

CORRESPONDENCE

EPSTEIN-BARR VIRUS IN CONCOMITANT GASTRIC CARCINOMA AND ADULT T-CELL LEUKEMIA/LYMPHOMA

To the Editor:

Epstein-Barr virus is associated with Burkitt lymphoma and nasopharyngeal carcinoma (1). However, recent evidence suggests associations with Hodgkin disease, lymphomas in immunocompromised patients, and gastric, breast, lung, and hepatocellular carcinomas (1–6). We report a patient with concomitant gastric carcinoma and adult T-cell leukemia/lymphoma in whom Epstein-Barr virus-infected cells were detected.

A 50-year-old Japanese man presented with weight loss and a 3-week history of high fever. On physical examination, superficial lymphadenopathy was noted in the neck and axillary regions. A mass about 4 cm in diameter was found in the occipital region. His white blood cell count was $6.2 \times 10^9/L$ with 1% abnormal lymphocytes that had cleaved nuclei. Levels of serum lactate dehydrogenase and calcium were normal. The serum soluble interleukin-2 receptor level was high (8600 U/mL; normal, 220 to 530 U/mL). Serum antibody to human T-lymphotropic virus type I (HTLV-I) was positive. Serological titers for Epstein-Barr virus were as follows: immunoglobulin (Ig) G antiviral capsid antigen, 1:80; IgM viral capsid antigen, <1:10; IgG anti-early antigen, <10; and antinuclear antigen, 1:10. Gastrofiberscopic examination revealed a superficial, depressed-type lesion at the angle of the stomach body. Partial gastrectomy was performed, and the diagnosis based on histology was early gastric cancer (moderately differentiated adenocarcinoma) (Figure). There was no infiltration of atypical lymphocytes. A biopsy specimen of the neck

lymph node showed diffuse infiltration of small to medium lymphocytes with mild nuclear irregularity and scattered CD30⁺ giant cells resembling Reed-Sternberg cells (Figure). No metastasis of gastric cancer was found. Although the histological picture resembled that of Hodgkin disease, infiltration of CD4⁺ lymphocytes, monoclonal integration of HTLV-I proviral deoxyribonucleic acid (DNA) as detected by Southern blot analysis, and rearrangement of the T-cell receptor gene suggested incipient adult T-cell leukemia/lymphoma (7,8). The patient was treated with combination chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisolone, etoposide, vindesine, ranimustine, and mitoxantrone), which led to partial remission.

We performed in situ hybridization for Epstein-Barr virus–encoded ribonucleic acid (EBER) on paraffin sections. EBER was detected not only in lymph node giant cells but also in stomach cancer cells (Figure). We also used genomic DNA from the affected lymph node and stomach tissues to determine the presence of Epstein-Barr virus DNA by polymerase chain reaction using primers that targeted the *BamW* region. Virus-specific DNA was detected in both of the tissues. Clonality of the genome in the lymph node was also analyzed by Southern blot analysis with the Epstein-Barr virus terminal fragment probe (9). A major single band was demonstrated, indicating that the infecting virus was monoclonal.

It is now believed that Epstein-Barr virus is not restricted to lymphoproliferative disorders, and that it may also play a pathogenetic role in epithelial cancers. Adult T-cell leukemia/lymphoma occurs endemically in some areas of the world, including Japan, where approximately 20% of affected patients have Epstein-Barr virus–positive cells (10). In comparison, 5% to 15% of patients worldwide

who have gastric carcinomas are infected with the Epstein-Barr virus (1–3). Our observation suggests that Epstein-Barr virus infection may have been an etiological cofactor of gastric cancer and adult T-cell leukemia/lymphoma in this patient.

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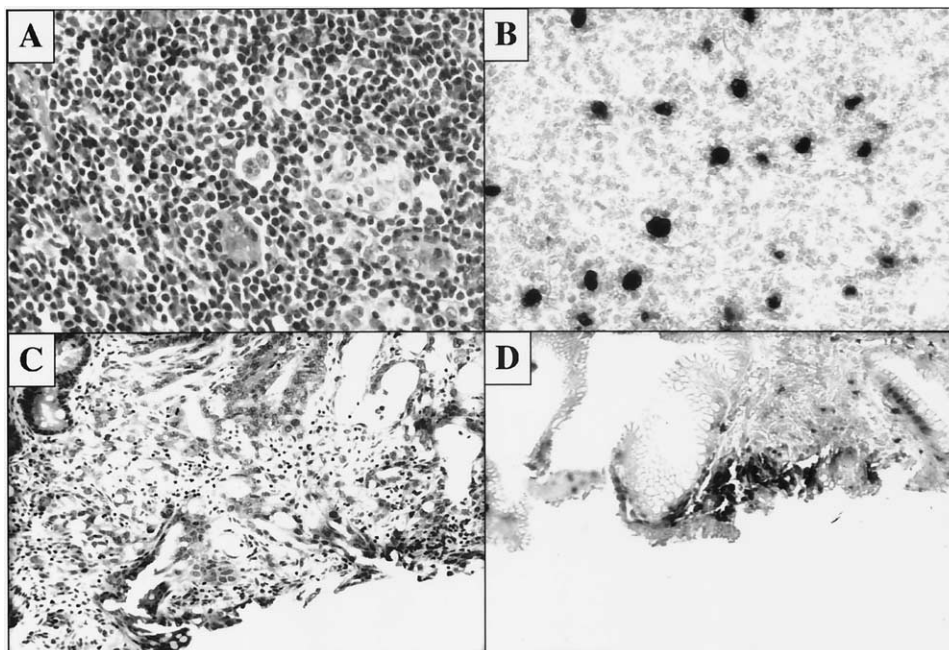


Figure. A: Biopsy specimen of the lymph node showing diffuse infiltration of lymphocytes with mild nuclear irregularity and scattered giant cells resembling Reed-Sternberg cells (hematoxylin-eosin, original magnification $\times 400$). B: In situ hybridization showing giant cells positive for Epstein-Barr virus–encoded ribonucleic acid (EBER) (methyl green, original magnification $\times 200$). C: Histology of the resected gastric tissue showing moderately differentiated adenocarcinoma (hematoxylin-eosin, original magnification $\times 100$). D: In situ hybridization showing that the cancer cells were positive for EBER (methyl green, original magnification $\times 100$).

GEOGRAPHY OF RANDOMIZED CONTROLLED TRIALS IN GENERAL INTERNAL MEDICINE: IS THE UNITED STATES' SHARE DECLINING?

To the Editor:

Contributions by the United States to highly reputed basic science, general medicine, nuclear medicine, and ophthalmology journals have decreased in the last decade (1–3). Several factors may be responsible for this unexpected downward trend. A decline in research funding may be the main reason. Increased high-quality research by researchers from other countries may also have a role. For this purpose, we sought to identify randomized controlled trials by country, which were published in the top seven general internal medicine journals during the last decade, as well as the publication trend over time.

We selected the following journals from the category “General, and General Internal Medicine” established by the Institute for Scientific Information (4): *The New England Journal of Medicine*, *The Journal of the American Medical Association*, *The Lancet*, *Annals of Internal Medicine*, *Archives of Internal Medicine*, *British Medical Journal*, and *The American Journal of*

Medicine. We searched MEDLINE in November 2002 to obtain the country affiliation of the randomized controlled trials published from 1991 to 2000 in these journals. We manually searched hard copies of articles if the affiliation data were not available on MEDLINE. Nonparametric tests for trend were performed using STATA statistical software, version 7 (STATA

Table. Publication of Randomized Controlled Trials in the Top Seven General Internal Medicine Journals (1991 to 2000) For the Top Ten Countries

Country	1991	2000	1991–2000
	(n = 351)	(n = 395)	(n = 3500)
	Number (%)		
United States	175 (50)	186 (47)	1604 (46)
United Kingdom	50 (14)	72 (18)	634 (18)
Canada	15 (4)	25 (6)	171 (5)
Netherlands	16 (5)	17 (4)	156 (4)
France	8 (2)	12 (3)	109 (3)
Italy	9 (3)	6 (2)	102 (3)
Australia	10 (3)	11 (3)	83 (2)
Germany	7 (2)	9 (2)	76 (2)
Denmark	9 (3)	4 (1)	64 (2)
Sweden	6 (2)	6 (2)	60 (2)