INTRODUCTION

Peritoneal lesion can be caused by several diseases such as malignancies and inflammation (1, 2). Identification of the cause of peritoneal lesion is often critical for appropriate treatment and predicting prognosis. In patients with peritoneal thickening, the diagnosis is often made on the basis of multiple factors, including the patients’ symptoms, laboratory tests and ascitic fluid analysis. But in some cases it is hard to differentiate peritoneal carcinomatosis from chronic inflammation including tuberculous peritonitis (3-6).

Assessment of the pattern of peritoneal lesion in abdominal computed tomography (CT) may help to differentiate inflammatory involvement from malignant involvement. Indeed, smooth uniform peritoneal thickening is the prevalent pattern in inflammation, whereas nodular pattern is common in malignancies.
However, the images of benign inflammatory and malignant diseases could be overlapped; it makes the lesion hard to differentiate (7-9).

The fluorine-18-fluorodeoxyglucose ($^{18}$F-FDG) positron emission tomography/computed tomography (PET/CT) may help to differentiate peritoneal disease (10, 11). A standardized uptake value (SUV) of greater than 5.1 may help to differentiate peritoneal carcinomatosis from benign peritoneal inflammation, but is no entirely accurate (12). Thus, tissue biopsy for histopathological diagnosis is often needed. Diagnostic yield of laparoscopic peritoneal biopsy have shown a relatively high rate (13-16). However, laparoscopy requires complex manipulations with many complications and needs anesthesia in an operating room, thus posing a risk to the patients (17, 18).

An ultrasound (US)-guided biopsy of peritoneal lesions can be less invasive, safer and rapider (19-23). However, there have been no reports on the biopsy of peritoneal thickening of unknown cause visualized as infiltrated fat without apparent mass formation on abdominal CT, probably due to their soft and friable nature which makes it difficult to perform the US-guided biopsy. Thus, the purpose of our study is to evaluate the diagnostic usefulness and safety of US-guided peritoneal biopsy for solitary peritoneal thickening visualized as only infiltrated fat on CT scan.

**MATERIALS AND METHODS**

**Patient Population**

Research ethics approval was obtained in advance for this study (IRB 2017-05-004). As the study was retrospective, the need for informed consent was waived. Between March, 1998 and March, 2017, 57 patients underwent biopsy for thickened peritoneum in our hospital. Among them, 21/57 patients whose peritoneum was completely replaced with soft tissue or who had an apparent mass formation in other organs except the peritoneum on CT were excluded. 36 patients (16 males, 20 females; mean age, 51.7 years old, range 17 to 86 years old) who underwent US-guided peritoneal biopsy for solitary peritoneal thickening visualized as only infiltrated fat on CT scan at the time of US-guided peritoneal biopsy. All patients were referred for sonographic biopsy after solitary peritoneal thickening were identified on CT. 36 patients had various amounts of ascites at the time of US-guided peritoneal biopsy. Ascites presented around the pathway of biopsy in 28 patients. Prothrombin time, activated partial thromboplastin time, international normalized ratio, and platelet counts were checked before biopsy, and none of the patients had coagulopathies or thrombocytopenia. To determine possible minute or concealed procedure related intraperitoneal bleeding, blood hemoglobin (Hb) and hematocrit (Hct) values were checked before and one day after biopsy.

**Biopsy Technique**

For US guidance a 5-MHz convex or a 12-MHz linear array transducer (Gateway; Diasonics, Milpitas, CA, USA) or a 5-MHz convex or a 12-MHz linear array transducer (HDI 5000; Philips Medical Systems, Bothell, WA, USA) or a 5-MHz convex or a 12-MHz linear array transducer (iU22 or EPIQ 5G; Philips Medical Systems) were used. For tissue sampling, an 18-gauge automated needle device with a 17 mm throw biopsy gun (Manan pro-mag 2.2; Manan medical products, Northbrook, IL, USA) or an 18-gauge automated needle device with a 15 mm throw biopsy gun (Bard-Magnum Biopsy Instrument, Bard Medical, Covington, WA, USA) were used.

The biopsy was performed by one radiologist whose experience of radiology over 8 years. Before the biopsy, the doctor would first identify the thickest peritoneal lesion on abdominal CT and localized the lesion on gray scale US. The color Doppler US was also performed to assess the vascularity of the peritoneum and to identify vessels around the lesion (Fig. 1). Skin at the puncture site was sterilized with povidone-iodine. Skin and parietal peritoneum at the expected pathway of the biopsy needle were infiltrated with 2% lidocaine hydrochloride using a 25-gauge injection needle. A minimal skin incision was made at the needle puncture site. Free-hand needle placement technique was used in all patients. During the procedure, the angle of needle approach was adjusted to secure the shortest and safest route. The peritoneum far enough away from the adjacent bowel was selected for a biopsy to avoid unwanted passage of the needle through the gastrointestinal tract. When the thickness of the peritoneum...
was minimal the biopsy needle was approached more horizontally to obtain as much as sample possible (Fig. 2). Also a portion of overlying abdominal wall muscle was sampled together with parietal peritoneum for the minimally thickened peritoneal biopsy.

The patient was asked to hold his/her breath for a second, during the moment the biopsy needle was inserted into the lesion. And then the biopsy gun was quickly withdrawn after triggered. The amounts of obtained samples were macroscopically examined and two or three pieces of specimens were taken from each patient. The samples were fixed in formalin and sent to the department of pathology. After the procedure, US examination was performed for at least 5 minutes to exclude possible life-threatening bleeding. The patients were kept in bed for at least 4 hours with close monitoring of their vital signs and symptoms.

**Histopathological Analysis**

Tissue analysis was carried out by several experienced consultant pathologists. All biopsy specimens were fixed in formalin, processed by standard procedure, embedded in paraffin, cut and stained with hematoxylin and polyclonal antibodies were applied to the formalin-fixed samples using the Bond Polymer Refine Detection System method. Immunohistochemistry including cytokeratin 7, cytokeratin 20, thyroid transcription factor 1, mucicarmine, Hector Battifora mesothelial-1, c-kit was evaluated if pathologically needed.
Data Analysis

The histopathological diagnosis through the US-guided peritoneal biopsy was compared with final diagnosis. The final diagnosis was made by open biopsy \((n = 3)\) and clinical/CT follow-up \((n = 33)\). The duration between the final diagnosis and the US-guided biopsy is 10.9 days \((7–30 \text{ days})\).

In 12 patients who underwent integrated PET/CT using \(^{18}\text{F}\)-FDG during the follow-up period, PET/CT findings were also included for making final diagnosis.

The diagnostic usefulness of US-guided peritoneal biopsy was assessed by calculating the rate of specific histopathological diagnosis, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy for the diagnosis of malignant disease. The sensitivity was defined as the number of true malignancy determined by US-guided biopsy divided by the number of finally diagnosed malignancy. The specificity was defined as the number of true non-malignancy determined by US-guided biopsy divided by the number of finally diagnosed non-malignancy. PPV was defined as the number of true malignancy determined by US-guided biopsy divided by the number of malignancy determined by US-guided biopsy. NPV was defined as the number of true non-malignancy determined by US-guided biopsy divided by the number of non-malignancy determined by US-guided biopsy. Accuracy was defined as the
percentage of patients with same final diagnosis and the histopathological diagnosis made by US-guided biopsy. Statistical analysis was performed by using IBM SPSS Statistics version 20.0 software (IBM Corp., Armonk, NY, USA). Difference between Pre- and post-biopsy blood Hb and Hct values were compared between two groups; a group with ascites around the sampling tissue and the other group without ascites around the sampling tissue. The difference between two groups was tested using t-test.

RESULTS

With two to three samples taken from each patient, the technical success rate of the US-guided biopsy of the thickened peritoneum visualized as infiltrated fat on CT was 100% (36/36). With this procedure, a specific histopathological diagnosis was made in 31/36 (86.1%) including peritoneal carcinomatosis in 15/31 (48.4%), tuberculous peritonitis in 15/31 (48.4%) and panniculitis in 1/31 (3.2%). A non-specific histopathological diagnosis was made in 5/36 (13.9%); chronic inflammation in 4/5 (80%) and mesothelial hyperplasia in 1/5 (20%) (Table 1).

The US-guided biopsy of thickened peritoneum showed a sensitivity of 83.3%, specificity of 100%, PPV of 100%, NPV of 85.7%, and an accuracy of 86.1% for the diagnosis of malignant diseases (Table 2).

One patient diagnosed as mesothelial hyperplasia by US-guided biopsy was finally confirmed as peritoneal carcinomatosis from adenocarcinoma with unknown primary site. The patient’s 18F-FDG PET/CT performed 5 days after US-guided biopsy showed findings suggestive of peritoneal carcinomatosis; nodular peritoneal thickening with diffuse hypermetabolic uptake in the greater omentum (SUV max 12.2) without demonstrable primary malignancy. This patient underwent cytoreductive surgery and had an early postoperative intraperitoneal (anticancer) chemotherapy an 30 days after US-guided biopsy. The histopathological diagnosis by open biopsy was peritoneal carcinomatosis from adenocarcinoma.

Among four patients with nonspecific chronic inflammation by the US-guided biopsy; two patients’ disease were confirmed as peritoneal carcinomatosis and another two patients diseases were confirmed as tuberculous peritonitis. The first patient underwent PET/CT 2 days after US-guided biopsy. 18F-FDG PET/CT showed findings suggestive of peritoneal carcinomatosis; nodular peritoneal thickening in the greater omentum (SUV max 7.7) without demonstrable primary malignancy. This patient’s disease was finally diagnosed as peritoneal carcinomatosis by clinical and radiologic follow-up because of rapid aggravation of the peritoneal thickening resulted in omental mass formation despite chemotherapy. The second patient’s 18F-FDG PET/CT 1 day after US-guided biopsy showed no definite hypermetabolic lesion in the peritoneum as well as in the whole body but CA-125 was elevated in ascites. Thus the patients underwent breast ultrasonography 20 days after US-guided peritoneal biopsy and breast cancer was found in her left breast. This patient’s disease was finally diagnosed as peritoneal carcinomatosis from the breast cancer. This patient’s follow-up abdominal CT 50 days after US-guided biopsy showed prominent nodular thickening in the peritoneum, consistent with peritoneal carcinomatosis.

Table 1. Underlying Disease, Histopathological Diagnosis by US-Guided Peritoneal Biopsy and Finalized Diagnosis

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Underlying Disease</th>
<th>Histopathological Diagnosis by US-Guided Biopsy</th>
<th>Finalized Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–14</td>
<td>Unknown</td>
<td>Peritoneal carcinomatosis</td>
<td>Peritoneal carcinomatosis</td>
</tr>
<tr>
<td>15</td>
<td>Endometrial cancer</td>
<td>Peritoneal carcinomatosis</td>
<td>Peritoneal carcinomatosis</td>
</tr>
<tr>
<td>16–30</td>
<td>None</td>
<td>Tuberculous peritonitis</td>
<td>Tuberculous peritonitis</td>
</tr>
<tr>
<td>31</td>
<td>None</td>
<td>Panniculitis</td>
<td>Panniculitis</td>
</tr>
<tr>
<td>32</td>
<td>Unknown</td>
<td>Mesothelial hyperplasia</td>
<td>Peritoneal carcinomatosis</td>
</tr>
<tr>
<td>33</td>
<td>Breast cancer</td>
<td>Chronic inflammation</td>
<td>Peritoneal carcinomatosis</td>
</tr>
<tr>
<td>34</td>
<td>Unknown</td>
<td>Chronic inflammation</td>
<td>Peritoneal carcinomatosis</td>
</tr>
<tr>
<td>35–36</td>
<td>None</td>
<td>Chronic inflammation</td>
<td>Tuberculous peritonitis</td>
</tr>
</tbody>
</table>

US = ultrasound

Table 2. The Sensitivity, Specificity, PPV, NPV, and Accuracy of Diagnosing Malignant Peritoneal Disease

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>US-guided biopsy (%)</td>
<td>83.3</td>
<td>100</td>
<td>100</td>
<td>85.7</td>
<td>86.1</td>
</tr>
</tbody>
</table>

NPV = negative predictive value; PPV = positive predictive value; US = ultrasound
which is suggestive of peritoneal carcinomatosis. The third patient’s 18F-FDG PET/CT 6 days after US-guided biopsy showed no definite hypermetabolic lesion in the peritoneum. This patient was clinically diagnosed as tuberculous peritonitis. Because, the patient's serum-ascites albumin gradient was 1.0 with high adenosine deaminase (48 IU/L) and the peritoneal thickening was resolved after anti-tuberculosis medication. Last patient had no 18F-FDG PET/CT and clinically diagnosed as tuberculous peritonitis because this patient's peritoneal thickening and ascites were resolved after anti-tuberculosis medication.

There were no serious procedure-related complications in all of the patients. Among the 28 patients who had ascites around the biopsy route, brisk bleeding was observed as moving echogenic dots emerged from the site of biopsy on US in 7 patients (Fig. 3). All of these bleedings were stopped within 5 minutes without specific management. Post-biopsy blood Hb levels were only slightly decreased by an average of 0.8 g/dL (range, 0.1–2.2 g/dL) compared with pre-biopsy blood Hb levels; 0.8 g/dL (range, 0.1–1.8 g/dL) in the group with ascites around the biopsy route, 0.9 g/dL (range, 0.1–2.2 g/dL) in the group without ascites around the biopsy route. Post-biopsy Hct levels were also only minimally decreased by an average of 2.1% (range, 0.4–6.4%) compared with pre-biopsy Hct levels; 1.9% (range, 0.4–6.0%) in the group with ascites around the biopsy route, 2.3% (range, 0.4–6.4%) in the group without ascites around the biopsy route. There were no statistical differences between two groups in post-biopsy Hct or Hb changes.

**DISCUSSION**

Peritoneum can be involved by variety of disease processes. Among them, metastatic carcinoma from gastrointestinal, and genitourinary organs, or from unknown primary sites are the most common (2). Peritoneal seeding of a malignant disease usually indicates an advanced disease and poor prognosis. Another important disease process involving peritoneum is tuberculous peritonitis especially in endemic areas of tuberculosis. Tuberculous peritonitis is occurring less than 4% of patients with pulmonary tuberculosis (25). However, pulmonary tuberculosis is still a major cause of morbidity and mortality, particularly in developing countries in the endemic areas (26). In western countries, about 80% of cases are occurring in association with acquired immunodeficiency syndrome (AIDS) but it is still occasionally encountered in non-AIDS patients (27).

Early and accurate diagnosis of the peritoneal disease is clinically important. In cases of metastatic cancer, specific histopathological diagnosis is required for selection of chemotherapeutic agents. Furthermore, tuberculous peritonitis is one of the few diffuse peritoneal diseases with a proper and effective therapy. The differentiation between peritoneal carcinomatosis and chronic inflammation particularly tuberculous peritonitis is sometimes very difficult by imaging findings alone. Peritoneal biopsy may be the only diagnostic option, especially if the peritoneal disease is the only finding and the primary tumor is not defined (cancer of unknown primary).

There are a few methods of obtaining peritoneal tissues such
as open surgery, laparoscopy and image guided biopsy. Nowadays laparoscopic peritoneal biopsy is being considered the gold standard test for the pathologic diagnosis of the peritoneal disease. The diagnostic yield of laparoscopic peritoneal biopsy has shown a relatively high rate and less invasive than open biopsy (13-15). However, this procedure poses a risk to the patients by various manipulations including induction of pneumoperitoneum, insertion of trocar, using thermal and mechanical instruments (17, 18). Therefore US-guided peritoneal biopsy can be an attractive alternative method.

There are several studies on the diagnostic usefulness of US-guided peritoneal biopsy (19-23). But there have been no report of US-guided biopsy of solitary thickened peritoneum visualized as infiltrated fat without apparent mass formation on abdominal CT. Our results showed slightly lower diagnostic accuracy than those of previous studies (20-22). We believe that this discrepancy could be attributed to the difference of included patients’ peritoneal lesions. While previous studies included patients with completely replaced peritoneal fat tissue by pathology involving peritoneum as well as patients with thickened peritoneum with only infiltrated fat. In our study, only patients with peritoneal thickening visualized as infiltrated fat on CT scans were included and patients with apparent peritoneal mass formation such as ‘omental cake’ or lymph nodal mass or other apparent mass formation in other organs were excluded.

The peritoneal thickening, which is seen as infiltrated fat on CT, might be less fixed and more fragile than apparent mass. Especially, if the thickness of peritoneum is minimal, it is hard to get sufficient tissue for histopathological diagnosis by US-guided biopsy. We tried to modify US-guided technique to obtain sufficient tissue sample and minimize possible complications. First, when the thickness of the targeted peritoneum was minimal, biopsy pathway was adjusted more horizontally toward targeted peritoneum in order to get as much as tissue possible. Second, we used free hand technique without using guiding device. With this method entire needle pathway could be more easily visualized on ultrasonography during the procedure. And it also made possible to avoid adjacent bowels loop so as to prevent inadvertent intestinal transit or biopsy of the bowel wall. Third, we used color Doppler examination routinely to monitor bleeding after biopsy, as well as to view pre-biopsy assessment of a safe pathway.

Despite these efforts, there were 5/36 (13.9%) patients with nonspecific histopathological diagnosis; chronic inflammation in 4/5 (80%) and mesothelial hyperplasia in 1/5 (20%). Furthermore, three of five patients were finally diagnosed as peritoneal carcinomatosis. This histopathological misdiagnosis of peritoneal carcinomatosis as chronic inflammation can be explained by strong association with cancer and inflammation (28). In peritoneal carcinomatosis, implantation of cancer cells causes inflammatory reactions. A prominent inflammatory reaction before the formation of apparent mass in the early stage of peritoneal carcinomatosis may be a factor in lowering the diagnostic accuracy of US-guided peritoneal biopsy. The reason why peritoneal carcinomatosis is misdiagnosed as mesothelial hyperplasia is as follows. When cancer cells metastasize to the lymphatic vessels, the lymphatic channels are obstructed and then ascites can occur. In this situation, mesothelial cells can be proliferated to absorb the ascites (29). Only tissues with proliferated mesothelial cells were obtained instead of cancer cells in this patient.

The major complications of percutaneous abdominal biopsy reported previously include bleeding, infection, bowel perforation, and seeding of the needle tract with tumor cells (30). A case of arteriovenous fistula in the greater omentum was reported after inadvertent passage of biopsy needle during liver biopsy (31). However, complications directly associated with peritoneal biopsy has not been reported (32).

With aforementioned modification of biopsy technique, no clinically significant complications were observed in all of our patients. In 28 patients who had ascites around the targeted peritoneum, active bleeding was depicted on the gray scale US immediately after withdrawal of biopsy needle in 7 patients. However, bleeding stopped spontaneously without specific management. No significant bleeding occurred in all patients. The mean decrease in Hb and Hct values was minimal and there was no difference between patients with ascites around the biopsy route and the patients without ascites. Though the number of our patients is small we assume that the presence of ascites without coagulopathy does not increase post-biopsy bleeding. Furthermore, we think ascites around the targeted peritoneum can be helpful to avoid bowel loops.

There are some limitations recognized in our study. First, this study is a retrospective study of long duration. Therefore, tech-
The Usefulness of Peritoneal Biopsy

Technical variability (used biopsy gun, US machine) and experience of the radiologist or pathologist could cause influence on the results. Second, all the standard reference was not histopathological examination by open or laparoscopic biopsy. Further large prospective studies, with histopathological examination as reference standard, needed to confirm our results and determine whether they can be applied to patients with incidentally discovered peritoneal thickening.

In conclusion, US-guided peritoneal biopsy is safe and fairly accurate diagnostic method even for minimally thickened peritoneum depicted as infiltrated peritoneal fat on CT image. It has a high PPV for the diagnosis of malignant peritoneal disease. It can be used as an initial biopsy method for the differential diagnosis of only minimally thickened peritoneum of unknown cause before performing laparoscopic or open surgical biopsy.

REFERENCES

CT 스캔에서 지방침윤만 보이는 원인 불명의 비후된 복막에 대한 초음파 유도하의 복막조직 생검의 진단적 유용성

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목적: CT 스캔에서, 복막에 지방 침윤만 보이는 원인 불명의 비후된 복막에 대한 초음파 유도하의 복막조직 생검의 진단적 유용성에 대해 알아보고자 하였다.

대상과 방법: CT 스캔에서 분명한 종괴 형성이 없이 복막에 단지 지방 침윤만 보이는 원인 불명의 비후된 복막이 있으며 초음파 유도하 복막조직 생검을 받은 36명의 환자(남성 16명, 여성 20명, 평균 연령 51.7세)를 대상으로 후향적으로 연구를 하였다. 병리조직학적으로 특이진단이 가능한지 알아보았으며, 악성 질환의 진단에 있어서의 정확도를 조사하였다.

결과: 병리조직 검사가 가능한 조직 채취는 모든 환자에서 가능하였다. 특이적 병리조직 진단은 36명 중 31명(86.1%)에서 가능하였다: 31명 중 15명(48.4%)은 복막암증, 31명 중 15명(48.4%)은 결핵성 복막염, 31명 중 1명(3.2%)은 지방층염이었다. 36명 중 5명(13.9%)에서는 비특이적 병리조직 진단만 가능하였다: 5명 중 4명(80%)은 만성 염증, 5명 중 1명(20%)은 중피세포 증식증이었다. 악성질환 진단에 있어서 민감도 83.3%, 특이도 100%, 양성예측치 100%, 음성예측치 85.7%, 그리고 정확도 86.1%를 보였다.

결론: 초음파 유도하의 복막조직 생검은 복막에 지방 침윤으로만 보이는 원인 불명의 경한 복막 비후에 대해서도 비교적 정확한 진단 방법으로 생각되어 복강경 또는 수술적 조직생검에 앞서 우선적으로 시도될 수 있을 것으로 생각된다.

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