

# The Disappearance of Lymph Node Metastasis from Neuroendocrine Carcinoma after Endoscopic Ultrasound-guided Fine Needle Aspiration

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## Abstract

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A 75-year-old Japanese man was referred to our hospital to undergo the examination of an enlarged peripancreatic lymph node. Computed tomography (CT) showed a lymph node 47 mm in size that was located above the pancreas head and beneath the liver. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) of the enlarged lymph node was performed, and an immunohistological examination of the sample confirmed a histological diagnosis of neuroendocrine carcinoma (NEC). The patient refused treatment with chemotherapy and instead chose to undergo observation. However, the lymph node the previously enlarged lymph node was not visible on CT at 12 months after the examination.

**Key words:** spontaneous regression, neuroendocrine carcinoma, endoscopic ultrasound-guided fine needle aspiration

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## Introduction

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The spontaneous regression of malignant tumors is defined as the partial or complete disappearance of a malignant tumor without therapy. This definition suggests that spontaneous regression applies to cases in which cancer is not always cured permanently (1). Iwanaga estimated that spontaneous regression occurred in approximately 1 in 120,000 cancer cases per year in Japan in 2011 (2). In addition, his report showed that the spontaneous regression of gastric cancer, which accounts for 8% of cases of spontaneous regression, is very rare and that regression of aggressive gastric cancers such as neuroendocrine carcinoma (NEC) is especially unlikely. We herein report a case in which a lymph node metastasis of NEC disappeared after endoscopic ultrasound-guided fine needle aspiration (EUS-FNA).

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## Case Report

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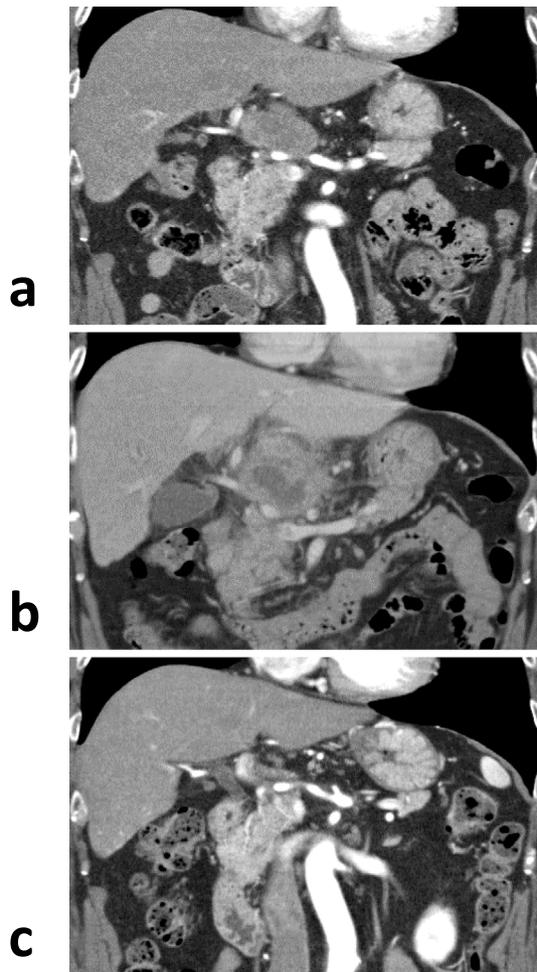
A 75-year-old Japanese man was referred to our hospital to undergo an examination of an enlarged peripancreatic lymph node, which had been incidentally detected on abdominal ultrasonography that was performed to investigate pollakiuria. He had been relatively healthy with a past medical history of colon polyps. His family history was unremarkable. The patient was asymptomatic when he visited our hospital. His physical examination and laboratory data including tumor marker levels (carcinoembryonic antigen, carbohydrate antigen 19-9) showed no abnormalities. Computed tomography (CT) showed a lymph node of 47 mm in size that was located above the pancreas head and beneath the liver (Fig. 1a, 2a). This lymph node was located beneath the gastric antrum and not in contact with the stomach. Upper gastrointestinal endoscopy showed a submucosal tumor with ulceration at the gastric antrum (Fig. 3). An immunohistological examination of the gastric biopsy specimens re-

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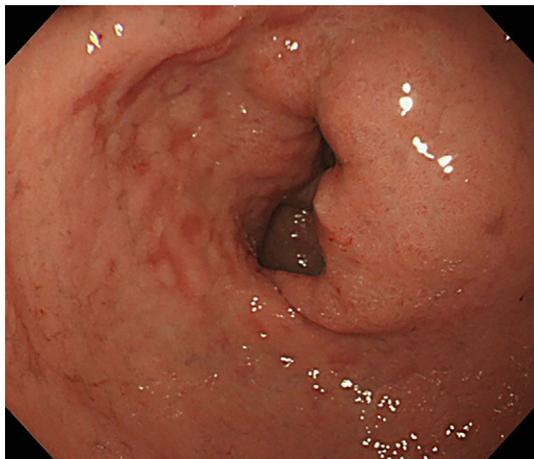
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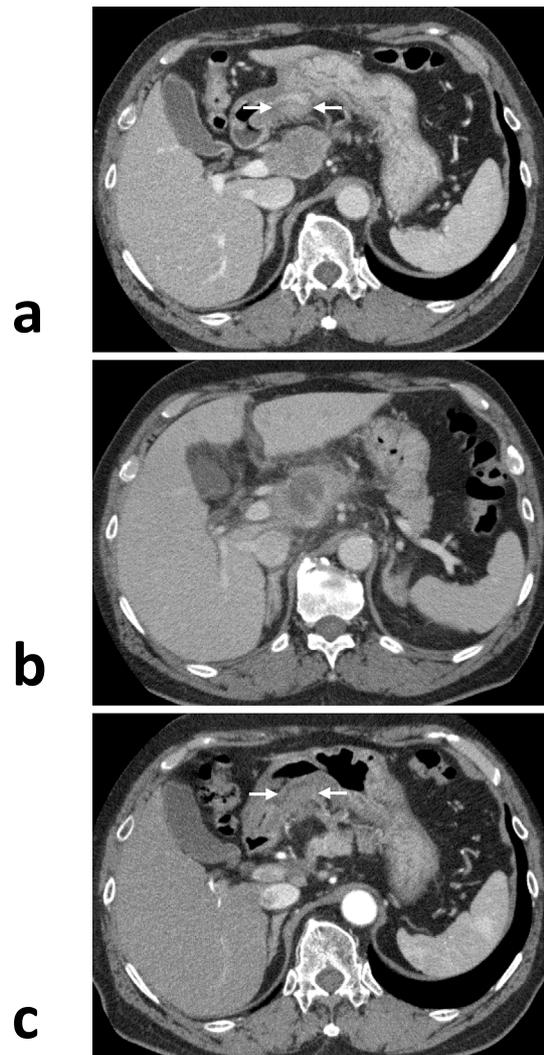
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**Figure 1.** Coronal dynamic computed tomography images showing the sequential changes before and after endoscopic ultrasound-guided fine needle aspiration (EUS-FNA). An enlarged lymph node is seen beneath the caudate lobe of the liver before EUS-FNA (a). The lymph node developed a central necrotic area at 10 days after EUS-FNA (b), and was not detectable at 12 months after EUS-FNA (c).



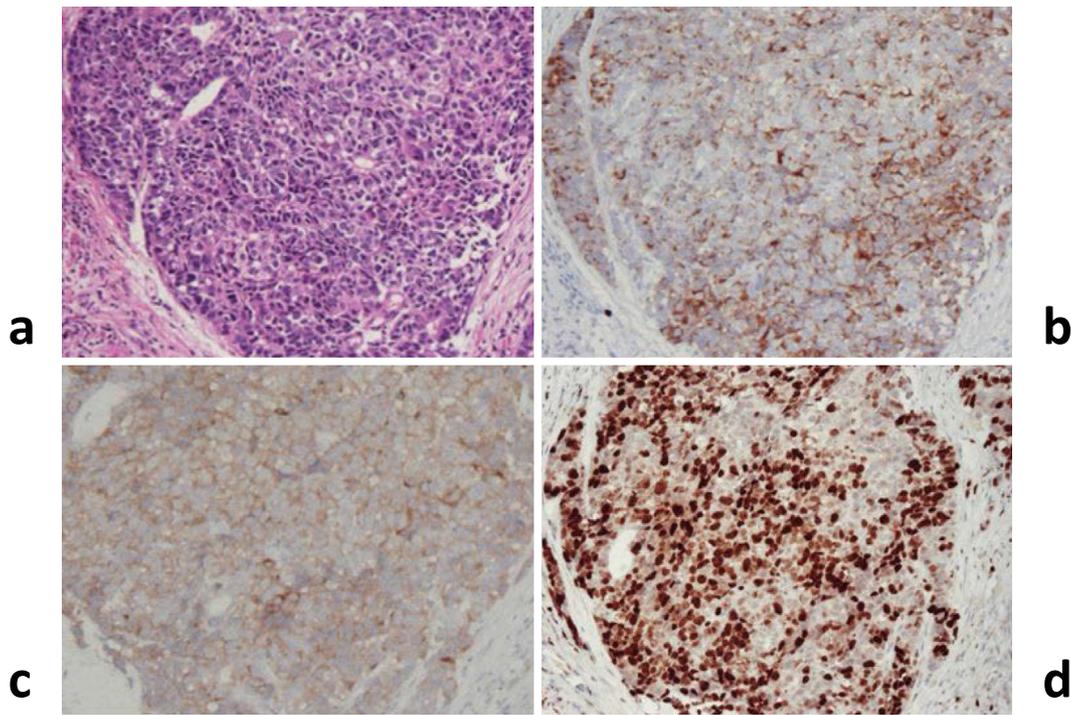
**Figure 3.** The endoscopy view of the submucosal tumor at the gastric antrum.



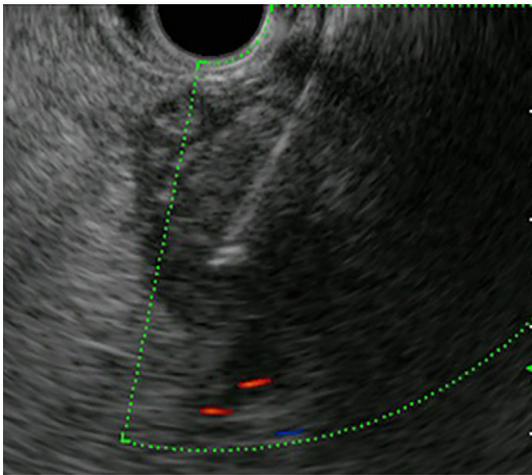
**Figure 2.** Horizontal dynamic computed tomography images showing the sequential changes before and after endoscopic ultrasound-guided fine needle aspiration (EUS-FNA). An enlarged lymph node is seen beneath the gastric antrum before EUS-FNA (a). The lymph node developed a central necrotic area at 10 days after EUS-FNA (b), and was not detectable at 12 months after EUS-FNA (c). Furthermore, the gastric tumor (white arrows) had become slightly larger in size over the 12-months period (a, c).

vealed a diagnosis of NEC that was positive for chromogranin-A and synaptophysin, with a Ki-67 index of more than 80% (Fig. 4). EUS-FNA of the enlarged lymph node was performed (Fig. 5). The examination of the sample obtained from the lymph node confirmed the immunohistological diagnosis of NEC (Fig. 6). Treatment with chemotherapy was discussed with the patient, but he rejected this opinion and instead chose observation.

A week after the EUS-FNA procedure, the patient experienced a high fever (temperature of 40°C) and was readmitted. A laboratory analysis revealed that his white blood cell count and C-reactive protein level were abnormally elevated. Two positive blood cultures revealed infection with *Streptococcus constellatus*. CT demonstrated a peripherally en-



**Figure 4.** Histological sections of the gastric biopsy specimen ( $\times 100$ ). A stained section (Hematoxylin and Eosin staining) showing the histological characteristics of neuroendocrine carcinoma, grade 3 (a). The specimens were diffusely positive for chromogranin-A (b), synaptophysin (c), and Ki-67 (d).



**Figure 5.** EUS-FNA of the enlarged lymph node was performed.

hanced low density mass at the location of the enlarged peripancreatic lymph node (Fig. 1b, 2b). We suspected that he had bacteremia and an abscess due to EUS-FNA, and treatment with tazobactam/piperacillin (4.5 g q6h) was started and continued for 16 days. He recovered after 3 weeks. At his request, no further treatment was initiated and a repeat CT was performed 6 months later. Surprisingly, the lymph node that had been subjected to EUS-FNA had disappeared. The lymph node remained undetectable at a follow-up CT examination that was performed at 12 months after EUS-FNA (Fig. 1c, 2c).

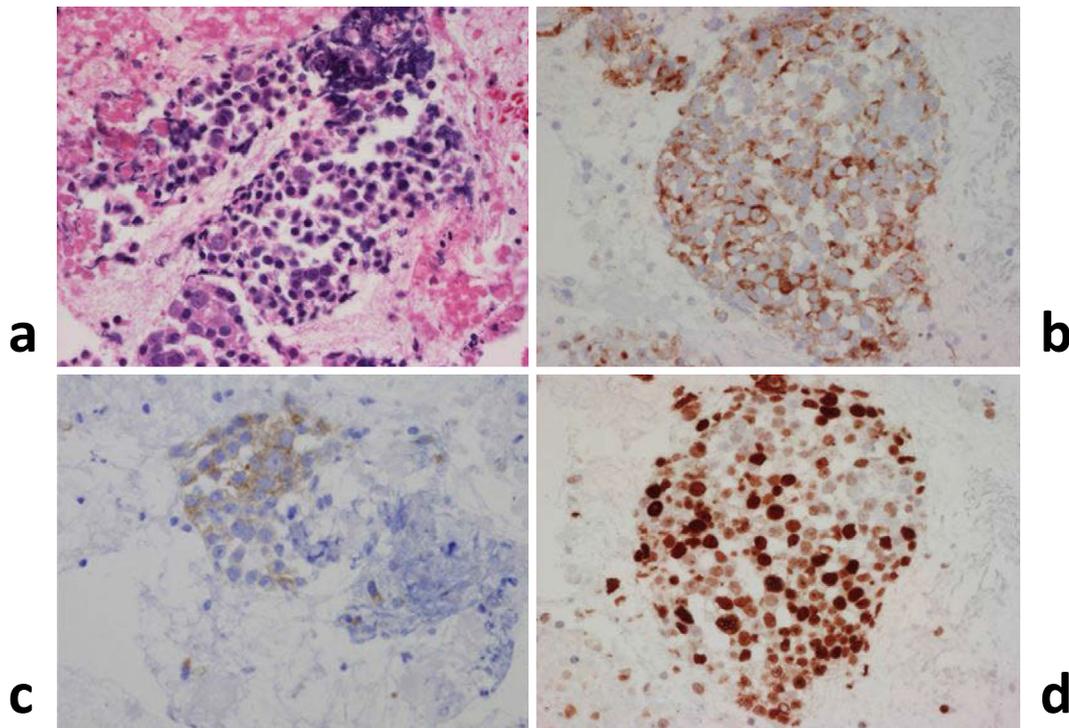
However, 18 months after EUS-FNA, the patient pre-

sented with general malaise. The lymph node remained undetectable, but CT showed multiple liver tumors and that gastric tumor had increased (from 50 mm on the first CT to 60 mm) (Fig. 2a and c). The patient refused to undergo follow-up upper gastrointestinal endoscopy; consequently, we did not evaluate the gastric tumor. We diagnosed the hepatic lesions as metastatic tumors from the gastric NEC. The patient was managed according to the best supportive care policy and gradually worsened. He died of multiple organ failure 19 months after undergoing the EUS-FNA procedure.

## Discussion

Bacteremia is a rare complication after diagnostic endoscopy. Several early studies showed an incidence rate of approximately 0-8% (3). EUS-FNA is a relatively safe method for diagnosing and evaluating gastrointestinal and non-gastrointestinal malignancies. Prophylactic antibiotics are therefore not recommended for the FNA of solid masses and lymph nodes (4). *Streptococcus constellatus*, which was detected in our case, is a member of the *Streptococcus milleri* group. These organisms reside as part of the normal flora in the human oral cavity and the gastrointestinal tract and have the ability to cause systemic infection.  $\beta$ -lactam agents remain the treatment of choice for *Streptococcus milleri* infections (5); thus, treatment with tazobactam/piperacillin was effective in our case.

We could not confirm the disappearance of metastatic lymph node after EUS-FNA. The patient died because of the progression of the primary gastric cancer; however, we con-



**Figure 6.** Histological sections of the tissue obtained by EUS-FNA ( $\times 100$ ). Stained section (Hematoxylin and Eosin staining) showing the histological characteristics of neuroendocrine carcinoma, grade 3 (a). The specimens were diffusely positive for chromogranin-A (b), synaptophysin (c), and Ki-67 (d).

sidered that the metastatic lymph node might have become undetectable after EUS-FNA due to “spontaneous regression.” To date, according to a key word survey of the PubMed database, several studies have reported disappearance of metastatic lymph nodes in cancer patients after FNA or biopsy procedures (6, 7). In addition, the infiltration of inflammatory cells was found at the site of tumor regression. Some reports have described the accumulation of T cells and natural killer (NK) cells in the histological specimens of regressed tumors (7, 8). Taking into account the above points, we considered that the immunological responses might have promoted the disappearance of the metastatic lymph node in our case. We hypothesize that the EUS guided-fine needle injection of drugs promoting T cells and NK cells activities may be effective in the treatment of malignant tumors. Chang et al. have already reported the first attempt of fine needle injection under EUS guidance in patients with advanced pancreatic cancer (9). Various anti-tumor agents may be considered for immunological therapy. Certain types of cancer advance by down-regulating T cell activation and evade the immune system by expressing immunosuppressive programmed death 1 (PD-1) ligands (10). Several studies have shown that the anti-PD-1 antibody is a key immune checkpoint drug. The anti-PD-1 antibody plays a key role in tumor therapy (11); hence, it may play a critical role in EUS guided-fine needle injection for tumor immunotherapy.

In conclusion, although definite evidence is lacking, immune modulation caused by the EUS-FNA procedure might

have contributed to local tumor regression. We considered that EUS-FNA and the ensuing bacterial infection stimulated an immunological phenomenon and caused the death of the cancer cells in the lymph node. Although further experiments are needed to confirm this hypothesis, the fine needle injection of immune-promoting drugs may be a useful as a tumor reduction therapy in the future.

**The authors state that they have no Conflict of Interest (COI).**

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