Digestive and Liver Disease 47 (2015) 417–422

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

Prevalence and outcomes of cystic lesion of the pancreas in immunosuppressed patients with solid organ transplantation

Saowanee Ngamruengphong[a], Kristina M. Seeger[b], Luke M. McCrone[b], Maria Moris[a], Stephen J. Garrison[c], Surakit Pungpapong[a,d], Andrew P. Keaveny[a,d], Massimo Raimondo[a,*]

[a] Division of Gastroenterology and Hepatology, Mayo Clinic, Jacksonville, FL, United States
[b] Department of Internal Medicine, Mayo Clinic, Jacksonville, FL, United States
[c] Department of Radiology, Mayo Clinic, Jacksonville, FL, United States
[d] Department of Transplant, Mayo Clinic, Jacksonville, FL, United States

ARTICLE INFO

Article history:
Received 4 December 2014
Accepted 21 February 2015
Available online 28 February 2015

Keywords:
Immunosuppressive therapy
Organ transplantation
Pancreatic cystic neoplasms

ABSTRACT

Background: Solid organ transplant recipients have an increased risk of cancer due to immunosuppressive therapy. Pancreatic cystic lesions are increasingly being detected, some with malignant potential. We aimed to determine the prevalence of these lesions and describe their clinical course in these patients.
Methods: We identified the presence of pancreatic cystic lesions in a retrospective cohort of 3188 consecutive solid organ transplant recipients from 2000 to 2013 and compared lesion characteristics at initial and follow-up imaging, when available.
Results: Lesion prevalence was 11.4% (365/3188), and increased with age. Median diameter of the largest lesions was 7 mm (range: 1–31 mm). We noted worrisome features in two patients (0.54%) at the time of cyst diagnosis. Of 155 patients who underwent follow-up imaging, the cysts size remained stable in 80%, increased in 16%, and decreased in 4%. Two patients (1.3%) developed features concerning for cancer. One underwent pancreatic surgery, and pathology confirmed the presence of high-grade dysplasia. The other continued with conservative management due to multiple comorbidities.
Conclusions: Pancreatic cystic lesions are common in solid organ transplant recipients. In lesions without high-risk features, the development of features worrisome for cancer is rare. These lesions can be managed conservatively, and their presence should not affect transplant eligibility.

1. Introduction

Solid organ transplantation (SOT) is a lifesaving procedure in patients with end-organ diseases. Based on Organ Procurement and Transplantation Network data, in 2013 a total of 28,954 transplants were performed in USA. Although recipient survival rates have improved considerably over time, chronic immunosuppressive therapy administered to prevent graft rejection results in substantial morbidity. Malignancy is one of the most common causes of mortality after transplantation [1].

Pancreatic cystic lesions (PCL) have been increasingly recognized due to widespread use of high quality imaging techniques. The prevalence of pancreatic cysts has been estimated to be 3–14% based on imaging studies [2–4]. Their spectrum is widely variable and includes benign, premalignant and malignant pathologies. Among resected cysts, serous cystic neoplasms (SCNs) (32–39%), mucinous cystic neoplasms (MCNs) (10–45%), and intraductal papillary mucinous neoplasm (IPMNs) (21–33%) represent the majority of the cases encountered in practice [5,6]. Their malignant potential varies according to histologic type. SCNs have a benign natural history and do not require surgical resection, unless symptomatic. In contrast, IPMNs and MCNs are considered neoplasms with malignant potential. IPMNs that involve the main pancreatic duct have a higher malignant potential compared to the branch duct IPMNs (BD-IPMNs) [7]. Although SCNs, BD-IPMNs, and main duct IPMNs have typical imaging features that can be readily distinguished from other types of PCL, current diagnostic tests cannot reliably differentiate between benign and potentially malignant cysts [8].

Several epidemiologic studies have demonstrated an increased incidence of various cancers among transplant recipients as a result of poor immune control of known oncogenic infection, loss of

* Corresponding author at: Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224, United States. Tel.: +1 904 953 6982; fax: +1 904 953 7260.
E-mail address: raimondo.massimo@mayo.edu (M. Raimondo).

http://dx.doi.org/10.1016/j.dld.2015.02.011
1590-8658/

immune surveillance, or carcinogenic effects of immunosuppressive medications [9]. Because a significant proportion of PCL have malignant potential, there have been concerns that immunosuppression may accelerate their malignant transformation. To date, the natural history of PCL in organ transplant recipients is unknown. Furthermore, there are limited data on the prevalence of pancreatic cysts in organ transplant recipients. There are established guidelines for the management of PCL based on the risk of developing a malignancy [7,10]. However, it is unclear whether the frequency of disease progression and malignant transformation in immunosuppressed patients is similar to that of the general population and whether published guidelines are applicable to transplant recipients.

The aims of this study were to determine the prevalence of incidental PCL in the SOT population and describe their clinical course in patients on chronic immunosuppressive therapy.

2. Materials and methods

This study was approved by the Mayo Clinic Institutional Review Board.

Using databases of the Department of Transplant at Mayo Clinic Florida, we retrospectively reviewed medical records of all patients who received a SOT ($n = 3893$) [liver or combined liver–kidney ($n = 2190$), kidney ($n = 1099$), heart ($n = 203$), or lung ($n = 401$) transplant] between January 2000 and August 2013. Of these, 3226 underwent cross-sectional imaging [computed tomography (CT) scan, MRI, or endoscopic ultrasound (EUS)]. Records of cross-sectional imaging were searched for the diagnosis of pancreatic cysts. We also manually reviewed radiographic imaging to confirm the presence of PCL.

Thirty-eight patients were excluded from the analysis because of clinical and/or imaging features of pancreatic pseudocysts, symptoms related to the pancreas, history of pancreas transplantation or pancreatic cancer, previous pancreatic surgery, or a diagnosis of chronic pancreatitis (because PCL in these patients are more likely to be pseudocysts than cystic neoplasm). This left 3188 patients for analysis.

2.1. Data acquisition

We recorded demographic information, including date and type of SOT, presence of symptoms attributable to PCL, and laboratory data, including cyst fluid analysis and cytology, when available. Baseline information on the cystic lesions, including date of examination, size, location, and development of features concerning for malignancy (see below) was recorded.

2.2. Study definitions

The cysts were measured at their largest diameter on cross-sectional imaging. Pancreatic duct dilatation was considered present if the main pancreatic duct was >6 mm in diameter. MCNs were diagnosed when macrocystic lesions, sometimes with septations and wall calcifications and without any demonstrable communication to the main pancreatic duct were present. BD-IPMNs were diagnosed when an imaging study showed one or more pancreatic cysts communicating with the main pancreatic duct, grape-like cyst shape, or pathology, when available. SCNs were diagnosed when the cysts were microcystic or honeycombed with a central scar or sunburst calcification on imaging or EUS. In the absence of typical imaging features, the lesions were considered "indeterminate".

For cystic lesions suspicious for IPMN, the following criteria were used as risk factors of malignant pancreatic cysts, so called "high-risk stigmata", including enhanced solid component and main pancreatic duct size of ≥10 mm, or "worrisome features", including thickened enhanced cyst walls, non-enhanced mural nodules, abrupt change in the main pancreatic duct calibre with distal pancreatic atrophy, main pancreatic duct size of 5–9 mm and lymphadenopathy" [10]. An increase in cyst size was also recorded, although it is still debatable as to whether an increase in size alone is a risk factor for malignant evolution [11,12].

2.3. Follow-up outcome

We evaluated outcomes of patients with pancreatic cysts ≥5 mm in maximal size that had follow-up imaging after SOT ($n = 155$). We excluded patients with cystic lesions when follow-up post-transplant imaging was not available for comparison ($n = 113$), as well as patients with cysts <5 mm in size ($n = 97$) from outcome analysis. For the lesions <5 mm, it is difficult to differentiate pancreatic intraepithelial neoplasia from IPMN. Therefore, we chose to evaluate clinical outcomes of patients with pancreatic cysts ≥5 mm. None of these excluded patients showed worrisome features at the time of cyst diagnosis. Follow-up imaging consisted of CT, MRI, or EUS with or without fine-needle aspiration (FNA). The sizes of the largest cyst at diagnosis and at the latest imaging study were compared. We used the same imaging modality whenever possible for purposes of comparison. Interval changes of the maximum cystic diameter and the development of worrisome features during the observation periods were recorded. Cyst size was considered to have changed if there was a difference of more than 5 mm.

Follow-up was defined as the time between the diagnosis of PCL and one of the following end points: (1) the first imaging showing sign of worrisome features/high-risk stigmata of malignancy; (2) pancreatic surgery for pancreatic cyst(s); (3) last imaging test in patients with an uneventful follow-up.

2.4. Statistical analyses

We performed a descriptive analysis to determine the prevalence of incidental pancreatic cysts in our SOT population undergoing cross-sectional imaging. For normally distributed variables, means and (±) standard deviation were reported, whereas for non-normal data we reported medians and interquartile ranges (IQR). The prevalence of cysts by age, race, sex, and type of SOT was examined. Statistical comparisons were performed using Student's t test, chi-squared test, Fisher's exact test, and Mann–Whitney U test, as appropriate. The Pearson Correlation coefficient was calculated to measure the strength of correlation between the prevalence of pancreatic cyst and age, and cyst size and age. For patients with multiple cystic lesions, the data from the largest cyst was used in the analysis. All data were analyzed using SPSS Statistics software (version 16; SPSS Inc., Chicago, Illinois, USA). A p value <0.05 was considered statistically significant.

3. Results

A total of 3188 patients met the selection criteria. The mean age of these patients was 55 years (±11.7) and 1119 (31%) were female. Overall, 11.4% (365/3188) of the patients had at least one incidental PCL detected in the imaging studies. The clinical data of patients with pancreatic cysts are shown in Table 1.

The prevalence of PCL increased with age from 1.9% in patients younger than 29 years to 18.5% in patients who were 70 years and older ($r = 0.99$, $p < 0.001$). Patients with incidental PCL were significantly older than those without incidental PCL (59.5 ± 9.3 years vs. 55.1 ± 11.4 years; $p < 0.001$). The prevalence of PCL in female patients (14.7%) was 1.5 times higher than in male patients (9.7%) ($p < 0.001$). No racial difference in prevalence was noted ($p = 0.07$).