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Chronic immunosuppression does not potentiate the malignant progression of mucinous pancreatic cystic lesions

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ABSTRACT

Background: Premalignant mucinous pancreatic cystic lesions (mPCLs) are increasingly identified.
Aims: In this study, we aim to assess the effect of selected immunosuppressive therapies on the progression of mPCLs, including side-branch intraductal papillary mucinous neoplasms and mucinous cystic neoplasms.
Methods: We performed a retrospective cohort study of patients with mPCLs diagnosed over a 24-year period who received chronic immunosuppression. Controls were matched on age at cyst diagnosis (±11 yrs) and cyst size (±8 mm). Measured outcomes included increase in cyst size, development of "worrisome features" as defined by consensus guidelines, progression to malignancy, and rate of surgical resection.
Results: 39 patients (mean age 60 yrs) with mPCLs were on immunosuppression. Leading indications for immunosuppression were solid organ transplant (n = 14), inflammatory bowel disease (n = 6), and rheumatoid arthritis (n = 5). 33% were on biologics, 77% on antimetabolites and 79% on multiple medications. Mean cyst size increased from 12.6 mm to 17.8 mm over a median of 16.5 months. 6 patients elected for surgical resection, and none ultimately developed malignancy. 26 cases with follow-up were matched to control subjects, with no significant differences among cases and controls in initial cyst size (12.8 mm vs 11.9 mm, P = 0.69), mean size increase (6.9 mm vs 5 mm, P = 0.47), follow-up interval (24.3 months vs 21.5 months, P = 0.44). No significant differences in the rate of worrisome features, malignancy, or surgical resection.
Conclusions: Patients with mPCLs exposed to immunosuppressive medications did not have higher rates of malignancy or development worrisome features in the short term. This suggests that patients with mPCLs can be initiated or maintained on these agents without changes to surveillance practices.

1. Introduction

Premalignant mucinous pancreatic cystic lesions (mPCLs), including intraductal papillary mucinous lesions (IPMNs) and mucinous cystic neoplasms (MCNs), are increasingly being recognized with routine cross-sectional imaging [1,2]. The reported incidence of pancreatic cysts varies widely ranging from 2.6% to 13.5% with increasing prevalence with age [3,4]. The malignant potential of mPCLs is variable [5]. Increased age, male sex, and malignant cytology from endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) have been proposed as predictive factors for identifying malignancy within mPCLs [6].

Management recommendations for mPCLs have evolved over the past decade as we learn more about the natural history of these lesions. The established consensus criteria for the management of mPCLs were initially published in 2006 and updated in 2012 [7,8]. Operative resection is generally offered for those with MCNs due to the uncertain natural history of the disease, although this practice has recently been challenged in the literature [9]. Branch duct IPMNs (BD-IPMNs) are considered to have a much lower risk of malignant transformation. Given the reduced risk of malignancy arising from these lesions, many BD-IPMNs are now followed under a surveillance protocol with regular cross-sectional imaging with either computed tomography or magnetic resonance imaging [8,10]. Operative resection is currently only recommended if a BD-IPMN is associated with symptoms, high-risk stigmata, or development of worrisome features.

Because of the increased detection of BD-IPMNs and established

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criteria calling for surveillance of these lesions with serial cross-sectional imaging, the natural history of mPCLs is now better characterized [1]. The long-term surveillance of these lesions in a varied patient population has produced new clinical conundrums that have only begun to be explored in the literature. A commonly encountered question concerns the effect of immunosuppression on the malignant potential of these mPCLs.

It is unknown if immunosuppressive therapy can be safely initiated or continued chronically in individuals with mPCLs, as there is limited evidence characterizing rates of malignant transformation in cystic lesions. Some data suggest that the risk of pancreatic malignancy is not increased in liver transplant recipients with BD-IPMNs on chronic immunosuppression [11,12]. However, the risk of progression of BD-IPMNs in individuals on other immunosuppressive therapies including biologic therapies, anti-TNF agents, and antimetabolites, which have been associated with increased risk of other malignancies, has never been described. Likewise, the risk of malignancy in immunosuppressed patients with MCNs is unknown.

This study aims to assess the effect of selected immunosuppressive therapies including biologics, antimetabolites, and glucocorticoids on the progression of BD-IPMNs and MCNs.

2. Methods

2.1. Study design and setting

The study was approved by the Institutional Review Board of the University of Pennsylvania. A retrospective matched-cohort study was performed with patients with mPCLs diagnosed between January 1, 1990 and June 1, 2014 at the Hospital of the University of Pennsylvania. A stratified design was employed: among a cohort of individuals with mucinous pancreatic cysts, we identified those who had received 2 or more months of immunosuppressive therapy. These individuals were then matched by age and cyst size in 1:1 fashion to individuals who had not received these agents.

2.2. Study population

For our exposed cohort, we identified individuals within the electronic medical record who were 18 years of age or older with an ICD-9-CM code for pancreatic cyst (577.2, 577.8, 577.9) and greater than 2 months of exposure to any of the following immunosuppressive agents: glucocorticoids, biologics (abatacept, etanercept, infliximab, adalimumab, certolizumab, golimumab, ustekinumab, and rituximab), or antimetabolites (azathioprine, 6-mercaptopurine leflunomide, methotrexate). Only patients with branch-duct IPMNs and mucinous cystic neoplasms were included. Patients with main-duct IMPNs and non-mucinous leions (ie, serous cystadeoma) were excluded. Further, only individuals with serial imaging were included for analysis. Patients were excluded if the pancreatic lesion was characterized as a pseudocyst or serous cyst by the radiologist or treating physician, or if the cystic lesion already met any of the study outcomes at the time of cyst diagnosis (see below). Patients were also excluded if they had a lesion arising from the main pancreatic duct, as these are already associated with a high rate of malignant transformation and are generally referred for surgical excision without long-term surveillance.

For the unexposed cohort, individuals 18 years of age or older using the same ICD-9-CM codes for pancreatic cysts who had not received immunosuppressive therapy were identified. In addition, a Research Electronic Data Capture (REDCap) database of individuals with pancreatic cystic lesions hosted at University of Pennsylvania was queried. Similar exclusion criteria were applied. Those individuals receiving any class of immunosuppressive therapy were not considered to be eligible as potential controls. One-to-one matching was then performed using the closest match to age and cyst size in the exposed cohort. Between cases and controls, cyst size at the time of initial diagnosis was preferentially matched within 4 mm, and age at time of diagnosis within 6 years. When those criteria for a match could not be used, the closest size cyst match within 8 mm and the closest age match within 11 years of age was used.

2.3. Data collection

The following covariates of interest were extracted via manual review of the medical record for both exposed and unexposed individuals: demographic information including age at time of cyst diagnosis, sex, and ethnicity; cyst type and location; size of the largest cyst at time of diagnosis and at the end of follow-up, with care taken to note whether the largest cyst at the end of follow-up was the same cyst as the largest cyst at initial diagnosis; and duration of cross-sectional imaging follow-up. Data on results of endoscopic ultrasound were obtained when available, including any concerning findings such as solid/enhancing component, mural nodule, main pancreatic duct (MPD) >5 mm, or new mass. If fine needle aspiration was attempted, the cytology results were also recorded. If the cyst was resected surgically, the date of the operation and surgical pathology were noted. Additionally, because solid organ transplant recipients are often on calcineurin inhibitors or mTOR inhibitors, exposure to these medications were also recorded. The time between initial and subsequent imaging was recorded.

2.4. Primary outcome

The primary outcome of interest was pancreatic cyst progression on subsequent cross-sectional imaging defined by criteria demonstrating need for surgical resection, including: (i) obstructive jaundice in a patient with cystic lesion of the head of the pancreas, (ii) enhancing solid component within cyst, or (iii) main pancreatic duct diameter measuring 10 mm or larger; or the development of "worrisome features" defined as: (i) cyst 3 cm or larger, (ii) thickened/enhancing cyst walls, (iii) main pancreatic duct size 5–9 mm, (iv) non-enhancing mural nodule, or (v) abrupt change in caliber of pancreatic duct with distal pancreatic atrophy.

2.5. Secondary outcomes

Secondary outcomes included the rate of malignancy, diagnosed by either surgical resection or positive fine needle aspiration, and the rate of cyst growth among cases on immunosuppression versus age- and cyst size-matched non-immunosuppressed controls.

2.6. Analysis

All statistical analyses were conducted using Microsoft Excel (Version 2011, Redmond, WA) as well as Stata 13 (StataCorp, College Station, TX, USA). Descriptive statistics were calculated stratified on exposure status for all covariates and outcomes including *t*-test, chi-square test, and Fisher's exact test where appropriate. Risk ratios were calculated comparing rates of the primary outcome for matched cases and controls using the cs match routine [13].

Time-to-event analyses were conducted accounting for time to follow up study or outcome, whichever came first. In these analyses, those who did not experience the primary outcome were censored at follow up imaging study. Kaplan Meier curves were calculated and log-rank testing was performed comparing exposed to unexposed individuals. Univariate Cox proportional hazards models with frailty were performed to calculate hazard ratios while accounting for prior 1:1 matching of age and cyst size.