Gastric Involvement in Patients with Primary Mediastinal Large B-Cell Lymphoma

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Abstract. *Gastric involvement is unusual in primary mediastinal large B-cell lymphoma (PMLBCL), which has not yet been adequately studied. The aim of this retrospective study was to investigate the frequency of gastric involvement in 204 consecutive patients with PMLBCL that presented at 23 hospitals in Greece. Two out of 204 patients (1.0%) had gastric involvement at presentation. The first patient had symptomatic gastric disease manifested as upper gastrointestinal (GI) hemorrhage, which was the presenting symptom (first case reported in the literature). The second patient underwent positron emission tomography/computed tomography (PET/CT) at baseline staging which revealed abnormal gastric uptake. Histological examination revealed discordant lymphomatous involvement (MALT lymphoma, in a 33-year old female). The estimated frequency of gastric involvement by conventional staging was 1/204 (0.49%), but no cases were identified among asymptomatic patients. Among asymptomatic patients who underwent PET/CT at baseline staging, the PET/CT-based frequency of gastric involvement was 7.1%, but lymphomatous gastric involvement was discordant. Finally, the frequency of gastric involvement in primary progressive or relapsed disease was 2.2%. Our study shows that gastric involvement is uncommon but can be seen in different clinical settings at presentation or at progression/relapse of PMLBCL. PET/CT-based staging may provide more accurate information regarding the true incidence of sub-clinical gastric involvement in this entity, but histological confirmation is essential in order to confirm the diagnosis.*

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Primary mediastinal large B-cell lymphoma (PMLBCL) has been categorized as a distinct entity in the recent WHO classification (1). The disease presents by definition with a mediastinal mass, causing cough, dyspnea and frequently, superior vena cava syndrome and affects almost exclusively young and middle-aged adults, predominantly females. At presentation, the disease is restricted to the thorax in the vast majority of patients, at least by conventional staging. Multiple, contiguous extranodal involvement is common (lung, pleura, pericardium, sternum *etc.*), typically representing stage IIE disease. Extranodal involvement outside the thorax is very uncommon at presentation, with approximately 5% of the patients suffering from renal or liver involvement. However, it is a unique feature of PMLBCL that peculiar extrathoracic extranodal involvement is not uncommon at relapse or progression (1, 2). The kidney and central nervous system (CNS) are the most frequently affected unusual extranodal sites, which are involved in the setting of relapsed/refractory disease, but ovaries, adrenals, intestine and other organs have also been reported (2, 3). Herein, we describe three patients with PMLBCL and gastric

involvement who were identified through searching our multicenter database: two patients had gastric involvement at initial presentation (one with discordant histology) and one at relapse, 6 months after the end of the initial treatment.

Patients and Methods

In 23 hospitals in Greece, 204 consecutive patients (113 patients came from four Centers) with PMLBCL were treated with rituximab, cyclophosphamide, adriamycin, vincristine and prednisone (R-CHOP), or similar regimens, with or without radiotherapy (RT) from the time of introduction of rituximab until 2013. The medical records of these patients were retrospectively reviewed for the presence of gastric involvement either at presentation or at relapse.

Clinical staging was based on conventional methods, including history and physical examination, chest X-rays, cervical, thoracic and abdominal/pelvic computed tomographic (CT) scans and unilateral bone marrow biopsy. Other imaging or endoscopic methods were infrequently used according to clinical indications. During the most recent years, 14 patients had additional baseline staging by positron emission tomographic/ computed tomographic (PET/CT) scan. PET/CT scans were performed at each treating physician's discretion. Staging procedures at progression or relapse were similar to those at baseline.

Results

Patients' characteristics. The present series of R-CHOP-treated patients reflected a typical patient population with PMLBCL (4, 5). The median age was 31 years [range=17-85 years; only 10/204 (5%) were more than 60 years old], 129/204 (63%) were females; 172/196 (88%) had stage I/II disease, 64/196 (33%) had B-symptoms, 31/183 (17%) had a performance status (PS) of 2 or more, 107/174 (62%) had bulky disease defined as a mass of 10 cm or more, 153/193 (79%) had an elevated serum lactate dehydrogenase (LDH) level and 41/189 (22%) had high/intermediate or high-risk age-adjusted International Prognostic Index (aaIPI=2-3).

Frequency of gastric involvement at presentation. Two out of 204 patients (1.0%) had gastric involvement at presentation. A detailed description of these two cases is provided below (cases 1 and 2). The first patient had symptomatic gastric disease manifested as upper gastrointestinal (GI) hemorrhage, which was the presenting symptom. The second patient underwent PET/CT baseline staging which revealed abnormal gastric uptake. Discordant lymphomatous involvement was histologically confirmed by endoscopic biopsy [discordant involvement versus concomitant mucosa-associated lymphoid tissue (MALT) lymphoma].

Based on the above data, the frequency of gastric involvement by conventional staging was 1/204 (0.49%), but no cases were identified among asymptomatic patients. Since 14 patients had baseline PET/CT staging, the PET/CT-based frequency of gastric involvement in patients with no upper GI symptoms was 7.1%.

Frequency of gastric involvement at progression/relapse. One out of 45 patients (2.2%) with primary progressive or relapsed disease had gastric involvement by conventional staging. This case was identified by CT and was confirmed by PET/CT and histological examination, as described below (case 3).

Description of Cases

Case 1: Upper GI hemorrhage as initial presentation of PMLBCL. A 36-year-old woman presented at the Emergency Department with upper GI hemorrhage. The complete blood count was as follows: hematocrit 26.5%, hemoglobin 8.4 g/dl, red blood cells 3.03×10^{12}/lt, white blood cells 9.46×10^{9}/l (polynucleated cells 68%, lymphocytes 22%, monotypes 8%, eosinophils 2%), platelets 326×10^{9}/lt. The serum biochemical profile was normal, except for an elevated LDH level (564 U/lt, with an upper normal limit of 248 U/l, *i.e.* 2.27-fold). Chest X-rays revealed a large mediastinal mass and a left pleural effusion. Upper GI endoscopy revealed a large ulcerative gastric lesion arising from the cardia and extending towards the fundus and the beginning of the pyloric antrum, which was the cause of the hemorrhage (Figure 1A). An endoscopic biopsy led to the diagnosis of diffuse large B-cell lymphoma (DLBCL). Complete staging with CT scans demonstrated nodular-polypoid thickening of the gastric wall (the fundus and the greater curvature), polypoid lesions in the remaining stomach, peripancreatic lymphadenopathy and enlargement of the right kidney, a large mediastinal mass with associated left pleural and pericardial effusions, as well as paracardiac lymphadenopathy (Figure 1B-D). Bone marrow biopsy was negative for infiltration. Eastern Cooperative Oncology Group (ECOG) PS was 0. According to these data, the clinical stage was IVA and the IPI was 3, while the aaIPI was 2, both falling into the high/intermediate-risk group.

Although the diagnosis of DLBCL had already been established, we were concerned about the possibility of PMLBCL, since the patient was a young female at the typical age of PMLBCL presentation, she had a large mediastinal mass with associated pleural effusion, and enlargement of the right kidney was also present. CD23 was positive and immunoglobulin was not expressed by the neoplastic cells, suggesting that the gastric neoplasm was an unusual localization of PMLBCL. Additional immuno-histochemical analysis was also performed for nuclear proto-oncogene c-REL and tumor necrosis factor receptor-associated factor 1, (TRAF1), which were positive, thus confirming the clinical suspicion of PMLBCL.

The patient was treated with eight cycles of R-CHOP, with a rapid response. Following completion of chemotherapy, upper GI endoscopy was normal, and abdominal lymphadenopathy, right kidney enlargement and pleural and pericardial effusions had resolved. The mediastinal mass had

been reduced to 3.5×3 cm (starting from an initial maximal diameter of 10 cm). However, the mass was still weakly-positive on (18)F-fluorodeoxyglucose (^{18}F-FDG) PET/CT (Maximum standardized uptake value, SUVmax=4.6). The patient underwent additional RT to the mediastinum at a dose of 4000 cGy. The residual mediastinal abnormality further regressed to 3×2.5 cm and then 3×1.5 cm, but still remained ^{18}F-FDG positive (SUVmax=3.6). Despite PET/CT positivity, the size of the residual mediastinal mass continued to decrease, until its disappearance at 23 months post diagnosis. No further PET/CT evaluation was carried out. The patient remains in complete response (CR) at five years following the diagnosis.

Case 2: PET/CT-identified, asymptomatic, discordant gastric involvement at diagnosis of PMLBCL. A 33-year-old woman was diagnosed with stage IIEA PMLBCL in August 2012. Two months earlier she had noticed a right supraclavicular swelling and a dry cough. Radiological evaluation revealed a 10-cm mediastinal mass, additional enlarged mediastinal nodes at various sites, right-sided pleural effusion, pericardial effusion and right supraclavicular lymphadenopathy. Histological confirmation was based on a right supraclavicular lymph node biopsy. The tumor was characterized by diffuse medium and large cell infiltration with prominent sclerosis. The immunophenotype of the neoplastic cells was: $CD20^+$, $CD79A^+$, $PAX5^+$ and $CD23^+$ in 100% of cells; $CD10^-$, $CD5^-$, CIG^-, $CD30^+$, $CD15^-$, B-cell lymphoma 2 $(BCL2)^+$ and Multiple myeloma 1/ Interferon regulatory factor 4 protein $(MUM1/IRF4)^+$ in 30% of cells. ECOG PS was 0. Serum biochemistry was normal except for an elevated LDH level (544 U/lt or 2.54-fold normal). The aaIPI was 1, falling in the low-intermediate risk category. A PET/CT was performed at the initial staging of the disease: lesions that were detected conventionally were verified (SUV_{max}=21.5), but there were also additional disease sites, including left supraclavicular lymphadenopathy, pericardial hypermetabolic foci, and increased FDG uptake at the gastric wall (Figure 2A and B). An endoscopic biopsy confirmed that gastric FDG uptake was due to lymphomatous infiltration. However, lymphoid cells were predominantly small-sized with a relatively small number of scattered large cells and a focal lymphoepithelial lesion. The neoplastic cell immunophenotype was $CD20^+$, $CD79a^+$, $PAX5^+$, $BCL6^-$, cyclin $D1^-$ and $MUM1/IRF4^-$. These findings were interpreted as marginal-zone B-cell lymphoma, MALT-type. Due to limitations of tissue material availability, it was not possible to study the identity of the two B-cell clones. The patient was treated with eight cycles of R-CHOP-21, achieving a CR on CT scan, which was confirmed by a negative PET/CT (Figure 2C) and a negative upper GI endoscopy. She then received additional mediastinal and gastric RT at a dose of 3,600 cGy. She remains in CR at 15 months following diagnosis.

Case 3: Gastric involvement at relapse of PMLBCL. A 33-year-old woman was diagnosed with stage IVA PMLBCL in August 2011. She had dry cough, dyspnea and superior vena cava syndrome due to a huge (14 cm) upper anterior mediastinal mass, as well as bilateral supraclavicular lymphadenopathy. Two parenchymal lung lesions and a small pleural effusion were also present at baseline CT scan. ECOG PS was 1. Serum biochemistry was normal except for an elevated LDH level (1189 U/lt or 2.58-fold normal). The aaIPI was 2, falling in the high/intermediate-risk category. She was treated with eight cycles of R-CHOP-21, with good partial remission on CT scan (max diameter 6.6 cm). PET/CT remained positive, with an SUV_{max} of 5. She received additional mediastinal RT at a dose of 3,800 cGy. PET/CT scan restaging 3 months after the end of RT was normal except for increased uptake in the stomach, which was attributed to post-RT gastritis (Figure 3). Six months after the end of the treatment, the patient complained of abdominal discomfort and appetite loss. Restaging with CT-scan revealed disease relapse with mediastinal mass, multiple parenchymal lung lesions, thickening of the stomach wall, abdominal lymphadenopathy, and peritoneal and liver infiltrates (Figure 4). An endoscopic biopsy of the gastric lesion was compatible with PMLBCL. The patient received salvage therapy with two cycles of Rituximab- etoposide- methylprednisolone-cytarabine- cisplatin (R-ESHAP) and achieved CR that was confirmed by PET/CT and verified by a negative gastric biopsy. Subsequently, she underwent high-dose chemotherapy with carmustin, etoposide, cytarabine and melphalan, (BEAM) and autologous stem cell transplantation (auto-SCT). She remains in CR 10 months after the confirmation of relapse/progression.

Discussion

The stomach is the most common primary extranodal localization in DLBCL (6). However, gastric involvement is not a common manifestation in patients who present with DLBCL diagnosed in other anatomic sites, either localized or disseminated. On the other hand, gastric involvement in PMLBCL has not been adequately studied.

To our knowledge, case 1 is the first reported case of PMLBCL presenting with upper GI hemorrhage due to gastric involvement. In addition, case 2 shows that the application of PET/CT-based staging can detect gastric involvement in asymptomatic patients where conventional staging procedures are negative. However, as suggested by this case, gastric lesions that are incidentally discovered during PET/CT staging of PMLBCL should be histologically examined, since the possibility of an alternative pathology (other lymphoma or even non-lymphomatous) exists. Indeed, a concomitant diagnosis of gastric MALT lymphoma was made. However, MALT lymphomas are unusual in this age group (7, 8) and limitations of tissue material did not permit the comparison of the two B-cell clones.

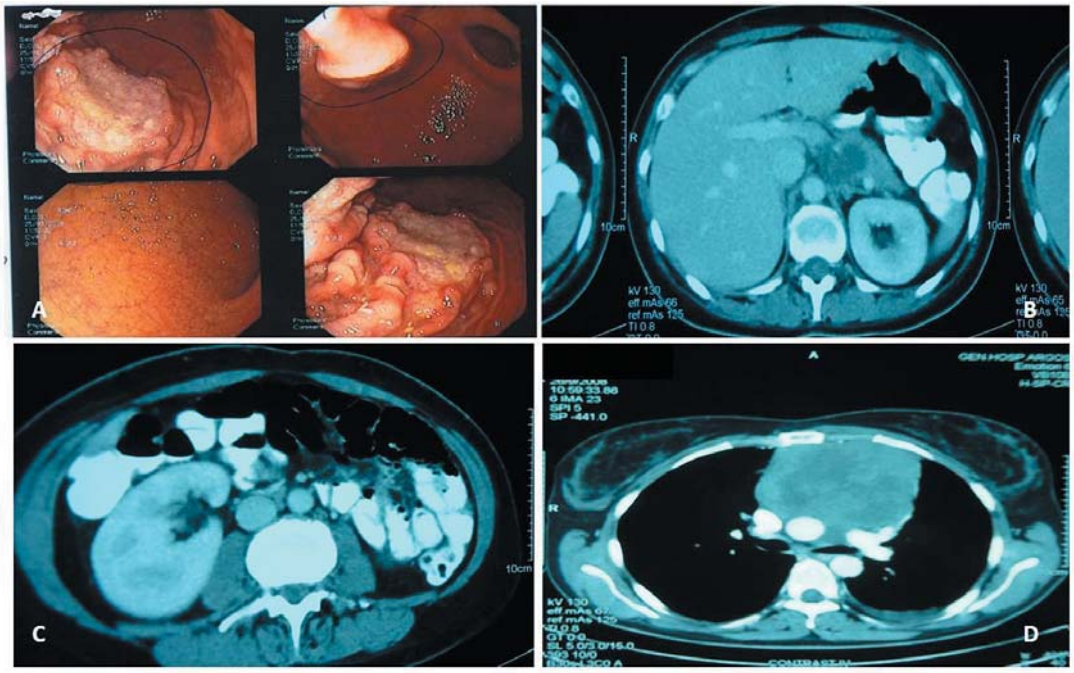

Figure 1. *A: Upper gastrointestinal (GI) endoscopy of case 1. Endoscopic appearance of the large ulcerative lesion due to primary mediastinal large B-cell lymphoma (PMBCL) infiltration of gastic cardia and fundus, which also extended to the pyloric antrum. B-D: Computed tomographic (CT) scan of case 1, showing thickening of the gastric wall and retropancreatic lymphadenopathy with central necrosis (B), enlargement of the right kidney with associated hypodense lesions (C), and a large mediastinal mass with multiple foci of necrosis and an associated small left pleural effusion (D).*

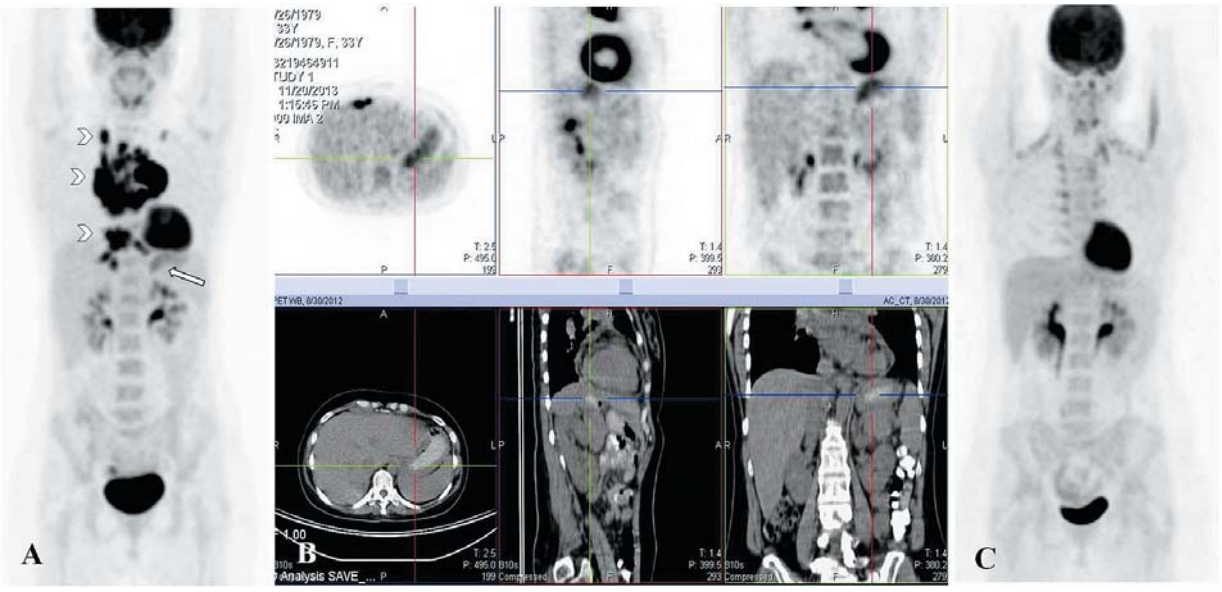

Figure 2. *A: Pre-treatment positron emission tomography/ computed tomography (PET/CT) maximum intensity projection (MIP) indicating a large, strongly-hypermetabolic mediastinal mass (Maximum standardized uptake value, SUV_{max} 21.5) with other associated hypermetabolic mediastinal and supraclavicular nodal localizations (arrowheads). A lower intensity uptake is evident at the gastric wall (SUV max 5.1) just below the left ventricle (arrow). B: Multiplanar depiction of the hypermetabolic gastric wall lesion at the level of the fundus (PET/CT MIP and CT reconstructions). C: Post-chemotherapy PET/CT MIP indicating complete resolution of all lymphomatous sites, including the gastric one. There is evidence of activated brown fat with thoracic paraspinal and supraclavicular foci of (18)F-fluorodeoxyglucose (^{18}F-FDG) uptake bilaterally, without clinical significance.*

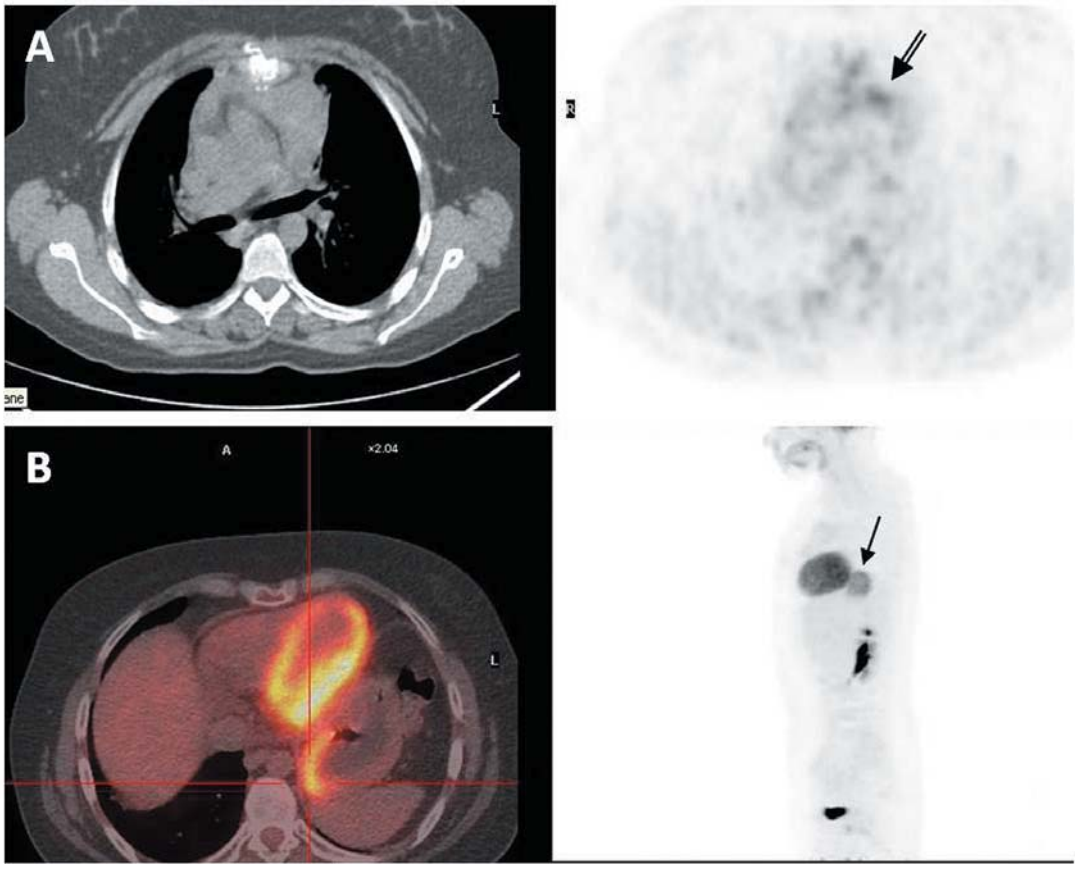

Figure 3. *A: Post-treatment PET/CT images indicating mild but persisting ^{18}F-FDG uptake (SUV_{max} 5) higher than that of the mediastinal blood pool in the mediastinal mass (open arrow). B: Post radiation PET/CT (fused and MIP images) indicating normal ^{18}F-FDG uptake in the mediastinal mass but increased uptake in the stomach (black and white arrows).*

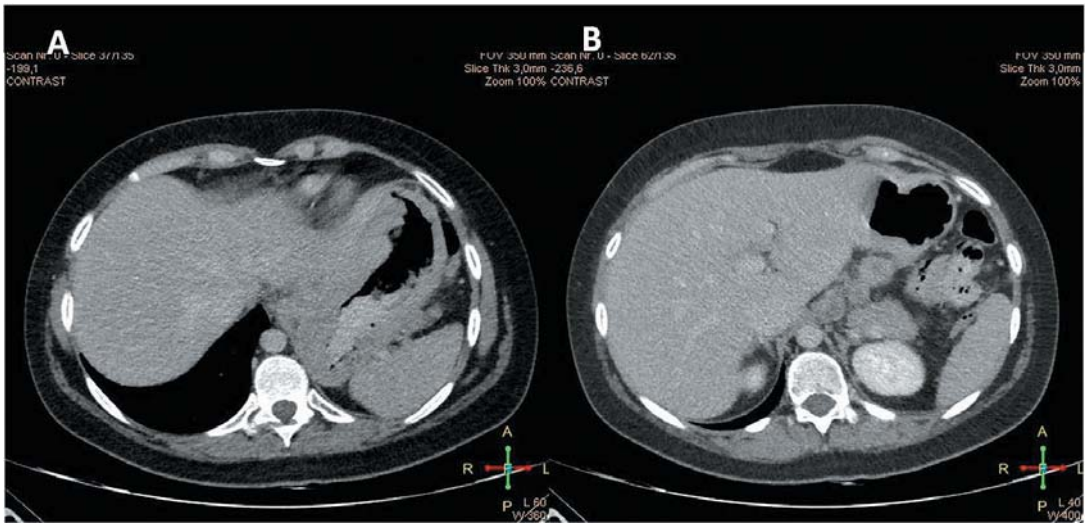

Figure 4. *Computed tomographic (CT) scan of case 3 at relapse, showing nodular thickening of the gastric wall (A), and abdominal lymphadenopathy (B).*

Gastric involvement is not evaluated by routine conventional staging in patients with PMLBCL in the absence of relevant symptoms. Since upper GI endoscopy is not included in the clinical staging procedures for PMLBCL, the true incidence of subclinical gastric involvement at the diagnosis of the disease is not known. The occurrence of gastric involvement is not reported in most published series (9- 11). Some series published during the 1990s (including patients diagnosed even earlier) have provided data on the frequency of gastric involvement in this disease: Lazzarino et al. found one case out of 106 (0.94%) and Massoud et al. 1/108 (0.93%) (12, 13). On the other hand, Bishop et al. reported gastric involvement in 2/23 patients (9%), but in their study, there was a strong selection of patients with unfavorable prognosis due to referral bias (14). Data from series including patients diagnosed more recently (for example beyond 2000) are not available. All the patients that are reported here were diagnosed after 2001 based on established modern diagnostic criteria and the incidence of clinically-evident gastric involvement was 1/204 (0.49%), which is similar to the rates reported by Lazarino et al. and Massoud et al. The true incidence of asymptomatic gastric involvement (as suggested by PET/CT staging) in PMLBCL is not known. In this study, only one out of 14 (7%) PET/CT-staged patients had gastric involvement, although this case might not represent PMLBCL localization but a concomitant MALT lymphoma, and this percentage needs further verification in larger patient cohorts.

Case 3 underlines the potential occurrence of latent or even clinically evident gastric involvement at first progression or relapse of PMLBCL. This is not unexpected, since peculiar extranodal localizations are rather common in the setting of relapsing or progressing disease. However, other sites such as kidneys, adrenal glands, central nervous system, and ovaries are usually involved (2, 3, 14). Data on gastric involvement at relapse are virtually absent. Only Bishop *et al*. reported one such case out of 14 patients (7%), with the limitations of this study discussed above (14). In our series, there was only one case out of 45 (2.2%) cases of relapsed/progressed disease evaluated by conventional staging. We consider this figure as a more close approximation of the true incidence of gastric involvement in this setting, but PET/CT-based data, which could also uncover occult cases, are lacking.

R-CHOP is probably the standard-of-care in PMLBCL, since R may obviate the need for more aggressive chemotherapy in most cases: at least 75% of patients are cured with R-CHOP, although a variable proportion of them also undergo consolidative RT (5, 15). Gastric involvement is certainly a marker of truly disseminated disease, but in our limited experience, it did not confer an adverse prognosis. With the finding of discordant histology in mind, both patients with gastric involvement at initial diagnosis were cured with R-CHOP and RT. Furthermore, the patient with relapse achieved a PET/CT-negative CR with salvage immunochemotherapy, permitting us to consolidate this favorable response with high-dose therapy and auto-SCT.

In summary, gastric involvement is uncommon and can be seen in different clinical settings at presentation or at progression/relapse of PMLBCL. PET/CT-based staging may provide more accurate information regarding the true incidence of subclinical gastric involvement in this entity, but histological confirmation is essential in order to draw safe conclusions.

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