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Brief Articles

Acute Cholecystitis Is a Common Complication after Allogeneic Stem Cell Transplantation and Is Associated with the Use of Total Parenteral Nutrition

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A B S T R A C T

The incidence and risk factors for acute cholecystitis after allogeneic hematopoietic stem cell transplantation (HSCT) are not well defined. Of 644 consecutive adult transplants performed at our institution between 2001 and 2011, acute cholecystitis occurred in the first year of transplant in 32 patients (5.0%). We conducted 2 retrospective case-control studies of this population to determine risk factors for cholecystitis after HSCT and to evaluate the performance of different methods of imaging to diagnosis cholecystitis in patients undergoing HSCT compared with non-HSCT patients. In the HSCT population, development of cholecystitis was associated with an increased 1-year overall mortality rate (62.5% versus 19.8%, $P < .001$). The risk of developing cholecystitis was higher in patients who received total parenteral nutrition (TPN) (adjusted odds ratio, 3.41; $P = .009$). There was a trend toward more equivocal abdominal ultrasound findings in HSCT recipients with acute cholecystitis compared with nontransplant patients (50.0% versus 30.6%, $P = .06$). However, hepatobiliary iminodiacetic acid (HIDA) scans were definitively positive for acute cholecystitis in most patients in both populations (80.0% of HSCT recipients versus 77.4% of control subjects, $P = .82$). In conclusion, acute cholecystitis is a common early complication of HSCT, the risk is increased in patients who receive TPN, and it is associated with high 1-year mortality. In HSCT recipients with findings suggestive of acute cholecystitis, especially those receiving TPN, early use of HIDA scan may be considered over ultrasound.

INTRODUCTION

Patients who undergo allogeneic hematopoietic stem cell transplantation (HSCT) are susceptible to infections, leading to increased morbidity and mortality [1,2]. One infectious complication of HSCT is acute cholecystitis, a condition characterized by inflammation of the gallbladder with or without gallstone obstruction in the cystic duct [3]. Although biliary sludge formation [4-6] and cholelithiasis [5,7,8] are known to occur in HSCT patients, the incidence of acute cholecystitis and its risk factors in this population are not well described [9-12].

Prompt recognition of acute cholecystitis is critical in both immunocompetent and immunosuppressed patients. However, the diagnosis of acute cholecystitis is often delayed in the HSCT population, because transplant patients are prone to multiple hepatobiliary complications that have similar clinical presentations and the typical signs of inflammation/infection may be masked by immune and marrow suppression [5]. In the present study, we reviewed 644 consecutive patients undergoing HSCT to identify patients who experienced acute cholecystitis. We subsequently performed 2 separate retrospective case-control analyses: the first to define the risk factors for development of acute cholecystitis after HSCT and the second to determine the diagnostic utility of radiographic modalities at presentation of this disease in the transplant population.

METHODS

Study Population

Between January 2001 and December 2011, 644 patients underwent allogeneic HSCT at the Hospital of the University of Pennsylvania. Medical records of these patients were screened for International Classification of

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Table 1
Baseline Demographic and Clinical Characteristics

Demographic Characteristic	HSCT Acute Cholecystitis Patients (n = 32)	HSCT Non-Cholecystitis Control Subjects (n = 96)	Non-HSCT Cholecystitis Control Subjects (n = 96)	*P*
Median age at HSCT, yr (range)	52.2 (24-75)	52.0 (20-76)	52.5 (18-78)	
Men	21 (65.6)	63 (65.6)	63 (65.6)	
Women	11 (34.3)	33 (34.4)	33 (34.4)	
Underlying disease				
ALL	5 (15.6)	11 (11.5)		.971
AML	13 (40.6)	39 (40.6)		.442
CLL/lymphoma	4 (12.5)	16 (16.7)		1
MDS	3 (9.4)	11 (11.5)		.532
MM	2 (6.3)	8 (8.3)		.420
PMF	3 (9.4)	3 (3.1)		1
CML	2 (6.3)	4 (4.2)		.144
Other	0	4 (4.2)		.926
Graft source				
Bone marrow	6 (18.8)	28 (29.2)		.283
Peripheral blood	26 (81.2)	68 (70.8)		
Sibling donor	15 (46.9)	53 (55.2)		.414
Conditioning regimen				
TBI-containing	14 (43.8)	43 (44.8)		.918
Myeloablative	18 (56.2)	53 (55.2)		.919
Reduced intensity	14 (43.8)	43 (44.8)		
ABO compatible graft	21 (67.7)	46 (49.0)		.162
GVHD prophylaxis				
Tac containing	23 (71.9)	70 (72.9)		.909
Tac/MTX	19 (59.4)	57 (59.3)		
Tac/MTX/ maraviroc	4 (12.5)	13 (13.5)		
CsA/MTX	6 (18.8)	15 (15.6)		
CsA/steroids	1 (3.1)	3 (3.1)		
CsA/mycophenolate	1 (3.1)	7 (7.3)		
None	1 (3.1)	1 (1.0)		
TPN	20 (64.5)	37 (39.8)		.019
CMV reactivation	5 (15.6)	22 (23.3)		.371
Weight loss >10%	13 (46.4)	38 (42.3)		.489

ALL indicates acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CLL, chronic lymphocytic leukemia; MDS, myelodysplastic syndrome; MM, multiple myeloma; PMF, primary myelofibrosis; CML, chronic myelogenous leukemia; TBI, total body irradiation; tac, tacrolimus; MTX, methotrexate; CsA, cyclosporine.
Values are number of cases with percents in parentheses, unless otherwise indicated.

Diseases, 9th revision (ICD-9) diagnosis codes for "acute cholecystitis" and all conditions related to acute cholecystitis, including gallbladder calculus, bile duct calculus, chronic cholecystitis, perforation or obstruction of gallbladder, cholecystectomy, and cholecystostomy. Detection of 1 or more of these conditions after the date of transplantation triggered a manual chart review to confirm cases of acute cholecystitis in the first year after HSCT. Cases were defined as (1) having ≥1 imaging modality interpreted by a radiologist as definitively positive for acute cholecystitis, including abdominal ultrasound (US), abdominal computed tomography (CT), or hepatobiliary iminodiacetic acid (HIDA) scan, or (2) having surgical gallbladder pathology consistent with acute cholecystitis. Patients with an ICD-9 code related to acute cholecystitis but without 1 of the 2 above inclusion criteria were excluded. The institutional review board approved this study.

Data Collection and Study Design

To identify risk factors for development of acute cholecystitis, we conducted a nested case-control analysis with control subjects randomly selected through incidence density sampling of the institutional transplant cohort (N = 644) and assigned to cases at a rate of 3:1, matching for age and sex. We then evaluated multiple potential risk factors for the development of acute cholecystitis, including type of underlying hematologic malignancy, graft source, donor type, ABO incompatibility, conditioning intensity, conditioning regimen containing versus not containing total body irradiation, graft-versus-host disease (GVHD) prophylaxis regimen, weight loss >10% compared with day +0 body weight, any total parenteral nutrition (TPN) use, and cytomegalovirus (CMV) reactivation, the latter defined as serum PCR positivity. Cases were counted as having 1 of the above risk factors if present before diagnosis of acute cholecystitis, whereas control subjects were counted as having a risk factor if present within the first year of transplant. In an exploratory analysis, we also compared the 1-year survival rate of cases and control subjects using a chi-square test.

In a second, separate case-control analysis, we compared the radiographic findings of US, CT scan, and HIDA scan in HSCT recipients (n = 32) versus non-transplant control subjects (n = 96) diagnosed with acute cholecystitis at our institution. Nontransplant control subjects were randomly selected from our institution's medical record system by screening for ICD-9 diagnostic codes for 'acute cholecystitis' and all conditions related to acute cholecystitis, including gallbladder calculus, bile duct calculus, chronic cholecystitis, perforation or obstruction of gallbladder, cholecystectomy, and cholecystostomy, entered between 2001 and 2011. As in the first case-control study, cases of acute cholecystitis were confirmed through manual chart review. Control subjects were assigned to cases at a rate of 3:1 and matched for age and sex. In these 2 populations, we compared the number of abdominal US, CT, and HIDA scans performed and the proportion of these radiographic studies interpreted by an attending radiologist as positive, negative, or equivocal for acute cholecystitis. Positive studies were those in which acute cholecystitis was stated by the interpreting radiologist as the final diagnosis, and negative studies were those in which a normal gallbladder was seen or there were no radiographic findings of acute cholecystitis. Equivocal studies were those in which a definitive radiographic diagnosis was not made. In these equivocal studies, a differential diagnosis was provided with acute cholecystitis as one of several diagnostic considerations, or, alternatively, the radiologist stated that the diagnosis of acute cholecystitis was equivocal.

Statistical Analysis

Cases and control subjects were compared with chi-square or Fisher's exact tests as appropriate. $P < .05$ was accepted as statistically significant. Logistic regression analysis was used to adjust for covariates when assessing risk factors for development of acute cholecystitis.

RESULTS

In our transplant cohort of 644 patients (630 first transplants, 13 second transplants, and 1 third transplant), 32 patients (5.0%) had radiographic and/or pathologic evidence of acute cholecystitis in the first year after HSCT and were counted as "case" patients. Baseline characteristics of these patients and each of the 2 control groups are listed in Table 1.

For each of these characteristics, data were successfully collected for all patients with the following exceptions: post-transplant weights were unavailable for 10 patients (4 cases, 6 control subjects), ABO incompatibility status was unavailable for 1 patient (case), CMV reactivation was unavailable for 1 patient (control), and TPN use was unavailable for 4 patients (1 case, 3 control subjects). Patients had a mean age of 52 years, and most (65.6%) were men. There were no significant baseline differences between cases and transplant control subjects with regard to underlying hematologic malignancy, graft source, donor type, conditioning regimen, ABO incompatibility, GHVD prophylaxis regimen, CMV reactivation, or weight loss after transplant.

Of those patients who developed acute cholecystitis in the first year after HSCT, the median time between day of transplantation and diagnosis of acute cholecystitis was 56.5 days (range, 6 to 342). Of note, 21 of 32 cases (65.6%) occurred within 90 days of transplant. Twelve patients (37.5%) were confirmed as having acute cholecystitis by positive imaging alone (none of these patients underwent cholecystectomy), 4 cases (12.5%) were confirmed by pathology but had negative or equivocal imaging studies (these patients ultimately went to surgery based on high clinical suspicion), and 16 (50%) had both imaging and pathology that were consistent with cholecystitis. As detected by pathology and/or imaging, 21 patients (65.6%) had acalculous cholecystitis, whereas the other 11 (34.4%) had evidence of cholelithiasis. Twenty cases of acute cholecystitis (62.5%) were treated with cholecystectomy, whereas 7 (21.9%) underwent cholecystostomy tube