Gastrosplenic fistula occurring in lymphoma patients:
Systematic review with a new case of extranodal NK/T-cell lymphoma

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Abstract

AIM
To provide the overall spectrum of gastrosplenic fistula (GSF) occurring in lymphomas through a systematic review including a patient at our hospital.

METHODS
A comprehensive literature search was performed in the MEDLINE database to identify studies of GSF occurring in lymphomas. A computerized search of our institutional database was also performed. In all cases, we analyzed the clinicopathologic/radiologic features, treatment and outcome of GSF occurring in lymphomas.

RESULTS
A literature search identified 25 relevant studies with 26 patients. Our institutional data search added 1 patient. Systematic review of the total 27 cases revealed that GSF occurred mainly in diffuse, large B-cell lymphoma (n = 23), but also in diffuse, histiocytic lymphoma (n = 1), Hodgkin’s lymphoma (n = 2), and NK/T-cell lymphoma (n = 1, our patient). The common clinical presentations are constitutional symptoms (n = 20) and abdominal pain (n = 17), although acute gastrointestinal bleeding (n = 6) and infection symptoms due to splenic abscess (n = 3) are also noted. In all patients, computed tomography scanning was very helpful for diagnosing GSF and for evaluating the lymphoma extent. GSF could occur either post-chemotherapy (n = 10) or spontaneously (n = 17). Surgical resection has been
INTRODUCTION

Gastrosplenic fistula (GSF) is a rare and potentially fatal complication of various diseases, including lymphoma, gastric adenocarcinoma, Crohn’s disease, splenic abscess, and trauma[1]. Lymphoma is the most common cause of GSF. Of these diseases, the majority have occurred in patients with diffuse, large B-cell lymphoma (DLBCL), and there has been no patient with NK/T-cell lymphoma. In our hospital, a tertiary cancer center, we recently encountered a patient with GSF developed in NK/T-cell lymphoma.

A multidisciplinary team was organized in our hospital for management of this patient. Our team performed an extensive literature search, however, and determined that the characteristics of GSF occurring in lymphoma patients have not been thoroughly investigated due to its extreme rarity. In contrast, the number of case reports regarding these patients has increased over the last 10 years[1-24].

Despite the increasing number of these patients, there has been no systematic review to summarize the variable presentations of GSF occurring in lymphomas. Therefore, we performed the current, systematic review with the addition of our single patient in order to provide a perspective regarding this rare disease entity.

MATERIALS AND METHODS

Systematic literature search

A computerized search of the MEDLINE database was conducted to find relevant studies published prior to February 10, 2017. Studies were eligible for inclusion if they described the clinicopathologic features, imaging findings, treatment and outcome of the cases with regard to GSF occurring in lymphoma. The following search terms were used: “GSF” and “lymphoma”. To expand the search, the bibliographies of articles that remained after the selection process were screened for other potentially suitable articles. We did not limit the language of the articles.

Institutional data search and case presentation

Our institutional review board approved the search of the electronic medical records for this study. Informed consent was waived from our institutional review board. We performed a systematic computerized search of our institutional database from January 2000 to January 2017 using the diagnostic codes of “GSF”, “splenic fistula”, and “lymphoma”. Using these search terms, we identified only one case which we recently encountered, as described below. In our institutional database, the patient’s record was anonymized and provided to us. We present here the clinical course, pathologic findings, and imaging features of this case. We also included this case in the systematic review of GSF of lymphoma.

Analysis of clinicopathologic and radiologic features

For patients with GSF occurring in lymphoma identified in the literature and at our institution, we analyzed their clinicopathologic features, imaging findings, treatment and outcome.

RESULTS

Literature selection

Our study selection process is shown in Figure 1. The literature search in the MEDLINE database generated 24, initial candidate articles. After reviewing the titles and the abstracts, all 23 articles were included. One study was subsequently excluded due to the lack of a full-text manuscript. Therefore, we reviewed the full text of all 23 articles, including 2 written in Spanish and 1 written in Korean. Search of the bibliographies of these articles found two, additional, eligible studies[8,14]. Therefore, a total of 25 articles were included in our
systematic review. Of these articles, 24 described one case, while 1 described two cases. Therefore, a total of 27 cases were retrieved from the systematic literature search.

Presentation of our case

A 50-year-old man was admitted to our hospital for a biopsy-proven NK/T-cell lymphoma of the right anterior nasal cavity. On contrast-enhanced computed tomography (CT), there was an ill-defined, homogeneous, enhancing, soft-tissue mass in the right anterior nasal cavity. There was no significantly enlarged lymph node in his neck, chest or abdomen-pelvis. However, hepatosplenomegaly was noted with numerous, ill-defined, low, attenuating nodules in the liver. His spleen measured 15.5 cm in the longest dimension. Hypermetabolic enlargement of the liver and spleen was revealed on positron emission tomography scanning. These findings were indicative of lymphoma involvement in the liver and spleen.

The patient was subsequently started on the combination of a SMILE chemotherapy regime consisting of methotrexate, leucovorin, ifosfamide, etoposide, and L-asparaginase followed by autologous stem-cell transplantation (ASCT). After completing the ASCT, complete remission was confirmed by a bone marrow biopsy and CT scans with resolution of the nasal cavity mass, hepatosplenomegaly, and focal liver lesions.

Two months later, follow-up CT showed a huge splenomegaly measuring 17.5 cm in its longest diameter, which was indicative of lymphoma recurrence (Figure 2). Chemotherapy was started for the lymphoma recurrence. Tumor lysis syndrome occurred, and the patient underwent dialysis treatment.

He then soon experienced left, upper quadrant, abdominal pain and nausea/vomiting. Follow-up abdominal CT showed a diffusely enlarged spleen with nearly total splenic infarction. A huge fistula track was also seen between the gastric lumen and the infarcted spleen (Figure 3).

He underwent emergency surgery for gastric wedge resection and splenectomy. During the surgery, a large GSF was observed and there was adhesion between the infarcted spleen and the stomach. These surgical findings suggested that the extensive lymphoma lysis due to chemotherapy resulted in disruption of the splenic capsule, adhesion to the adjacent gastric fundus, and eventually led to the large GSF. In the gross and microscopic specimen, there was extensive hemorrhagic infarction in the spleen with a large GSF. The atypical lymphoma cells, which were positive for CD3 on immunohistochemistry stain and positive for Epstein-Barr virus (EBV) on EBV RNA stain, were found in the stomach wall near the GSF as well as in the whole spleen (Figure 4). The histopathological diagnosis was NK/T-cell lymphoma and these findings suggest that lymphoma cells may infiltrate from the spleen to the stomach wall through the adhesion/perforation site.
In all 27 cases, the GSF was depicted or suspected on CT scans, as there was a defect in the gastric wall and splenic capsule where the stomach and spleen were closely attached. Of these, 10 cases described the size of the GSF which ranged from 0.25 cm to 6 cm (mean size: 2.87 cm). In 21 cases, endoscopy was performed to confirm the diagnosis of GSF and to evaluate the bleeding or other concomitant disease, such as a gastric ulcer.

The CT scan was excellent for identifying the extent of lymphoma involvement. The splenic involvement was most commonly noted as a moderate to massive splenomegaly ($n = 13$). Five of seven cases specifically noted the gastric lymphoma as a diffuse/segmental, gastric wall thickening or mass. There were five cases with extensive lymphoma masses in the left upper quadrant, including diaphragm involvement.

The CT scan was also very helpful for identifying any associated GSF complications. Indeed, a splenic abscess was diagnosed on CT in three cases. Acute bleeding was seen as leakage of contrast agent in the gastric lumen. Even when there was no leakage of contrast agent seen on CT, the presence of a hematoma in the stomach and/or spleen could suggest a recent hemorrhagic event.

Regarding the treatment, surgical resection was performed in 23 patients (88.9%). Two patients underwent chemotherapy without surgery, and one patient refused any treatment.

Figure 4 Microscopic specimen of the spleen and stomach. A: Atypical lymphoma cells were found in the spleen on hematoxylin-eosin stain (left). These cells showed positivity for CD3 on immunohistochemistry stain (middle) and EBV on EBV RNA stain (right). There was also extensive coagulative necrosis indicative of splenic infarction; B: Lymphoma cells were found in the stomach wall near the gastrospenic fistula on hematoxylin-eosin stain (left), and which also showed positivity for CD3 (middle) and EBV (right). NK/T-cell lymphoma was diagnosed. These findings suggested that lymphoma cells may have infiltrated from the spleen to the stomach wall through the perforation site. EBV: Epstein-Barr virus.
### Table 1 Summary of the 27 cases of gastrospenic fistula occurring in lymphomas

| Ref.          | Diagnosis                   | Sex/age | Size of lymphoma | Disease status | Presentation                              | Diagnostic modality                          | Intervention/therapy                           | Outcome                                      |
|---------------|-----------------------------|---------|------------------|----------------|-------------------------------------------|---------------------------------------------|-----------------------------------------------|----------------------------------------------|
| Bubenik et al (1983) | Diffuse histiocytic lymphoma | Male/58 | Not available     | Post-CTx       | Nonspecific LUQ discomfort                 | CT abdomen followed by endoscopy of upper GI tract | Splenectomy, gastric greater curvature resection, distal pancreatectomy | Uneventful post-operative period; no further details |
| Hiltunen et al (1991) | Gastric DLBCL | Male/36 | Not available     | Post-CTx       | Hematemesis, splenomegaly                 | CT abdomen followed by endoscopy             | Laparotomy without details                    | Followed-up over 3 yr                        |
| Blanchi et al (1995) case 1 | Splenic DLBCL | Male/62 | Not available     | Initial presentation | Left abdominal pain and fever            | Endoscopy of upper GI tract followed by CT abdomen | Resection of spleen, tail of pancreas, and involved stomach | At 6 mo after the operation, the patient was in complete remission after CTx |
| Blanchi et al (1995) case 2 | Splenic DLBCL | Male/45 | Not available     | Initial presentation | Epigastric pain and weight loss         | Endoscopy of upper GI tract followed by CT abdomen | Laparotomy, but no further details.               | No further details                           |
| Carolin et al (1997) | Splenic DLBCL | Male/46 | Not available     | Initial presentation | Epigastric pain, fatigue, weight loss and splenomegaly | Endoscopy of upper GI tract followed by CT abdomen | Spinal artery embolization, near total gastrectomy and splenectomy | Disease-free after three cycles of CTx; no further details |
| Bird et al (2002) | Splenic DLBCL | Male/36 | Not available     | Initial presentation | Hematemesis, melena, fatigue, weight loss and splenomegaly | Endoscopy of upper GI tract followed by CT abdomen | CT abdomen followed by endoscopy of upper GI tract/biopsy, gastric wedge resection, and distal pancreatectomy | Not available |
| Choi et al (2002) | Splenic DLBCL | Male/24 | Not available     | Initial presentation | LUQ pain and constitutional symptoms (splenic mass) | CT abdomen followed by endoscopy of upper GI tract | Splenectomy, gastric wedge resection, and distal pancreatectomy | After surgery, the patient underwent CTx |
| Yang et al (2002) | Gastric and splenic DLBCL | Male/21 | Not available     | Initial presentation | LUQ pain, fatigue, weight loss, fever, and splenomegaly | CT abdomen followed by endoscopy of upper GI tract | Splenectomy, gastric wedge resection, and distal pancreatectomy | Died after 2 mo of CTx |
| Puppala et al (2005) | DLBCL | Female/66 | Not available     | Initial presentation | LUQ pain | CT abdomen oral contrast | CTx | Died after 2 mo of CTx |
| Kerem et al (2006) | DLBCL | Male/57 | 10 cm × 7 cm × 2 cm in the stomach and 8 cm × 5 cm × 4 cm in the spleen | Initial presentation | Abdominal pain, epigastric tenderness and splenomegaly | CT abdomen followed by PET/CT and endoscopy of upper GI tract | Splenectomy, proximal gastrectomy, esophagectomy, proximal pyloroplasty followed by CTx | Uneventful post-op period; underwent chemotherapy. |
| Al-Ashgar et al (2007) | Hodgkin’s lymphoma (nodular sclerosis)-IIIS | Female/16 | Not available     | Initial presentation | LUQ pain, constitutional symptoms and splenomegaly | Endoscopy of upper GI tract, barium swallow, CT abdomen | Laparoscopic surgical repair followed by seven cycles of CTx | Alive and in remission after 1 yr |
| Aribas et al (2008) | DLBCL | Male/25 | Not available     | Post-CTx       | Abdominal pain, weight loss, fever, chill and splenomegaly | CT cystography followed by USG | Gastric wedge resection, fistulectomy and splenectomy | Discharged after a month and died 2 mo later due to progression of lymphoma and infection due to pancreatic and gastric fistulas |
| Palmowski et al (2008) | DLBCL | Male/36 | 15 cm of spleen | After three cycles of CTx | Fever and signs of acute infection (splenic mass) | CT abdomen | Splenectomy with partial gastric resection | Finished six cycles of CTx |
| Selb et al (2009) | Hodgkin’s lymphoma | Male /49 | 3.6-cm splenic mass | Relapsed post-CTx | LUQ pain and constitutional symptoms (splenic mass) | CT abdomen | Partial gastrectomy and fistulectomy | Died after 5 mo |
| Name et al. Year | Gender/Age | Tumor Size | Presentation | Symptoms | Imaging | Surgical Procedure | Additional Details |
|------------------|------------|------------|--------------|----------|---------|------------------|-------------------|
| Moran et al. 2009 | Male/35    | 5.4 cm x 5.3 cm | Initial | LUQ pain and constitutional symptoms | CT abdomen followed by endoscopy of upper GI tract | Abscess drainage; splenectomy, total gastrectomy, Roux-en-Y esophagojejunostomy followed by CTx | Received CTx after surgery; no further details available |
| Maiko et al. 2009 | Female/76  | Not available | Initial | Massive hematemia, fever and fatigue (spleenic abscess) | CT abdomen followed by endoscopy of upper GI tract | Splenectomy, partial gastrectomy, diaphragmatic primary repair, drainage chest tube and feeding tube jejunostomy | At 2 mo later the patient developed a pulmonary infection and died because of multi-organic failure |
| Garcia et al. 2009 | Male/76    | Not available | Initial | Epigastric pain, weight loss and splenomegaly | CT abdomen followed by endoscopy of upper GI tract | Total gastrectomy, splenectomy and distal pancreatectomy CTx | Remained asymptomatic at the 36-mo follow-up; no further details available |
| Khan et al. 2010  | Male/43    | 18.9 cm x 10 cm x 8.6 cm | Initial | Upper abdominal pain and constitutional symptoms (spleenic mass) | Endoscopy of upper GI tract followed by CT | Surgical en bloc resection followed by chemotherapy | Complete remission after two cycles of CTx; no further details available |
| Rothermel et al. 2010 | Male/74    | Not available | Initial | Fever, chill and weight loss | Endoscopy of upper GI tract followed by CT | Splenectomy, stapled gastric-sleeve resection | After surgery, the patient underwent CTx; good prognosis for long-term survival |
| Dellaportas et al. 2011 | Male/68    | Not available | Initial | Hematemesis (spleenic mass) | Endoscopy of upper GI tract followed by CT abdomen | CT abdomen followed by endoscopy of upper GI tract | Surgical en bloc resection followed by chemotherapy |
| Jain et al. 2011  | Male/55    | Not available | Post-CTx | Progressive weakness, fatigue, melena and splenomegaly | CT abdomen followed by endoscopy of upper GI tract | CT abdomen followed by endoscopy of upper GI tract | CT abdomen followed by endoscopy of upper GI tract |
| Ding et al. 2012  | Male/62    | 7 cm | Initial | LUQ pain with constitutional symptoms and splenomegaly | Endoscopy of upper GI tract followed by CT | Splenectomy, gastric wedge resection, and distal pancreatectomy followed by CTx and RT | Well at follow-up; no further details available |
| Favre Rizzo et al. 2013 | Male/35    | Not available | Initial | Hematemesis, epigastric pain, weight loss and splenomegaly | CT abdomen | Partial gastrectomy, splenectomy and distal pancreatectomy | After surgery; no further details available |
| Senapati et al. 2014 | Male/57    | Splenomegaly of 15 cm | Post-CTx | No symptom but splenomegaly | PET/CT followed by endoscopy of upper GI tract | Refused any surgical intervention | Lost to follow-up |
| Gentili et al. 2016 | Female/66  | 7.5 cm x 3 cm | Post-CTx | Weakness, fatigue, weight loss and splenomegaly | Endoscopy of upper GI tract followed by CT | Gastric wedge resection, splenectomy | Discharged after surgery; no further details available |
| Sousa et al. 2016  | Male/52    | Not available | Post-CTx | Hematemesis | Endoscopy of upper GI tract followed by CT | Total gastrectomy, splenectomy, distal pancreatectomy | Patient was lost to follow-up after discharge |
| Present case      | Male/50    | 11 cm x 5 cm x 13 cm | Post-CTx | LUQ pain, nausea, vomiting and splenomegaly | CT abdomen | Gastric wedge resection and splenectomy | At 3 mo later, gastric perforation occurred and the patient expired due to sepsis |

CT: Computed tomography; CTx: Chemotherapy; DLBCL: Diffuse large B-cell lymphoma; GI: Gastrointestinal; LUQ: Left upper quadrant; PET: Positron emission tomography; RT: Radiation therapy; USG: Ultrasonography.

Among the 27 cases, death was reported in 5 patients due to a gastric perforation (n = 1), progression of lymphoma and infection (n = 1), pulmonary infection with multi-organic failure (n = 1), and no further details (n = 2). The time to death ranged from 2-5 mo after the initial surgery or diagnosis. In 18 cases, the patients were alive at that time or were discharged. Patient outcomes were not reported for three patients, and two patients were lost to follow-up.

**DISCUSSION**

GSF is a very rare complication of lymphoma, as only 27 cases have been reported including the present case. It is very difficult to identify the spectrum of presentation,
As our systematic review includes all of the available articles in PubMed without the limitation of language, it is the largest reported series of GSF cases occurring in lymphomas. Although there was a diversity in the clinicopathologic features, imaging features and outcomes, we can summarize that GSF occurs mainly in DLBCL (85.2%) and it can occur either post-chemotherapy (37%) or spontaneously (63%). GSF can also cause fatal complications such as acute bleeding and splenic abscess. Once these fatal complications in the acute illness stage are controlled, the long-term outcome is good.

Regarding the pathologic type, DLBCL is the most common type associated with GSF. The present case of GSF occurred in extranodal NK/T-cell lymphoma of the nasal type and, to our knowledge, is the first reported case. In general, NK/T-cell lymphoma occurs in the nasal cavity. If NK/T-cell lymphoma involves an area outside the nasal cavity, the gastrointestinal tracts and skin are common and preferential extranodal organs of lymphoma involvement [26]. Rare sites of involvement include the spleen, prostate, pancreas and adrenal glands [27]. From this perspective, our case demonstrated a very rare complication of GSF which occurred in a rarely involved site of NK/T-cell lymphoma of the nasal type.

In general, NK/T-cell lymphoma is characterized by its aggressive behavior and with an angiocentric/angiodestructive growth pattern. In our case, we at first postulated that the GSF might occur due to these aggressive behaviors. Thereafter, a multidisciplinary discussion at our medical center indicated that extensive tumor lysis from chemotherapy might also be an important causative factor of GSF. The spleen parenchyma and capsule were largely infiltrated by NK/T-cell lymphoma cells, and thus caused splenomegaly. When the enlarged spleen was attached to the adjacent gastric fundus, tumor cells might infiltrate into the gastric wall. When chemotherapy caused tumor lysis and necrosis, the defect in the spleen capsule and gastric wall occurred, eventually leading to the GSF.

When we systematically reviewed the literature reports, we discovered that there has been a commonly proposed theory of GSF development, i.e., necrosis of lymphoma tissue involving the spleen or stomach may cause GSF. According to this theory, invasion of the gastric wall and splenic capsule is required. If the lymphoma predominantly involves the spleen, the tumor cells should also infiltrate the gastric wall, and vice versa. The rapid necrosis of infiltrated lymphoma cells in the gastric wall and splenic capsule may result in the formation of GSF which may occur either spontaneously or post-chemotherapy [6,28]. Most of the GSFs described in the published literature are small. However, if a larger part of the stomach is infiltrated, it is possible for a large opening in the stomach wall to arise, as was reported in our case.

As the initial presentations of GSF occurring in lymphomas are somewhat non-specific, such as constitutional symptoms and abdominal pain, the diagnosis of GSF may be difficult and delayed. CT scanning can have an important role in the diagnosis of GSF, can identify GSF-associated complications such as abscess or bleeding, and can evaluate the disease extent and surgical planning. If the diagnosis and treatment of GSF are delayed, the clinical outcome might not be favorable, as GSF in lymphomas recover spontaneously. Therefore, radiologists should be aware of this rare disease entity and should notify physicians when GSF is suspected in patients with lymphoma involving the spleen or stomach.

There are various therapeutic options for managing GSF. Surgery is regarded as the most important and curative treatment in the vast majority of literature reports. The surgical method can be determined based on the tumor extent and the surgeon’s preference. The most common surgical method in the literature reports is partial gastrectomy (mostly laparoscopic) with/without splenectomy. However, in some cases with a large tumor extent, near-total gastrectomy and splenectomy has also been performed. When patients were too ill to have surgery or refused it, the outcome was not good. Once patients had surgery and overcame the acute illness status, the long-term outcome was generally good. Considering all of these cases, we propose that aggressive surgery at the early stage of disease might be the best way to save patients with GSF occurring in lymphomas.

In conclusion, this systematic review provides an overview and spectrum of GSF occurring in lymphomas and covering the clinicopathologic features, radiologic features, treatment and outcome. We also included a rare case of GSF occurring in extranodal NK/T-cell lymphoma. This information will be helpful for physicians so that they can become aware of this rare disease entity.
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in lymphomas were analyzed.

**Innovations and Breakthroughs**

This systematic review includes all of the available articles in PubMed without the limitation of language and it is the largest reported series of GSF cases occurring in lymphomas. It provides a systematic summary and overview of GSF occurring in lymphomas in order to understand the spectrum of presentation, clinicopathologic/radiologic features and outcome in this type of extremely rare disease entity. The authors also added our present case of GSF occurring in extranodal NK/T-cell lymphoma of the nasal type and, to our knowledge, this is the first reported case of this type.

**Applications**

When lymphoma patients present symptoms or signs of constitutional symptoms, such as weight loss, fever and fatigue, abdominal/flank pain, acute gastrointestinal bleeding, such as hematemesis or any infection signs with or without history of chemotherapy, computed tomography scanning was very helpful for diagnosing GSF and evaluating the lymphoma extent. GSF could occur either post-chemotherapy or spontaneously. Surgical resection has been the most common treatment. Once patients have recovered from their acute illness status after undergoing surgery, their long-term outcome has been good. The authors should be aware of GSF, which is a rare disease entity in patients with lymphoma, especially involving the spleen or stomach.

**Terminology**

GSF is a communication between the stomach lumen and spleen parenchyma.

**Peer-review**

This manuscript systematically reviewed a very rare complication of GSF occurring in lymphomas. The review analyzed the current literature regarding the clinicopathologic/radiologic features, treatment and outcome of GSF. It therefore provides useful recording of the disease.

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