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Case Report

Fourth malignancy after treatment of Hodgkin's lymphoma: a case report

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Abstract: Objective: To evaluate the incidence and treatment of the fourth malignancy in a Hodgkin's lymphoma (HL) patient. Methods: We reported a HL patient after treatment that developed the second, third, and fourth malignancies (chronic myeloid leukemia, chronic lymphocytic leukemia, and gastric adenocarcinoma) in relatively short time (75 months). The diagnosis was confirmed by pathology, bone marrow morphology, flow cytometry, karyotype and fusion gene examination. Results: He received surgery and chemotherapy. He achieved good response for triple malignancies. After diagnosis with gastric cancer, he orally administered compound tegafur capsule, apatinib and imatinib. Conclusion: The fourth malignancy of HL patient is extremely rare. We recommend a strict follow-up, for HL to detect multiple malignancies.

Keywords: Fourth malignancy, Hodgkin lymphoma, chronic myeloid leukemia, chronic lymphocytic leukemia, gastric adenocarcinoma

Case report

A 55-year-old male was admitted to our hematological department in April 2014 with asthma and abdominal mass for 2 months. His past medical history revealed HL41 months ago. Personal history: He smoked one pack of cigarettes per day for 25 years. At beginning of disease, he was admitted to outside hospital with chest suppress for 2 weeks. The magnetic resonance imaging (MRI) showed an anterior mediastinal mass 9.7×7 cm (**Figure 1**). He underwent resection of mediastinal mass. According to consult of our pathologist, tumor cells were positive for CD15, CD30, Ki67, and negative for CD3, CD5, CD20, CD99, TdT, AE1/AE3. The diagnosis of nodular sclerosis classical Hodgkin lymphoma (cHL-NS) was confirmed. He received ABVD regimen (Epirubicin, bleomycin, vinorelbine and dacarbazine) for 4 cycles. He achieved CR. In this hospitalization, physical examination presented splenomegaly (AB line 6 cm, AC line 8 cm, DE line -4 cm). The laboratory tests revealed that blood routine showed leukocytosis (WBC 275.6×10^9/L, with neutrophils 73.5%, blasts 3%, eosinophils 7.5%, basophils 9%, lymphocytes 2%), hemoglobin (HGB) 97 g/L, platelet (PLT) 496×10^9/L. The lactic dehydrogenase (LDH) 731 U/L, β2-microglobulin (β2-MG) 4.93 mg/L, Epstein-Barr virus (EBV), cytomegalovirus (CMV), liver and renal function were normal. The immune function was low ($CD3^+$ $CD4^+$ 26.81%, NK cell 15%, $CD3^-$ $CD19^+$ 30.8%). Bone marrow (BM) smears showed hypercellular with blasts 3.5%, granulopoietic lineage 74%, eosinophils 9%, basophils 4%, lymphocytes 1%, megakaryocytes 620/per slid. The granulocyte/erythroid ratio was 38.1. Flow cytometry (FCM) of BM showed myelocytic lineage 85.31%, $CD34^+$ $CD117^+$ 2.1%, $CD10^+$ 22.7%, partial expression for CD56, CD15 (dim), basophils 3.75%. The cytogenetic analysis performed according to G banding. Twenty cells were evaluable and characterized by presence of 46XY, t(9;22)(q34;q11) (**Figure 2**). The molecular biologic study performed by the fluorescence quantity polymerase chain reaction (FQ-PCR) technique demonstrated the fusion gene BCR-ABL p210 rearrangement and negative for 8 types fusion genes (AML1-ETO, PML-RARa etc.). The computed tomography (CT) showed splenomegaly with 10 rib unit. He was diagnosed as ① CML, chronic phase (CP) intermediate risk group. ② cHL-NS. CR. He orally administered imatinib 400 mg/day.

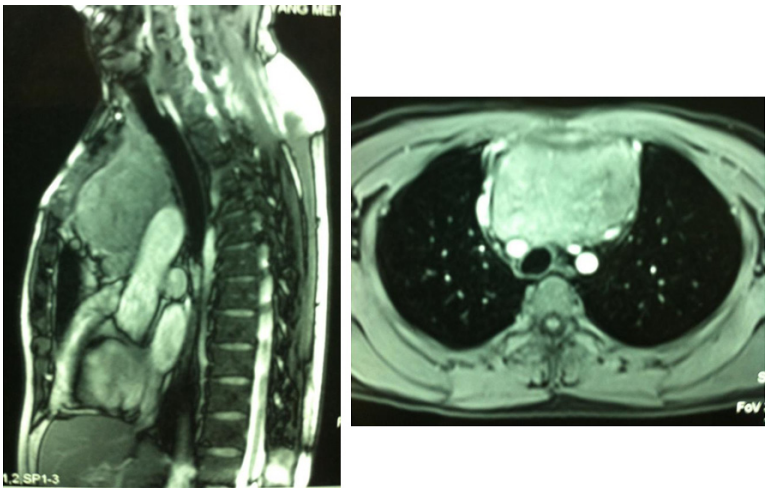

Figure 1. Sagittal and axial MRI of chest showing a anterior mediastinal mass.

In April 2015, he was admitted to our hematological department with bloody stool and tired for 3 days. Physical examination presented pallor, no superficial lymphadenopathy or hepatosplenomegaly. The laboratory tests showed HGB 63 g/L, WBC 13.65×10^9/L with neutrophils 33%, lymphocytes 66%, the absolute value of lymphocyte was 9.07×10^9/L, PLT 161×10^9/L, LDH 149 U/L, β2-MG 2.3 mg/L. Occult blood in the stool was positive. The immune function was low ($CD45^+$ $CD3^+$ 5.7%, $CD3^+$ $CD4^+$ 2.5%, $CD3^+$ $CD8^+$ 2.9%, NK cell 4.5%, $CD3^-$ $CD19^+$ 89.9%). The gene rearrangement examination of peripheral blood showed positive for B-cell lymphoma IGH and IGK rearrangement. BM smear showed prolymphocytes 3.5%, lymphocytes 55% (**Figure 3**). megakaryocytes 3/per slid. The granulocyte/erythroid ratio was 1.16:1. FCM of BM showed $CD19^+$ $CD5^+$ 36.6%. The cells were positive for CD5, CD19, CD20, CD23, CXCR4, CD22 (dim), and negative for CD7, CD10, CD11C, CD15, CD25, CD30, CD33, CD34, CD38, CD103, CD125, CD138, (**Figure 4**). The karyocyte showed 46XY. The fusion gene demonstrated BCR-ABLp210/ABL 0.85%. The CT revealed bilateral cervical anterior, mediastinal, interval gap of trachea and carina lymph nodes enlargement (maximum lymph node size 1.0 cm), without splenomegaly. He was diagnosed as ① CLL Rai I, Binet B stage. ② CML, complete hematological response and major cytogenetic response. ③ cHL-NS, CR. He was orally administered imatinib 400 mg/day.

According to the International Workshop on Chronic Lymphocytic Leukemia guidelines, this stage of CLL requires only monitoring without treatment.

In February 2017, he was admitted to our hematological-department with anorexia and weight lost 6 kg for 1 month. Physical examination presented pallor, no hepatosplenomegaly, bilateral cervical and inguinal lymph nodes enlargement (maximum lymph node size 1 cm). The laboratory test showed HGB 110 g/l, WBC-14.3×10^9/L, with neutrophils 19.6%, lymphocytes 78.30%, the absolute value of lymphocyte 11.24×10^9/L, PLT 146×10^9/L. The liver and renal functions, LDH, β2-MG, EBV, CMV, were normal. Occult blood in the stool was positive. Tumor marker revealed normal for CEA, CA199, CA242, CA724, AFP, CA50. The immune function was low ($CD45^+$ $CD3^+$ 5.6%, $CD3^+$ $CD4^+$ 2.3%, $CD3^+$ $CD8^+$ 31%, NK cell 2.1%, $CD3^-$ $CD19^+$ 92.6%). Contrast Enhanced Computed Tomography (CECT) scan revealed pulmonic hilus and iliac lymph nodes enlargement (maximum lymph node size 3×2 cm) and small ascites. A gastroscopic examination showed mucosa erosion and white coat of upper part of gastric corpus (**Figure 5**) and positive for helicobacter pylori (HP). The biopsy confirmed gastric low differential adenocarcinoma (**Figure 6**). He was diagnosed as ① gastric adenocarcinoma (pT3N0M1 stage III), ② CML, complete hematological response and major cytogenetic response. ③ CLL Rai I, Binet B stage, ④ cHL-NS, CR. He orally administered compound tegafur capsule, apatinib, and imatinib. Otherwise, he received omoprazole, amoxicillin, and clarithromycin for HP infection.

Discussion

Today, successful treatment has improved the life expectancy of HL patients and the risk of late treatment affects is becoming an important issue. After treatment of HL patients, the second malignant neoplasm (SMN) was more common. The third malignant neoplasm is rare. To best of our knowledge, a fourth malignant neoplasm has never been reported in relatively

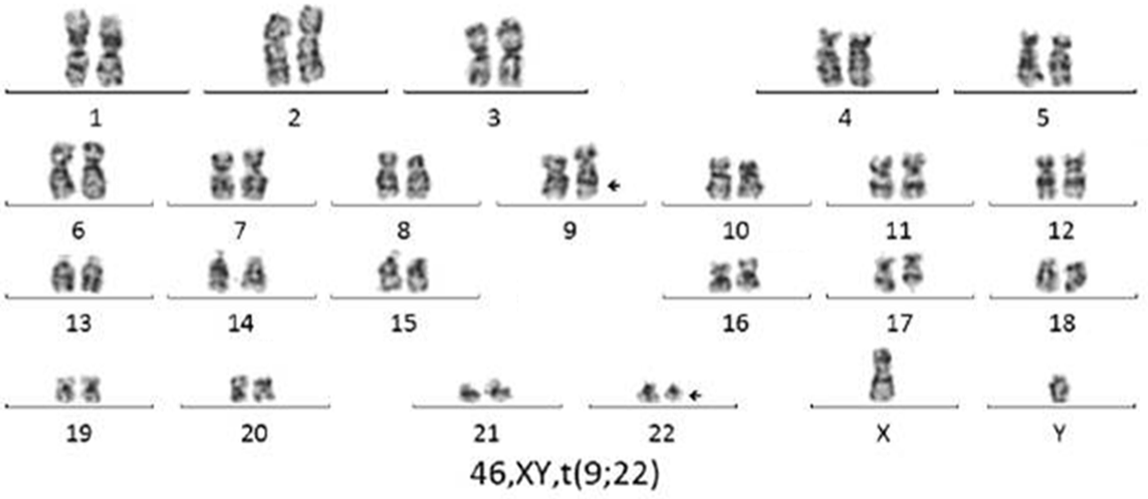

Figure 2. Karyotype of bone marrow showing philadelphia positive.

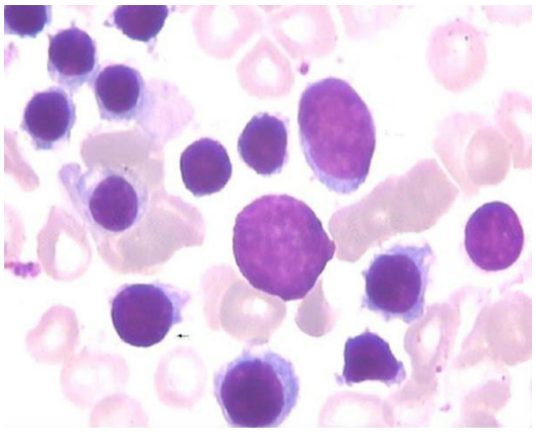

Figure 3. Bone marrow smear showing lymphocytosis (Wright-Giemsa×1000).

short time. Robinson etal reported 209 patients with HL. Among them, 22 patients (10.5%) presented SMN, including patients of 16 solid tumors, 3 lymphoma, 2 acute myelogenous leukemia (AML) and 1 CML. Owing to SMN, 13 patients died, including 2 (0.96%) of a third malignancy [1]. Beaty etal described 499 HL patients. After treatment, 25 patients (5.5%) developed SMN, including patients of 19 solid tumors, 4 AML, 1 non-Hodgkin lymphoma and 1 CML. Among them, 3 (0.65%) patients had a third malignancy [2]. In SMN patients, there was no CLL. The third malignancy of HL mainly based on the case report in the literature. Grudeva-Popova etal reported an 11-year old HL patient after treatment with chemotherapy and radiotherapy. In 24 years duration, he underwent the second and third solid malignancy [3]. Giannopoulos et al reported 13-year-old HL patient achieved CR after radiation. Seventeen years later, the second tumor was gastric sarcoma. Twenty months later, the third tumor was ductal invasive carcinoma of the breast. Author reviewed the data of several investigators. The development of blood malignancies was conformed during the first decade following HL treatment and of solid tumors after 15 years [4]. Our patient with metachronous blood and solid malignancies was very rare in relatively short time.

The ABVD regimen is lower toxicity than BEACOPP regimen. The SMN of HL patients with ABVD regimen occurred in 0.4% [5]. The relationship between the use of alkylating agents, anthracycline, and in particular topoisomerase II inhibitors hasbeen associated with the development of SMN [6-8]. Each cytotoxic agent may damage DNA, which may lead to various cytogenetic abnormalities and contribute to various biological characteristics.

The unfavorable factors of our patient included over 50 years old, smoke, ABVD and imatinib chemotherapy, HP infection, and low immune function. Our data suggest that clinical observations remind us to investigate the possibility of multiple primary cancers. The long term monitoring should be considered for lymphoma survivors.

Acknowledgements

The informed consents of all patients were obtained and Ethics Committee approval of

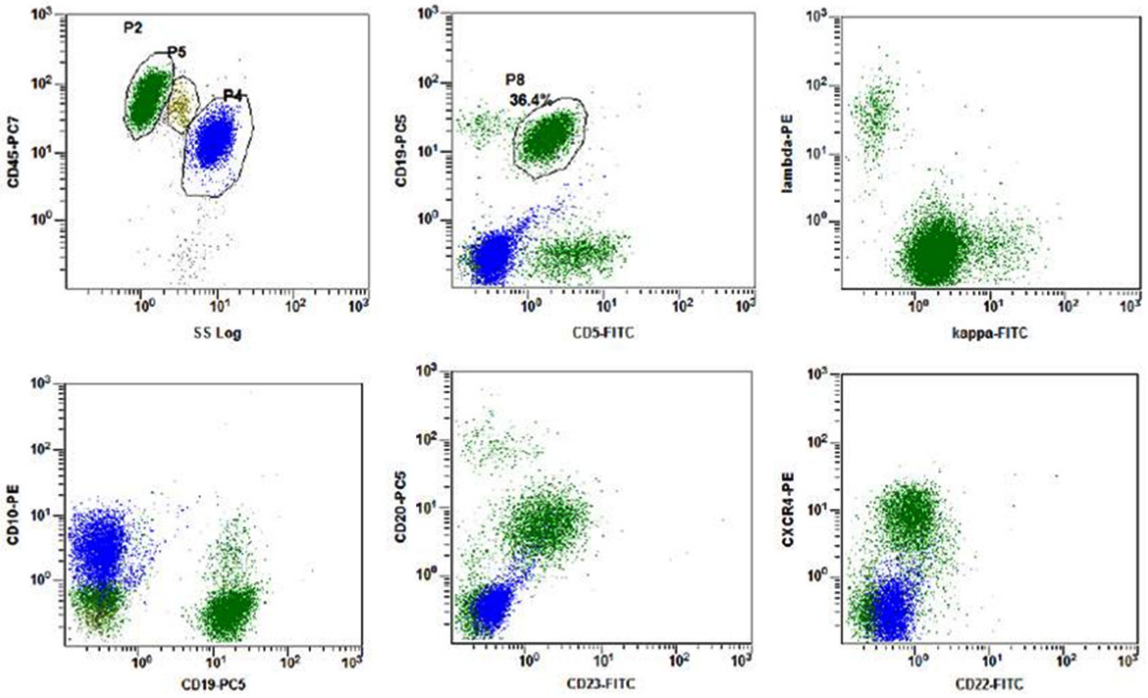

Figure 4. FCM of bone marrow showing positive for CD5, CD19, CD20, CD22, CD23.K

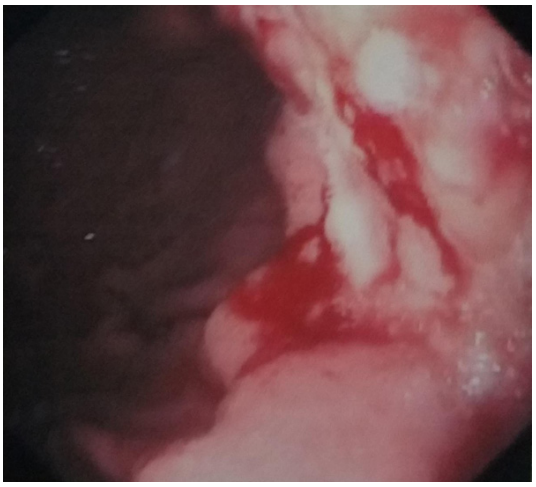

Figure 5. Gastroscope showing mucosa erosin and white coat in upper part of gastric corpus.

Shanxi Tumor Hospital was received. Written informed consent was obtained from the patient's family for publication of this case study.

Disclosure of conflict of interest

None.

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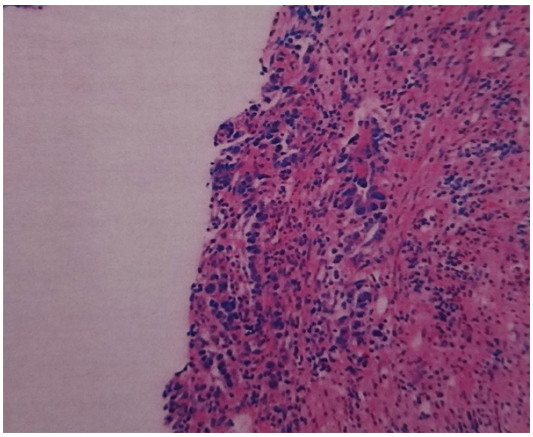

Figure 6. Pathological figure showing gastric adenocarcinoma grad 3 (H&E×400).

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