Hemophagocytic Syndrome as the Initial Performance of CD20 (+) B Cell Non-Hodgkin's Lymphoma with EGFR (+) Lung Adenocarcinoma: A Case Report and Literature Review

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Abstract

We reported one case of CD20 (+) B-cell non-hodgkin's lymphoma (NHL) with hemophagocytic syndrome (HLH) as the initial manifestation, which was located on a 50-year-old female. After being treated with R-CHOP regimen chemotherapy, HLH caused by NHL was controlled, but the chest CT of this patient showed no significant changes in the left upper lung lesions. Later, the patient was diagnosed as lung adenocarcinoma after percutaneous lung biopsy and exon 21 L858R in EGFR gene mutated. The patient received R-GDP scheme chemotherapy and Icotinib targeted therapy and chest CT showed that the upper left lung cancer lesions were absorbed more than before.

Keywords: Hemophagocytic Syndrome, CD20(+), Non-Hodgkin's Lymphoma, EGFR(+), Lung Adenocarcinoma

Introduction

Hemophagocytic syndrome (HLH) is a very serious syndrome in clinical which needs timely diagnosed and treated. 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 and so on, which is common in adults [1]. According to statistics, the most common cause of adult HLH is lymphoma and EB virus, followed by bacteria, fungi and tuberculosis, etc [2,3].

The incidence of lung cancer has increased in recent years and has become one of the leading causes of cancer death. For those patients with advanced Non-Small Cell Lung Cancer (NSCLC), chemotherapy is the major treatment, the effective rate of which is about 35% ～ 45% [4]. In recent years, molecular targeted therapy with EGFR as the target has become a new therapeutic method for NSCLC [5]. Icotinib is a new small molecule targeted high efficiency specific EGFR- tyrosine kinase inhibitor (TKI) anticancer drug with China intellectual property right, its physical and chemical properties, mechanism and clinical effectiveness of treatment of NSCLC and other aspects are all comparable with Gefitinib and Erlotinib. Moreover, its safety is better than the above 2 drugs [6,7].

This paper aimed at mastering the diagnosis and treatment of this kind of repeat cancer through reporting a case of rare CD20 (+) B-cells non-hodgkin's lymphoma (NHL) with HLH as the initial manifestation and complicated with lung adenocarcinoma and its diagnosis and treatment.

Case Report

The patient a 51-year-old woman, was admitted to the department of Respiration in our hospital out of "fever for 5 days". 5 days before that, the patient began with fever due to a cold, the highest temperature reached up to 40℃, accompanied by cold, a little cough, white
colour sputum, no abdominal pain and diarrhea, no dysuria, urinary frequency and urgency, she came to our hospital for emergency treatment. There is no obvious improvement after anti-infection therapy with cefotaxin, patient was then transferred to the department of Respiration for hospitalization.

After being admitted to the department of Respiration, the patient accepted illness evaluation and the blood test showed that WBC 4.9 × 10⁹/L, HB 110 g/L, Plt 207×10⁹/L; Blood coagulation routine showed that PT 13.6s, APTT 42s, D-dimer 2620 μg/L, Fib 482 mg/dl, 3P-negative; Blood biochemical examination showed that creatinine 87.1 μmol/L, direct bilirubin 9.8 mmol/L, indirect bilirubin 7.7 mmol/L, albumin 35.6 g/L, AST 63 u/L, triglycerides 1.73 mmol/L, LDH 3130/L; Ferritin 3189.6 ug/L; procalcitonin 0.28 ng/ml. Abdominal ultrasonography detection: liver mass increased, the maximal oblique diameter of right liver was 15.4 cm, the spleen thickness was around 4.3 cm. Chest CT detection: patchy clouding increased bronchovascular shadows were found in two upper lobe of lung, the periphery lesions of the upper left lung were surrounded by ground glass shadows; A number of grinding glass small nodules and solid nodules could be seen in two lung upper lobe, the boundary is still clear; Small patchy high density shadows could be seen in the middle lobe of right lung, the boundary is unclear. There is no significant enlargement of hilar and mediastinal lymph nodes, the bilateral pleural fluid density (Figure 1a).

![Figure 1: Chest CT: a and b showed that there was no significant change in the left upper pulmonary lesions after treatment with anti-bacteria, fungi and tuberculosis. c: The lesions in the left upper lung cancer were more absorbed than before 4 months after treatment of icotinib oral (arrow).](image)

After admission, the patient was given Sulperazone 3.0g Q8H and intravenous injection combined with Moxifloxacin 0.4g QD intravenous infusion anti-infection treatment for 1 week, but the patient still had an continuous fever and the body temperature fluctuated between 40.8 and 37.9 degrees Celsius and the blood routine test showed that WBC, HB and Plt counts decreased progressively, multiple blood cultures showed no bacteria, Urine culture and stool culture were negative, three lines of hepatitis B were positive, Hepatitis A, C, D and E antibodies were negative, AIDS antibody, syphilis antibody were negative, Tuberculosis antibody and T-SPOT were negative, Anti-nuclear antibodies, ANCA and rheumatoid factor were negative, detection of EB virus, cytomegalovirus and Coxsackie virus DNA were negative, Blood smear did not find Plasmodium. Fungus (1, 3) - beta -D dextran assay: 13.72 pg/ml (0 - 60). Aspergillus immunity test: 0.233 (0 - 0.5). Nutrition support like infusion of gamma globulin, plasma were taken. Sulperazone and Moxifloxacin were stopped, instead, Teranex 1.0g q8h intravenous drip, Cancidas 50 mg qd intravenous drip, Vancomycin 1.0 q12h intravenous drip were combined to anti-infection. And the blood routine test: WBC 1.4 × 10⁹/L, HB 63 g/L, Plt 31 × 10⁹/L. Coagulation routine: PT 19.1s, APTT 55.6s, Fib

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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 3.42 mmol/L, lactate dehydrogenase 170 IU/L, Na+135 mmol/Ls CD25: 10080 U/ml. Examination of bone marrow was carried on and abnormal cells were found in the smear, consider lymphoma cells (Figure 2); Bone marrow biopsy showed active bone marrow tissue proliferation, lymphocytes increased significantly and cells were relatively large, Immunohistochemistry: CD20(+), CD79a(+) Combining clinical, lymphoma involving bone marrow was taken into consideration (Figure 3). Detection of antigen in bone marrow cell type: HLA-DR, CD 2, CD 3, CD 4, CD 5, CD 7, CD 8, CD 10, CD 11b, CD 13, CD 14, CD 15, CD 16, CD 19, CD 20, CD 22, CD 33, CD 34, CD 38, CD 56, CD 64, CD 71, CD 117, CD 123, sKappa, sLambda and CD 45, hints: an analysis of the design of the CD45/SSC point map, the area of original cells is about 1% of the nuclear cells and CD34+ cells occupy about 0.80% of the nuclear cells, the distributions of them were scattered. Lymphocytes occupy about 8.5% of nuclear cells, ratio decrease, CD4/CD8 = 0.82, the distribution of each lymph node was approximately normal; Monocytes occupy about 1.5% of nuclear cells, phenotype mature; Granulocyte occupies about 78% of nuclear cells, some of the cells were considered to have developmental abnormalities. Chromosomes are normal karyotype, IgVH and IgK gene rearrangements were detected in bone marrow (Figure 4), TCR gene rearrangement was not detected. Clinical considered of lymphoma causing macrophage cell syndrome, Patient was then transferred to the Department of Hematology. According to the above diagnosis: 1. CD20 (+) B cells NHL IV B group; 2. HLH; 3. pulmonary infection.

**Figure 2:** Bone marrow routine: abnormal cells (arrow) were found in the smear, consider lymphoma cells, ×1000.

**Figure 3:** Bone marrow biopsy: A Lymphocytes increased significantly and cells were relatively large, consider lymphoma cells, HE stain, ×1000. Immunohistochemistry: B: CD20(+), C: CD79a(+), ×400.
Figure 4: PCR test: IgVH and IgK gene rearrangements were detected in bone marrow. The 1st, 2nd, 3rd, 4th, 5th, 6th, 7th, 8th Lane are respectively IgVH-A, IgVH-B, IgVH-C, IgDH-A, IgDH-B, IgK-A, IgK-B and control gene (The bands from the bottom to the top: 100 bp, 200 bp, 300 bp and 400 bp). Among them, the 1st, 2nd, 3rd, 6th, 7th lane are positive.

Considering that CD20 (+) B cells NHL induced HLH and the patient was in critical condition and couldn't receive PET/CT and other further auxiliary examination. Patient was immediately treated with modified R-COPE regimen for chemotherapy on 15th August (rituximab 500 mg d0+CTX 0.6g d1, 0.4g d4+VDS 4 mg d1+DXM 15 mg d1-5, 7.5 mg d6-8+Vp16 0.05g d1, d3), after chemotherapy, patient’s pleural and peritoneal effusion was significantly absorbed. Blood routine and blood coagulation returned to normal. No lymphoma cells were found in the bone marrow routine and bone marrow biopsy. IgVH and IgK gene rearrangements were not detected in the bone marrow. R-CHOP regimen (rituximab 500 mg d0+CTX1.0g d1+ Epirubicin 80 mg d1+VDS 4 mg d1+DXM15 mg d1-5) was used twice for chemotherapy on 13th September 2014 and 30th October 2014. Because the patient has a lesion on the left lung, after consultations in the department of Tuberculosis, the patient received HRZE therapy.

However, after being treated with active anti-bacteria, anti-fungal and anti-tuberculosis treatment, patient’s chest CT examination showed no absorption of left upper pulmonary lesion, but no pleural effusion (Figure1b). According to the clinical manifestations, lung cancer should be taken into consideration. The patient refused surgical resection, but agreed to perform percutaneous lung biopsy and received CT guided percutaneous lung biopsy on 22nd December 2014. Puncture biopsy pathology showed: Well-differentiated adenocarcinoma (Figure 5). The patient was CD20 (+) B cell NHL combined with multiple primary malignant tumor of lung adenocarcinoma with HLH as the initial manifestation and received R-GDP regimen for chemotherapy on 1st January 2015 (rituximab 500 mg d0+ Gemcitabine 1.5g d1, 8+ Cisplatin 30 mgd1-3+DXM30 mg d1-4), treatment went smoothly. Then EGFR gene mutation was performed in percutaneous lung biopsy specimens of the patient on 6th November 2015. ARMS showed that EGFR gene exon 21 L858R mutation. The patient began to receive icotinib 125 mg TID oral treatment since 31st March 2016. The review of pulmonary CT examination showed that the lesions in the left upper lung cancer were more absorbed than before on 26th July 2016 (Figure 1c).
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Discussion and Conclusion

Multiple cancer is also known as multiple primary malignant tumors, multiple carcinomas and multiple primary cancers. Diagnostic criteria for repeated cancer: (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) Must rule out metastasis or recurrence [8].

Some researchers have reported cases of lymphoma complicated with lung cancer, such as cases of coexistence of T cell lymphoma and primary lung cancer reported by Miyahara and others [9]. While Hoshi R and others have reported cases of lymphoepitheloid lymphoma complicated with lung adenocarcinoma [10]. Hatzibougias and others also have reported cases of lung adenocarcinoma and pleural mantle cell lymphoma existing at the same time. But literature has rarely reported cases of B cell NHL combined with lung adenocarcinoma with HLH as the initial manifestation [11].

HLH were characterized by fever, hepatosplenomegaly, pancytopenia, hypofibrinogenemia, hypertriglyceridemia and the phenomenon of macrophage phagocytosis of blood cells etc. It is a very serious syndrome in clinical practice and needs timely medical diagnosis and treatment [1]. HLH 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 and so on, which is common in adults [1].

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 [12], so the clinical diagnosis was HLH. For clinical diagnosis of HLH patients, searching for the cause is necessary. According to statistics, the most common cause of adult HLH is lymphoma and EB virus, followed by bacteria, fungi and tuberculosis, etc [2,3]. The patient’s examinations including bone marrow biopsy and bone marrow routine showed HLH, excluding virus infection. So at that time, we first considered that HLH was caused by NHL and it was secondary HLH.

The patient's chest CT showed no changes in the upper left lung lesions after receiving regular anti-bacterial, fungal and empirical anti-tuberculosis treatment. If it was lung NHL, patient’s pulmonary lesions must 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, puncture biopsy to lung was performed. Postoperative pathological examination showed lung highly differentiated adenocarcinoma. So the patient was NHL combined with multiple primary carcinoma of lung adenocarcinoma. Clinically, doctors need to improve the understanding of the multiple primary carcinoma. In particular, for the diagnosis of cancer patients who have had chemotherapies, don’t blindly jump to the diagnosis of metastasis or recurrence. Pathological tissue need to be gotten as much as possible to confirm the diagnosis.

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After being treated with 1 R-COPE and 2 R-CHOP regimen for chemotherapy, the patient’s clinical symptoms turned better apparently. Blood routine, bone marrow and other examinations returned to normal. There were no changes in lung adenocarcinoma. So HLH was caused by NHL, lung adenocarcinoma did not participate in the occurrence of HLH. This result is in accordance with the results of literatures [2].

There are no unified standard for how to treat CD20 (+) B cell NHL combined with lung adenocarcinoma yet. Multiple primary carcinoma should be based on radical cure as its aim, Choose therapy which mainly consisted of surgery and/or combined with radiotherapy and chemotherapy and other multi-discipline coordination according to the patient’s condition, disease period, location, nature and pathological type, striving to achieve the purpose of cure [8]. Radical treatment is an independent prognostic factor for the overall survival of patients with multiple primary carcinoma [13]. Some scholars have reported that the longest life expectancy of multiple primary carcinoma can be up to 35 years [14]. So, the patient’s treatment needs to take into account both NHL and lung adenocarcinoma. At present, the common treatment for these two tumors are respectively R-CHOP and GP [15,16]. GDP regime is mainly used for second-line treatment of diffuse large B cell lymphoma and peripheral T cell lymphoma [17]. Therefore, when the patient was diagnosed as CD20 (+) B cell NHL with HLH as the initial manifestation, R-COPE and R-CHOP regime were adopted. When diagnosed with lung adenocarcinoma, the patient received R-GDP regime.

EGFR is a transmembrane receptor tyrosine kinase, there are over expression and (or) mutations in NSCLC [18,19]. The EGFR gene contains 28 exons, among which exon 18 - 21 is in the region of encoding tyrosine kinase [20]. The study showed that the EGFR gene was distributed in the whole tyrosine kinase region, deletion mutations of exon 19 and L858R mutations of exon 21 were the most common types of mutations [20]. A number of studies at home and abroad have pointed out the results that EGFR-TKI, like Gefitinib and Erlotinib, have good clinical curative effect and good safety in the treatment of patients with advanced lung adenocarcinoma [21]. At the same time, several researches pointed out that Icotinib can also make survival benefit for patients and the overall incidence of adverse reactions is lower than Gefitinib and Erlotinib. Therefore, Icotinib has become the first-line standard selection for EGFR mutation of advanced lung adenocarcinoma in China [22]. There is a mutation of EGFR gene exon 21 L858R in patient's lung biopsy, so after receiving EGFR-TKI Icotinib treatment for about 4 month, review of chest CT showed that the left lung cancer lesions were more absorbed than before, illustrating that Icotinib treatment was effective.

Overall, the patient is CD20 (+) B-cells NHL combined with EGFR (+) lung adenocarcinoma with HLH as the initial manifestation, which is very rare in clinical. The treatment should be based on controlling HLH and treating NHL at first. After the condition is stable, treatment needs to take into account both NHL and lung adenocarcinoma.

Disclosure
The authors report no conflicts of interest in this work.

Bibliography

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