

Fever of Unknown Origin Associated with Intrabdominal Lymphadenopathy, the Efficiency of Laparoscopic Biopsy

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Abstract

Introduction: Prolonged fever is a difficult to diagnose febrile disorder appositely termed Fever of Unknown Origin. Abdominal lymphadenopathy mandates diagnostic set up with tissue biopsy in cases where percutaneous biopsy is not feasible or it fails to establish diagnosis. The aim of this study is to evaluate the safety, efficacy and diagnostic yield of laparoscopic lymph node biopsy in patients with Fever of Unknown Origin associated with intrabdominal lymphadenopathy.

Materials and methods: The medical records of patients subjected to laparoscopic lymph node biopsy from August 2005 to December 2011 were revised retrospectively. Data collected from our prospective database included patient demographics, anatomical site of lymph node biopsy, operative time, conversion rate, morbidity, mortality, hospital stay and pathology results.

Results: During the study period 32 patients were subjected to laparoscopic lymph node biopsy. The mean operative time was 40min. No intraoperative complications were recorded. There was no conversion to open. The root of the mesentery was the most common site of biopsy and non-Hodgkin lymphoma was the most common diagnosis. All patients had an uneventful recovery and the mean length of stay was 1.8 days. Diagnosis was successfully established in all but one patient where tissue sample was insufficient (diagnostic yield: 96.9%).

Conclusion: Laparoscopic lymph node biopsy is a safe procedure with a high diagnostic yield. It can be performed on an outpatient basis and it should be offered in all patients with Fever of Unknown Origin associated with intrabdominal lymphadenopathy when percutaneous techniques are unsuccessful or not feasible.

Keywords: Fever of unknown origin; Laparoscopy; Biopsy; Intrabdominal lymphadenopathy; Lymph node

Introduction

Prolonged fever is a difficult to diagnose febrile disorder appositely termed Fever of Unknown Origin (FUO). Fever of unknown origin was first termed "prolonged and perplexing fevers" by Kiefer and Leard [1] and may be defined as disorders with temperatures greater than 38.3°C (101°F) on several occasions with a duration of fever greater than three weeks that were not diagnosed after one week of intensive in-hospital investigation [2]. Durack and Street proposed a new definition that categorizes FUO into four groups according to patient subtype, with each group having unique causes of fever [3]. The most common causes of classic FUO are infection, noninfectious inflammatory diseases and malignancy. Physical examination of the patient is crucial for the diagnosis. When lymphadenopathy is present lymph node biopsy is useful to diagnose lymphomas, lymphogranuloma venereum, toxoplasmosis, Kikuchi's arteritis and even a granulomatous disorder.

Abdominal lymphadenopathy without a known cause is a pathologic entity that implies the need for tissue sampling. In cases where peripheral lymphadenopathy is also present, biopsy can be easily performed under local anesthesia. In any other case an invasive procedure in the abdominal cavity is required. Currently, ultrasound or computed tomography (CT)-guided biopsies are the gold standard for tissue sampling since they are minimally invasive procedures that are associated with low morbidity and acceptable diagnostic yield [4-6]. Nevertheless, in some cases tissue extraction via core-needle biopsy is not sufficient or tissue architecture is jeopardized and diagnosis cannot be established [6,7]. Furthermore, the proximity of an enlarged pathologic lymph node to vital structures such as major blood vessels, bowel or other viscera makes percutaneous biopsy technically difficult and dangerous even in the hands of an experienced radiologist [8]. In

such occasions laparotomy needs to be performed in order to access and obtain adequate tissue. However, the latter is an invasive procedure which is associated with a prolonged convalescence and a delay in the final treatment. Lately, laparoscopy has been increasingly applied for the biopsy of abdominal lymph nodes [9,10]. The profound advantages of this approach are the excellent diagnostic accuracy, the minimal surgical trauma and the fast recovery [10].

The aim of this study is the evaluation of safety, efficacy and diagnostic accuracy of laparoscopic lymph node biopsy in patients with Fever of Unknown Origin associated with intrabdominal lymphadenopathy.

Materials and Methods

The medical records of all patients subjected to laparoscopic lymph node biopsy at the time period of August 2005 to December 2011 were revised. Data collected from our prospective database included patient demographics, preoperative diagnosis, physical laboratory and imaging evaluation, anatomical site of lymph node biopsy, operative time, conversion rate, morbidity, mortality, hospital stay and the final pathology results.

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The data of all patients satisfied the criteria of FUO, prior to the operation, were included in this study. All patients with prolonged fever remained undiagnosed preoperatively after at least one week of extensive physical, laboratory and imaging evaluation. Furthermore all patients included in this study were subjected to a thorough physical examination in order to rule out peripheral lymphadenopathy. Patients subjected to laparoscopic lymph node biopsy with a preoperative diagnosis other than FUO were excluded from the study.

All imaging studies were discussed in depth with an experienced interventional radiologist and the final treatment plan regarding percutaneous or operative lymph node biopsy was established. For patients with an inconclusive percutaneous biopsy result an operative lymph node biopsy was offered. As soon as the decision for surgery was taken all patients were informed in detail about the benefits and the risks of laparoscopy and a written signed informed consent form was obtained.

All procedures were performed under general anesthesia with the patient in the supine position. An orogastric tube and a Foley catheter were inserted at the induction of anesthesia and were both removed at the conclusion of the procedure. A single dose of a second generation cephalosporin and metronidazole were given at the induction of anesthesia. Pneumoperitoneum was established with a Verres needle which was placed left subcostally. A 10 mm optical trocar was placed periumbilically and a thorough exploration of the abdominal cavity was carried out with a 30° angled laparoscope. Thereafter, two additional 5 mm working ports were placed in sites directed by the lesion site. The specimen was gently grasped and dissected from the surrounding tissues with a hook electrocautery or bipolar forceps. In all cases, every possible effort was made to excise the entire lymph node with an intact capsule. In case of multiple pathologic or small size nodes at least three of them were excised in order to achieve definite diagnosis. However, in case of lymph node masses with no discrete anatomical borders incisional biopsies were obtained. Hemostasis was achieved in the vast majority of cases with electrocautery and in few cases with clip application. The excised lymph nodes were removed in an endo-bag and then sent for pathology study.

Results

During the study period 32 patients with FUO and intraabdominal lymphadenopathy were subjected to laparoscopic lymph node biopsy. Patient demographics are shown in Table 1. Twenty-four of our patients were primarily deemed poor candidates for percutaneous biopsy due to the anatomical location of the lymph node. The rest of our patients (n=8) had an earlier unsuccessful percutaneous biopsy. In all patients, lymph node biopsy was successfully accomplished by means of laparoscopy

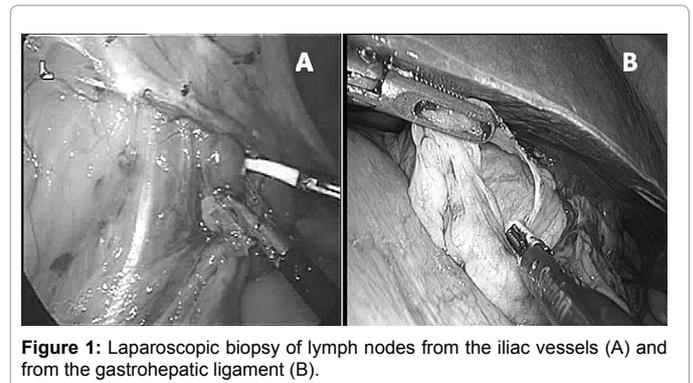
Gender	n (%)
Male	13 (40.6)
Female	19 (59.4)
Age, years (range)	61.2 (24-81)
Classification of FUO	n (%)
Classical FUO	28 (87.5)
HIV	2 (6.25)
Neutropenic	2 (6.25)
Peripheral lymphadenopathy	0 (0)
Previous unsuccessful percutaneous biopsy, n (%)	8 (25)
Poor candidates due to anatomic location, n (%)	24 (75)

FUO: Fever of Unknown Origin, HIV: Human Immunodeficiency Virus

Table 1: Patient demographics and FUO Classification.

Operative time (range) (min)	40 (25-70)
Conversion to std laparoscopy, n (%)	0 (0)
Mortality/Morbidity (%)	0/0
Length of hospital stay (range) (days)	1.8 (1-3)
Site of biopsy n (%)	
Mesentery	13 (40.6)
Para-aortic	6 (18.7)
Gastrohepatic ligament	6 (18.7)
External iliac	5 (15.6)
Retroperitoneal	2 (6.2)
Nodes excised n (%)	
Segmental Biopsy	3 (9.4)
1 node	6 (18.8)
2 nodes	6 (18.8)
3 nodes	15 (46.9)
4 nodes	2 (6.3)

Table 2: Perioperative data



and no conversion was necessary. The mean operative time was 40 min (range 25-70 min). No intraoperative complications were recorded and blood loss was minimal (Table 2).

The root of the mesentery was the most common site of biopsy (Table 2 and Figure 1). In three occasions where a compact lymph block was revealed an incisional biopsy was performed (9.4%). In six occasions a single node was excised (18.8%), in other six occasions two nodes (18.8%), in 15 patients three nodes (46.9%) and in two patients four nodes (6.3%). Postoperatively no antibiotics were given and liquid diet was instituted the same evening of the operation. Intravenous analgesia was supplied postoperatively upon patient request. All patients had an uneventful recovery and the mean length of stay was 1.8 days (range 1 to 3 days).

Diagnosis was successfully established in all but one occasion. In the latter case an incisional biopsy has been performed in a male patient whose tissue specimen was deemed inadequate. Due to the unique location of the pathology the patient was subjected to a second laparoscopy and the whole lymph block was carefully removed. Eventually a successful diagnosis was established. Thus, in our cohort the diagnostic yield of laparoscopy reached 96.9%.

Histopathology tests revealed non-Hodgkin lymphoma in 11 patients, Hodgkin lymphoma in 5 patients, tuberculosis in 3 patients, while 9 patients had malignant infiltration by a primary or metastatic tumor and 4 patients had benign lymphadenopathy. The latter group of patients had a close follow up with a sequence of CTs for at least 3 years in order to assess the progression of lymphadenopathy.

Discussion

Unexplained fever regardless of an extended work up frequently sets a clinical challenge. The presence of lymphadenopathy in the majority of cases poses the need of lymph node biopsy which is useful in order to diagnose lymphomas, lymphogranuloma venereum, toxoplasmosis, Kikuchi's arteritis and even a granulomatous disorder [11,12]. Abdominal lymphadenopathy is a common clinical concern that requires management with accurate histological typing and immunophenotyping [13]. The advent of technology with the development of instrumentation as well as the improvement of laparoscopic surgical skills have made it possible for laparoscopy to displace laparotomy as the surgical intervention of choice in the diagnostic set up of abdominal lymphadenopathy [14]. Frequently at the time of laparotomy, a large number of patients with F.U.O are in bad general condition, resulting in high perioperative risk such as wound infection and seroma. Takahashi in his study reported an operative morbidity of 12% and a mortality of 4% [15]. Due to the high laparotomy related morbidity and the longer convalescence which leads to further delay in the definitive treatment, we have recently shifted to laparoscopy for abdominal lymph node biopsy.

By early 1980s minimally invasive techniques such as ultrasound or computed tomography guided percutaneous biopsies were employed for the diagnosis of abdominal lymphadenopathy. Furthermore PET-CT has a known role in the diagnostic strategies for identifying the causal source of F.U.O [16,17]. Hypermetabolic PET lesions like pathologic lymph nodes may be identified and hence the site for the lymph node biopsy better specified. Unfortunately in our institution (and the wider health district) a PET-CT scan could not be performed. Computed tomography guided biopsies have been associated with a low morbidity and an acceptable diagnostic yield [6,7,18]. For these reasons percutaneous techniques are the gold standard in the diagnostic set up of abdominal lymphadenopathy. However, percutaneous biopsy is not feasible when anatomical obstacles, like vital structures, are situated adjacent to the targeted lymph node. Furthermore tissue sampling via fine needle or core biopsy may be inadequate for histopathologic and immunochemical assay [10]. When the above criteria are met surgical intervention is required. In the present cohort, after assessment of the CT scans by an experienced interventional radiologist, 24 patients (75%) were deemed poor candidates for percutaneous biopsy due to the anatomic location of the lesion. The rest of patients in the cohort (25%) had been subjected earlier in a percutaneous biopsy where diagnosis could not be established due to insufficient tissue sampling.

At the hands of an experienced surgeon, lymph node biopsy by means of laparoscopy is not technically demanding in the vast majority of cases. However, in some occasions the anatomic location of the lymph node as well as undesirable events such as bleeding from the biopsy site may necessitate conversion of the procedure to open. In the present cohort we were able to achieve a zero conversion rate but according to the literature the latter could be high enough reaching 17-20% [9,10,19]. Careful interpretation of the preoperative CT scans as well as the standardization of the technique are vital steps for avoiding conversions. Furthermore, though not applied in current study, laparoscopic ultrasonography has been shown to be a valuable tool in the identification of retroperitoneal lymph nodes and it should be used when available [10].

In the literature, the rate of false negative diagnoses after laparoscopic lymph node biopsy ranges from 0% to 14% [20-23]. According to Asoglu the proximity of the pathologic nodes to vital structures such as the duodenum, the pancreas and the aorta can increase the prevalence

of false negative diagnoses due to inadequate tissue sampling [19]. In agreement with the aforementioned study we had a false negative diagnosis in a patient with a periaortic lymph block where an incisional biopsy was performed. Due to the presence of enlarged mediastinal lymph nodes in a CT scan, malignant disease could not be excluded and this patient was subjected to a second laparoscopy where the entire periaortic lymph block was excised. Eventually, laboratory analysis revealed malignant lymphoma.

The mean hospital stay was 1.8 days (range 1-3). No adverse events were recorded intraoperatively and postoperatively all patients had an uneventful recovery. Initially in our cohort we were reluctant to fast track surgery in these patients. However, as our experience has increased, we have now shifted to a day surgery protocol where patients are discharged the day after the procedure provided that mobilization is sufficient and pain is minimal. We believe that this fast patient trading is a significant advantage of laparoscopy since there is no delay in the final systemic therapy.

In conclusion, laparoscopic lymph node biopsy is a safe procedure with a high diagnostic yield. It can be performed on an outpatient basis and it should be offered in all patients with Fever of Unknown Origin associated with intraabdominal lymphadenopathy when percutaneous techniques are unsuccessful or not feasible.

References

1. Keefer C, Leard S (1955) Prolonged and perplexing fevers. Boston: Little, Brown
2. Petersdorf RG, Beeson PB (1961) Fever of unexplained origin: report on 100 cases. *Medicine (Baltimore)* 40: 1-30.
3. Durack DT, Street AC (1991) Fever of unknown origin--reexamined and redefined. *Curr Clin Top Infect Dis* 11: 35-51.
4. Zornoza J, Cabanillas FF, Altoff TM, Ordonez N, Cohen MA (1981) Percutaneous needle biopsy in abdominal lymphoma. *AJR Am J Roentgenol* 136: 97-103.
5. Erwin BC, Brynes RK, Chan WC, Keller JW, Phillips VM, et al. (1986) Percutaneous needle biopsy in the diagnosis and classification of lymphoma. *Cancer* 57: 1074-1078.
6. Ben-Yehuda D, Polliack A, Okon E, Sherman Y, Fields S, et al. (1996) Image-guided core-needle biopsy in malignant lymphoma: experience with 100 patients that suggests the technique is reliable. *J Clin Oncol* 14: 2431-2434.
7. Pappa VI, Hussain HK, Reznick RH, Whelan J, Norton AJ, et al. (1996) Role of image-guided core-needle biopsy in the management of patients with lymphoma. *J Clin Oncol* 14: 2427-2430.
8. Cowles RA, Yahanda AM (2000) Laparoscopic biopsy of abdominal retroperitoneal lymphadenopathy for the diagnosis of lymphoma. *J Am Coll Surg* 191: 108-113.
9. Diulus L, Chalikhonda S, Pitt T, Rosenblatt S (2009) Efficacy of laparoscopic mesenteric/retroperitoneal lymph node biopsy. *Surg Endosc* 23: 389-393.
10. Casaccia M, Torelli P, Cavaliere D, Panaro F, Nardi I, et al. (2007) Laparoscopic lymph node biopsy in intra-abdominal lymphoma: high diagnostic accuracy achieved with a minimally invasive procedure. *Surg Laparosc Endosc Percutan Tech* 17: 175-178.
11. Sinclair S, Beckman E, Ellman L (1974) Biopsy of enlarged, superficial lymph nodes. *JAMA* 228: 602-603.
12. Dorfman RF, Remington JS (1973) Value of lymph-node biopsy in the diagnosis of acute acquired toxoplasmosis. *N Engl J Med* 289: 878-881.
13. Bain BJ (1995) Routine and specialised techniques in the diagnosis of haematological neoplasms. *J Clin Pathol* 48: 501-508.
14. Arch-Ferrer JE, Velázquez-Fernández D, Sierra-Madero J, López-Karpovitch X, Angeles-Angeles A, et al. (2003) Laparoscopic approach to fever of unknown origin. *Surg Endosc* 17: 494-497.
15. Takahashi T, Herrera MF, Onuma L, Calva JJ, Sánchez-Mejorada G, et al. (1991) Diagnostic laparotomy in fever of unknown origin. *Rev Invest Clin* 43: 25-30.

16. Balink H, Collins J, Bruyn GA, Gemmel F (2009) F-18 FDG PET/CT in the diagnosis of fever of unknown origin. *Clin Nucl Med* 34: 862-868.
17. Keidar Z, Gurman-Balbir A, Gaitini D, Israel O (2008) Fever of unknown origin: the role of 18F-FDG PET/CT. *J Nucl Med* 49: 1980-1985.
18. Buscarini L, Cavanna L, Fornari F, Rossi S, Buscarini E (1985) Ultrasonically guided fine-needle biopsy: a new useful technique in pathological staging of malignant lymphoma. *Acta Haematol* 73: 150-152.
19. Asoglu O, Porter L, Donohue JH, Cha SS (2005) Laparoscopy for the definitive diagnosis of intra-abdominal lymphoma. *Mayo Clin Proc* 80: 625-631.
20. Strickler JG, Donohue JH, Porter LE, Habermann TM (1998) Laparoscopic biopsy for suspected abdominal lymphoma. *Mod Pathol* 11: 831-836.
21. Porte H, Copin MC, Eraldi L, Roumillac D, Jaillard-Thery S, et al. (1997) Retroperitoneoscopy for the diagnosis of infiltrating retroperitoneal lymphadenopathy and masses. *Br J Surg* 84: 1433-1436.
22. Mann GB, Conlon KC, LaQuaglia M, Dougherty E, Moskowitz CH, et al. (1998) Emerging role of laparoscopy in the diagnosis of lymphoma. *J Clin Oncol* 16: 1909-1915.
23. Gossot D, de Kerviler E, Brice P, Mariette X, Meignin V, et al. (1998) Surgical endoscopic techniques in the diagnosis and follow-up of patients with lymphoma. *Br J Surg* 85: 1107-1110.