Original Study

Incidence, Management, and Implications of Visceral Thrombosis in Pancreatic Ductal Adenocarcinoma

Angel Mier-Hicks,[1] Michael Raj,[2] Richard Kinh Do,[2] Kenneth H. Yu,[4] Maeve A. Lowery,[3] Anna Varghese,[3] Eileen M. O'Reilly[3,4]

Abstract

In a cohort analysis evaluating patients with pancreatic adenocarcinoma who presented with or developed visceral thrombosis, including portal, mesenteric, and splenic vein, as well as thrombi in renal or gonadal veins, among the 95 patients analyzed, 154 visceral thrombosis events (VTE) occurred. VTE frequently presented as an incidental finding on routine abdominal imaging, with the most common location being portal vein, followed by mesenteric and splenic vein. Patients who received systemic anticoagulation had a low bleeding complication rate.

Background: Visceral or splanchnic thrombosis is defined as thrombi within the hepatoportal venous system, including portal (PV), mesenteric (MV), and splenic vein (SV), as well as thrombi in renal or gonadal veins. There are limited data to evaluate the prognostic significance, incidence, and clinical management of visceral thromboses in patients with pancreatic ductal adenocarcinoma (PDAC). **Patients and Methods:** We conducted an analysis of 95 patients treated at Memorial Sloan Kettering Cancer Center with PDAC who had a visceral thrombosis. **Results:** A total of 153 visceral thromboses (VsT) were identified in 95 patients (n = 51, 54% woman). A total of 36 patients (37%) had locally advanced disease, and n = 59 (62%) had metastatic disease. Systemic therapies received included FOLFIRINOX (n = 57, 60%) and GC/PTX (n = 27, 28%). All VsT events were incidentally detected. Overall survival of cohort was 12.3 months (range, 10.2-14.4 months). Visceral thrombosis incidence in the cohort was as follows: portal vein (PV) (45%), MV (26%), SV (17%), and gonadal veins (8%). Time to develop first VsT was 4.3 months (range, 3-5.6 months), and time to death from VsT development was 1.87 months (range, 0.8-2.8 months). Forty-five patients (47%) developed a second VsT. Sixty percent had a Khorana risk score of > 3. Thirty-nine patients (41%) were treated with short-term anticoagulation (AC) (< 1 month) (low-molecular-weight heparin, n = 34). Forty-five patients (47%) were treated with long-term AC (> 1 month) (low-molecular-weight heparin, n = 32; 23 were transitioned to an oral anticoagulant). Twenty-two patients (23%) were not treated with AC. Eight patients (8%) had a bleeding complication from AC. Portal vein thrombosis had the shortest overall survival at 3.6 months (range, 2.3-4.8 months). **Conclusion:** In PDAC, VsT can frequently present as an incidental finding on routine abdominal imaging. The most common location is PV, followed by MV and SV. We observed that AC is underutilized in this setting despite a low bleeding complication rate. PV was associated with the least overall survival of the VsT. Future large prospective studies should explore the role of AC and value in this setting.

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Introduction

Pancreatic ductal adenocarcinoma is one of the most common malignancies associated with thromboses.[1,2] Recent literature reports indicate an incidence between 17% and 36%.[1,3-7] This high risk is potentiated by the pancreatic cancer cell, which intrinsically promotes tumor growth and angiogenesis by increasing platelet activation and expression of procoagulant factors, including tissue factor and thrombin.[8] Usually thrombi can originate in any of the

[1]Department of Medicine, University at Buffalo, Buffalo, NY
[2]Department of Diagnostic Radiology
[3]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY
[4]Department of Medicine, Weill Cornell Medicine, New York, NY

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Address for correspondence: Eileen M. O'Reilly, MD, Department of Medicine, Gastrointestinal Oncology Service, Memorial Sloan Kettering Cancer Center, 300 E 66th St, Office 1021, New York, NY 10065
Fax: (646) 888-4542; e-mail contact: oreillye@mskcc.org

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venous vasculatures, although is frequently observed in the deep venous system (as in deep vein thromboses [DVT]), the pulmonary vasculature (pulmonary embolism [PE]), and the venous portal system located in the abdominal cavity. When thrombi develop in the portal venous system, different terminology may also be used, such as splanchnic, abdominal, or visceral thrombosis.[9-13]

Typically these visceral thromboses (VsT) are observed in the main veins, such as portal (18%), splenic (14%), and/or mesenteric vein system (13%), while the renal vein (1%) and gonadal vein (1%) can also be affected.[14] In the general population, VsT is an infrequent event; most incidents occur in patients with concomitant comorbidities. From a large international registry with unselected patients diagnosed with VsT, Ageno et al[15] observed a high incidence in patients with hepatic cirrhosis (27.8%), genetic hypercoagulable mutations (20.1%), and/or solid tumors (22.7%, 136/609). A total of 8% patients (12/136) were diagnosed with pancreatic cancer.

When examining the cancer literature, the incidence of VsT appears to be much higher in an oncologic population, with a reported incidence of 22.9% (31/89) in pancreatic ductal adenocarcinoma (PDAC).[14] Evidence demonstrates that this high incidence is associated in part with a rise of incidental detection of VsT with computed tomography (CT) scan for diagnosis and staging of pancreatic cancer.[16] These incidental findings of VsT have led to an increased interest in the clinical significance of VsT and an interest in defining paradigms. While there is some evidence that points toward decreased survival in PDAC,[9,13] the evidence for this is limited. There are no standard guidelines for management of VsT in patients with PDAC.

We therefore conducted this retrospective cohort study to determine the impact of VsT in patients with PDAC. We examined the time to develop first VsT, the implications of VsT in future thromboses, and survival outcomes. In addition, we evaluated the role of systemic anticoagulation (AC), type of AC utilized, and duration of AC for each patient. The intent of our study was to extend the knowledge of VsT in PDAC and to elucidate treatment paradigms.

Methods

Setting and Study Design

The institutional review board and the privacy board at Memorial Sloan Kettering Cancer Center reviewed this single-center retrospective cohort study. Patients who underwent imaging and received care at the center who were diagnosed between January 1, 2013, and December 31, 2015, with pathologic confirmation of PDAC who developed a VsT (mesenteric vein [MV], portal vein [PV], splenic vein [SV], renal veins [RV], or gonadal veins [GV]), either at presentation or during the disease course, comprised the study population.

Search Strategy and Selection Criteria

An institutional database (DARWIN) was used to retrospectively obtain medical records from patients diagnosed with pancreatic cancer who were identified by using the International Classifications of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) with the following codes: C259 pancreas ca, C250 pancreas ca-head, C251 pancreas ca-body, C252 pancreas ca-tail, C258 pancreas ca-overlapping lesion. The ICD-10 only has a specific code (I81) for portal vein thrombosis (PVT), so we therefore included patients that had any of the following ICD-10 codes along with their pancreatic cancer diagnosis: I82.3 (other venous embolism and thrombosis of renal vein), I82.891 (chronic venous embolism and thrombosis of other specified veins), I82.890 (acute venous embolism and thrombosis of other specified veins), I82.91 (other venous embolism and thrombosis of unspecified site), and K55.0 (acute vascular disorders of intestine).

Data Extraction

A.M.H. and E.O.R. performed electronic medical record review and data abstraction, and data were stored on a secure drive. Imaging reports and images were manually reviewed by the radiology co-authors (M.R. and R.D.), who evaluated the CT scans of the abdomen/pelvis to corroborate the correct date of diagnosis and location of the visceral thrombi (PV, MV, SV, GV, RV). Detailed demographic and clinical information was extracted, including date of cancer diagnosis, presenting symptoms, American Joint Committee on Cancer (AJCC) stage at presentation, performance status (ECOG) at presentation, sites of metastases at presentation, primary tumor location, treatment modalities (surgery, systemic therapy), types of systemic therapy received, lines of treatments, interval between diagnosis of pancreatic cancer and occurrence of thrombosis, presenting symptom of VsT, method of diagnosis of VsT, ECOG at diagnosis of first VsT, laboratory variables required to calculate Khorana score (cell blood count, comprehensive metabolic panel, coagulation studies), type and duration of systemic AC, complications of therapies, and survival outcomes.

Statistical Analysis

Baseline patient characteristics, clinical findings at diagnosis of VsT, and laboratory evaluation at the time of VsT diagnosis are summarized in Table 1. Overall survival (OS) was calculated from date of diagnosis to date of death. Median OS and 95% confidence interval (CI) were estimated by Kaplan-Meier methods. All P values were based on 2-tailed statistical analysis, and $P < .05$ was considered to indicate statistical significance. All analyses were performed by SPSS 24 (IBM SPSS, Chicago, IL).

Results

Demographic and Clinical Characteristics

A total of 1484 patients with PDAC were identified from January 1, 2013, to December 31, 2015. The analyzed cohort (n = 95) was later identified with one of the ICD diagnoses previously described. These patients with PDAC had developed any type of VsT either at presentation or during the course of the disease. Figure 1 illustrates the flow of patients that comprised the analyzed cohort. Descriptive characteristics of the study cohort are summarized in Table 1. Forty-six percent (n = 44) were men, and median age of PDAC diagnosis was 60.5 years (range, 38-86 years). Sixty-two percent (n = 59) presented with metastatic PDAC, 16% (n = 15) had locally advanced PDAC (stage III), and 22% (n = 21) had resectable disease at presentation (stages I-IIB). Primary pancreatic tumor was located in the head (53%, n = 51), body (17%, n = 16), and tail (16%, n = 15). Surgery was performed in 10% (n = 9) of patients, 6% (n = 6) had a Whipple procedure, 3% (n = 3) had other type