

# EBV-positive Diffuse Large B-cell Lymphoma as a Secondary Malignancy Arising in a Myelodysplastic Syndrome Patient who Was Treated with Azacitidine

Naruko Suzuki<sup>1</sup>, Junji Hiraga<sup>1</sup>, Hiroki Kato<sup>1</sup>, Yusuke Takagi<sup>1</sup>, Nobuko Ujihira<sup>2</sup>,  
Michihiko Narita<sup>2</sup> and Yoshitoyo Kagami<sup>1</sup>

---

## Abstract

---

We report a case of secondary diffuse large B-cell lymphoma (DLBCL) after azacitidine (AZA) treatment in a 63-years-old man with myelodysplastic syndrome. The patient suffered from febrile neutropenia after 10 cycles of AZA treatment. Despite the performance of a whole-body CT scan, which showed a multifocal low-density area in the liver and a multifocal nodular shadow in the lung, no malignant neoplasms could be detected. An autopsy was performed 6 months later, and a histopathological examination of the lesions of the liver and lung revealed the infiltration of large round-shaped tumor cells with necrotizing lesions. Immunohistochemically, the tumor cells were positive for CD20 and EBER, indicating EBV-positive DLBCL as a secondary malignancy.

**Key words:** myelodysplastic syndrome, azacitidine, secondary malignancy

(Intern Med 56: 1711-1713, 2017)

(DOI: [10.2169/internalmedicine.56.7865](https://doi.org/10.2169/internalmedicine.56.7865))

---

## Introduction

---

Myelodysplastic syndrome (MDS) represents a heterogeneous spectrum of disorders of the hematopoietic stem cells that is characterized by cytopenias, dysplastic hematopoiesis and the possible development of acute myeloid leukemia (AML). The hypomethylating agent azacitidine (AZA) has improved the cytopenia of high-risk MDS patients and prolonged their overall survival (1, 2). Although AZA has been widely used in the treatment of MDS, there are no reports of the occurrence of secondary malignancies other than AML following its use. We herein present a case of diffuse large B-cell lymphoma (DLBCL) that arose after AZA treatment.

---

## Case Report

---

A 63-year-old man with autoimmune hemolytic anemia (AIHA) had been receiving maintenance therapy with prednisolone (PSL; 5 mg, daily) for 3 years. In July 2013, the

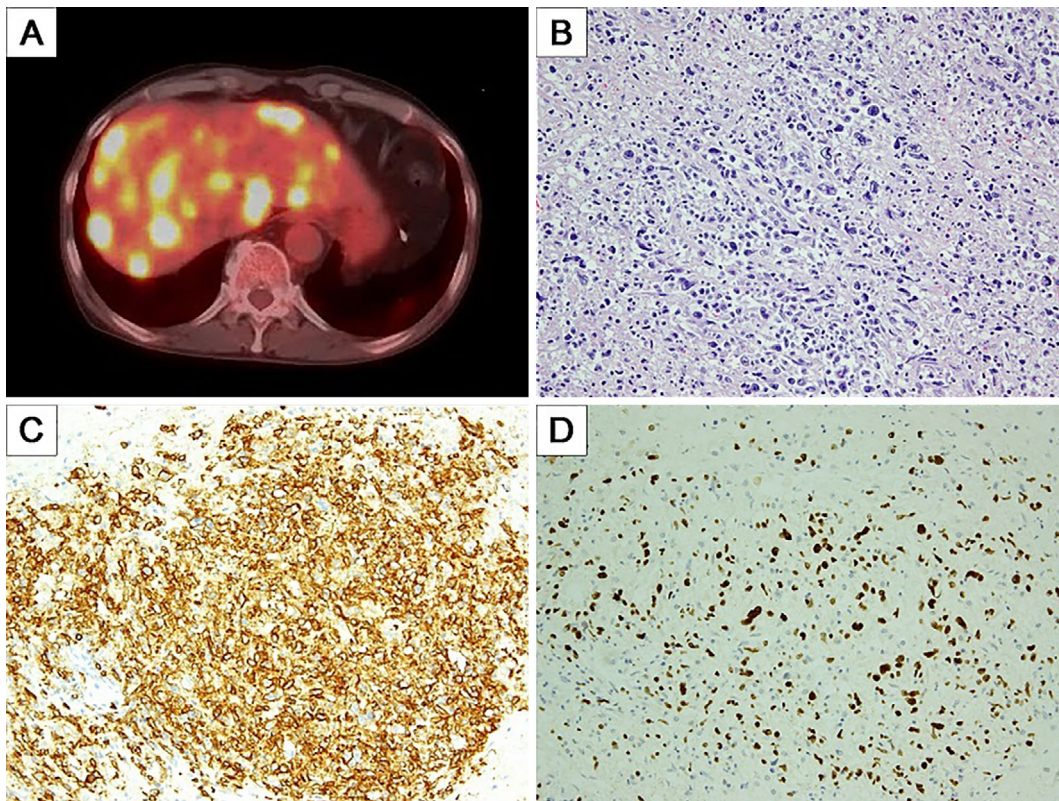
patient's anemia was observed to progress without hemolysis, and bone marrow aspiration showed MDS (refractory anemia with ringed sideroblasts; WHO classification 2008). He became transfusion-dependent, and was classified as intermediate risk according to the Revised International Prognostic Scoring System (IPSS-R). Eight cycles of AZA were administered at a dose of 75 mg/m<sup>2</sup> for 7 days, after which he became free of transfusion. Six months later, he became transfusion-dependent again and AZA was re-administered. During the 9th cycle of AZA treatment, he suffered from febrile neutropenia. Pneumonia was also found by a whole-body CT scan; however, the patient was negative for all fungus antigen and tumor markers. He received antibiotics and granulocyte-colony stimulating factor, and his fever declined. Two months later, after an X-ray revealed that the patient's pneumonia had disappeared, a 10th cycle of AZA was administered, because the patient's anemia had not improved. However febrile neutropenia occurred again. A whole-body CT scan showed a multifocal low-density area in the liver and a multifocal nodular shadow in the lung. The level of carbohydrate antigen 19-9 (CA19-9) was in-

---

<sup>1</sup>Department of Hematology, Toyota Kosei Hospital, Japan and <sup>2</sup>Department of Pathology, Toyota Kosei Hospital, Japan

Received for publication June 16, 2016; Accepted for publication October 28, 2016

Correspondence to Dr. Junji Hiraga, [j-hiraga@toyota.jaaikosei.or.jp](mailto:j-hiraga@toyota.jaaikosei.or.jp)



**Figure.** A PET/CT image and the histological appearance of DLBCL in the liver at autopsy. **A:** PET/CT detected an abnormal uptake in the multifocal liver lesions. **B:** Hematoxylin and Eosin staining, 200×magnification. Multiple lesions in his liver showed the destruction of the hepatic lobule and its replacement with large tumor cells. **C:** Immunohistochemical staining with CD20, 200×magnification. The tumor cells were CD20-positive. **D:** Immunohistochemical staining with EBER, 200×magnification. The tumor cells were EBER-positive.

creased to 65 U/mL (normal range: <37 U/mL). The level of lactate dehydrogenase (LDH) was within the normal range, but at 448 mg/dL, the IgG level was low. Gastroscopic and colonoscopic analyses detected no malignant lesion. PET/CT imaging detected an abnormal uptake in the left pulmonary hilar lesion as well as in the multifocal liver lesion (Figure A). A transbronchial lung biopsy and ultrasound-guided liver biopsy were performed, but identified mostly necrotizing tissues, and immunohistochemical staining could not identify a malignant neoplasm. His liver function was impaired and he had severe thrombocytopenia, and was not eligible for a further examination or chemotherapy. He received palliative care for a cancer of unknown primary. His LDH and CA19-9 levels were elevated to 1,515 U/mL and 1,287 U/mL respectively, and he required regular transfusions of red blood cells and platelets. He suffered from infections on several occasions, and required antibiotics treatment. The patient died 6 months after the 10th cycle of AZA. A CT scan performed 1 month before his death showed the enlargement of multiple nodular lesions of his liver and lung. After his death, an autopsy was performed. The microscopic examination of the multiple nodular lesions in his liver showed the destruction of the hepatic lobule and its replacement with large round-shaped tumor cells with necrotizing lesions (Figure B). Immunohistochemical staining

indicated that the tumor cells were positive for CD20 (Figure C), CD79a, and EBER (Figure D), and were negative for CD3, CD5, CD10, AE1/AE3 and CAM5.2. The percentage of Ki67-positive cells was nearly 70%. The same microscopic findings were observed in his left lung, mediastinal lymph nodes, and epicardium. The dilatation of the intrahepatic bile ducts and bile ductile proliferation were observed in his liver, and fibrosis was found in the portal canal area. The autopsy revealed that the cause of death was EBV-positive DLBCL, as a secondary malignancy.

## Discussion

There have been several reports on malignant lymphoma arising as a second malignancy in patients with hematological malignancies (3-5); however, malignant lymphoma arising from MDS following treatment with AZA is rare. EBV-positive DLBCL that is not related to HIV was almost classified among the “other iatrogenic immunodeficiency-associated lymphoproliferative disorders” or as “EBV-positive diffuse large B-cell lymphoma of the elderly” in the WHO 2008 criteria. Immunosuppression-related medication or aging may influence the course of lymphomagenesis. In this case, during maintenance therapy with AIHA, the only received PSL (5 mg, daily) for 3 years, and did not seem to

be immunosuppressed. After receiving 10 cycles of AZA, the patient's immunoglobulin level declined, which may have induced immunosuppression and caused DLBCL. The patient in the present case also had a high CA19-9 level, which often indicates pancreatic cancer or cholangiocarcinoma. There have been few reports on CA19-9 elevation in patients with malignant lymphoma (6, 7). An increase in the intrahepatic bile ducts and bile ductile proliferation might have been the cause of the CA19-9 elevation. The further accumulation of reports on secondary malignancies arising from AZA treatment is necessary.

**The authors state that they have no Conflict of Interest (COI).**

## References

1. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomized, open-label, phase III study. *Lancet Oncol* **10**: 223-232, 2009.
2. Götze K, Platzbecker U, Giagounidis A, et al. Azacitidine for treatment of patients with myelodysplastic syndromes (MDS): practical recommendations of the German MDS Study Group. *Ann Hematol* **89**: 841-850, 2010.
3. Higuchi M, Sasaki S, Kawadoko S, et al. Epstein-Barr virus-positive diffuse large B-cell lymphoma following acute myeloid leukemia: a common clonal origin indicated by chromosomal translocation t(3;4)(p25;q21). *Int J Hematol* **102**: 482-487, 2015.
4. Xu X, Hassan A. Extranodal marginal zone lymphoma arising in a patient with chronic myelogenous leukemia on long-term tyrosine kinase inhibitors. *Leuk Lymphoma* **55**: 715-717, 2014.
5. Chim CS, Choi PT, Lee WK, et al. Hodgkin's lymphoma as a second cancer in multiple myeloma never exposed to lenalidomide. *Ann Hematol* **92**: 855-857, 2013.
6. Peng JX, Wang LZ, Tan ZJ, et al. Concomitant non-Hodgkin's lymphoma in colon and liver: report of a rare case and review of literature. *Int J Clin Exp Pathol* **8**: 3257-3261, 2015.
7. Wang YJ, Jeng CM, Wang YC, Chang PP, Wang TH. Primary pancreatic Burkitt's lymphoma mimicking carcinoma with obstructive jaundice and very high CA19-9. *Eur J Gastroenterol Hepatol* **18**: 537-540, 2006.

The Internal Medicine is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).

---

© 2017 The Japanese Society of Internal Medicine  
<http://www.naika.or.jp/imonline/index.html>