Tuberculosis is a Common Cause of Post-Liver Transplant Ascites: An Observational Study

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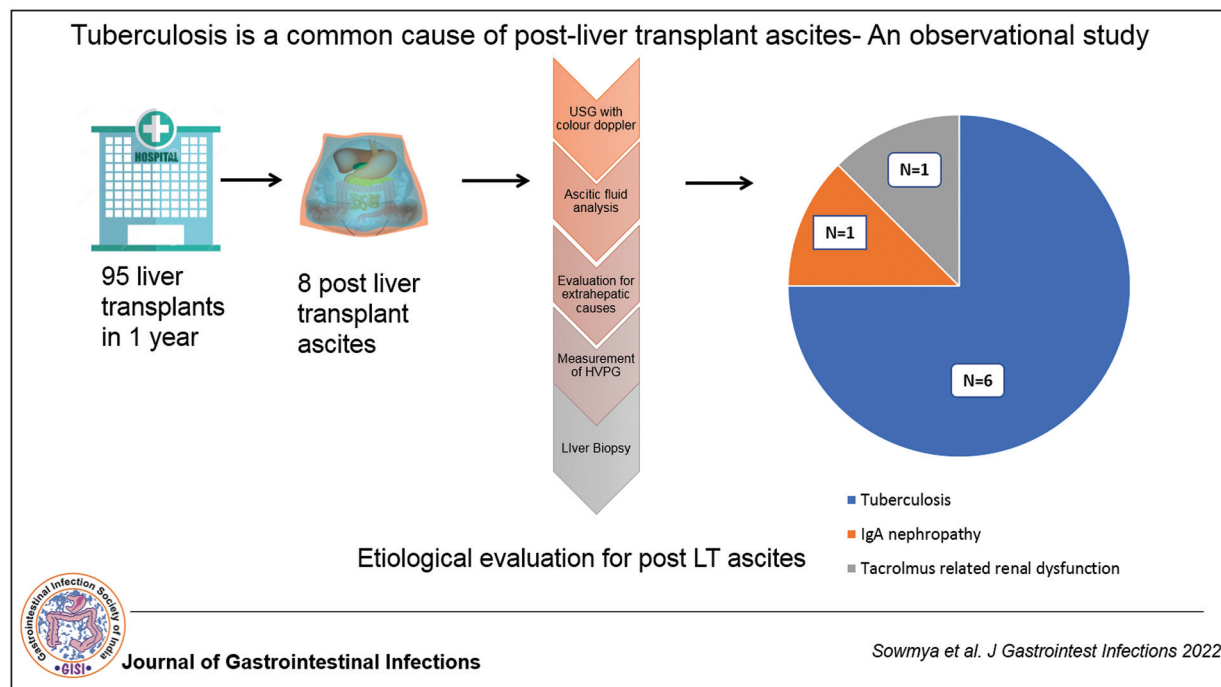Nageshwar Reddy[3]   Padaki Nagaraja Rao[1]

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Tuberculosis is a common cause of post-liver transplant ascites- An observational study

95 liver transplants in 1 year → 8 post liver transplant ascites → USG with colour doppler / Ascitic fluid analysis / Evaluation for extrahepatic causes / Measurement of HVPG / Liver Biopsy

Etiological evaluation for post LT ascites

- Tuberculosis (N=6)
- IgA nephropathy (N=1)
- Tacrolmus related renal dysfunction (N=1)

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Abstract

Background   Ascites is expected to resolve within 2 to 4 weeks following orthotopic liver transplantation. New-onset ascites after transplant is associated increased morbidity and affects quality of life. The risk of opportunistic infections is high in transplant recipients due to immunosuppressive drugs.

Objective   The objective was to assess the incidence of new-onset ascites in the transplant recipients and describe the cause and course of the same.

Methods   We retrospectively collected data of all the patients who underwent liver transplantation at our center from April 1, 2020 to April 1, 2021. The details of patients developing ascites post-liver transplantation were retrieved. The patients were followed up for 1 year after transplant.

Keywords
► liver transplantation
► mycobacterium tuberculosis (MTB)
► IgA nephropathy
► post-transplant tuberculosis
► tuberculous peritonitis
► peritoneal tuberculosis

Results   A total of 95 patients underwent living donor liver transplantation at our center. The incidence of new-onset ascites was 8.42% (8/95). Six out eight patients were diagnosed with tubercular ascites of whom one had disseminated tuberculosis. None of the patients had concomitant pulmonary tuberculosis. Ascites secondary to hypoalbuminemia was reported in two patients. Immunoglobulin A nephropathy and tacrolimus therapy were the underlying causes of proteinuria.

Conclusion   Tuberculosis was the leading cause of ascites in post-transplant period in our study. Tuberculosis should be considered as a differential diagnosis while evaluating these patients especially in the Asia-Pacific region. Being a potentially curable cause, timely diagnosis and treatment significantly improves graft survival.

Introduction

Refractory ascites is one of the common indications for liver transplantation (LT). Ascites is expected to resolve within 2 to 4 weeks following orthotopic liver transplant as the reversal of hemodynamic changes occur by then.[1,2] New-onset ascites post-LT is associated with significant morbidity and reduced graft survival. Ascites after liver transplant is defined as the presence of free fluid in the peritoneum for more than 4 weeks after a successful LT, which is rare and is reported in 3 to 7% of cases.[1,3,4] Pretransplant portal hypertension, operative techniques (inferior vena cava anastomosis by piggyback vs. classical technique), hepatic inflow or outflow obstructions, graft rejection, and prolonged cold ischemia time also play a major role in the development of ascites post-LT.[1,4–6] The causes of ascites post-LT may differ in India. The diagnostic and management strategies also need to be modified in our settings. Early diagnosis and treatment of specific cause may improve the graft survival. However, there is insufficient data regarding the causes for post-liver transplant ascites in Indian scenario.

Immunosuppressant medications administered during the post-transplant period make patients most susceptible to opportunistic infections. Underlying sarcopenia and malnutrition in cirrhotic patients add to the risk. Latent tuberculosis (TB) is highly prevalent in India and has a risk of activation of infection following immunosuppression. We aimed to assess the incidence, etiology, and management of new-onset ascites post-LT in our settings. Furthermore, we also describe the challenges faced during the treatment of TB in the post-liver transplant period.

Methods

Setting
We conducted a retrospective study in the Department of Hepatology of AIG Hospitals, Hyderabad, Telangana, India. Data of all patients developing ascites after liver transplant over 1 year was obtained.

Patient Workup
Pretransplant protocol of our institution is mentioned in ►**Supplementary Table S1** (available in the online version). Ascitic fluid analysis was done in all patients as a part of pretransplantation workup, and infections were ruled out. Latent TB should ideally be evaluated; however, lack of definite guidelines in pretransplant workup coupled with limited reliability of tuberculin sensitivity tests and interferon-gamma release assays (IGRA) in patients with cirrhosis, curtails its incorporation into pretransplant workup.

Post-Transplant Follow-Up
After transplantation, all patients were started on standard triple immunosuppression regimen as per institution protocol (steroids + mycophenolate mofetil + tacrolimus). Ascites after LT was defined as presence of free fluid in the peritoneal cavity after 4 weeks of LT, and it was confirmed using ultrasonography in all patients during their follow-up visits after transplantation. Ascites after liver
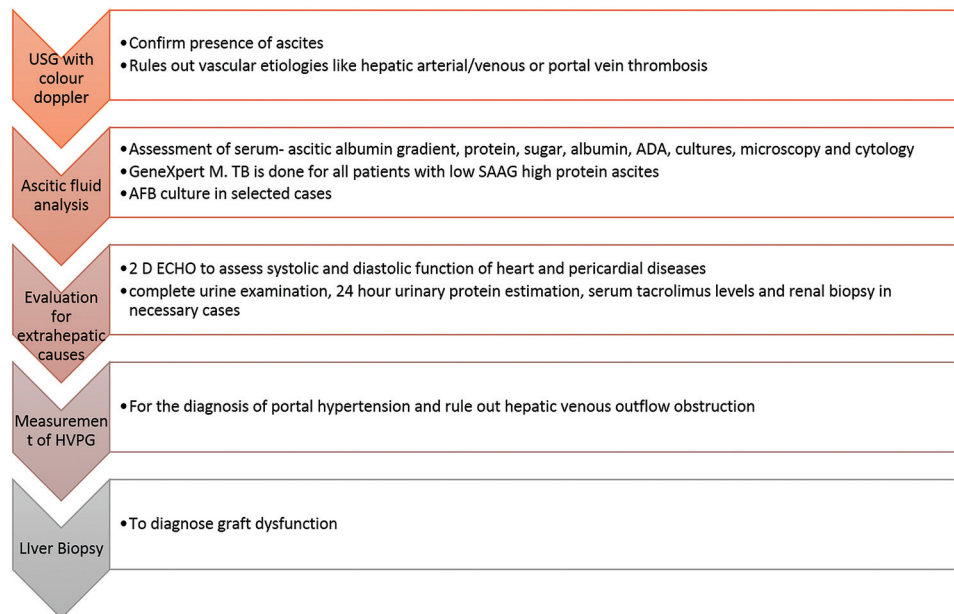
Fig. 1 Step-wise approach in the evaluation of post-liver transplant ascites in our institution. Ultrasonography of abdomen with Doppler confirmed the presence of ascites and ruled out vascular thrombosis. Ascitic fluid analysis was performed in all cases to understand the nature of ascites and rule out tuberculosis. Patients in whom the etiology of ascites was not identified after ascitic fluid analysis were further evaluated for cardiac or renal dysfunction causing ascites. Furthermore, measurement of HVPG and liver biopsy were considered in undiagnosed cases of ascites. ADA, adenosine deaminase; AFB, acid-fast bacilli; MTB, mycobacterium tuberculosis; HVPG, hepatic venous pressure gradient.

transplant were evaluated by an institutional protocol described in ►**Fig. 1**.

Any patient presenting with abdominal distention after LT underwent ultrasonographic examination of abdomen with color Doppler. Vascular etiologies were ruled out with the help of Doppler studies. Ascitic fluid analysis for protein, sugar, albumin, adenosine deaminase (ADA), cytology, gram stain, microscopic examination for acid-fast bacilli (AFB), and culture sensitivity were done. ADA levels were considered as indirect evidence for TB. Values of < 20 IU/L were considered negative for TB. Values between 20 and 40 IU/L were suspected for TB. Any value > 40 IU/L was considered diagnostic of TB.[7]

Serum ascitic albumin gradient (SAAG) was calculated in all patients. Value < 1.1 was considered as low SAAG ascites and more than 1.1 was considered high SAAG ascites.

GeneXpert mycobacterium tuberculosis (MTB) (a cartridge-based nucleic-acid amplification technique for rapid diagnosis of MTB along with rifampicin resistance) was done in patients with low SAAG (< 1.1) and high protein (> 2.5 g/mL). Any positivity to GeneXpert studies or AFB on microscopy were diagnostic of TB. However, negativity of either test could not rule out TB where AFB culture was performed.[8]

High SAAG low protein ascites with low ADA were further assessed by hepatic venous pressure gradient (HVPG) measurement for portal hypertension. Low SAAG high protein ascites with high ADA were presumed as TB which was further confirmed by GeneXpert MTB. For those who had negative test report for GeneXpert MTB were further evaluated by AFB culture meanwhile started on empirical antitubercular therapy (ATT).

For patients in whom diagnosis could not be arrived after ascitic fluid analysis were further evaluated for extrahepatic causes. Two-dimensional echocardiography was done to assess systolic and diastolic cardiac functions and for pericardial diseases. Complete urine examination, renal function test with blood urea, serum creatinine, serum electrolytes, 24-hour urinary protein excretion, and urinary albumin creatinine ratio were done in necessary cases. Patients with significant proteinuria (> 300 mg/g of urine albumin–creatinine ratio) underwent renal biopsy as a gold standard test for diagnosis.

Further in the evaluation, HVPG measurement to rule out portal hypertension and liver biopsy to diagnose graft dysfunction are considered as a part for ascites evaluation in undiagnosed cases.

Results

Patients

Out of 95 patients who underwent living donor LT (LDLT) in our institution, 8 (8.4%) developed ascites. Mean age of these patients was 43 ± 17 years. Four were males. Three (37.5%) patients underwent LDLT for alcohol-related liver cirrhosis, and one each for (12.5%) for nonalcoholic steatohepatitis, chronic hepatitis B, Budd–Chiari syndrome, autoimmune hepatitis, and Wilson disease (►**Table 1**).

Pretransplant Factors

All the patients had ascites prior to LT of whom 6 (75%) had refractory ascites. Five (62.5%) of them had hepatorenal syndrome prior to transplant. Two (25%) of them had

Table 1 Pre- and posttransplant characteristics of all patients with ascites after LDLT

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Age (y)	62	23	65	50	54	22	46	19
Sex	Female	Female	Male	Male	Female	Female	Male	Male
Indication for transplant	NASH	Chronic Budd–Chiari syndrome	AUD-related	AUD-related	Chronic hepatitis B	Wilson's disease	AUD-related	AIH-related
Ascites before LT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Refractory ascites	Yes	Yes	No	Yes	Yes	No	Yes	Yes
Shunt surgery prior to LT	No	Yes	No	No	Yes	No	No	No
CIT	105 min	95 min	118 min	120 min	85 min	65 min	98 min	86 min
Early resurgery	Hepatic artery thrombosis – Thrombectomy on POD1	Yes – Trans gastric bilioma drainage	No	No	No	No	No	No
Time for onset of ascites	3 mo	2 mo	2.5 mo	3 mo	3.5 mo	3 mo	3 mo	4 mo
USG Doppler	Normal hepatic blood flow	Normal hepatic blood flow	Normal hepatic blood flow	Normal hepatic blood flow	Normal hepatic blood flow	Normal hepatic blood flow	Normal hepatic blood flow	Normal hepatic blood flow
Ascitic fluid analysis	High protein low SAAG	High protein low SAAG	High protein low SAAG	High protein low SAAG	High protein low SAAG	High protein, high SAAG	High protein low SAAG	High protein low SAAG
ADA (u/dL)	37	33	6	40	23	5	33	45
Cell count (cells/hpf)	800	750	100	350	400	200	560	1160
Cell type	95% lymphocytes	95% lymphocytes	93% lymphocytes	95% lymphocytes	80% lymphocytes	95% lymphocytes	98% lymphocytes	87% lymphocytes
Cultures	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Others	–	–	Renal biopsy- IgA nephropathy	MTB PCR positive	GeneXpert MTB positive. Triglycerides in AF (ascitic fluid) - 518 mg/dL	Renal biopsy showed chronic tubulointerstitial nephritis	GeneXpert MTB positive	Concomitant pleural effusion GeneXpert for mycobacterium tuberculosis positive
2D ECHO	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
HVPG	Not done	9 mm Hg	10 mm Hg	Not done	Not done	Not done	Not done	Not done
Liver biopsy	Not done	Not done	Normal	Not done	Not done	Not done	Not done	Done after 1-year follow up- showing chronic rejection
Diagnosis	Tubercular ascites	Tubercular ascites	IgA nephropathy	Tubercular ascites	Tubercular ascites	Tacrolimus-induced proteinuria and CKD	Tubercular ascites	Tubercular ascites and pleural effusion

Abbreviations: 2D ECHO, two-dimensional echocardiography; ADA, adenosine deaminase; AIH, autoimmune hepatitis; AUD, alcohol use disorder; CIT, cold ischemia time; CKD, chronic kidney disease; HVPG, hepatic venous pressure gradient; IgA, immunoglobulin A; LDLT, living donor liver transplantation; LT, liver transplantation; MTB, mycobacterium tuberculosis; NASH, nonalcoholic steatohepatitis; PCR, polymerase chain reaction; POD, postoperative day; SAAG, serum ascitic albumin gradient; USG, ultrasonography.

undergone transjugular intrahepatic portosystemic shunt procedure prior to transplant, which had failed.

Intraoperative Factors

Cold ischemia time was 96.5 ± 17 minutes. One patient had hepatic artery thrombosis in the postoperative period and underwent thrombectomy on postoperative day 1. One patient had intra-abdominal bilioma formation which was drained through transgastric endoscopic procedure.

Postoperative Period

Most common complaint among all the patients was progressive abdominal distension followed by fever in two (25%) patients. Mean time to the development of ascites was 3 ± 0.6 months.

All patients had normal splenoportal Doppler study.

Ascitic fluid analysis was done in all patients. Ascitic fluid protein was high in all patients (> 2.5 g/dL). Six (75%) patients had low SAAG (< 1.1). Two patients had high SAAG (> 1.1). Two patients with high SAAG also had normal ascitic fluid ADA and cytology reports.

All six patients with low SAAG ascites had leukocytosis with lymphocyte predominance in ascitic fluid. However, only two patients had high ADA levels (> 40 IU/L). Out of these six patients, three had (50%) positive reports for GeneXpert for MTB and the diagnosis of tubercular ascites was made. One patient had concomitant pleural effusion. Although ascitic fluid was negative for GeneXpert MTB in this patient, pleural fluid analysis was positive and hence diagnosis of disseminated TB was made. Remaining two patients tested negative for TB by direct microscopy and GeneXpert studies. AFB was sent for culture (AFB culture). However, empirical ATT was started considering low SAAG and lymphocyte-predominant picture on ascitic fluid analysis. All six patients were started on ATT. On follow-up of these two patients who were started on empirical ATT, although AFB culture was negative after 6 weeks, there was a clinical response to treatment with the disappearance of ascites and hence tubercular ascites was confirmed retrospectively. Mean ADA for tubercular ascites in the posttransplant period was 35.2 ± 7 µ/dL.

None of the patients had drug-resistant TB. None had concomitant pulmonary TB which was confirmed by normal chest imaging and sputum smear-negative reports. Rifampicin, levofloxacin, and ethambutol were initiated with the gradual introduction of isoniazid over the next 15 days. Subsequently, pyrazinamide was introduced and quinolone was withdrawn. One of the patients developed ATT-induced liver injury related to rifampicin and subsequent graft dysfunction. Due to drug interaction with immunosuppressant medications, rifampicin was replaced with rifabutin. He was treated with N-acetylcysteine and had delayed recovery with conservative management.

Two patients with high SAAG ascites had proteinuria on routine urine examination. Twenty-four-hour urinary protein excretion and urine albumin–creatinine ratio were elevated (24-hour urine protein 1.2 and 1.5 g/day and urine albumin–creatinine ratio were 0.9 and 1.2, respectively). Both underwent renal biopsy. One patient had immunoglobulin A (IgA) nephropathy and the other had tubulointerstitial nephritis. HVPG was normal in these cases. One patient underwent liver biopsy to rule out graft dysfunction, which was reported normal. Diagnosis of ascites secondary to renal dysfunction and proteinuria was made in these cases. Tubulointerstitial nephritis was attributed to tacrolimus and the drug was discontinued, following which his renal function improved.

One patient with tubercular ascites had chylous nature of ascites with high triglyceride levels in ascitic fluid. She responded to medium-chain triglycerides diet. On long-term follow-up for 1 year after diagnosis was made, one of these patients with posttransplant ascites succumbed due to sepsis, one had chronic graft rejection (►**Table 2**).

Table 2 Clinical characteristics of ascites in post-liver transplant period

Characteristic	Value
Age (mean ± SD) (y)	43 ± 17
Males	50%
Indication for liver transplant	
Alcohol-related liver cirrhosis	3 (37.5%)
NASH-related cirrhosis	1 (12.5%)
Wilson's disease with cirrhosis	1 (12.5%)
Chronic hepatitis B-related cirrhosis	1 (12.5%)
Chronic Budd–Chiari syndrome-related cirrhosis	1 (12.5%)
Autoimmune hepatitis-related cirrhosis	1 (12.5%)
Follow-up duration since transplant	1 year
Mean duration for development of ascites	3 ± 0.6 months
Symptoms	
Progressive abdominal distension	8 (100%)
Fever	2 (25%)
Fatigue	6 (75%)
Etiology of ascites	
Tubercular	6 (75%)
Proteinuria-related to IgA nephropathy	1 (12.5%)
Tacrolimus-related chronic kidney disease	1 (12.5%)
Outcomes at 1 year	
Alive	7 (87.5%)
Death	1 (12.5%) due to sepsis
Graft dysfunction	1 (12.5%)

Abbreviations: IgA, immunoglobulin A; NASH, nonalcoholic steatohepatitis; SD, standard deviation.

Discussion

The present study shows that TB is the most important cause of post-liver transplant ascites accounting for 75% of such cases. Our findings would suggest the need to treat latent TB prior to liver transplant so as to reduce posttransplant activation of TB due to drug-related immunosuppression. Extrapulmonary TB is common in posttransplant period and the treatment of active TB in posttransplant period may be challenging. This is because of the hepatotoxicity of the drugs and interactions with immunosuppressant medications, especially with rifampin. Ascites post-LT can lead to chronic graft dysfunction. Importantly, normal levels of ADA may not rule out tubercular ascites. Low SAAG is the most consistent feature in tubercular ascites after liver transplant. Absence of microbiological evidence cannot definitively rule out tubercular ascites and the positivity of Xpert Mtb/Rif is usually only in one-third of cases of tubercular ascites.[9]

Earlier studies also confirm that the risk of TB in patients with transplantation is at its highest during the first year; however, the mean time of occurrence of TB is approximately 9 months posttransplantation.[10,11] Tuberculin skin testing (TST), QuantiFERON test, or any IGRA have poor sensitivity and specificity in liver disease patients.[12] There is a lack of information on managing patients with positive TST results.[13] Universal national BCG (bacillus Calmette-Guerin) vaccination program for TB can make interpretation of TST results less accurate. Earlier studies on TST before renal transplantation in India suggested a very low positive predictive value of 5.2 to 23.8% for the development of posttransplant TB.[14] However, similar data on LT is insufficient. Recent studies have reported that there is no difference between TST and IGRA in the diagnosis of latent TB among LT recipients, especially in the areas with widespread BCG vaccination.[15] Concomitant pulmonary TB was not seen in any of our patients, as well as occurrence of disseminated TB was only seen in one patient in contrast to previous studies, which have demonstrated a higher incidence of pulmonary and disseminated TB.[16–18] ►Supplementary Table S2 (available in the online version) shows the pattern of TB in posttransplant period in other studies compared with our study.

The number of cases in our series is small to arrive at any definitive conclusion; however, considering the higher prevalence of TB in India routine pretransplant screening for latent TB might be helpful in avoiding active TB in posttransplant period. Explanted liver should be cautiously examined for any granulomatous lesions or for microbiological evidence of TB. Treatment of latent TB might pose challenges in pretransplant period as the drugs used may cause hepatotoxicity or the patient may not sustain decompensated liver cirrhosis for the long treatment duration of latent TB. In such cases, latent TB treatment may be considered starting from immediate postoperative period. Recommended regimens for latent TB in cirrhosis includes Isoniazid administration at 300 mg/day with pyridoxine supplementation for 6 months.

Tacrolimus is known to cause renal dysfunction. There have been few reports of tacrolimus-induced nephrotoxicity leading to anasarca. Plausible explanation for tacrolimus nephrotoxicity could be due to high concentration of tacrolimus binding proteins in the kidney (higher than in the liver and spleen). At the cellular level, morphologic observations suggest that tubular epithelial cells, vascular endothelial cells, arteriolar myocytes, and interstitial fibroblasts are all targets for tacrolimus nephrotoxicity. This leads to proteinuria and development of ascites.[19] As well, the studies have shown that tacrolimus is involved in the development of sinusoidal obstruction syndrome after LT which may subsequently result in ascites.[20,21]

IgA nephropathy is common in alcohol-related liver disease patients in the pretransplant period. Previous studies have reported IgA nephropathy in post-LT period. Up to 9% renal biopsies from liver transplant recipients with renal impairment can have IgA nephropathy.[22]

In conclusion, although global data suggest vascular etiologies as the common cause of ascites posttransplant, in Indian scenario TB should always be considered as a differential diagnosis while evaluating these patients. Being a potentially curable cause, it significantly improves graft survival after treatment. Future studies on validity of routine screening for latent TB and its role in preventing active TB in posttransplant period are needed.[23,24]

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