An Autopsy Case of an Elderly Patient with Classic Hodgkin Lymphoma Presenting with a Plethora of Clinical Symptoms and Signs

Authors' Contribution:
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Data Collection B
Statistical Analysis C
Data Interpretation D
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Conflict of interest: None declared

Patient:	**Female, 88-year-old**
Final Diagnosis:	**Hodgkin lymphoma**
Symptoms:	**Fever • weight loss • dypnea**
Medication:	**—**
Clinical Procedure:	**—**
Specialty:	**Pathology**

Objective: **Unusual clinical course**

Background: Hodgkin lymphoma (HL) is a potentially curable disease with favorable outcomes. However, elderly patients with HL usually have more adverse prognostic factors and hence a much worse prognosis than younger patients.

Case Report: The patient was a woman in her 80s. She reported high fever, anorexia, and a weight loss of 8 kg within 5 months. She had been on treatment for diabetes mellitus and hypertension. She had undergone percutaneous coronary intervention and pacemaker implantation to treat acute coronary syndrome and sinus arrhythmia, respectively. Blood tests showed elevation of alkaline phosphatase, C-reactive protein, leukocyte count, CA 19-9, and carcinoembryonic antigen. Computed tomography did not show tumors in the liver, and cholangitis and sepsis were suspected. Aspartate transaminase, alanine aminotransferase, and total bilirubin gradually increased through the course of the patient's hospital stay. Despite treatment, her condition deteriorated and she died 22 days after hospital admission. At autopsy, we found stage IV HL with lymph node swelling on both sides of the diaphragm, as well as diffusely disseminated nodules in the liver and spleen.

Conclusions: Our patient had several poor prognostic factors including B symptoms, comorbidity, advanced stage, Epstein-Barr virus infection, and expression of programmed death-ligand 1 and interleukin-6, all of which were closely connected with her advanced age. Her age and comorbidities may have been the most adverse prognostic factors for her illness. An effective HL screening method for elderly individuals should be developed to ameliorate poor prognosis and adverse outcomes.

MeSH Keywords: **Antigens, CD274 • Epstein-Barr Virus Infections • Hodgkin Disease • Interleukin-6 • Prognosis**

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Background

Hodgkin lymphomas (HLs) are lymphoid neoplasias that usually affect lymph nodes. Although primary extranodal involvement is rare, dissemination to more than one organ, such as the liver, bone marrow, or lungs, is associated with advanced (stage IV) disease [1]. Owing to advances in chemotherapy and radiation therapy, outcomes for patients with early-stage HL are excellent, and prognosis in advanced-stage disease is also very good [2–4].

Nevertheless, the 5-year survival rate of elderly patients (60 years or older) is much worse than that of younger patients (15 to 39 years old) [5,6]. In elderly individuals, HLs are characterized by aggressive disease and unfavorable prognostic features including advanced age, advanced stage, comorbidity, histological subtype, Epstein-Barr virus (EBV) positivity, the number of macrophages and programmed death-ligand 1 (PD-L1)-positive cells, and serum levels of interleukin (IL)-6 [7–11]. Thus, the choice of treatment for HL in the elderly is a major challenge [4,7].

Despite a low rate of autopsies, a few recent reports describe HL cases that were diagnosed after death [12–14]. An autopsy study for unrecognized HL revealed a number of unfavorable prognostic factors that are common findings among patients who died of HL [15]. We found advanced HL at autopsy in an elderly patient in whom acute cholangitis and sepsis had been suspected. The patient had also exhibited worsening diabetes mellites and an elevation of tumor markers such as CA19-9 and carcinoembryonic antigen (CEA). This case had almost all the adverse prognostic factors mentioned above.

In this report, we discuss the prognostic factors that may have adversely affected the course of the patient. We also discuss the pathophysiological relation of HL with worsening diabetes mellites and suspected cholangitis. HL is a rather common, but vicious disease in elderly individuals [7,11]. However, screening methods to identify elderly patients with HL are lacking [16–18]. A new modality of the effective screening method is needed to ameliorate poor prognosis and adverse outcomes for elderly individuals with HL.

Case Report

The patient was a woman in her 80s. She had been treated for diabetes mellites and hypertension with medications. She had also undergone percutaneous coronary intervention and pacemaker implantation to treat acute coronary syndrome and sinus arrhythmia, respectively, 7 months before presentation. She reported anorexia and weight loss from 41 kg to 33 kg within 5 months, and she was brought to the hospital because she was experiencing breathing difficulty.

Upon physical examination on admission, her body temperature was 38.6°C; blood pressure, 110/70 mmHg; heart rate, 101 bpm; and SpO_2, 99% under nasal cannula with oxygen (3 L/min). Her skin and extremities were normal, and no superficial lymph nodes were palpable. There were no abnormal cardiac or respiratory sounds on auscultation. The abdomen was flat and soft with no tenderness. The chest X-ray showed a cardiothoracic ratio of 62.7% and no findings of pulmonary edema. Electrocardiogram did not reveal any abnormal changes.

Blood tests (Table 1) demonstrated elevated value of alkaline phosphatase (1291 U/L), C-reactive protein (15.34 mg/L), leukocyte count (9900/µL), blood glucose (405 mg/dL), hemoglobin A_{1c} (10.0%), CA 19-9 (80.76 U/mL), and CEA (5.51 ng/mL). On the patient's second day in the hospital, endoscopic retrograde cholangiopancreatography was performed because cholangitis was suspected. The examination indicated biliary sludge in the common bile duct and narrowing of the pancreatic duct in the area of the papilla of Vater. Stents were placed in the biliary and pancreatic ducts. The patient was treated with fasting, fluid replacement, meropenem hydrate, and insulin.

A high fever up to 39°C continued, and the daily difference was sometimes more than 2°C. On the fourth day, when her systolic blood pressure fell to less than 70 mmHg, she was treated with continuous intravenous dopamine for suspected septic shock. Her blood pressure became normal in 5 days and her disturbance of consciousness also recovered when her blood sugar normalized 2 weeks after her hospital stay.

Computed tomography (CT) imaging revealed moderate swelling of mediastinal and retroperitoneal lymph nodes (Figure 1A, 1B). Enhanced CT imaging was not available, but simple CT imaging did not reveal any specific tumors in the liver or spleen (Figure 2A, 2B). We did not conduct any workups for lymphoid malignancy in the nodes because the swellings were considered to be a reactive change to cholangitis and sepsis. Despite the clinical possibility of pancreatic carcinoma indicated by elevated tumor markers CA 19-9 and CEA as well as worsening diabetes mellitus, no pancreatic tumor was found on CT. Aspartate transaminase, alanine aminotransferase, and total bilirubin gradually increased through the course of her illness, while total protein and albumin decreased to around 4.0 g/dL and 1.0 g/dL, respectively, at the terminal stage. The patient's condition gradually deteriorated, and she died of respiratory failure without any aggressive life-saving procedures.

Autopsy findings

Macroscopic inspection revealed many swollen lymph nodes up to 3×3 cm in size in the mediastinal, retroperitoneal, hepatic hilar, and peripancreatic regions. These lymph nodes were grayish white in color and had an elastic consistency. The

Table 1. Blood test results.

Test	Result
Comprehensive metabolic panel	
Sodium	143 mEq/L
Potassium	4.1 mEq/L
Chloride	104 mEq/L
Blood urea nitrogen	47.9 mg/dL
Creatinine	1.24 mg/dL
Estimated glomerular filtration rate	33 mL/min
Total protein	6.5 g/dL
Albumin	2.2 g/dL
C-reactive protein	15.34 mg/dL
Hemoglobin A1c	10.0%
Blood glucose	405 mg/dL
Liver function panel	
Lactate dehydrogenase	185 U/L
Total bilirubin	0.5 mg/dL
Aspartate transaminase	46 U/L
Alanine transaminase	99 U/L
Alkaline phosphatase (ALP)	1291 U/L
ALP1	21%
ALP3	5%
γ-Glutamyltransferase	22 U/L
Hepatitis B surface antigen	Negative
Hepatitis C virus antibody	Negative
Lipid and thyroid panels	
Total cholesterol	87 U/mL
Triglycerides	46 mg/dL
Low-density lipoprotein cholesterol	134 U/mL
High-density lipoprotein cholesterol	46 U/mL
Thyrotropin	0.16 μIU/mL
Free triiodothyronine	1.00 pg/mL
Free thyroxine	0.63 ng/mL

Test	Result
Complete blood count and coagulation panel	
White blood cells	9900/mm^3
Neutrophils	90.0%
Basophils	0%
Eosinophil	0%
Lymphocytes	2.0%
Monocytes	6.0%
Red blood cells	422×10^4/mm^3
Hemoglobin	12.2 g/dL
Hematocrit	37.2%
Platelets	28.4×10^4/mm^3
Prothrombin time, international normalized ratio	1.20
Prothrombin time%	52%
Prothrombin time	14.2 s
Activated partial thromboplastin time	31.6 s
D-dimer	1.3 μg/mL
Fibrinogen	434 mg/dL
Tumor marker panel	
Serum amylase	59 U/L
Pancreatic amylase	54 U/L
CA 19-9	80.86 U/L
Carcinoembryonic antigen	5.51 ng/mL
Elastase	1006 ng/dL
DUPAN-2	108 U/mL

inspection also detected numerous white to brownish white nodules in the liver (915 g) and spleen (151 g) that were a few millimeters in size (Figure 3A, 3B). Both lungs had more than a dozen nodules of several millimeters in size (left: 297 g, right: 420 g). The right kidney had 2 nodules (7×7 mm) in the cortex, while the left kidney had no tumors. There was an elevated mucosal tumor (2×3 cm) at the base of the gall bladder. We did not observe any tumors or nodules in the pancreas. The pacemaker terminal was implanted in the right ventricle, and the stent was in the anterior descending branch of the left coronary artery. All 3 main branches of the coronary artery had

severe atherosclerosis, with 65% to 90% occlusion of the lumens. Cut sections of the heart (285 g) showed an infarction scar (5.5×1.0 cm) in the posterolateral area of the left ventricle and a few smaller scars affecting the septum and anterior area. Yellow and translucent anasarca was seen: ascites of 700 mL, pleural effusions of 350 mL (left) and 300 mL (right), and pericardial effusion of 60 mL. Mild to moderate bronchopneumonia was observed in the lungs.

Histology of the lymph nodes, liver, spleen, lungs, right kidney, and bone marrow similarly demonstrated scattered infiltration of atypical large cells with a dense admixture of inflammatory cells including small lymphocytes, plasma cells, and macrophages (Figure 4A). The atypical cells had large single nuclei or multiple nuclei with pale chromatin and prominent eosinophilic nucleolus. Neither geographical necroses nor angiocentric or angiodestructive lesions were seen. Immunohistochemically, the atypical cells were diffusely positive for CD15, CD30, and
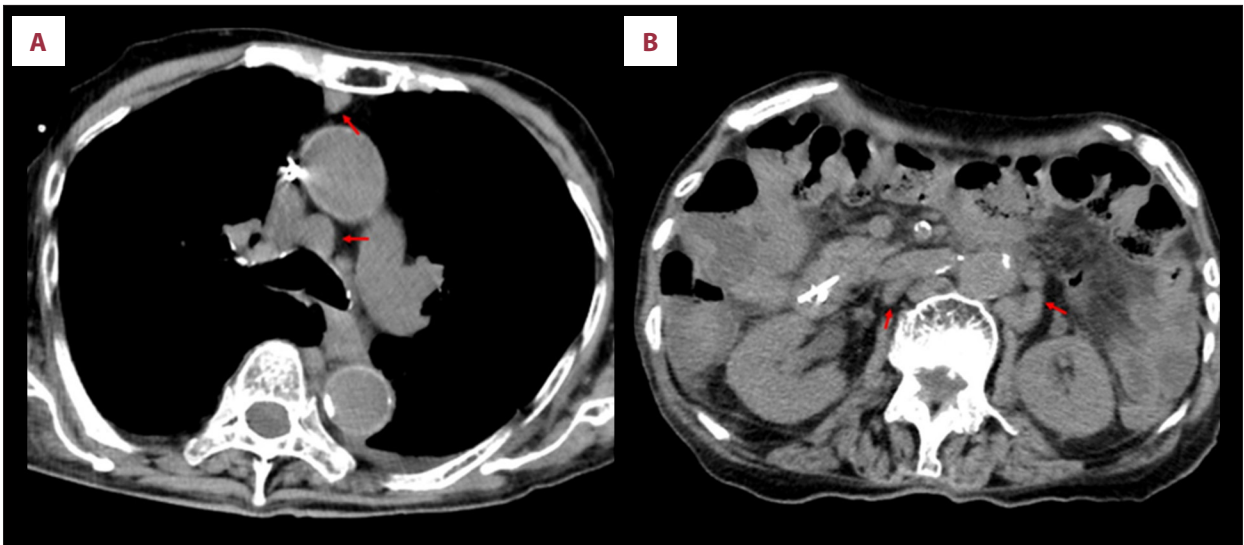
Figure 1. (**A**) Simple computed tomography image showing swollen lymph nodes, up to 2 cm in size, in the anterior mediastinum and pretracheal area (red arrows). (**B**) The computed tomography image showing swollen lymph nodes, approximately 2 cm in size, in the paraaortic area (red arrows).
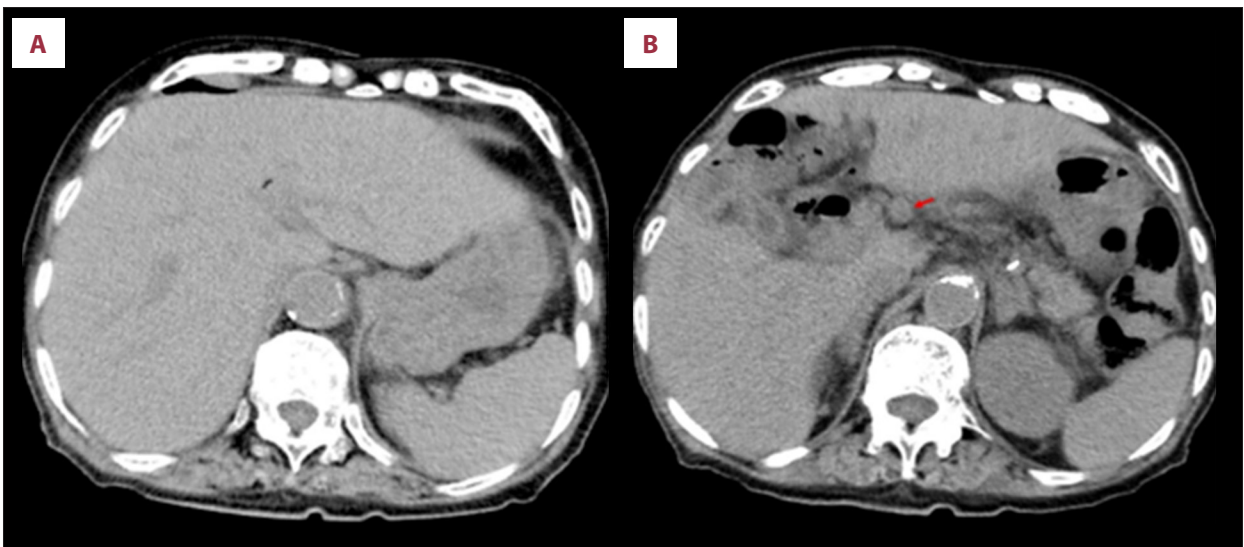

Figure 2. (**A, B**) Computed tomography imaging did not clearly show any intrahepatic lesions. However, a 2-cm swollen lymph node is visible in the hepatic hilum (**B**, red arrow).

Mum1 (Figure 4B–4D); focally positive for CD138; and negative for CD3, CD4, CD8, CD20, and CD79a. We diagnosed the case as mixed-cellularity classical HL (MCCHL). We performed immunostaining with PAX5 (Leica 1EW) twice and could not obtain the proper immunohistochemical results owing to no positive staining of Hodgkin and Reed/Sternberg (HRS) cells and the background lymphocytes.

In situ hybridization analysis with Epstein-Barr virus-encoded RNA (EBER; Leica BOND EBER probe) showed strong positivity for many HRS cells (Figure 5A). Many macrophages in the tumor microenvironment were positive for CD-68 (Agilent

KP1; Figure 5B). HRS cells positively stained strongly for PD-L1 (Ventana SP142; Figure 5C) and IL-6 (Leica 10C12; Figure 5D), moderately for LMP1 (Dako CS.1–4) and granzyme B (Leica 11F1), and weakly for tumor necrosis factor (TNF)-α (Abcam P/T2). A large number of the inflammatory cells were also positive for PD-L1 and IL-6 (Figure 5C, 5D). Monoclonal or oligoclonal proliferation of plasma cells was not seen with immunohistochemistry of kappa and lambda light chains of immunoglobulin.

In the liver, HRS cells and the reactive components heavily infiltrated the portal tracts (Figure 6A). Many hepatic bile ducts were positive for CA 19-9 (Figure 6B) but not for CEA. The gall
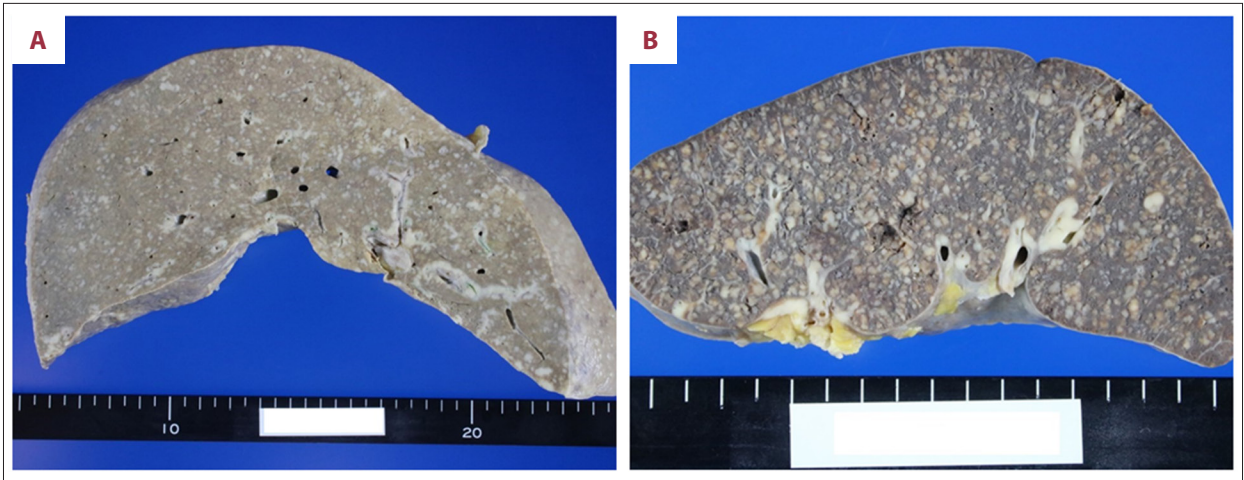
Figure 3. (**A**) A cut section of the liver with many nodules that were a few millimeters in size. Some nodules had evident distribution along the portal tracts. (**B**) A cut section of the spleen revealed numerous nodules that were up to 5 mm in size.
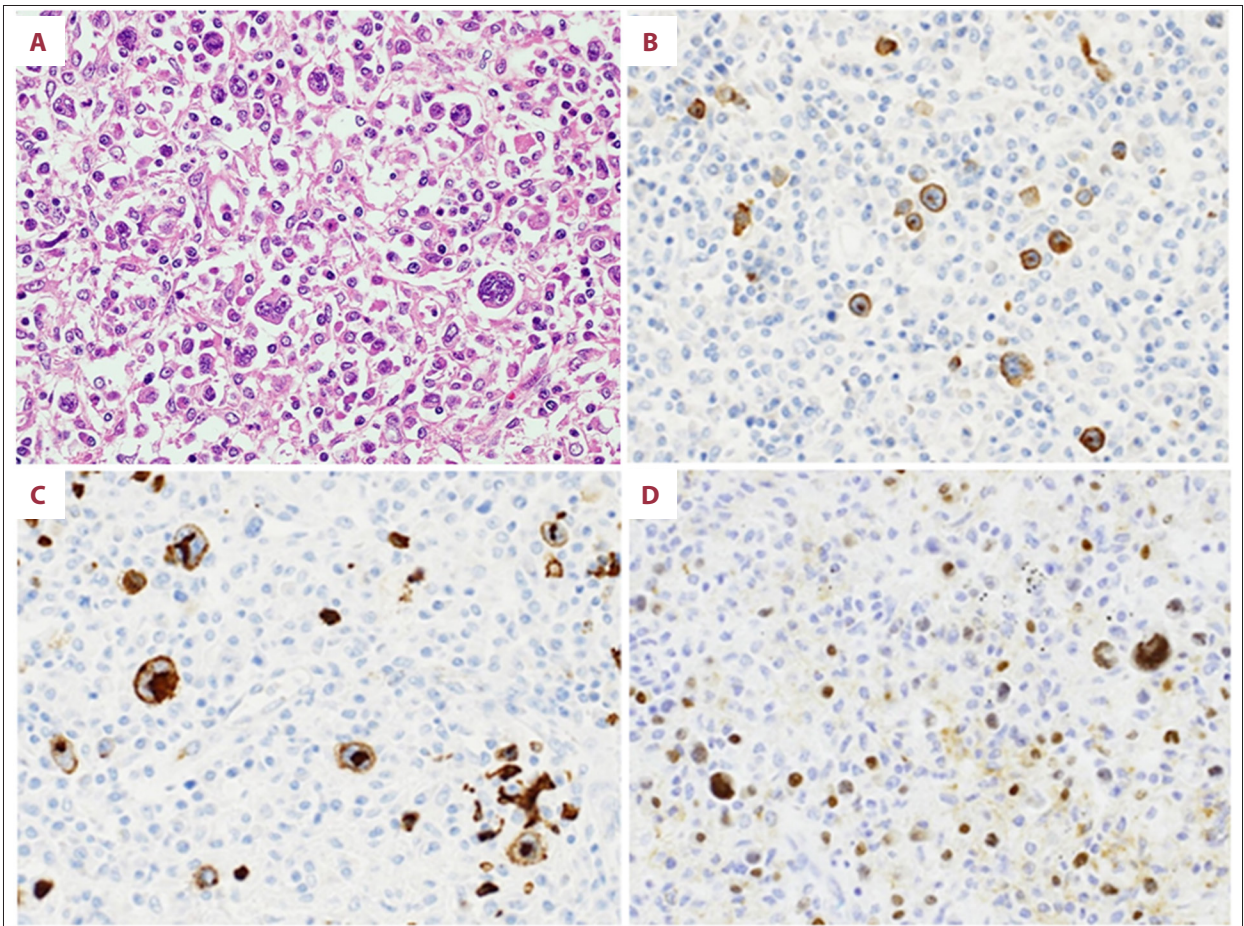

Figure 4. (**A**) Atypical large cells with a single nucleus or multiple nuclei were seen and were densely admixed with small lymphocytes, plasma cells, and macrophages in the tumor microenvironment. Hematoxylin and eosin stain; magnification, ×400. (**B–D**) The tumor cells (Hodgkin and Reed/Sternberg cells) were positive for CD30 (**B**), CD15 (**C**), and Mum1 (**D**). Magnification, ×400.
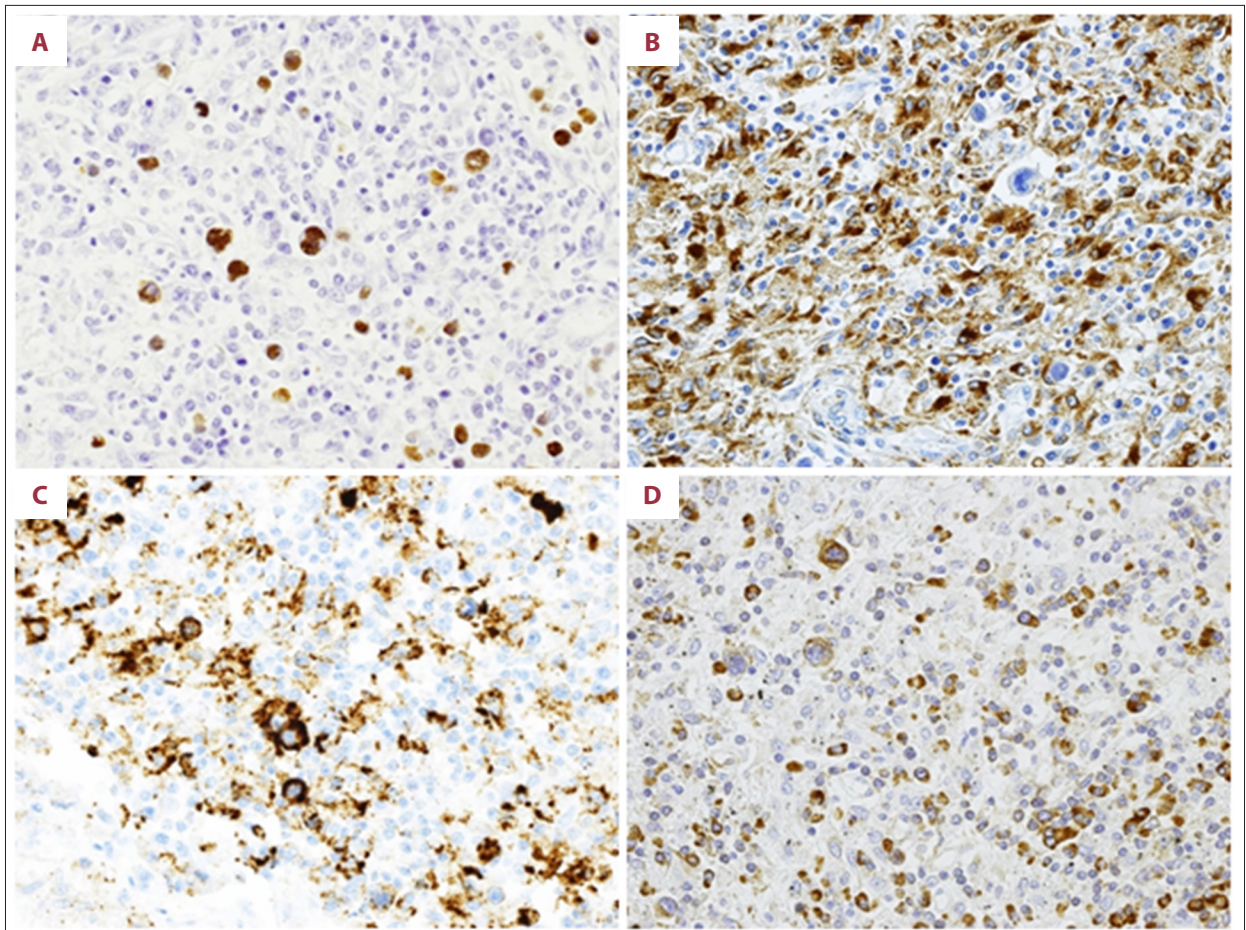
Figure 5. (**A**) *In situ* hybridization of Epstein-Barr virus-encoded RNA demonstrated positivity in the nuclei of Hodgkin and Reed/Sternberg cells but not in the inflammatory cells. Magnification, ×400. (**B**) Many CD68-positive macrophages were intermingled with CD68-negative Hodgkin and Reed/Sternberg cells and small lymphocytes. Magnification, ×400. (**C, D**) Programmed death-ligand 1 (**C**) and interleukin-6 (**D**) were strongly positive for the tumor cells and inflammatory cells. Magnification, ×400.

bladder tumor was histologically identified as adenoma with severe dysplasia/carcinoma *in situ*, and the neoplastic cells were immunohistochemically positive for CEA.

Discussion

In a surveillance study with more than 21 500 HL cases, multivariate analyses suggested that adverse prognostic factors included age (>19 years old), histologic subtypes (mixed cellularity and lymphocyte-depleted), stage IV, presence of B symptoms, no reported use of radiation, and non-white race [19]. In the International Prognostic Score, only age (≥45 years) and hemoglobin level retained independent significance in multivariate analyses of advanced-stage HL [20]. Elderly patients (≥60 years of age) with HL have disproportionately worse survival rate compared with younger patients [21]. Net survival gradually decreases with age, and the 5-year survival is the

highest (over 90%) in the youngest individuals (15 to 39 years), approximately 50% in patients aged 70 to 79 years, and less than 30% in those aged 80 years or older [5]. Accordingly, age is considered as one of the most important prognostic factors in HL, and it is intrinsically associated with HL biology [22].

According to van Sporsen et al. [23], 21% of HL patients younger than 60 years have serious comorbid conditions compared with 58% of the older patients. Comorbid conditions chiefly comprise cardiovascular disease, hypertension, chronic obstructive pulmonary disease, and diabetes. In multivariate analyses of elderly HL patients, comorbidity, but not age (60 or older), was regarded as a significant factor of overall survival, whereas the presence of a comorbidity, stage, and presence of B symptoms were each independently correlated with inferior survival [24]. The presence of comorbidity as an independent prognostic factor is particularly relevant for older patients. Moreover, the presence of severe comorbidity may
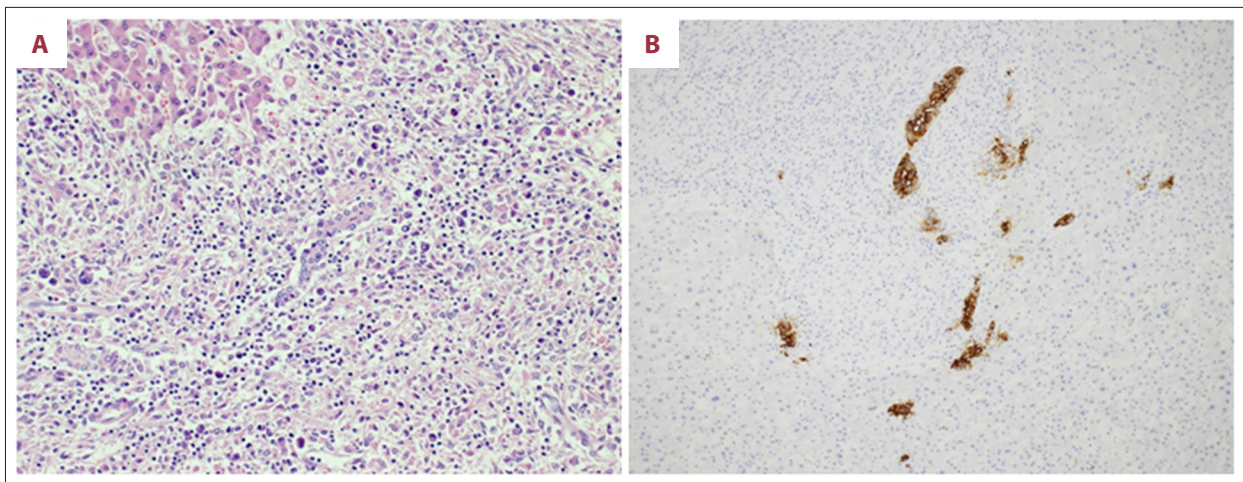
Figure 6. (**A**) Many inflammatory cells and several Hodgkin and Reed/Sternberg cells mainly infiltrated the portal tracts, with moderate distortion of the bile ducts and the neighboring hepatic cords. Magnification, ×200. (**B**) Immunohistochemistry demonstrated positivity of bile ducts for CD19-9. Magnification, ×200.

distract the patient, clinician, or both, such that the early symptoms of tumor growth may go unnoticed, leading to delayed diagnosis [25]. Our patient had actually undergone percutaneous coronary intervention and pacemaker implantation for acute coronary syndrome and sinus arrhythmia, respectively, 7 months earlier. She did not present with any symptoms and signs of HL at that time. In addition, there is no true consensus for treatment of elderly patients with HL, primarily owing to intolerance of curative treatment caused by comorbidities. Therefore, the choice of treatment is a major challenge [4,7].

It has been recognized that the number of tumor-infiltrating CD68+ and CD163+ macrophages constitutes a major biomarker that is predictive of inferior progression-free and overall survival [8,26]. Several studies have confirmed this observation [27–29]. CD68 and CD163 expression in classical HL (CHL) is related to increased age, EBER positivity, and MCCHL [28]. Old age is associated with a high frequency of presence of EBV and MCCHL [22,30]. Immunosenescence may be an explanatory factor for the presence of EBV in older patients [22,30]. MCCHL has a close relationship with EBV infection [1], and older patients with EBV-positive HL have significantly poorer outcomes compared with those with EBV-negative HL [30,31].

The natural function of signaling between PD-1 and PD-L1 is to limit certain T-cell-mediated immune responses. T-cell exhaustion is essential to the pathogenesis of HL [32,33]. Nonetheless, PD-L1 and PD-L2 on HRS cells have no prognostic significance [34]. In several tumor types, especially CHL and other tumors with a marked inflammatory infiltrate, a major component of PD-L1 expression within the total cellularity is supposed to derive from tumor-infiltrating macrophages [9,33,35]. Thus, in addition to the CD68 and CD163 expression, the number of PD-L1-positive cells in formalin-fixed paraffin-embedded

tissue can be considered as an adverse prognostic factor for elderly patients with HL [9,36].

IL-6 expression in HRS cells, as detected by immunohistochemistry, correlates with B symptoms [10,37]. The expression in background cells independently predicts poor response and freedom from treatment failure in pediatric HL [38]. Although we could not examine serum IL-6, we believe that it was probably elevated in the serum because HRS cells and many inflammatory cells immunohistochemically showed strong positivity for IL-6. The serum level of IL-6 as well as those of IL-1 and TNF-α offers an unfavorable prognosis [10,39]. In addition, patients with increased IL-6 and IL-2R have a significantly higher risk of early relapse and death [10]. However, further studies are needed to clarify virus-associated cytokine effects on poor prognosis in elderly patients with HL [30].

On the other hand, the serum level of TNF-α or IL-6 increases when glucose tolerance is impaired in diabetics compared with nondiabetics [40–42]. Worsening of glucose control positively and linearly correlates with high levels of IL-6 and leptin [43]. There are a few reported cases with IL-6-producing tumors, including lung cancer and adrenal pheochromocytoma, that exacerbated glucose tolerance in diabetic or non-diabetic patients [44–46]. Worsening of glucose tolerance in our patient may have been caused by excess production of IL-6 by HRS cells and inflammatory cells. Nonetheless, the relationship between IL-6 production and abnormal glucose tolerance in HL patients remains to be unraveled with more cases.

While liver diseases occur as a hepatic manifestation of paraneoplastic syndrome in HL [47–49], the frequency of direct involvement with HL ranges from 2% to 20% at the time of diagnosis [1,50,51] and up to two-thirds of the cases at autopsy

or necropsy [15,52]. The portal tracts are the most common site for HL involvement [52]. The involvement more typically manifests as miliary lesions (<1 cm) than as masses on CT [47]. Hence, enhanced CT and positron emission tomography (PET) imaging may be required to detect them. The lesions are more frequently seen in portal areas than in hepatic parenchyma in liver biopsy [53]. The histology of portal involvement sometimes suggests acute cholangitis and nonspecific large (≥1 mm) inflammatory infiltrates [53]. The frequency of liver involvement differs in subtypes of CHL. Lymphocyte-depleted CHL (LDCHL) has involvement of the bone marrow (11%) and liver (19%) significantly more often than the other subtypes [50]. Although LDCHL has a much poorer prognosis than the other subtypes, LDCHL and MCCHL are viewed as 2 grades of a single disease entity, often occurring in the setting of HIV infection and conferring a significantly worse prognosis [39].

Finally, HL is not a very rare disease among elderly individuals. The percentage of patients aged over 60 years ranges between 15% and 35% [7,11]. Cases in this population are characterized by aggressive disease and unfavorable prognostic features, which many authors have reported. An effective screening method to detect HL in elderly patients at an early stage and in younger patients is expected in the near future [17,18]. Less toxic and effective therapies are also needed [6,11], in addition to next-generation strategies to prevent and treat EBV infection as a means to control EBV-associated diseases [54–56]. These efforts will result in filling the disproportionately large gap between young and older patients in terms of the effectiveness of treatment and disease prognosis.

Conclusions

We reported an autopsy case of HL in an elderly woman. Such reports are very rare probably because of a low rate of autopsies. We suspected excessive production of IL-6 as the cause of worsening diabetes mellites in our case. Study of a larger number of cases is needed to unravel the relationship between IL-6 production and abnormal glucose tolerance in HL patients. HL may often involve the liver as miliary lesions occur along the portal tracts, which can be confused with cholangitis. Thus, enhanced CT and PET imaging may be required to detect them.

Elderly patients with HL usually have more adverse prognostic factors than younger patients. We discussed the adverse factors, including comorbidity, CD68+ macrophages, EBV infection, and PD-L1 and IL-6 expression in the cells of tumor microenvironment. All of these factors appear to be closely connected with advanced age and pose a major challenge in the clinical management of elderly patients. A new modality of screening for HL in elderly individuals is needed.

Acknowledgment

Conflicts of Interest

None.

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