Two Cases of Intravascular Lymphoma Diagnosed by Gastrointestinal Endoscopic Biopsy

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Abstract

Two cases of intravascular lymphoma (IVL) were diagnosed by endoscopic biopsy. Both patients were admitted to our hospital with a fever of an unknown origin. An elevated serum level of soluble interleukin-2 receptor antibody suggested IVL. An upper gastrointestinal endoscopy was performed. A biopsy of both the reddened and normal gastroduodenal mucosa (Case 1) and a biopsy of a gastric antral ulcer, multiple polyplloid lesions resembling submucosal tumors in the duodenum, and the patient’s normal mucosa (Case 2) revealed vascular infiltration by CD20-positive atypical lymphocytes, confirming the diagnosis of IVL. The performance of a gastrointestinal biopsy for suspected IVL is important, even if there are no visible endoscopic abnormalities.

Key words: intravascular lymphoma, gastrointestinal endoscopic biopsy

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Introduction

The World Health Organization (WHO) classification defines intravascular lymphoma (IVL) as an extranodal diffuse large B cell lymphoma with tumor cells infiltrating the blood vessels (1). Tumor cells are rarely found in the peripheral blood, and the diagnosis of IVL is difficult due to the absence of superficial lymphadenopathy. In fact, IVL is usually identified at autopsy (2). In recent years, however, an increasing number of living patients are diagnosed (3). While the definitive diagnosis of IVL has been achieved by bone marrow biopsy and random skin biopsy (4, 5), there are no previous reports of diagnosis by endoscopic biopsy.

Case Reports

Case 1

A 64-year-old man was referred to our hospital with a fever of unknown origin and the elevation of the biliary enzymes. Abdominal ultrasonography and computed tomography (CT) did not show any specific findings. His fever did not respond to the administration of intravenous antibiotics, but his fever subsided (but later recurred) when oral prednisolone (20 mg/day) was administered for suspected autoimmune disease. On admission, the patient exhibited pancytopenia, the elevation of serum soluble interleukin-2 receptor (sIL2R) antibody to 5,006 U/L (normal: 135-483), and the elevation of biliary enzymes. There was no evident lymphadenopathy and no abnormal accumulation of 18F-fluorodeoxyglucose on positron emission tomography (PET)/CT, but abdominal CT revealed splenomegaly. IVL was sus-
obvious lymphadenopathy. Liver and bone marrow biopsies of the patient’s interleukin 2 receptor (IL2R) level without expected due to the fever of unknown origin and the elevation of the patient’s interleukin 2 receptor (IL2R) level without obvious lymphadenopathy. Liver and bone marrow biopsies were therefore performed simultaneously because of the importance of a rapid diagnosis due to the poor prognosis. In the liver biopsy specimen, there was considerable variation in the cells of the sinusoids (Fig. 1A), revealing the effect of prednisolone. Asian variant IVL (6) was considered possible, due to the presence of CD20-positive large B lymphocytes and the observation of hemophagocytosis in both the liver (Fig. 1) and the bone marrow biopsy specimens (Fig. 2). Upper gastrointestinal endoscopy was performed to investigate the patient’s anemia. We obtained 6 random biopsy specimens, including 1 specimen of the patient’s apparently normal duodenal mucosa (Fig. 3A), 1 specimen of reddened duodenal mucosa (Fig. 3A), 2 specimens of reddened gastric mucosa (Fig. 3B), 1 specimen of apparently normal gastric mucosa (Fig. 3B), and 1 specimen of reddened anastomotic mucosa (Fig. 3B).

All 6 of the biopsy specimens revealed vascular infiltration by CD20-positive atypical lymphocytes (Fig. 3C, D), confirming the diagnosis of IVL. JH rearrangement was not investigated because IVL was diagnosed by pathological examination. Chemotherapy was initiated with cyclophosphamide, doxorubicin, vincristine, and prednisolone. Rituximab was added from the second course and remission was achieved after 8 courses. However, the disease recurred and the patient died 40 months after the initial diagnosis.

Figure 1. The liver-biopsy findings in Case 1. A: An Hematoxylin and Eosin (H&E) staining liver biopsy specimen displaying various cells in the sinusoids. Large B lymphocytes and hemophagocytosis are observed, but there is no proliferation of atypical lymphocytes in the vessels. Magnification: ×20. B: The immunostaining of a liver biopsy specimen shows CD20-positive lymphocytes. No proliferation of atypical lymphocytes in the vessels is observed. Magnification: ×20.

Figure 2. The bone marrow biopsy findings in Case 1. A: An H&E staining bone marrow biopsy specimen shows large B lymphocytes and hemophagocytosis, but there is no proliferation of atypical lymphocytes in the vessels. Magnification: ×20. B: The immunostaining of a bone marrow biopsy specimen shows CD20-positive lymphocytes. No proliferation of atypical lymphocytes in the vessels is observed. Magnification: ×20.
Case 2

A 64-year-old woman was admitted with a fever of 2-3 weeks in duration and a weight loss of 15 kg over 2 months. Her serum level of sIL2R antibody was found to be elevated to 1,950 U/L on admission. There was no detectable lymphadenopathy, no abnormal accumulation on PET/CT, and no lymphadenopathy or splenomegaly on abdominal CT. Malignant lymphoma was suspected because the patient had a fever of unknown origin and an increase of the blood vessels, confirming the diagnosis of IVL. JH rearrangement was not investigated in case 2 because IVL was diagnosed by the pathologic findings. We performed 6 courses of chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone. The patient is currently alive at 12 months after the initiation of chemotherapy.

Discussion

IVL was first described as “angioendotheliomatosis proliferans systemisata” by Pfleger and Tappeiner in 1959 (7). In the 1980s, it was recognized to be a malignant tumor of the vascular endothelial cells and was called “angiotropic lymphoma.” This disease was subsequently reclassified as “IVL” by Wick et al. (8, 9). IVL is an independent disease entity in the WHO classification and its clinical features have been clarified (1, 6, 10, 11). In Japan, Asian variant IVL (6) accounts for 60% of cases. The features of Asian variant IVL are anemia, thrombocytopenia, hepatomegaly/splenomegaly on CT or ultrasonography, and the absence of lymphadenopathy or hemophagocytosis. Patients can present with gen-
**Figure 4.** The endoscopic findings in Case 2. A: Endoscopy demonstrates polypoid lesions resembling submucosal tumors in the second part of the duodenum. Biopsy specimens were obtained from a polypoid lesion (white arrow) and from the normal mucosa (black arrow). B: Endoscopy demonstrates polypoid lesions resembling submucosal tumors in the duodenal bulb. Biopsy specimens were obtained from a lesion (white arrows) and from the normal mucosa (black arrow). C: Endoscopy reveals polypoid lesions resembling submucosal tumors in the gastric antrum. Biopsy specimens were obtained from a lesion (white arrows). D: Endoscopy reveals an ulcer in the posterior gastric antrum. Biopsy specimens were obtained from the ulcer border (white arrow). E: Endoscopy shows the normal mucosa in the gastric body; a biopsy specimen was obtained at the indicated site (black arrow). F: Endoscopy demonstrates Candida esophagitis in the lower esophagus. Biopsy specimens were obtained from a Candida esophagitis lesion (white arrow) and the normal mucosa (black arrow).

**Figure 5.** Findings in Case 2. A: H&E staining biopsy specimen shows the invasion of atypical lymphocytes into the capillaries. Ulcer border; Magnification: ×20. B: The immunostaining of a biopsy specimen displays capillary invasion by CD-20 positive atypical lymphocytes. Ulcer border; Magnification: ×20.
eral symptoms (fever of unknown origin and fatigue), skin symptoms (eruptions and erythema), and/or neurological symptoms (disturbance of consciousness). The clinical course is varied, but the disease is highly malignant and the prognosis is poor. Laboratory tests reveal the elevation of sIL2R in over 80% of IVL patients. A definitive diagnosis of IVL is usually made by bone marrow biopsy or random skin biopsy (4, 5), but both procedures are painful and cause scarring. In contrast, we found that an endoscopic biopsy was useful for the definitive diagnosis of IVL in our two patients. A search of PubMed from 1949 to 2014 using the terms “intravascular lymphoma” and “gastrointestinal endoscopic biopsy” suggested that this is the first report on the diagnosis of IVL by gastrointestinal endoscopic biopsy. IVL involving the intestine has not been reported thus far. We speculate that there have been no previous reports of gastric IVL because endoscopic biopsy of the apparently normal gastric mucosa has not been previously performed in IVL patients. We do not know whether IVL is always associated with gastric lesions, because there have been no previous reports of such lesions in IVL patients. We detected gastric lesions in Case 1 by performing endoscopic biopsies from sites that were thought to be normal. It seems important to perform biopsies when IVL is suspected, even if there are no visible endoscopic abnormalities. On endoscopic examination, the gastric lesions in IVL patients may be seen as an ulcer or as a submucosal tumor as in Case 2 [similar to the findings in conventional gastric lymphoma (12)] or the mucosa may range from normal to reddened as was observed in Case 1. All 6 biopsy specimens obtained from the duodenum and stomach in Case 1 and 11 of the 12 specimens obtained from the duodenum, stomach, and esophagus in Case 2 yielded a diagnosis of IVL. These findings suggest that it is possible to diagnose IVL by random upper gastrointestinal biopsy - something that is already known to be possible for skin biopsy - although more patients will need to be investigated. The chief pathologic feature of IVL is tumor cells infiltrating the blood vessels. This is distinct from the invasion of skin lesions and from the other types of gastric lymphoma. There have been some reports (13, 14) indicating that the analysis of immunoglobulin gene rearrangement is useful in the diagnosis of lymphoma. However, our cases were diagnosed by the pathologic examination of endoscopic biopsy specimens and thus we did not analyze immunoglobulin gene rearrangement.

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