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Case Report

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Temporary Spontaneous Disappearance of Diffuse Large B Cell Lymphoma in Patient with Hepatitis C Virus

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1. Abstract

An 80-year-old male, diagnosed with chronic hepatitis C and received interferon (IFN) treatment, but was a non-responder. Abdominal contrast CT for screening revealed a hypovascular liver tumor in the liver with para-aortic and intraperitoneal lymphadenopathy. Pathologically, biopsy of the tumor revealed mild infiltration of only inflammatory cells in the portal region and no tumorous change was recognized. Esophagogastroduodenoscopy showed multiple well-delineated elevated lesions with a depression at the center at the middle to lower gastric body. Biopsy of these lesions revealed infiltration of only inflammatory cells pathologically. Blood tests revealed mild anemia and elevated soluble IL-2 receptor but no elevation in tumor markers. After 3 months, abdominal CT showed a marked reduction in size of liver tumor and the para-aortic lymph node. Esophagogastroduodenoscopy also revealed obvious disappearance of the intragastric lesions. One year after, cervical lymphadenopathy appeared, and diagnosis was eventually made as DLBCL by biopsy of a swollen cervical lymph node.

2. Introduction

The number of new patients with malignant lymphoma was 13.3 per 100,000 and have been increasing every year in Japan [1]. Diffuse large B cell lymphoma (DLBCL) is the most common disease type of all kinds of non-Hodgkin lymphoma (NHL) and accounts for 30 – 40% [2]. The relationship between Hepatitis C Virus (HCV) infection and malignant lymphoma has been suggested for a while and occurrence of malignant lymphoma in cases with chronic hepatitis C has been reported [3, 4]. Spontaneous remission of low-grade malignant lymphoma has often been reported [5], but spontaneous remission of DLBCL which is high-grade malignant lymphoma has not been reported. We experienced a case that first developed liver tumors, para-aortic lymphadenopathy, and multiple gastric elevated lesions during the follow-up of chronic hepatitis C, which spontaneously disappeared temporarily. Then, cervical lymphadenopathy later appeared, and diagnosis was eventually made as DLBCL by biopsy of a swollen cervical lymph node. We reported such a rare case with DLBCL.

3. Case Report

An 80-year-old male, diagnosed with chronic hepatitis C at the medical check-up around 1990, received interferon (IFN) treatment, but was a non-responder. Because, Hepatocellular Carcinoma (HCC) was detected in the liver section 8, he has received partial hepatectomy and continued a periodical visit to the clinic. 10 years after the resection, abdominal contrast CT (Figure 1A and 1B) for screening revealed a hypovascular tumor 18 mm in diameter in the liver section 5 with para-aortic and intraperitoneal lymphadenopathy, and he was referred to our hospital. Esophagogastroduodenoscopy (Figure 1C and 1D) showed multiple well-delineated elevated lesions with a depression at the center at the middle to lower gastric body. Biopsy of these lesions revealed infiltration of only inflammatory cells pathologically, and no obvious lymphadenopathy was observed.

Liver tumor biopsy was considered and he was admitted to the hospital for further examination. On admission, blood tests revealed mild

anemia and elevated soluble IL-2 receptor but no elevation in tumor markers. Compared with previous abdominal CT, the liver tumor was 10 mm in size with an obvious shrinking tendency. Pathologically, biopsy of the tumor revealed mild infiltration of only inflammatory cells in the portal region and no tumorous change was recognized (Figure 2A). Three months after biopsy, abdominal CT showed a marked reduction in size of liver tumor and the para-aortic lymph node (Figure 2B) and it was judged that EUS/FNA was difficult to carry out. Since esophagogastroduodenoscopy also revealed obvious disappearance of the intragastric lesions and he was followed-up at the outpatient clinic (Figure 2C and 2D).

One year later, cervical lymph node swelling was observed (Figure 3A), and biopsy of the lymph node was enforced. Atypical large lymphoid cells were found with chromatin-rich nuclei (Figure 3B). These cells were positive for CD10, CD20, and CD23. These results led to the diagnosis of DLBCL. CHOP with rituximab was started and the same treatment is ongoing.

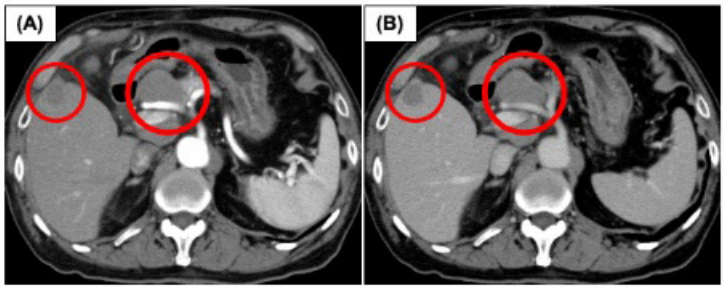

Figure 1A & 1B: Computed tomography (CT) scan showing a hypovascular liver tumor and para-aortic and intraperitoneal lymphadenopathy (red circles).

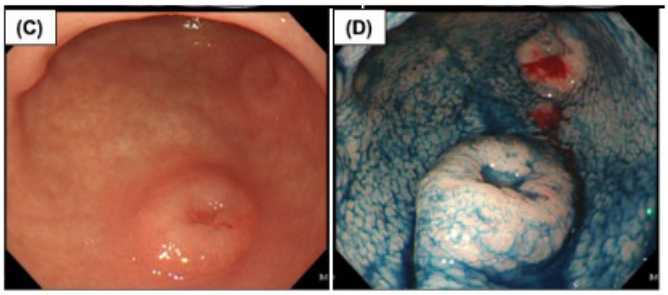

Figure 1C & 1D: Esophagogastroduodenoscopy showed multiple well-delineated elevated lesions with a depression at the center at the middle to lower gastric body.

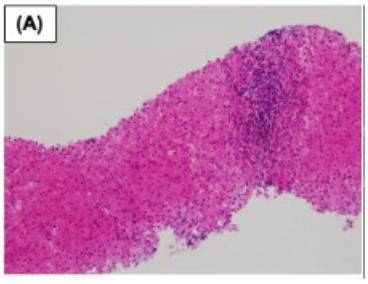

Figure 2(A): Microscopic picture of the tissue from liver tumor (Hematoxylin & Eosin staining) at x100 magnification.

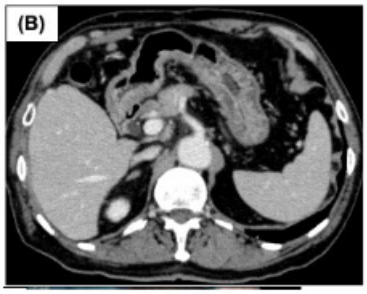

Figure 2(B): CT scan 1 months after the tumor biopsy.

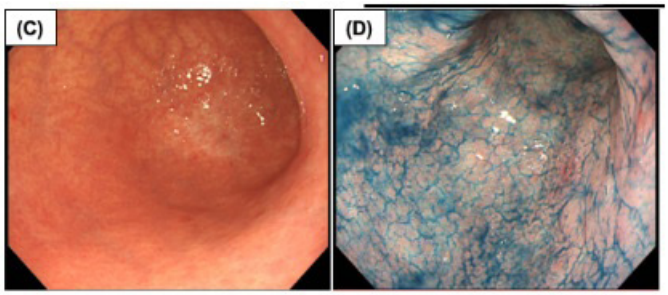

Figure 2(C, D): Esophagogastroduodenoscopy 3 months after tumor biopsy.

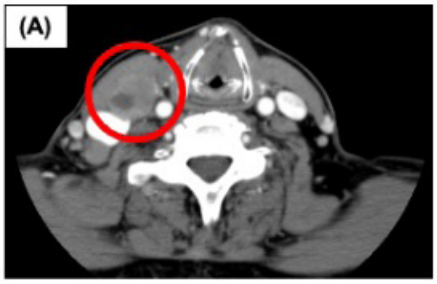

Figure 3 (A): CT for cervical lymphadenopathy (red circle).

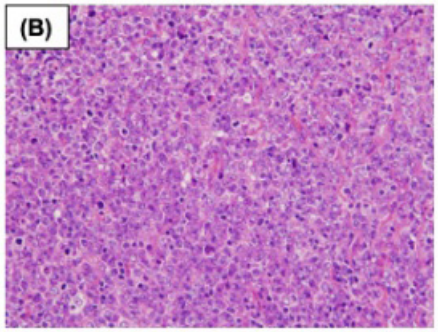

Figure 3(B): Microscopic picture of the tissue from cervical lymph node (Hematoxylin & Eosin staining) at x400 magnification.

4. Discussion

It is known that extrahepatic lesions that are developed by the virus per se or host immune response at the time of HCV infection are present. However, the onset mechanism remains poorly understood [6]. Extrahepatic manifestations include cryoglobulinemia, membranous proliferative glomerular nephritis, porphyria cutanea tarda, Sjogren syndrome, Mooren's corneal ulcer, malignant lymphoma, and myositis, and the relationship of chronic hepatitis C with NHL, in particular, B cell lymphoma has often been suggested. It was reported that the infection rate of HCV in cases with B cell lymphoma was 0.5 – 25% in the world [7]. Ferri et al. investigated the occurrence rate of lymphoma in 500 cases with chronic hepatitis C, and DLBCL was concurrently observed in 14 cases (2.8%) [4]. Of mixed-type cryoglobulinemia with a monoclonal and polyclonal immunoglobulin increase (type II and III), the frequent onset of DLBCL is known in type II cryoglobulinemia [8]. It has been elucidated that some cases with chronic hepatitis C accompany type II cryoglobulinemia as one of the extrahepatic manifestations, and the relationship with the occurrence of DLBCL has been suggested [9]. Both DLBCL and mixed-type cryoglobulinemia are induced as a result of activation of B cells in a multiple-step pathway [10]. With regard to the onset mechanism of NHL in cases with HCV infection, since HCV is not incorporated into the host cell genome due to the absence of reverse transcriptase in HCV and existence of oncogenes has yet to be proven, the following hypotheses have been suggested: HCV directly infects B cells and induces the disease [11]; E2 protein in the envelope of HCV binds CD81 expressed on the hepatocytes and B cells and activation of the complex induces the activation of B cells [12]; and activation of the systemic immune system or the suppressed state by HCV infection influences malignant transformation of B cells [10]. However, the precise mechanism remains unclear. Since B cells proliferated monoclonally in the intrahepatic lymphoid follicles in cases with chronic hepatitis C and immunostaining revealed overexpression of proliferation markers such as bcl-2 and Ki-67, it was speculated that accumulation of lymphocytes in the portal region in the liver with chronic hepatitis was a precursor lesion of malignant lymphoma [13]. In B cell lymphoma associated with HCV infection, IFN treatment eliminated HCV and induced a remission of malignant lymphoma [14], which suggested the relationship between HCV infection and malignant lymphoma. Although it is known that spontaneous remission is observed during the follow-up in some cases with systemic malignant lymphoma, spontaneous disappearance of highly malignant DLBCL is rare [15-17]. The leading hypothesis regarding spontaneous remission in relation to NHL involves modulation of the host immune system to viral or bacterial infection and traumatic effects including biopsy but the mechanism remains unclear [6].

Most patients with DLBCL are cured with a combination of rituximab with anthracycline-based chemotherapy, such as the R-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab; immunochemotherapy) regimen [18]. Rituximab is a monoclonal antibody targeting CD20, a common B-cell marker that is present on the majority of malignant lymphoma cells in DLBCL [19]. Although its mechanism of action has not been completely elucidated, several actions have been postulated, including complement-mediated toxicity [20]. Zuckerman et al., reported the disappearance of B-cell clones from the blood of HCV-infected patients after antiviral therapy [21]. In cases of HCV-related splenic marginal zone lymphoma, antiviral treatment with IFN and ribavirin proved to be an effective option [22]. But, in HCV-infected patients with DLBCL, larger therapeutic trials of antiviral therapy were not reported.

5. Conclusion

We experienced a case with highly malignant DLBCL in association with chronic hepatitis C. Although the lesion spontaneously disappeared temporarily, a lesion re-appeared one year later, and biopsy led to the diagnosis of DLBCL. He did not hope IFN therapy, so a treatment regimen of CHOP with rituximab was selected.

It is markedly rare that B cell lymphoma associated with HCV infection spontaneously, though temporarily, disappears. Although certain immune reaction with B cells may potentially be involved, the mechanism of spontaneous disappearance remains unclear. Since it is highly likely that such malignant lymphoma may recur after spontaneous disappearance, periodical evaluation of the whole body by imaging modalities is considered necessary.

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