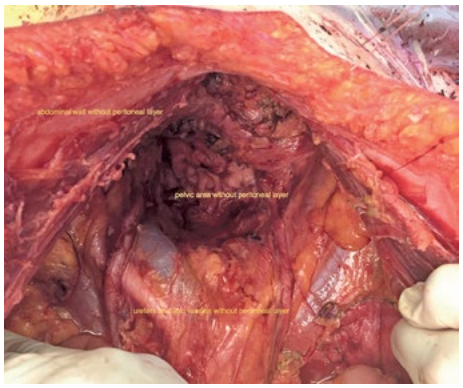

Fig. 2. Abdominal wall and pelvic space after, "en bloc" resection of the recto-sigmoidian tumor, the carcinomatous peritoneum and the involved organs.

recovery under intensive care therapy. These complications are known as side effects of oxaliplatin and the subsequent immunosuppression. The median postoperative hospital stay was 15 days. The median postoperative follow-up is now 117 days, all patients being alive, with no evidence of local or systemic recurrence.

We conclude that this technique is feasible with acceptable morbidity and mortality, as confirmed by the literature reports, while offering a realistic chance of survival for patients diagnosed with colorectal cancer and peritoneal carcinomatosis.

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Conflicts of interest: None to declare.

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Successful treatment of post-transplant hepatitis C virus cirrhosis with daclatasvir and asunaprevir

To the Editor,

Chronic hepatitis C virus (HCV) infection is a main cause of liver failure and a leading indication for liver transplantation (LT) [1]. Recurrence of HCV infection following LT is frequent and can lead to accelerated graft cirrhosis [2, 3]. The tolerance of interferon alpha-based regimens for recurrent HCV infection after LT is poor [4].

Direct-acting antiviral (DAA) agents have provided an opportunity to treat post-transplant HCV recurrence. Data on daclatasvir+asunaprevir use in LT patients are limited. We report a patient with LT who developed cirrhosis due to recurrent progressive HCV treated with daclatasvir and asunaprevir successfully.

A 55-year-old woman presented with HCV infection detected during screening. Genotype was 1b; she was given pegylated interferon and ribavirin. On the 3rd month, due to primary non-response, therapy was discontinued. On follow-up, she became decompensated, and a living-donor liver graft was transplanted. One month after LT she developed an acute flare; ALT was 630 U/L, HCV-RNA was 24,400,000 IU/mL. She was under mycophenolate mofetil (MMF) and steroid treatment; MMF was discontinued. She could not be given any antiviral therapy and ALT levels spontaneously decreased to 120-200 U/L and HCV-RNA to 2,320,000 IU/mL. One year after LT, a control liver biopsy revealed cirrhosis (Ishak's fibrosis score of 5/6).

The patient was given daclatasvir 60 mg per day and asunaprevir 100 mg twice a day for 24 weeks, the only available all-oral regimen provided for compassionate use in the country at that time. She was closely followed-up and the dose of immunosuppressive drug (steroid) was tapered since no drug-drug interaction data were available. During the 1st, 3rd and 6th (end of treatment) months, HCV-RNA remained negative. One month and three months after the end of treatment, it still was negative. After therapy, albumin level increased from 2.7 to 4.3 g/dL, platelets from 73,000 /mcL to 168,000/mcL and INR decreased from 2.02 to 0.98 (Fig. 1).

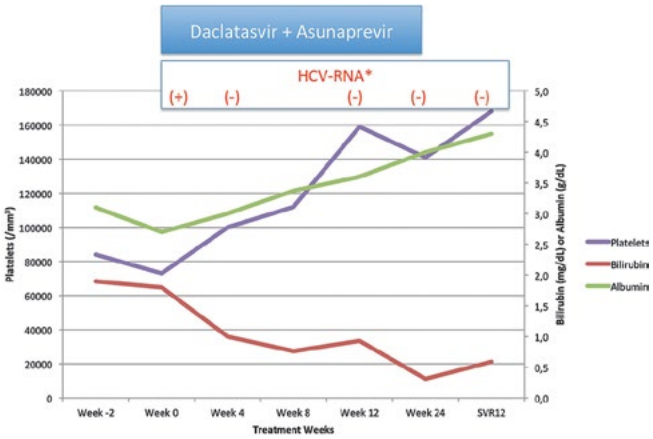

Fig. 1. Albumin and bilirubin levels and platelet counts with the therapy. *Week 0 HCV-RNA was 2,320,000 IU/mL, (-) represents HCV-RNA <20 IU/mL.

Hepatitis C virus leads to a more rapid progression in post-transplant setting, causing cirrhosis within the first 5-10 years in 20-30% of patients [2, 3]. However, interferon-based therapies are poorly tolerated and for triple therapy with telaprevir or boceprevir, drug interaction with immunosuppressive drugs is a big concern [4]. DAAs have provided high virological response rates with fewer side effects in post-transplant HCV recurrence [5, 6]. For genotype 1, the current guidelines recommend sofosbuvir+ledipasvir+ribavirin or sofosbuvir + daclatasvir + ribavirin or ritonavir-boosted paritaprevir + ombitasvir + dasabuvir + ribavirin or sofosbuvir + simeprevir + ribavirin [5, 6]. However, these drugs are not available in many countries.

Combination of daclatasvir, a non-structural protein 5A inhibitor and asunaprevir, a protease inhibitor provided virological response rates of 82-90% after 12-24 weeks of treatment in naïve or pegylated interferon+ribavirin nonresponder HCV genotype 1b patients [7]. However, asunaprevir is not recommended for patients with Child B or C cirrhosis in whom the maximum asunaprevir concentration is 5-fold and 23-fold higher than in healthy subjects, respectively [8].

In post-transplant settings, daclatasvir+asunaprevir was used for a patient with severe cholestatic hepatitis [9]. Our case represents the first use of daclatasvir with asunaprevir in post-transplant cirrhosis. Daclatasvir combined with asunaprevir seems to be an option for post-transplant HCV recurrence in patients, including compensated cirrhotics.

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Metabolomics for genomics: the role of vitamin D in nonalcoholic fatty liver disease

To the Editor,

Due to the increasing prevalence of NAFLD and the difficulties in selecting patients who require closer surveillance for fatty liver disease, various serum surrogate markers have been proposed [1, 2]. Vitamin D has already been reported to be pathogenically involved in different chronic liver disease. Lower levels of vitamin D were shown to correlate with NAFLD presence [3]. Moreover, vitamin D concentrations proved to be lower in NASH patients when compared to those with

simple steatosis and which were inversely correlated with liver histology [4].

The metabolic pathway of vitamin D implies (a) hydroxylation by 25-hydroxylase (CYP2R1) in the liver, leading to the formation of 25-hydroxyvitamin D [25(OH) D3], (b) transportation to the kidney where it undergoes (c) hydroxylation by 1 αhydroxylase (CYP27B1) to its active form 1,25-dihydroxyvitamin D [1,25(OH)2D3]. 25(OH)D3 is the form typically measured in the serum to assess the vitamin D status.

Metabolomics is a new emergent technique that can identify small molecules as final products of various metabolic pathways. It has been already used in patients with NAFLD, so that new metabolomic biomarkers for fatty liver become available, but they still need to be validated. We aimed to determine the role of vitamin D for the diagnosis of steatosis in a group of 30 patients compared to 20 healthy subjects and to evaluate the relationship between vitamin D levels and the polymorphism of *CYP27B1*.

We used the metabolomic approach for determining vitamin D levels by specific high performance liquid chromatography coupled with mass spectrometry (HPLC-MS) and principal component analysis (PCA) for the detection of polar molecules in the serum. As a reference we used the morphological analysis, which was estimated using the SteatoTest(R) (Biopredictive, Paris, France) for steatosis grading and the FibroTest(R) (Biopredictive) and transient elastography (Fibroscan®, Echosens, Paris, France) for fibrosis staging.

The NAFLD group had significantly lower levels of vitamin D (25(OH)D3) compared with the control group (35,827.00±4,304.37 vs 44,188.40±4,929.14, p<0.001), with high diagnostic accuracy (AUROC=0.890, cut-off=41,848 units). In NAFLD patients, the higher levels of 25(OH) D3 were significantly associated with the AA genotype of *CYP27B1* polymorphism (p=0.031). We also found a significant association between vitamin D levels and the noninvasive assessment of morphological features: steatosis grade (p=0.013 vs. SteatoTest) and fibrosis stage (p=0.030 vs. FibroTest and p=0.022 vs. Fibroscan).

An interesting observation was related to the presence of three patients having no steatosis at the SteatoTest (S0), as they were first enrolled in the NAFLD group based on ultrasound evaluation. In this setting, 25(OH)D3 had a high accuracy for confirming the presence of steatosis (patients with S0 vs S123): AUROC=0.905, p<0.001.

In conclusion, our pilot study suggest that vitamin D (assessed through metabolomics) could assist in the diagnosis of NAFLD and could be used to assess the disease severity (steatosis grade and fibrosis stage). It could also serve as a surrogate for *CYP27B1* polymorphism and eventually, it might be used as a substitute for the costly genetic method currently used to assess the vitamin D metabolism.

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Conflicts of interest: None to declare.

Acknowledgement: This study was performed under the framework of the European Social Fund, Human Resources Development Operational Programme 2007-2013, project POSDRU/159/1.5/S/138776.

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Hemorrhoidectomy and anal stenosis

To the Editor,

We recently examined three patients with anal stenosis after a Milligan-Morgan hemorrhoidectomy. All of them had in common the use of electrothermal bipolar vessel sealing (EBVS) devices. We reviewed our data and identified a total of five patients with anal stenosis where the overzealous removal of large areas of anoderm and hemorrhoidal mucosa could not be incriminated. Gentle lubricated dilation for a few weeks was sufficient in all but one case. We had to perform a Y-V advancement flap anoplasty with good results at a 3 month follow-up. A lateral sphincterotomy was associated to ease spasms. Sphincter relaxation and hygiene were provided by daily lukewarm sitz baths.

The EBVS devices provide safe hemostasis in hemorrhoid resection. Results reported with specially designed graspers were promising, with less postoperative pain, shorter hospitalization and faster wound healing compared to scissors or diathermy hemorrhoidectomy [1]. Several case reports have mentioned anal stenosis after the use of EBVS devices where the suspected pathogenesis consisted of partial-thickness burns of the anal margin [2]. Although the sealing system develops a tissue temperature of only 100°C and the lateral thermal spreading is limited at 1–2 mm, the contact time is longer than during resections with monopolar diathermy. Thus the perianal skin and mucocutaneous bridges sustain burns and gradual fibrosis occurs in the sub-cutaneous space of the anal canal [3].

Discomfort during defecation and stool narrowing are the main symptoms. It is difficult to perform a standard assessment of anal stenosis because quite frequently the patient is too anxious to accept a painful examination.

A simple scale describes a mild stenosis if examination is possible with the index finger, moderate if dilation is necessary for inserting the index and severe stenosis if the little finger cannot be inserted [4]. Depending on the length, stenosis may be diaphragmatic, ring-like or anular. The last two varieties are usually associated with hemorrhoid surgery [5]. Considering the level, stenosis can be low (0.5 cm below the dentate line), median (0.5 cm above and below the dentate line) and high (more than 0.5 cm above the dentate line). The low and median varieties account for the majority of postsurgical cases.

Prevention is the best treatment of postsurgical anal stenosis. A specific training for an appropriate use of EBVS devices and specially designed forceps for hemorrhoidectomy are mandatory. A proper pediculisation with cold dissection starting close to the mucosal margin and the retraction of the cutaneous margin exposed to the lateral thermic spread of the bipolar blades will minimize burns.

A close follow-up is mandatory to diagnose the stenosis before it is stabilized [4]. Early conservative treatment with daily lubricated dilations for 1-2 months and stool softeners will suffice in most situations.

Bipolar vessel sealing devices greatly improved hemorrhoidectomy, and postoperative anal stenoses can be avoided if thermal lateral lesions prevention is considered.

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Conflicts of interest: No conflict to declare.

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