LEFT-SIDED PORTAL HYPERTENSION SECONDARY TO LOCALLY ADVANCED PANCREATIC CANCER: CLINICAL CHARACTERISTICS, THERAPEUTIC APPROACH AND OUTCOME. MULTICENTRIC INTERNATIONAL REGISTER.

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Background and rationale

Left-sided portal hypertension (LSPH), also known as sinistral or segmental hypertension, is a localized form of portal hypertension (PH) that usually occurs as a result of splenic vein thrombosis (SVT) [1,2]. It represents less than 5% of all cases of PH, distinguished from other forms by preserved liver function and patent extrahepatic portal vein (3).

Due to its location along the pancreas, pancreatic disorders represent the main etiology of splenic vein (SV) occlusion. Acute and chronic pancreatitis are the most common pancreatic diseases associated, followed by pancreatic cancer. Other rare causes of LSPH are iatrogenic injury after liver transplantation, SV resection after pancreaticoduodenectomy and hereditary thrombophilia, among other [4]. Regarding pancreatic cancer, the incidence of LSPH has no connection with the tumor's primary site [3]. Nevertheless, it may be related to a high-grade malignancy and hence poor prognosis [5].

The incidence of LSPH has increased over the past decades due to increased awareness of the entity as one rare cause of gastrointestinal bleeding (GIB), as well as advances in diagnostic approach. In this context, borderline resectable (BR) and locally advanced pancreatic cancer (LAPC) are disorders related to LSPH in which the management, prognosis and complications have changed in the last years is.

Pancreatic cancer (PC) is a highly lethal malignancy, being the third leading cause of cancer-related death worldwide and projected to become the second leading cause of cancer death in the next ten years. Surgical resection and chemotherapy offer the only chance to prolong survival. Unfortunately, because of late presentation, 80–85% of patients present with locally advanced or metastatic disease and only 15-20% are resectable or borderline resectable PC candidates for pancreatectomy. Furthermore, even after a complete resection, prognosis is poor, with only 20% surviving 5 years following surgery [6]. Notwithstanding, these recent years, the prognosis of patients with BR and LAPC has experienced progress in increasing survival with neoadjuvant treatment [7]. Recent advances in surgical techniques and chemotherapy regimens, such as FOLFIRINOXm, have improved the overall survival rates in this group of patients, especially in BR and LAPC when no resection is possible. In LAPC patients, some series have reported median overall survival of 24 months after FOLFIRINOXm and up to 60% resection rate after downstaging [8].

Due to more extended survival, patients might develop more complications, such as LSPH secondary to SVT. In this scenario, the challenges brought by LSPH are getting more attention, because of the potential complications in peri-operation phase during the neoadjuvant chemotherapy period [3]. Some surgeons consider secondary LSPH as a potential risk for failure of radical operation. However, pancreatectomy seems to be safe and effective for patients with BR and LAPC who develop LSPH, even though the surgical strain may be increased [5]. Even though not all LAPC patients might be surgical candidates, it is important to assess the risk for LPSH-related complications in this group of patients, since a delayed chemotherapy treatment could lead to progression of the disease.

The diagnosis of LSPH should be contemplated in patients with BR and LAPC and GI bleeding. The first diagnostic approach is performed by Doppler ultrasonography (US), which is used to rule out isolated portal vein thrombosis and liver cirrhosis. Computed tomography (CT) and magnetic resonance imaging (MRI) are both valuable tools in assessing portal venous system and splenic vasculature [1]. Esophageal varices (EV) may be seen both radiologically and endoscopically; however, gastric varices (GV) may be more difficult to diagnose by either technique. Arteriography remains the gold standard diagnostic method, delimiting the exact location of the obstruction and the route of decompression [1]. Endoscopic ultrasound (EUS) has been increasingly used to confirm SVT when other diagnostic tools fail [2]. In some cases, a liver biopsy may be done to exclude cirrhosis [1].

Management of LSPH comprises treating both the underlying cause and PH-related complications. Variceal hemorrhage may be controlled endoscopically using sclerotherapy or band ligation [1]. An angiographic approach with variceal obliteration w/o thrombectomy can also be considered but has not been properly evaluated. Unresponsive bleeding may require urgent splenectomy [9], which the objective of decreasing splenic inflow through the collateral circulation and decompressing the resulting varices [10]. Splenic artery embolization is sometimes performed before splenectomy to decrease intraoperative blood loss [11], but its performance alone is not recommended because it may cause splenic infarction and abscess formation[1]. There is not enough evidence supporting prophylactic splenectomy in asymptomatic patients. Other less frequently used therapeutic options include SV reconstruction and stent placement. There is no consensus with the role of anticoagulation, but in patients considered susceptible of receiving anticoagulants, they should only be initiated after treatment of varices [2,4].

The incidence and mortality rate related to variceal bleeding is relatively low compared with patients with liver cirrhosis and generalized PH, and usually do not recur. Thus, the prognosis depends on the underlying disease.

Despite all this data, the real incidence of patients with BR and LAPC who develop LSPH is unknown and the best therapeutic approach remains controversial. Heretofore, most articles published in the literature are case reports or series involving a reduced number of patients, without a long-term follow-up.

The aim of our study is to assess the real incidence of GIB secondary to LSPH in BR and LAPC and to review the best therapeutic approach. Furthermore, we would like to identify risk factors in these patients to develop SVT and LSPH and whether the prognosis of these patients is influenced by the presence of LSPH.

References

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Objectives

Main objective

To assess the real incidence of GIB in patients with BR or LAPC and LSPH, and to review the best therapeutic approach.

Secondary

1) Identify risk factors in patients with BR and LAPC who have developed SVT and LSPH

2) Document the presence of other PH-related complications at follow-up

3) Establish the long-term survival

Design

A retrospective multicenter study is proposed. Patients with diagnosis of LSPH secondary to BR and LAPC will be included. The diagnosis will be based on clinical presentation, endoscopic and radiographic imaging, and operative findings. Patients with BR and LAPC, and SVT will be included. Patients with isolated fundal varices without demonstrated splenic vein occlusion or isolated portal vein thrombosis will also be considered as candidates for inclusion. Clinical history and diagnostic tools (including imaging tests, endoscopic procedures and angiography) will be reviewed. Management of both complications and underlying disease will be recorded, as well as outcome during follow-up.

Study population

Patients with diagnosis of BR and LAPC who develop LSPH secondary to SVT will represent the study population. The recruitment will be made by reviewing the patient database of every participating center.

Inclusion criteria

-Age ≥18 years.

- BR or LAPC proved by pathological examination.

-Portal hypertension defined by clinical, laboratory or endoscopic findings.

-Demonstration of splenic vein thrombosis or stenosis with or without portal vein involvement, either by imaging, endoscopic ultrasound, angiography, or intraoperatively. To achieve a better characterization of the disease and the technical methods used, isolated portal vein thrombosis will also be included.

-Isolated gastric varices (IGV) without demonstrated splenic vein occlusion will be also considered.

Exclusion criteria

-Liver cirrhosis.

-Isolated intrahepatic portal vein thrombosis.

Definitions

Thrombosis will be considered when a thrombus is visible by imaging (contrast-enhanced CT or MRI, but also eco-Doppler US).

Acute or **chronic** thrombus will be defined, when it is possible, according to the radiological aspect. A calcified thrombus or cavernous transformation will be defined as chronic.

Stenosis will be considered when the lumen vessel is occluded, usually due to an external compression (not caused by thrombus).

Left-sided portal hypertension (LSPH) will be diagnosed if indirect signs of portal hypertension are present, in the absence of liver disease. Indirect signs of portal hypertension could be splenomegaly, presence of collaterals, esophageal or gastric varices or ascites.

Parameters

Clinical data (prior history and basal clinical status), laboratory tests and diagnostic evaluation, surgical and non-surgical management, outcome and survival will be recovered from medical records. Follow-up will take into account the first diagnostic tool reporting alterations compatible with LSPH.

Data will be collected as follows:

1. Patient history:
    - Identification
    - Age; date of birth
    - Diabetes (yes/no)
    - Alcohol and smoking habits: yes/no/previous consumption
    - Known liver disease
    - Known prothrombotic disorder
    - Previous abdominal surgery: type (appendectomy; cholecystectomy; liver resection; pancreas resection: other -type-) and date (surgery performed 6 months near the diagnosis of thrombosis)

2. Oncological history:
    - Date of borderline resectable or locally advanced pancreatic cancer diagnosis
    - Localization (head/body/tail)
    - Size according to the maximum diameter
    - Stage
    - Biopsy
    - Laboratory tests:
        - Hemoglobin, Leucocytes, Platelets, Creatinine, Bilirubin, Liver enzymes, Albumin, INR (current anticoagulant treatment yes/no)
        - CA 19-9
    - Presence of thrombosis (partial/total; thrombus length; date of diagnosis; reason of diagnosis –asymptomatic finding, GI bleeding, ascites-)
        - Splenic vein: yes/no; partial/total
        - Portal vein: yes/no; partial/total
        - Mesenteric vein: yes/no; partial/total
        - Portal-esplenic-mesenteric confluent: yes/no; partial/total
        - Hepatic artery: yes/no; partial/total
        - Splenic artery: yes/no; partial/total
        - Portal cavernous transformation: yes/no
    - Thrombosis treatment:
        - Anticoagulation (date and type)
        - Thromboprophylaxis (date and type)
        - Thrombectomy (date)
        - Stent placement (date; anticoagulation or antiagregation)
        - Others
    - Presence of secondary porto-systemic collaterals: yes/no; type.
    - Oncological treatment:
        - Neoadjuvant treatment: yes/no
            - Starting date
            - Type of chemotherapy
            - Number of cycles
        - Locorregional treatment: yes/no
            - Starting date
            - Type of treatment
        - Surgery: yes/no

        - Date of surgery
        - Type of surgery
    - Second line chemotherapy:
        - Starting date
        - Type of chemotherapy
        - Number of cycles
    - Other lines of chemotherapy:
        - Starting date
        - Type of chemotherapy
        - Number of cycles

3. <u>Follow-up:</u>
    - Date of last follow-up
    - Response to treatment: yes/no; date; type of response (disease-free, partial)
    - Laboratory data: Hemoglobin, Leucocytes, Platelets, Creatinine, Bilirubin, Liver enzymes, Albumin, INR (current anticoagulant treatment)
    - Progression: yes/no; date
        - Type of progression: local, adenopatic affection, metastases
    - Thrombosis progression: yes/no
        - Date of diagnosis
        - Treatment
    - Death: yes/no; date
        - Cause of death:
            - Disease progression
            - Upper gastrointestinal bleeding due to LSPH
            - Others
4. <u>Portal hypertension and related complications:</u>
    - Date of LSPH diagnosis
    - Clinical manifestations of LSPH (abdominal pain, upper GIB, asymptomatic…)
    - Diagnostic approach (Doppler-US, abdominal CT or MRI, HVPG…)
    - Laboratory data: Hemoglobin, Leucocytes, Platelets, Creatinine, Bilirubin, Liver enzymes, Albumin, INR (current anticoagulant treatment)
    - Upper endoscopy: yes/no; date
        - Esophageal varices: yes/no; small/large
        - Gastric varices: localization (GOV1, GOV2, IGV1, IGV2)
        - Other findings (portal gastropathy, GAVE…)

- Acites: treatment and date
- Upper GIB during follow-up: yes/no
    - Date
    - Cause:
        - Esophageal varices
        - Gastric varices
        - Others
- Treatment (date):
        - Endoscopic local treatment (banding, sclerotherapy…)
        - Angiographic approach: Gastric varices embolization
        - Thrombectomy
        - Stent placement (plus anticoagulation or antiaggregation)
        - Splenectomy w/o splenic artery embolization
        - Specific medical treatment
        - In case of previous anticoagulation: date of interruption
    - Complications post-treatment (type and date)
    - Recurrence: yes/no
        - Date of recurrence
        - Type