Impact and safety of endoscopic ultrasound guided fine needle aspiration on patients with cirrhosis and pyrexia of unknown origin in India

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Background and aims: Etiologic diagnosis of pyrexia of unknown origin is important in patients with cirrhosis for optimal management and to prevent flare up of infectious disease after liver transplantation. However, there is very limited literature available on this subject. The present study aimed to examine the safety and impact of endoscopic ultrasound (EUS) guided fine needle aspiration (FNA) in patients with cirrhosis.
Methods: The study was conducted between January 2014 and January 2016 at a tertiary care center. A total of 50 (47 lymph nodes, 3 adrenal) EUS guided FNAs were performed in 46 patients. Data are presented as median (25–75 IQR).
Results: The study included 46 patients (40 males) whose mean age was 47.9 ± 11.1 (SD) years; mean Child-Turcotte-Pugh (CTP) score and mean MELD (Model for End-Stage Liver Disease) score were 10 (8–11) and 18 (12–20), respectively. The Child Pugh class was A in 4, B in 14,

and C in 28 (including three patients with adrenal FNAs). Indications for FNA were pyrexia of unknown origin and lymphadenopathy on CT imaging. The cytopathological diagnoses were metastatic disease in 1 (adrenal), granulomatous change in 10 (6 positive with acid fast bacilli stain), histoplasmosis in three (two adrenals, one lymph node), 32 lymph nodes were reactive and four lymph node FNAs showed inadequate cellularity. The pathologic nodes had significantly lower long-to-short axis ratio [1.25 (1.09–1.28) versus 1.46 (1.22–1.87), $P = 0.020$]; a higher proportion of hypoechoic echotexture (5 versus 3, $P = 0.017$), and sharply defined borders (4 versus 2, $P = 0.029$). Complications included mild hepatic encephalopathy related to sedation in two patients with Child's C status.
Conclusion: EUS guided FNA is safe in patients with cirrhosis and modified the management in 14/46 (30.4 %) patients.

Introduction
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Pyrexia of unknown origin (PUO) was defined in 1961 by Petersdorf and Beeson as (1) a temperature greater than 38.3° C (101° F) on several occasions, (2) more than 3 weeks' duration of illness, and (3) failure to reach a diagnosis despite 1 week of inpatient investigation [1,2]. Patients with cirrhosis and PUO offer several challenges with regard to management; obtaining a tissue diagnosis is difficult due to coagulopathy and collaterals. Differential diagnosis of PUO is very broad and often these patients are started on empirical anti-tubercular treatment (ATT) [3]. Tuberculosis is a common cause of PUO. Extrapulmonary tuberculosis is more common than pulmonary tuberculosis in patients with cirrhosis, thus patients present without pulmonary infiltrates and tissue diagnosis is required [4]. Empirical ATT has a risk of hepatotoxicity and this risk is higher in patients with cirrhosis and may cause

further decompensation of liver disease or acute-on chronic liver failure that is associated with high mortality [5–7]. Thus, it is not recommended to start empirical ATT. There is also a risk of exacerbation of tuberculosis after initiation of immunosuppressant treatment in liver transplant recipients, thus pretransplant diagnosis and treatment are necessary. The practice of empirical ATT is common in tropical countries such as India due to the high prevalence of tuberculosis. Excision biopsy from abdominal lymph nodes carries a high risk in patients with cirrhosis, and patients with Child Pugh class C are very poor candidates for such sampling (even laparoscopic) [8]. Empirical ATT may also delay the true diagnosis and thus may worsen the original disease. EUS guided FNA offers several advantages: it can be performed with conscious sedation, the FNA procedure is real time, vision guided, and vascular structures (or collaterals) can be safely avoided.

There are no literature reports with regard to EUS-FNA in these patients. A case report of cirrhosis with pyrexia of unknown origin which proved to be histoplasmosis on EUS-FNA was published by our institute [9]. The aim of this current study was to examine the safety and impact of EUS guided FNA in patients with cirrhosis.

Methods
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The study was conducted prospectively between January 2014 and January 2016 at a tertiary care center in North India (Delhi NCR). Out of 6104 patients with cirrhosis, 70 patients had PUO as shown in ● **Table 1**. Sixteen patients with PUO were in the ICU and were very critical, hence FNA was not done. Four patients did not give consent for the FNA procedure. In eight patients, lymph nodes were considered to be accessible by transabdominal ultrasound; four of these patients were referred for EUS guided FNA later due to intervening collaterals. Thus, 46 patients with cirrhosis and PUO with lymphadenopathy or adrenal enlargement on imaging who underwent EUS guided FNA, were included in the analysis (● **Table 1**). The study had approval from the institute's review board/ethics committee. The standard definition for PUO was used [2].

Three patients had cirrhosis with PUO and enlarged adrenals for which EUS FNA was done. All of the procedures were carried out under conscious sedation (Midazolam). EUS guided FNA was performed using a GF-UCT140 linear echo-endoscope (EUS scope, Olympus, Tokyo, Japan). Work-up for pyrexia included ascitic fluid analysis, urine culture, blood culture, malaria serology, chest X-ray, and contrast enhanced CT of the abdomen and thorax. Patients who had enlarged lymph nodes or adrenal/adrenals underwent EUS guided FNA. The following data were recorded for each patient: age, sex, site of lymph node, size of lymph node on its short and long axis, type and number of needle passes, number of slides, results of FNA, and complications from the procedure. In the presence of multiple lymph nodes, the node with larger size/with demarcated borders/hypoechoic in nature was preferred for FNA. A lymph node was considered reactive when FNA showed lymphoid cells in different stages of activation in the presence of adequate cellularity and the absence of granulomas/necrosis/malignant cells. We aimed to follow-up all these patients up to 6 months after the procedure.

EUS FNA procedure

A lymph node was selected based on the above mentioned criteria for FNA, if feasible (avoidance of vascular structures and vital organs). A linear array echo-endoscope was directly inserted into the esophagus. An EUS FNA needle with stylet was introduced into the working channel; Doppler was used to avoid any vascular structures in the needle path. The stylet was withdrawn slightly before puncture; it was reintroduced fully after puncture of the lymph node to displace any material in the needle (from the gastrointestinal wall). After that, the stylet was completely withdrawn; 10–20 to and fro movements of the needle were performed within the lymph node. The material inside the needle was gradually pushed onto slides with the help of the stylet. Two slides from each pass were immediately fixed in absolute alcohol and the remainder were air dried. The slides were stained with Papanicolaou, Giemsa stain and Ziehl-Neelsen stain (wherever required). The type of needle, method of FNA (suction, no suction or capillary), and number of needle passes (as no on-site cytopa-

Table 1   Break-up of PUO in patients with liver cirrhosis and accessibility of lymphadenopathy.

Total number of CLD patients screened in OPD/IPD	6104
CLD with PUO and lymphadenopathy	70
Not assessed for FNA (very sick/no consent)	20 (16/4)
Considered to be accessible for transabdominal ultrasound	8 FNA done in 4, not done in 4 due to intervening collaterals (EUS done in these 4 patients)
EUS guided FNA performed	46 (including 4 referred from transabdominal ultrasound)

CLD, chronic liver disease; EUS, endoscopic ultrasound; FNA, fine needle aspiration; IPD, inpatient department; OPD, outpatient department; PUO, pyrexia of unknown origin.

thologist facility was present) were operator-dependent. We used a 25G needle in the majority of the patients. The average number of passes was 3 (2–5). Patients received a platelet transfusion if the platelet count was <50000/cmm or fresh frozen plasma transfusion if INR >1.5. The patients were kept under observation for 6 hours in our dedicated endoscopy post-procedure area adjacent to the endoscopic suite. They were observed for vital examination, and immediate procedure or anesthesia related complications. The patients were followed up by phone or outpatient department (OPD) basis for 1 week for any complications including bleeding, infection, and fever. Further follow-up for 6 months was carried out to assess the clinical response to treatment.

Statistical methods

The data are shown as number, percentage, and median (25–75 IQR). Two groups were compared with Student's t test or Fishers exact test (nominal data). A two-tailed P value <0.05 was considered to be significant. All statistical analyses were performed with SPSS, version 16 (SPSS Inc., Chicago, Illinois, United States).

Results
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The study group comprised 46 patients (40 males). A total of 50 FNAs were done (47 lymph nodes and three adrenals). The parameters of liver disease severity were as follows: mean Child-Turcotte-Pugh (CTP) score 10 (8–11), mean Model for End-Stage Liver Disease (MELD) score 18 (12–20). The Child Pugh class was A in 4, B in 14, and C in 28 (including three patients with adrenal FNA). A total of 34 (73.9%) patients had ascites, platelet count was 1.2×10^5 (0.7–1.45 L)/cmm, and INR was 1.5 (1.17–1.65, maximum 3). The site of the sampled lymph node was mediastinal in 10 and abdominal in 37 patients; adrenal FNA was taken from the left adrenal in two patients with bilateral enlargement and the right adrenal (isolated right adrenal enlargement) in one patient. Six patients required a platelet transfusion; fresh frozen plasma was required in 22 patients before the EUS-FNA procedure. One of these patients also had renal failure (serum creatinine 7.4 mg/dL). After the EUS-FNA procedure, blood smearing of mucosa was seen in 18 patients (all abdominal lymph nodes); none of the patients had clinically significant bleeding/melena. A 25G FNA needle was used in the majority of patients (n=26, all patients with Child's C), a 22G needle was used in 17, and 19G was used in one patient who had a calcified
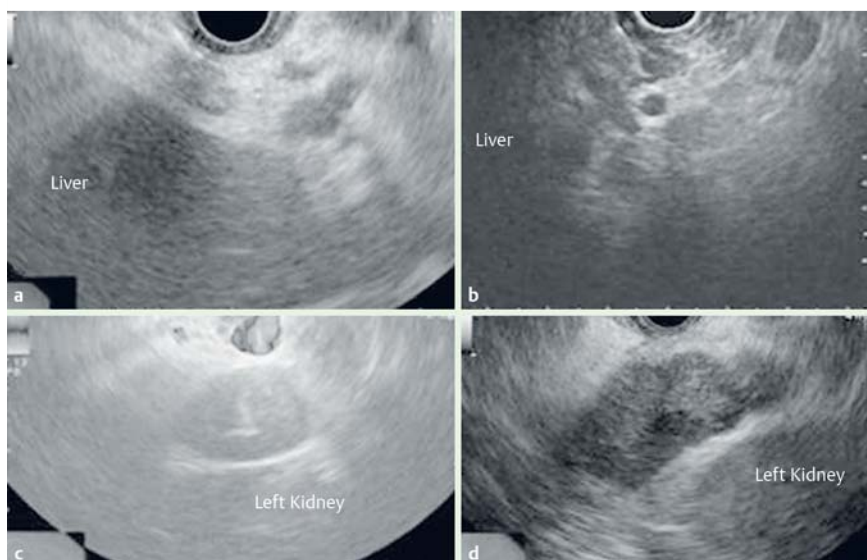
Fig. 1 **a** Tubercular lymph node. **b** Histoplasma positive lymph node. **c, d** Left adrenals positive for Histoplasma.

lymph nodal mass and in whom the 22 G needle had failed to yield an aspirate. The average number of passes was 3 (2 – 5). Cytopathological diagnoses were metastatic carcinoma in one (right adrenal), granulomatous change in 10 (six acid fast bacilli stain positive), histoplasmosis in three (two adrenals), and reactive changes in 32. One patient had a pre-liver transplant diagnosis of multiple small hepatocellular carcinomas and had pyrexia of unknown origin; his abdominal lymph node showed the presence of granulomas without necrosis or positive staining for tubercular bacilli. He was given anti-tubercular treatment which led to improvement in his condition. Liver transplantation was done after a few weeks and his explanted liver also showed the presence of granulomas. A total of 32 patients had a diagnosis of reactive lymph node. These patients were followed for a period of 6 months (4 patients for 3 months) and all had a benign course. Ten of these patients had a liver transplant and had a benign course (one died after 3 months due to intracranial bleeding). Four patients provided inadequate samples; one of these underwent biopsy of the inguinal node which was positive for lymphoma. When pathologically enlarged lymph nodes were compared to reactive lymph nodes, pathological nodes were larger along the small and large axes; however, none of these parameters reached statistical significance. Pathological lymph nodes tended to be less oblong and had a significantly higher proportion with hypoechoic echotexture and sharply defined borders. One of the lymph nodes was calcified and it was acid fast bacilli stain positive. Representative images from four patients are shown in ○ **Fig. 1**.

Adverse events were encountered in 4 % of the patients. Two developed mild hepatic encephalopathy related to sedation and both had Child's C cirrhosis and were inpatients at the time of the procedure. All of the possible precipitating factors for hepatic encephalopathy including infection, bleeding, constipation, dyselectrolytemia, and renal failure were excluded in these patients. None of the patients had clinically significant bleeding.

Discussion
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Patients with long standing PUO in the setting of cirrhosis pose a diagnostic challenge. While patients with compensated cirrhosis may have normal coagulation parameters, the presence of de-compensated cirrhosis is associated with coagulation abnormalities and collaterals. Diagnosis of the etiology of pyrexia is of utmost importance in patients with cirrhosis. The correct diagnosis has multiple implications: first treatment of the cause may lead to improvement in symptoms, and treatment of infectious disease is important before liver transplant (if needed) to prevent flare up after transplantation. Patients with liver cirrhosis are at increased risk of tuberculosis and also their prognosis is worse [10, 11], thus, timely diagnosis is important. Empirical ATT is often used in such patients; however, these patients have a higher risk of hepatotoxicity that may lead to acute-on liver failure which is associated with high mortality. Also, monitoring of drug-induced hepatitis is confounded by the presence of cirrhosis due to fluctuating liver function tests [12 – 14]. Patients with cirrhosis are immunosuppressed and thus may be more prone to develop histoplasmosis as shown in the current series [15]. There are no large published studies on FNA in patients with decompensated cirrhosis. EUS offers several advantages over other imaging modalities. It provides the option for real time FNA, and vascular structures can be avoided as seen in ○ **Fig.1c**. EUS also allows sampling from locations which are difficult to access by the percutaneous route. Obtaining a tissue diagnosis is also important to avoid a delay in diagnosis. Ten patients in the current series had tuberculosis. Three adrenal FNAs were performed in the current series and the procedure is safe as shown earlier by our group in non-cirrhotic patients [16]. It is important to work-up these patients by other means if EUS guided FNA is unable to provide a diagnosis as one of the patients in the present series who provided an inadequate sample had lymphoma.

We encountered mild hepatic encephalopathy as an adverse effect related to midazolam. A recent meta-analysis by Tsai et al. suggested that propofol sedation for endoscopy in cirrhotic patients provides more rapid sedation and recovery than midazolam, and efficacy is also superior. The risk of sedation-related side effects for propofol does not differ significantly from that of midazolam [17].

The strengths of the present study include its prospective nature and follow-up of patients. It is the first such kind of study that expands the horizons of EUS guided FNA. The sample size is small, however, as cirrhosis and long standing pyrexia are very uncommon indications of EUS guided FNA. The findings of the current study may not be applicable in Western countries where the

prevalence of tuberculosis is low. In conclusion, we present a series of 46 patients with cirrhosis who underwent EUS guided FNA of the lymph nodes or adrenals and management was modified in approximately one-third of the patients.

Competing interests: None

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