Case Report

Hemophagocytic syndrome as the initial manifestation of CD20(+) B-cell non-Hodgkin lymphoma with EGFR(+) lung adenocarcinoma: a case report and literature review

Wei Yang, Xue-Jin Zhang, Xiao-Feng Xu

Department of Hematology, Zhejiang Chinese Medicine and Western Medicine Integrated Hospital (Hangzhou Red Cross Hospital), 208# Huancheng East Road, Hangzhou 310003, Zhejiang, China

Received July 8, 2018; Accepted January 10, 2019; Epub May 15, 2019; Published May 30, 2019

Abstract: We report a case of CD20(+) B-cell non-Hodgkin lymphoma (NHL) with hemophagocytic syndrome (HLH) as the initial manifestation, which was found in a 51-year-old female. After being treated with R-CHOP regimen chemotherapy, the patient’s HLH was controlled, but the chest computed tomography (CT) showed no significant changes in the left upper lung lesions. The patient was diagnosed with lung adenocarcinoma after a percutaneous lung biopsy and the determination of the mutation of exon 21 L858R in the epidermal growth factor receptor (EGFR) gene. The patient received R-GDP scheme chemotherapy and icotinib targeted therapy. After the treatment, her chest CT showed that the left upper lung cancer lesions were more absorbed than before.

Keywords: Hemophagocytic syndrome, non-Hodgkin lymphoma, epidermal growth factor receptor, lung adenocarcinoma

Introduction

Hemophagocytic syndrome (HLH) is a very serious syndrome clinically which needs a timely diagnosis and treatment. It can be divided into two categories: one is primary or familial, which is common in children less than 2 years old; the other is secondary and caused by infection, rheumatic diseases, tumor, etc., which is common in adults [1]. According to reported statistics, the most common cause of adult HLH is lymphoma and the EB virus, followed by bacteria, fungi and tuberculosis [1, 2].

The incidence of lung cancer has increased in recent years and become one of the leading causes of cancer death. For those patients with advanced non-small cell lung cancer (NSCLC), chemotherapy is the principal treatment, the effective rate of which is about 35%–45% [3]. In recent years, molecular targeted therapy with epidermal growth factor receptor (EGFR) has become a new therapy for NSCLC [4]. Icotinib an anticancer drug whose patent is owned by China, is a new, small-molecule tyrosine kinase inhibitor (TKI) targeting EGFR with high efficiency. The drug's physical and chemical properties, mechanism, and clinical effectiveness for NSCLC are all comparable with those of gefitinib and erlotinib. Moreover, the safety of icotinib is better than the above two drugs [5, 6].

The paper aims to describe the best diagnosis and treatment for this kind of multiple cancer by reporting a case of rare CD20(+) B-cell NHL with HLH as the initial manifestation and complicated with lung adenocarcinoma.

Case description

The patient, a 51-year-old woman, was admitted to the Department of Respiration in our hospital because of “fever for five days”. Five days before hospitalization, the patient had fever due to a cold. The highest temperature reached 40°C, which was accompanied by a cold, a little cough, and white colored sputum. There was no
abdominal pain or diarrhea, no dysuria, urinary frequency, or urgency. She came to our hospital for emergency treatment. There was no obvious improvement after anti-infection therapy with Cefoxitin®. The patient was then transferred to the Department of Respiration for hospitalization.

After being admitted to the department of Respiration, the patient received an illness evaluation. The blood routine showed white blood cell (WBC) 4.9×10⁹/L, hemoglobin (HB) 110 g/L, platelet (PLT) 207×10⁹/L; the blood coagulation routine showed prothrombin time (PT) 13.6 s, activated partial thromboplastin time (APTT) 42 s, D-dimer 2620 μg/L, fibrinogen (Fib) 482 mg/dl, 3P-negative; the blood biochemical examination showed creatinine 87.1 μmol/L, direct bilirubin 9.8 mmol/L, indirect bilirubin 7.7 mmol/L, albumin 35.6 g/L, triglycerides 1.73 mmol/L, lactate dehydrogenase (LDH) 313 U/L, ferritin 3189.6 ug/L, procalcitonin 0.28 ng/ml. The abdominal B-mode ultrasonography showed that liver volume was increased, the maximal oblique diameter of the right liver was 15.4 cm, and the spleen thickness was around 4.3 cm. A chest computed tomography (CT) showed that patchy, density increased shadows were found in the two upper lobes of her lung, the periphery lesions of the upper left lung were surrounded by a ground glass shadow, and a number of grinding glass small nodules and solid nodules could be seen in the two upper lobes of her lungs with a clear boundary, small patchy high-density shadows could be seen in the middle lobe of right lung with an unclear boundary, there was no significant enlargement of the hilar or mediastinal lymph nodes, and a bilateral pleural effusion could be seen (Figure 1A).

After admission, the patient was given a Sulperazone® 2.0 g Q8H intravenous injection combined with Moxifloxacin® 0.4 g QD intravenous infusion anti-infection treatment for one week. However, the patient still had a continuous fever and her body temperature fluctuated between 40.8 and 37.9°C. The blood routine showed that her WBC, HB and PLT counts decreased progressively. Multiple blood cultures showed no bacteria; Her urine and stool cultures were negative. Her surface antibodies for hepatitis B were positive, hepatitis A, C, D, and E antibodies were negative; acquired immunodeficiency syndrome (AIDS) antibodies and syphilis antibodies were negative, and tuberculosis antibodies and T-SPOT were negative. Anti-nuclear antibodies, anti-neutrophil cytoplasmic antibodies, and rheumatoid factor were negative. DNA detection of the Epstein-Barr virus, cytomegalovirus, and coxsackie virus were all negative. The malaria parasite was not found in the blood smear. Fungus (1,3) - beta-D dextran assay: 13.72 pg/ml (0-60). Aspergillus immunity test: 0.233 (0-0.5). Plasma, gamma globulin and other supportive treatments were taken. Sulperazone® and Moxifloxacin® were stopped. Tienam® 1.0 g q8h intravenous drip, Cancidas®
Non-Hodgkin lymphoma with lung adenocarcinoma

50 mg qd intravenous drip and Vancomycin® 1.0 q12h intravenous drip were combined to anti-infection. And the blood routine: WBC 1.4×10⁹/L, HB 63 g/L, PLT 31×10⁹/L. Blood coagulation routine: PT 19.1 s, APTT 45.6 s, Fibrinogen 91 mg/dl, D-dimer 16080 μg/L. Biochemical routine: creatinine 87.1 μmol/L, Direct bilirubin 9.4 mmol/L, indirect bilirubin 13.2 mmol/L, albumin 32.7 g/L, glutamic-pyruvic transaminase 20 u/L, triglyceride 3.12 mmol/L, lactate dehydrogenase 170 U/L, Na⁺ 135 mmol/L. A bone marrow examination was carried on and abnormal cells were found in the smear, which were considered lymphoma cells (Figure 2A); A bone marrow biopsy indicated that bone marrow tissue hyperplasia was active, the number of lymphocytes increased significantly, and were relatively large (Figure 2B), immunohistochemistry: CD20(+) (Figure 2C), CD79a(+) (Figure 2D). Bone marrow cell immunophenotyping (with threshold analysis set on a CD45/side scatter point diagram) demonstrated the cells in the original area occupied about 1% of the nuclear cells, in which the CD34+ cells occupied about 0.8% of the nuclear cells, and were scattered; Lymphocytes occupied about 8.5% of the nuclear cells, with a reduced proportion, and the distribution of each lymphoid subgroup was generally normal, CD4/CD8 = 0.82; Mononuclear cells occupied about 1.5% of the nuclear cells, and the phenotype was mature; Granulocytes occupied about 78% of the nuclear cells, and some cells were considered to have developmental abnormalities. The chromosome was a normal karyotype. IgVH and IgK gene rearrangements were detected in the bone marrow with polymerase chain reaction (PCR) analysis (Figure 3), T-Cell receptor (TCR) gene rearrangement was not detected. Lymphoma was clinically considered to cause HLH, and the patient was then transferred to the Department of Hematology. According to the diagnosis above: 1. CD20(+) B cells NHL IVB; 2. HLH; 3. pulmonary infection.

Considering the CD20(+) B cell NHL and that the patient was in critical condition preventing her from receiving PET/CT and other auxiliary examination, she was immediately treated with a modified R-COPE regimen (rituximab 500 mg d0 + cyclophosphamide (CTX) 0.6 g d1, 0.4 g d4 + vindesine sulfate (VDS) 4 mg d1 + deta-
methasone (DXM) 15 mg d1-5, 7.5 mg d6-8 + acetoside (Vp16) 0.05 g d1, d3) for chemotherapy on August 15, 2014.

After chemotherapy, the patient’s pleural and peritoneal effusions were significantly absorbed. Blood routine and blood coagulation returned to normal. No lymphoma cells were found in the bone marrow routine or the biopsy. IgVH and IgK gene rearrangements were not detected in the bone marrow. An R-CHOP regimen (rituximab 500 mg d0 + CTX 1.0 g d1 + Epirubicin 80 mg d1 + VDS 4 mg d1 + DXM 15 mg d1-5) was used twice for chemotherapy on September 13, 2014 and October 30, 2014. Because the patient had a lesion on the left lung, after consultations in the department of Tuberculosis, the patient received isoniazid + rifampicin + pyrazinamide + ethambutol anti-tuberculosis treatment. However, after the active anti-bacterial, anti-fungal and anti-tuberculosis treatments, the patient’s chest CT examination showed no absorption of the left upper pulmonary lesion, and no pleural effusion (Figure 1B). According to the clinical manifestations, lung cancer was considered. The patient refused a surgical resection but agreed to allow a percutaneous lung biopsy. She received a CT-guided percutaneous lung biopsy on December 22, 2014. The puncture biopsy pathology showed a well-differentiated adenocarcinoma (Figure 1C). The patient began to receive icotinib 125 mg TID oral treatment on March 31, 2016. A review of her chest CT showed that the lesions in the left upper lung cancer were more absorbed than they were before on July 26, 2016 (Figure 1D).

Discussion

Multiple cancer is also known as multiple primary malignant tumors, multiple carcinomas and multiple primary cancers. The diagnostic criteria include: (1) Each kind of tumor must be confirmed as a malignant tumor; (2) Each kind of tumor must have its own unique pathological morphology; (3) Metastasis or recurrence must be ruled out [7].

Some researchers have reported cases of lymphoma complicated with lung cancer, such as the cases of coexistence of T-cell lymphoma and primary lung cancer reported by Miyahara and others [8]. Hoshi and others reported cases of lymphoepitheloid lymphoma complicated with lung adenocarcinoma [9]. Hatzi-bougias and others also reported a case of lung adenocarcinoma and pleural mantle cell lymphoma existing at the same time. However, the literature has rarely reported cases of B cell NHL with HLH as the initial manifestation combined with lung adenocarcinoma [10].

Figure 4. An ARMS assay showed that the EGFR gene exon 21 L858R of the lung puncture biopsy specimens was a mutation (green).
The clinical manifestations and the auxiliary examination of the patient met the new HLH diagnostic criteria established by the American Society of Hematology in 2009 [11], so the clinical diagnosis was HLH. For the clinical diagnosis of an HLH patient, it is necessary to find the cause. According to available statistical data, the most common cause of adult HLH is lymphoma and the EB virus [1, 2]. In this case, the patient’s examinations, including her bone marrow biopsy and bone marrow routine, showed HLH without any viral infection. So, at that time, we first considered that the HLH was caused by NHL and that it was secondary HLH.

The patient’s chest CT showed no changes in the upper left lung lesions after she received regular anti-bacterial, anti-fungal and anti-tuberculosis treatments. If it were lung NHL, the patient’s pulmonary lesions would have obvious changes after regular chemotherapy. Therefore, after the exclusion of pulmonary bacteria, fungi, tuberculosis infection, and pulmonary NHL, lung cancer was highly suspected. Since the patient could not tolerate open chest surgery, a puncture biopsy to lung was performed. The postoperative pathological examination showed highly differentiated adenocarcinoma in her lung. So, the patient was diagnosed with NHL combined with multiple primary carcinoma of lung adenocarcinoma. Clinically, doctors need to improve the understanding of the multiple primary tumors. In particular, for the diagnosis of cancer patients who have had chemotherapies, do not blindly jump to the conclusion of a recurrence of a primary tumor.

EGFR is a transmembrane receptor tyrosine kinase. There are overexpression and (or) mutations of the EGFP gene in NSCLC [12, 13]. The EGFR gene contains 28 exons, among which exons 18-21 are in the coding region of tyrosine kinase. Studies have shown that mutations in EGFR are scattered throughout the tyrosine kinase region. Deletion mutations of exon 19 and L858R mutations of exon 21 were the most common types of mutations [14]. A number of studies have pointed out that EGFR-TKIs, like Gefitinib and Erlotinib, have a good clinical curative effect and good safety in the treatment of patients with advanced lung adenocarcinoma [15]. At the same time, several studies have pointed out that icotinib can also have a survival benefit for patients, and the overall incidence of adverse reactions is lower than with gefitinib and erlotinib. Therefore, icotinib has become the first-line standard selection for the EGFR mutation of advanced lung adenocarcinoma in China [16]. There was a mutation of EGFR gene exon 21 L858R in this patient’s lung biopsy, so after receiving EGFR-TKI icotinib treatment for about 4 months, her chest CT showed that the left lung cancer lesions were more absorbed than they were before treatment, indicating that the icotinib treatment was effective.

Overall, the patient was CD20(+) B-cells NHL with HLH as the initial manifestation combined with EGFR(+) lung adenocarcinoma, which is clinically rare. The treatment was based on controlling the HLH and treating the NHL at first. After the condition became stable, the treatment targeted both the NHL and the lung adenocarcinoma.

Disclosure of conflict of interest

None.

Address correspondence to: Xiao-Feng Xu, Department of Hematology, Zhejiang Chinese Medicine and Western Medicine Integrated Hospital (Hangzhou Red Cross Hospital), 208# Huancheng East Road, Hangzhou 310003, Zhejiang, China. Tel: 13750830313; E-mail: hhxuxiaofeng@126.com

References

Non-Hodgkin lymphoma with lung adenocarcinoma


