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Case report

Primary gastric Burkitt's lymphoma presenting with *c-myc* gene rearrangement

Akira Andoh, Hiroki Takaya, Masamichi Bamba, Hitoshi Sakumoto, Tetsuya Inoue, Tomoyuki Tujikawa, Shigeki Koyama, Yoshihide Fujiyama, and Tadao Bamba

Department of Internal Medicine, Shiga University of Medical Science, Seta Tukinowa, Otsu 520-2192, Japan

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Abstract: A 54-year-old man with primary gastric Burkitt's lymphoma is described. He was evaluated for appetite loss and intermittent midepigastric pain. Upper gastroduodenal endoscopy detected an ulcer in the lesser curvature of the body, and biopsy specimens revealed infiltration of medium-sized lymphoblasts with "starry sky" macrophages. The infiltrated cells were positive for a B-cell marker. Abdominal computed tomography scan demonstrated marked enlargement of the gastric wall, but no enlargement of lymph nodes. These findings led us to diagnose primary gastric Burkitt's lymphoma. The patient responded dramatically to CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy, but 6 months after his initial admission, the disease recurred in the stomach and bone marrow. Lymphoblastic cells were positive for B-cell markers (CD 10, 19, 20, and human leukocyte antigen [HLA]-DR) and showed an abnormal karyotype, 47, XY, t(8;14)(q24;q32), +12. In these cells, the Epstein-Barr virus genome was detected by polymerase chain reaction. Southern blot analysis revealed rearrangement of Ig heavy and light chain genes. In addition, *c-myc* gene rearrangement was detected. Eight months after the beginning of chemotherapy, the patient died of central nervous system involvement. To our knowledge, this is the first description of a genetic analysis of primary gastric Burkitt's lymphoma.

Key words: EB virus, Southern blot, immunoglobulin gene

Offprint requests to: A. Andoh

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Introduction

Burkitt's lymphoma is an aggressive, diffuse non-Hodgkin's lymphoma of B-cell origin.[1] It was initially described as an endemic disease of central Africa, where it affects both children and young adults and usually presents as a jaw or retroperitoneal mass (African type). A sporadic form of this lymphoma (American type) presents with an intraabdominal mass located mostly in the ileocecal region.[1,2] Here we report a rare case of primary gastric Burkitt's lymphoma (American type) with an abnormal karyotype of t(8;14)(q24;q32) and *c-myc* gene rearrangement. To our knowledge, this is the first report of the genetic analysis of primary gastric Burkitt's lymphoma.

Case report

A 54-year-old man was evaluated at the hospital of Shiga University of Medical Science for appetite loss and intermittent abdominal pain. The abdominal pain was aching and midepigastric and was not affected by eating. His past medical and family histories were unremarkable.

Physical examination was normal, except for tenderness in the midepigastric region. Surface lymph nodes were not palpable. Fecal occult blood was positive.

Laboratory examination revealed mild anemia (hematocrit [Ht], 23.0%; normal range, 39–52%, and hemoglobin [Hb], 7.8 g/dl; normal range, 14–18 g/dl), and elevated lactic dehydrogenase (LDH, 818 IU/l; normal range, 50–400 IU/l). Chest X-ray was normal. Upper gastroduodenal endoscopy detected an ulcer with thick nodular borders in the lesser curvature of the lower body (Fig. 1a). A tumor-like swelling with folds was observed in the greater curvature of the lower body (Fig. 1b). Pathology findings of endoscopic biopsy specimens of the ulcers revealed infiltration of medium-sized lymphocytes with "starry sky" macrophages (Fig. 2a).

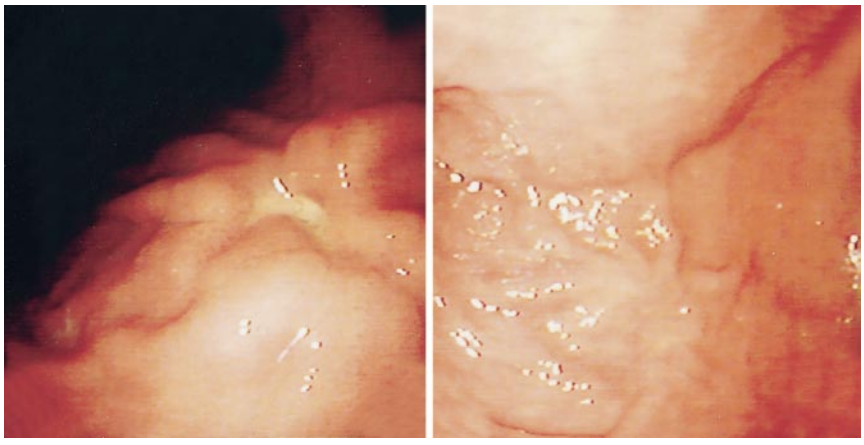

Fig. 1a,b. Endoscopic findings of the stomach. **a** Upper gastroduodenal endoscopy detected an ulcer in the lesser curvature of the body. **b** Tumor-like swelling with several folds was observed in the greater curvature of the lower body

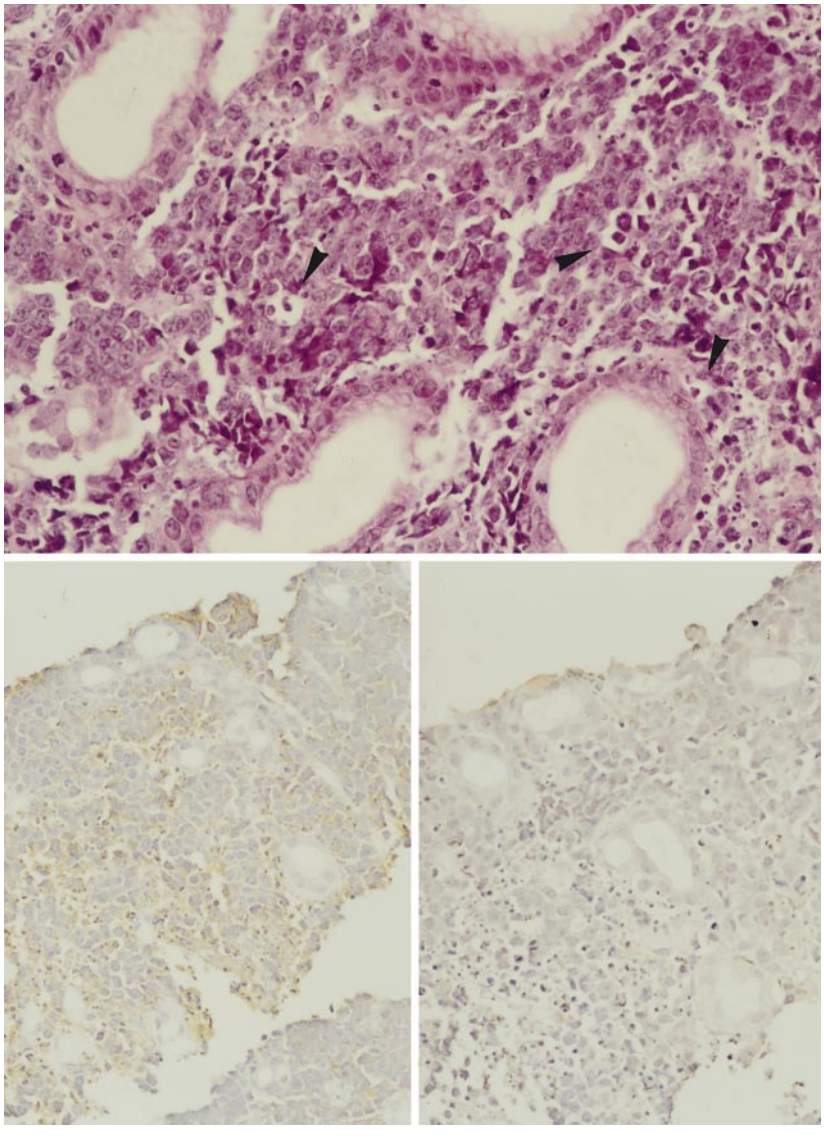

Fig. 2a–c. Pathology findings of biopsy specimens. Biopsy specimens had medium-size lymphocyte infiltration. **a** *Arrowhead* indicates "starry sky" macrophages. H&E, ×300. **b** The infiltrated cells were positive for the B-cell marker, L-26. ×150, but **c** negative for the T-cell marker UCHL-1. ×150

Immunohistochemical staining showed that the infiltrated cells were positive for the B-cell marker (DAKO Japan, Kyoto, Japan) L-26 (Fig. 2b), but negative for the T-cell marker (DAKO Japan) UCHL-1 (Fig. 2c). Bone marrow aspirate from the right iliac crests was normal. Abdominal computed tomography (CT) scan demonstrated marked enlargement of the gastric wall (Fig. 3). From these findings, we diagnosed gastric Burkitt's lymphoma. The patient was treated for 2 months with three courses of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) therapy. He responded dramatically, as detected by decreased enlargement in the gastric wall.

Six months after completion of the treatment, the patient had abdominal pain, nausea, and vomiting. Abdominal CT scan again revealed marked enlargement of the gastric wall, suggesting a relapse of the gastric Burkitt's lymphoma. The patient's LDH level was markedly elevated (39980 IU/l), and abnormal lymphoid cells appeared in the peripheral blood. Bone marrow from the right iliac crests was occupied by lymphoblastic cells (more than 90%) expressing multiple cytoplasmic lipid droplets (Fig. 4). These cells were positive for B-cell specific surface markers (CD10, 19, 20, and HLA-DR; COULTER, Miami, FL, USA). Cytogenetic analysis of bone marrow showed 47, XY, t(8;14)(q24;q32), +12 in 10/10 metaphases (Fig. 5). Polymerase chain reaction (PCR) analysis detected Epstein-Barr (EB) virus genome in these cells (Fig. 6). Southern blot analysis for the immunoglobulin (Ig) heavy chain gene, using a DNA probe specific for the constant (Cμ) region of this gene, revealed rearrangement bands with both *Bam*HI and *Hin*dIII digestion (Fig. 7a). Rearrangement of the Ig light chain (λ) gene was also detected (Fig. 7b). We also detected rearrangement of the *c-myc* proto-oncogene by Southern blot analysis, using a DNA probe specific for *c-myc* gene exon1 with *Eco*RI, *Sac*I, and *Bgl*II digestion (Fig. 8).

CHOP therapy was again initiated, but the patient died as a result of central nervous system involvement.

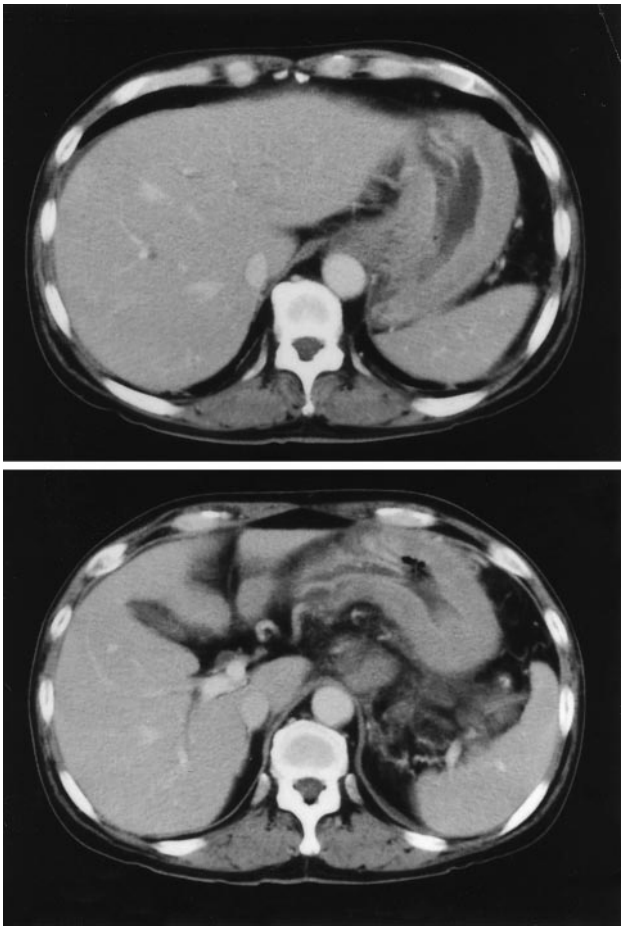

Fig. 3. Abdominal computed tomography scans. Marked enlargement of the gastric wall was detected

Discussion

Burkitt's lymphoma is an uncommon B-cell non-Hodgkin's lymphoma, with a pattern of clinical characteristics, rapid growth, and treatment response that places it in a distinct class.[1–6] Although there are notable clinical differences between the American and African types of Burkitt's lymphoma, diagnosis of this disease depends on the almost identical patterns of histological findings characterizing the two types.[1,4] In our patient, pathology examination of the biopsy obtained from gastric lesions revealed medium-sized lymphoblastic cells, which had infiltrated in tightly packed sheets with characteristic "starry sky" macrophages. The infiltrated

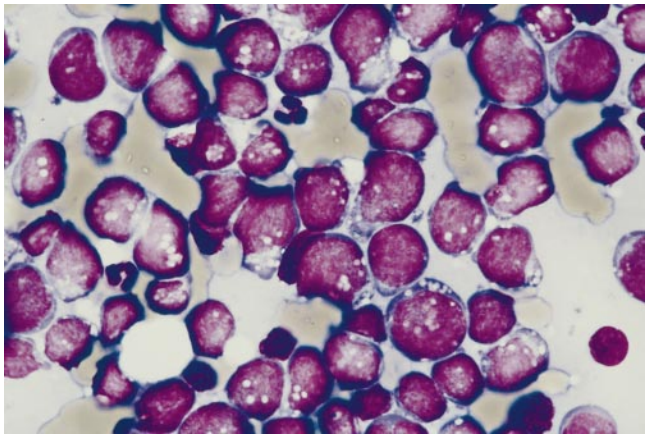

Fig. 4. Wright-Giemsa staining of the cells expanded in the bone marrow. Bone marrow was occupied by lymphoblastic cells with multiple cytoplasmic lipid droplets × 400

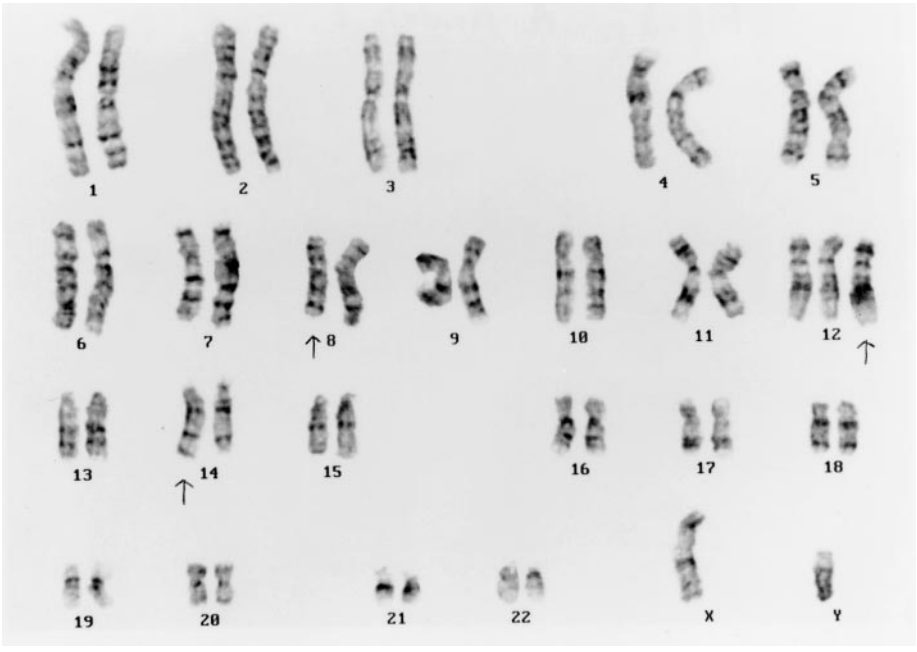

Fig. 5. Chromosomal analysis of the bone marrow cells

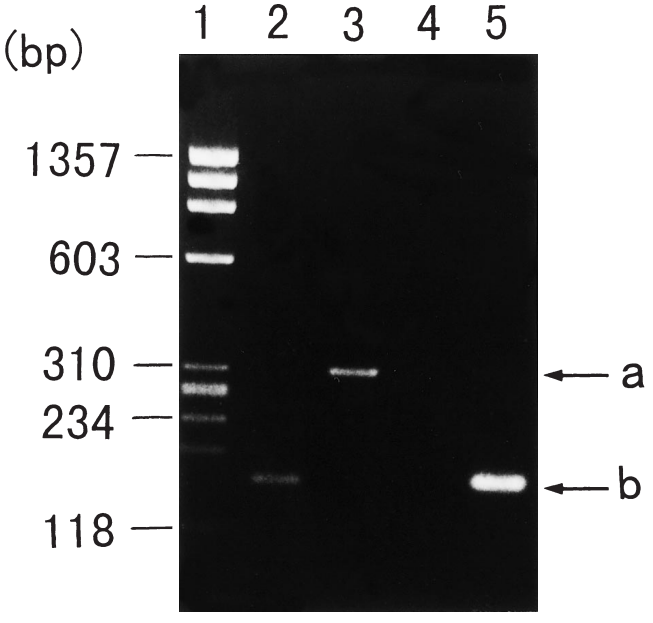

Fig. 6. Polymerase chain reaction (PCR) analysis of the bone marrow cells for Epstein-Barr virus (EBV) genome DNA. *Lane 1*, size marker; *lanes 2 and 3*, sample; *lane 4*, negative control; *lane 5*, positive control for EBV genome. *a* 309-bp PCR product of internal control (Duchenne muscular dystrophy gene). *b* 161-bp PCR product of EBV genome DNA

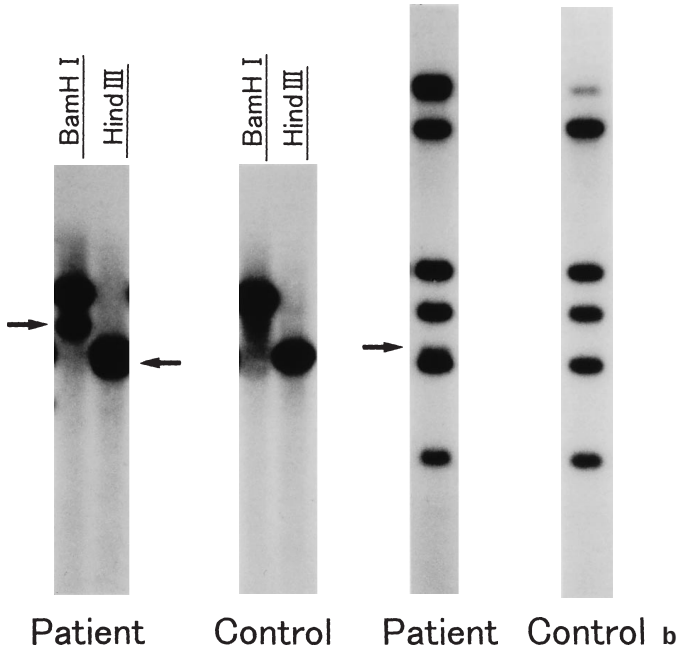

Fig. 7a,b. Southern blot analysis for the immunoglobulin **a** heavy and **b** light (λ) chain genes. *Arrows* show rearrangement bands

cells were positive for a B-cell marker. These findings were compatible with the histological findings of Burkitt's lymphoma.[1] At relapse, characteristic lymphoblastic cells were observed in the bone marrow. These cells contained multiple cytoplasmic lipid droplets expressing B-cell markers, and EB virus genome was detected in these cells. There is a close relationship between EB virus and Burkitt's lymphoma, with the EB virus present in more than 95% of African type of Burkitt's lymphoma cases and in 20% of the American type.[1] These observations confirmed our first diagnosis at admission.

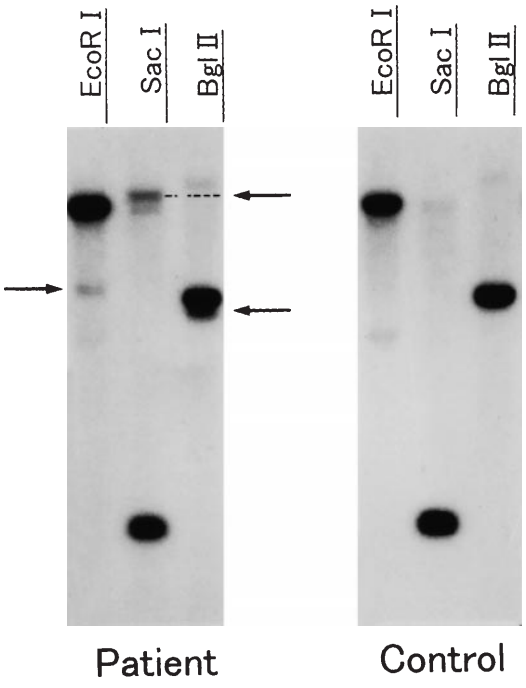

Fig. 8. Southern blot analysis for the *c-myc* gene. *Arrows show* rearrangement bands

The gastrointestinal tract is one of most common sites of extranodal malignant lymphoma, but primary gastrointestinal lymphomas are relatively rare.[3] Burkitt's lymphoma involves a variety of gastrointestinal sites, and 30%–80% of patients have involvement of the small bowel plus the colon, especially in the ileocecal region.[2–4] However, involvement of the stomach occurs in only 10% of patients and it usually appears late in the disease as an extension of a bulky tumor located elsewhere in the abdomen or lower gastrointestinal tract.[2,5,7] Predominant involvement of the stomach characterized our patient, suggesting primary gastric Burkitt's lymphoma. Primary gastric Burkitt's lymphoma is extremely rare and there have been only a few clinical descriptions reported.[2,7]

In previous reports, cytogenetic analysis of gastric Burkitt's lymphoma was not performed. Neoplastic cells in our patient expressed pan-B-cell markers including CD19 and 20. The restricted B-cell marker CD10 and the activation antigen HLA-DR were also expressed. In addition, Southern blot analysis demonstrated rearrangement of the Ig heavy and light chain genes. These data indicated that the neoplastic cells in our patient had an activated and differentiated pre-B-cell phenotype. To date, Burkitt's lymphoma has been considered as a B-cell lymphoid neoplasm, characterized by Ig-bearing phenotypes.[1,4,6] The phenotypic characterization in our patient was compatible with this concept.

Our patient demonstrated an abnormal karyotype, t(8;14)(q24;q32). In general, a characteristic feature of all Burkitt's lymphomas is t(8;14)(q24;q32) (76%) and variant t(8;22)(q24;q11) (16%), or t(2;8)(p11;q24) (8%) translocation between the *c-myc* oncogene on chromosome 8 and the Ig heavy chain gene on chromosome 14 or the light chain (λ and κ) gene on chromosomes 22 and 2, respectively.[1,8,9] While the overall karyotype appears in both the African and American types of the disease, the precise breakpoints are distinct for the two types.[10,11] In African type Burkitt's lymphoma, the breaks in chromosome 8 occur up to 75 kb upstream of the *c-myc* gene, whereas in the American type these breaks occur around exon 1 of the *c-myc* gene. It has been suggested that this translocation may induce *c-myc* gene activation through the enhancer activity of Ig genes, resulting in neoplastic growth. While we observed *c-myc* gene rearrangement in our patient, we could not analyze the structure of the *c-myc* breakpoint. Recent studies have suggested that a point mutation in the *c-myc* gene exon 1 also participates in the neoplastic transformation of Burkitt's cells,[12] and further studies addressing these possibilities are now being undertaken in our laboratory.

In conclusion, we believe this is the first description of the cytogenetic and molecular genetic features of primary gastric Burkitt's lymphoma. Since Burkitt's lymphoma is characterized by rapid growth and fulminant complications, accumulation of clinical and cytogenetic data related to this disease will the needed to help achieve prompt diagnosis and treatment in the future.

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