Treatment of grey zone lymphoma using the R-CODOX-M/R-IVAC protocol

Two case reports

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Abstract

**Rationale:** We report our experience with 2 patients diagnosed with grey zone lymphoma (GZL). The histopathological characteristics of lymphomatous tissues in these patients ranged between those of diffuse large B-cell lymphoma (DLBCL) and the classical Hodgkin lymphoma.

**Patient concerns:** A 52-year-old female presented to the hospital with a history of lower abdominal pain of metastatic origin for 2 days. She was diagnosed with acute appendicitis and had undergone emergency surgery. A 17-year-old male was admitted to the hospital because of acute left upper abdominal pain.

**Diagnoses:** Both patients are diagnosed of GZL primarily based on histopathology.

**Interventions:** Both patients were treated with R-CODOX-M/R-IVAC regimen for 4 to 6 cycles.

**Outcomes:** The short-term curative effect was complete response; no recurrence was observed as of 32-month follow-up.

**Lessons:** R-CODOX-M/R-IVAC regimen exhibited relatively good curative effect. International Prognostic Index score and lactate dehydrogenase level may correlate with prognosis of these patients.

**Abbreviations:** CHL = classical Hodgkin lymphoma, DLBCL = diffuse large B-cell lymphoma, GZL = grey zone lymphoma, PMBL = primary mediastinal large B-cell lymphoma.

**Keywords:** Burkitt lymphoma, chemotherapy, diffuse large B-cell lymphoma, grey zone lymphoma, morphology

1. Introduction

The 2008 World Health Organization classification of tumors of lymphoid tissues included a new clinical entity referred to as grey zone lymphoma (GZL). The condition refers to unclassifiable B-cell lymphoma with characteristics intermediate between those of diffuse large B-cell lymphoma (DLBCL) and the classical Hodgkin lymphoma (CHL). This entity includes lymphomas that are characterized by clinical, morphological, and immunophenotypic features that overlap with those of DLBCL, such as primary mediastinal large B-cell lymphoma (PMBL) and nodular sclerosis CHL. Although DLBCL, nodular sclerosis CHL, and GZL are closely related, these are distinct diseases. Although extramediastinal site was found in several studies, these lymphomas commonly present as mediastinal lesion with high aggressiveness.

The histomorphology of GZL is marked by sheet-like growth of neoplastic cells. Cell morphology ranges from that of immunoblastic or centroblastic B-cells to Hodgkin and Reed-Steinberg cell-like cells; localized or diffusely fibrotic stroma with polymorphous infiltrates of mature lymphocytes, eosinophils, and plasma cells are also observed. Immunohistochemically, the neoplastic cells show a blended phenotype of B-cell lymphoma (CD20, CD79a, PAX5, and OCT2) and CHL (CD15 and CD30).

This type of lymphoma has a typically aggressive growth and commonly presents as mediastinal lesions. However, several studies have reported that GZL may also present at extra-mediastinal sites. Owing to the relative rarity of these lymphomas, a consensus on the appropriate therapeutic approach is yet to be achieved. Current treatment approach is based on doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), while that for CHL and DLBCL requires addition of rituximab, based on CD20 expression of the neoplastic cells.

We report our experience with 2 patients with GZL, which overwhelmingly originated from B-cell lymphoma. Both patients were followed up for about 33 months.

2. Case report

The study was approved by the Institutional Review Board and Ethics Committee of Shanghai Xuhui district center hospital. Informed consent was obtained from all individual participants included in the study.

2.1. Case 1

A 52-year-old female presented to the hospital with a history of lower abdominal pain of metastatic origin since 2 days. She was diagnosed with acute appendicitis and had undergone emergency surgery. A mass measuring 5 × 6 cm was noted on the cecum along with enlarged lymph nodes at the corresponding mesangial
roots. Tumor invasion into the horizontal segment of duodenum was observed. She underwent right hemicolectomy and right adnexectomy along with right salpingectomy. A biopsy specimen from left ovary was also obtained. Histopathological examination of surgical specimen showed B-cell lymphoma at the ileocecal junction, which was difficult to distinguish from large B-cell lymphoma (DLBCL) and Burkitt lymphoma (BL). The tumor had invaded the full thickness of the intestinal wall. The immunophenotype was CD20+, PAX5+, Bcl-2+, Bcl-6+, CD10+, MUM1+, CD21+, CD23+, CD38+, CD5, AE1/AE3+, Ki67+ 100%. Serum level of lactic dehydrogenase (LDH) was 326U/L. Postoperative positron emission tomography/computed tomography (PET/CT) confirmed the absence of residual tumor. Bone marrow and cerebrospinal fluid examinations were normal. The disease was classified as stage IV A, and the International Prognostic Index (IPI) score was 3 (Fig. 1).

After excluding the contraindication, 1 month postsurgery, she received R-CODOX-M chemotherapy, including Rituximab 600 mg day (d) 0 + CTX 1.0 d1-2 + Mesna + VCR 2 mg d1, 8 + ADM 60 mg d1 + MTX 2.0 d10 1.0 civ23 d10. Ara-C 70 mg + DXM 5 mg were administered twice intrathecally. She developed degree IV granulocytopenia with fever and degree III thrombocytopenia, for which symptomatic treatment was administered. After 1 month, lower dosage R-IVAC regimen chemotherapy, including Rituximab 600 mg d0 + IFO 1.6 d1-5 + Mesna + Vp-16 60 mg d1-5 + Ara-C 1.5 g d1-2. MTX 12 mg was administered via intrathecal injection. She developed degree III leukocytopenia. Repeat evaluation showed a partial response.

She received another cycle of reduced R-CODOX-M regimen and R-IVAC regimen, which included MTX 12 mg and Dxm 5 mg intrathecal injection. She reported bottom-up numbness of lower limbs, together with dyskinesia and dysphoria. Brain and thoracic spinal cord magnetic resonance imaging (MRI) was unremarkable. Methylprednisolone and immunoglobulin were administered with no significant effect. The symptoms improved after 1 month and she recovered over the next 6 months. Repeat PET/CT showed complete response. She was followed-up for 32 months; no relapse occurred during this period.

2.2. Case 2

A 17-year-old male was admitted to the hospital because of acute left upper abdomen pain. Abdominal CT showed a soft mass measuring 15.1 x 9.4 cm anterior the stomach. It was suspected to be a sarcomatous invasion of peritoneum and spleen. Malignant lymphoma was considered in the differential diagnosis. He underwent splenectomy along with resection of tail of pancreas and greater omentum. The histopathology indicated spleen peripheral B-cell lymphoma, which was difficult to distinguish from DLBCL and BL. The immunophenotype was CD20+, PAX5+, Bcl-2+, Bcl-6+, CD10+, MUM1+, CD38+, UCHL-1+, LCA+, Ki67+ 100%, TDT-, MPO-, KP-1+. Serum level of LDH level was 322U/L. On the basis of PET/CT, bone marrow and cerebrospinal fluid examination the disease was staged as IIIS B; the IPI score was 2 (Fig. 2).

After excluding the contraindication, 1 month after surgery, he received R-CODOX-M chemotherapy, which included Rituximab 600 mg d0 + CTX 1.4 d1-2 + Mesna + VCR 2 mg d1, 8 + ADM 70 mg d1 + MTX 2.0 d10 1.0 civ23 d10. MTX 12 mg and Dxm 5 mg were administered twice intrathecally. Moreover, he received lamivudine oral treatment against hepatitis B virus. He developed degree III leucocytopenia, which was managed with symptomatic treatment. The abdominal mass showed significant decrease after chemotherapy. After 1 month, he was further treated with R-IVAC regimen, which
included Rituximab 600 mg d0 + IFO 2.5 d1-5 + Vp-16 100 mg d2-6 + Ara-C 3.4 g d2-3. MTX 12 mg and Dxm 5 mg were intrathecally injected. During the course of treatment, he developed degree III leucopenia. Repeat evaluation showed partial response.

Another cycle of R-CODOX-M and R-IVAC regimens was administered, which included MTX 12 mg and Dxm 5 mg intrathecal injection. PET/CT scan showed increased 18F-fluordeoxyglucose (FDG) metabolism in the retroperitoneal lymph nodes. The patient refused bone marrow transplantation and received another cycle of R-CODOX-M and R-IVAC regimens. He developed degree IV granulocytopenia with fever, which improved with anti-inflammatory medication. Repeat PET/CT performed at 1 year showed complete response. He was followed-up for 33 months; no relapse occurred during this period.

3. Discussion

GZL is a type of rare lymphoma that accounts for <5% of invasive lymphomas in adults.[10] In a reported case series, the median age at onset was 55 (range, 13–93) years. Most cases occurred in the age group of 41 to 68 years with similar incidence among men and women.[11] It is characterized by highly invasive growth; most patients are diagnosed at stage III-IV with bone marrow and central nervous system involvement.[12]

Both DLBCL and CHL have specific diagnostic criteria, while no clear diagnostic criteria have been proposed for GZL. The diagnosis is based on a comprehensive analysis of cell morphology, immunohistochemistry, and genetics. The neoplastic cells are often characterized as medium to large size in morphology, accompanied by sky star phenomena. The immunophenotype exhibits CD20, CD10, Bcl-2, and Bcl-6 positivity. It often demonstrates complicated karyotype changes with MYC shift and Bcl-2 suspicious positive in embryo. Double shift and triple whammy phenomena is observed. Thus, the cellular morphology of GZL exhibits characteristics of both BL and DLBCL. The complex karyotype distinguishes it from BL.

Cytoxan, Hydroxyrubicin (Adriamycin), Oncovin (Vincristine), Prednisone (chemotherapy regimen) (CHOP) or R-CHOP regimens for DLBCL show poor efficacy against GZL, especially in patients with MYC and Bcl-2 double shift. Median survival in
this subset of patients may be as short as 4.5 months. Intensive regimes such as CODOX-M/IVAC are now gradually accepted by numerous clinicians to treat HIV-associated BL. Although there is still a lack of randomized study, rituximab is often added to CODOX-M/IVAC chemotherapy to improve survival in the HIV-negative population without increasing the risk of toxicity.\[15\]\[16\]

Rituximab was related to a trend to enhance the response rate and reduce lymphoma progress and death. However, it still suffered from query because of a higher mortality in the rituximab arm from infectious complications, especially in those with a CD4+ cell count below 50 cells/μL. Lin et al\[14\] reported that the survival time of patients with MYC gene rearrangement treated with R-CHOP was shorter than that in patients treated with R-hyper CVAD or RCODOX-M. Corazzelli et al\[15\] reported improved disease-free survival with use of CODOX-M and Rituximab. The curative effect of hematopoietic stem cell transplantation is still unclear.

Short-course and high-intensive chemotherapy is the most commonly reported treatment approach.

Patients with IPI score 0 to 2 showed significantly better overall survival and disease-free survival than those with IPI score 3 to 5.\[16\] Patients with normal LDH level were reported to show good survival, while 17% patients with MYC gene rearrangement developed brain metastases.\[17\]

In this study, we reported 2 patients with GZL patients diagnosed by histopathology. Further MYC, Bcl-2, and Bcl-6 gene measurement may help to confirm diagnosis and predict prognosis. Their IPI scores were 2 to 3 and LDH levels were high, which were reported to be associated with a poor prognosis. Both patients were treated by R-CODOX-M/IVAC regimes and obtained complete response in the short term. No relapse was found after 32 to 33 months follow-up. R-CODOX-M/IVAC regimes exhibited good curative effect and were associated with relatively fewer complications in these patients. We recommend this regimen for patients with GZL, although more experience is needed to draw definitive conclusions.

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