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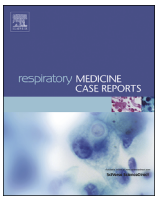

Case Report

Evans syndrome suggests disease progression in lung adenocarcinoma

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A B S T R A C T

We admitted a 60-year-old male patient diagnosed with lung adenocarcinoma who had a shrinking lung cancer mass after radiotherapy and 6 cycles of chemotherapy, but developed facial inflammation 2 weeks after the end of the final chemotherapy treatment, and was admitted to the hospital with anemia and thrombocytopenia, and diagnosed with Evans syndrome, and brain metastasis of lung cancer was found in the course of the consultation, which suggested disease progression. Evans syndrome was seen as a paraneoplastic syndrome.

1. Introduction

Paraneoplastic syndromes (PNS) are characterized by systemic responses that are indirectly linked to malignancies. Patients with cancer may appear with a range of hematologic characteristics, particularly if their malignancies have progressed. Evans syndrome, on the other hand, is an uncommon form of PNS in solid cancers. We describe the example of a patient with lung cancer who experienced a gradual drop in hemoglobin content after finishing radiation treatment and developing thrombocytopenia. Following platelet transfusion and infection management, anemia steadily deteriorated while platelets were high. After receiving adrenocorticotropic hormone therapy, intracranial metastases were discovered, but platelet counts and hemoglobin concentrations improved noticeably, allowing researchers to investigate the relationship between immunity and tumor progression.

2. Case presentation

A 60-year-old male patient with chronic Hepatitis B presented to our hospital on March 29, 2018, with chief complaints of cough, expectoration, and hemoptysis persisting for over a month. Physical examination revealed normal cardiac auscultation, coarse breath sounds in the right lung, and no palpable hepatosplenomegaly. Laboratory tests showed the following: white blood cells (leukocyte, WBC) at 7.22×10^9/L, hemoglobin concentration (Hb) at 143 g/L, and platelets (PLT) at 236×10^9/L. Enhanced chest computed tomography (CT) scan findings included: 1. Carcinoma in the lower lobe of the right lung with obstructive inflammation and atelectasis in the inner and anterior basal segments, 2. Enlargement of multiple lymph nodes in the right hilum and mediastinum, 3. Multiple small nodules in both lungs, Hepatic hilar lymph node metastasis? 4. A lateral adrenal nodule on the left side (Fig. 1), However, chest enhancement CT did not confirm hilar lymph nodes, bilateral lung nodules and left adrenal metastases.

Under the guidance of a chest CT, a lung mass biopsy was performed, and histopathological examination of the biopsy sample confirmed lung adenocarcinoma (Fig. 2). The diagnosis was lung adenocarcinoma T4N2M0 Stage IIIB. EGFR gene testing was negative. Brain MRI and SPECT showed no signs of metastasis. On April 27, 2018, the patient underwent radical concurrent chemoradiotherapy; radiotherapy (IMRT) was administered at 2 Gy per session for a total of 30 sessions, with concurrent “paclitaxel 60 mg + cisplatin 40 mg qw” for radiosensitization three times. Subsequent chest CT showed minimal tumor reduction, prompting a change to “cisplatin 40 mg + etoposide 80 mg qw” for two additional radiosensitization sessions. From June 2018, the patient received “peme-

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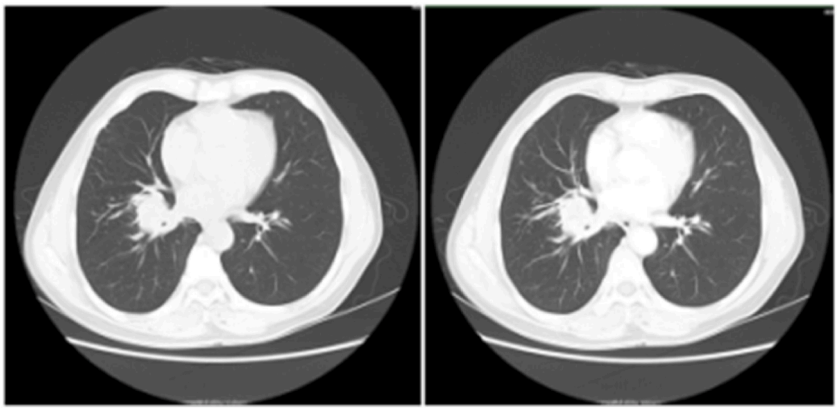

Fig. 1. A computed tomography (CT) scan of the chest reveals several enlarged lymph nodes in the mediastinum and right lung, as well as a 4.3 × 3.5 cm2 soft tissue density shadow in the lower lobe parenchyma of the right lung field. There was a 19 mm circular lesion in the hilum and an oval lump measuring 3 mm by 25 mm in the lateral part of the left adrenal gland.

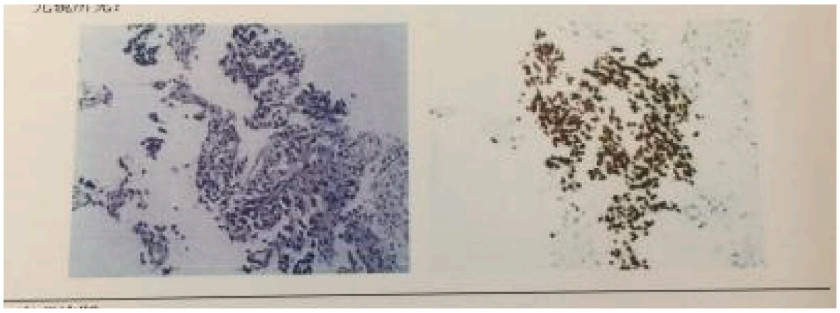

Fig. 2. CK5/6(−),CK7(−),Ki-67(5 %+), Napsin A(+),P40(−),TTF-1(+).

trexed disodium 0.8 + cisplatin 40 mg on days 1–3″ chemotherapy, with a cycle length of 21 days, for a total of six cycles. During this period, routine blood counts remained within normal ranges. The last chemotherapy session was completed on November 1, 2018. On November 15, 2018, the patient presented to our otolaryngology department with facial swelling for two days and was diagnosed with cellulitis. He was readmitted to our department and treated with "piperacillin-tazobactam 3.75g every 8 hours from November 15 to November 26 for 12 days" and "clindamycin 0.9g every 12 hours from November 16 to November 20 for 5 days." On November 16, 2018, a complete blood count showed a platelet count of 4×10^9/L; one therapeutic dose of apheresis platelets was transfused, but there was no improvement in the patient's platelet count. From November 20 to November 29, moxifloxacin 0.4g daily was administered, and from November 26 to December 9, meropenem 1g every 8 hours was given. During this period, the patient experienced a decrease in hemoglobin, and despite transfusing four therapeutic doses of apheresis platelets and undergoing blood agglutination, Coombs test, and cold agglutinin test which were all negative, the condition persisted. Antinuclear antibodies (ANA), anti-double-stranded DNA (dsDNA) antibodies, and anti-extractable nuclear antigen (ENA) antibody spectrum were also negative. HBV-DNA was $<1.00 \times 10^2$ IU/mL. Immunofixation electrophoresis did not reveal any abnormal monoclonal bands, and serum protein electrophoresis did not detect any M-protein. Bone marrow biopsy showed active proliferation of nucleated cells and no metastatic cancer cells (Fig. 3).

Given the patient's increased mean corpuscular volume (MCV), supplementation with folic acid, vitamin B12, and potassium chloride tablets was initiated, yet without effect, as the MCV continued to increase. Slight improvement was noted following warm baths, with no change in platelet count. Facial symptoms gradually improved, and C-reactive protein (CRP) levels progressively decreased (Fig. 4). However, compatibility in blood transfusion remained unsuccessful with a positive (3+) result in the irregular antibody screening test, and no red blood cells were transfused. The patient was treated with dexamethasone (Dex) 10 mg/day from November 24 to December 7, followed by 5 mg/day from December 7 to December 14, along with oral entecavir to prevent hepatitis virus activation. Anemia gradually improved and platelet levels normalized. Considering the potential for paraneoplastic syndrome (PNS), and the patient's headaches, an enhanced brain MRI was performed: it revealed multiple enhancing lesions indicative of widespread intracranial metastasis. Oral anlotinib (12 mg from day 1 to day 14) was administered for the treatment of brain metastases from lung cancer, with a 21-day cycle. At a 3-month follow-up, the lung cancer remained stable, and peripheral blood cell counts were normal.

3. Discussion

In this case, the patient was diagnosed with lung adenocarcinoma, and the complete blood count was normal at the time of diagnosis. During the course of radical concurrent chemoradiotherapy [1–3](IMRT [4], "paclitaxel + cisplatin" [5], and "cis-

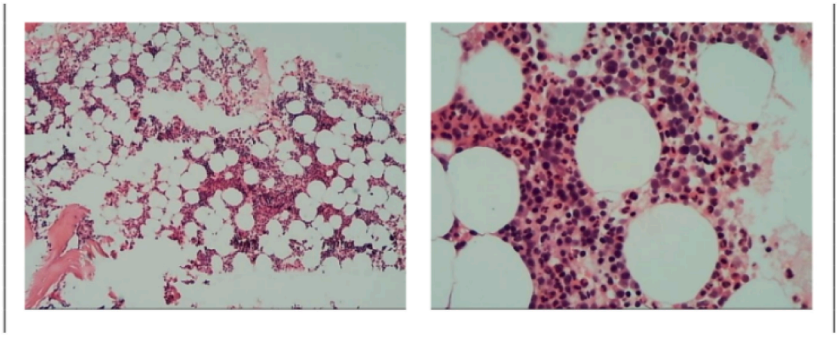

Fig. 3. Bone marrow biopsy.

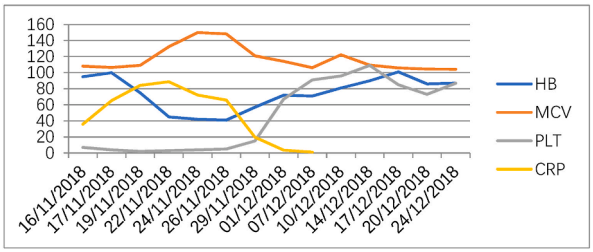

Fig. 4. Evans syndrome, progressive worsening of anemia, severely low platelet count, significantly elevated mean corpuscular volume (MCV), high levels of C-reactive protein. Following infection control, C-reactive protein levels return to normal, improvement in anemia, platelet count approaching normal, and decrease in MCV.

platin + etoposide" [6,7]), although there were fluctuations in platelet count and hemoglobin concentration, these levels quickly normalized. However, However, two weeks after the completion of therapy, the patient developed facial cellulitis, anemia, and thrombocytopenia. Following antibiotic treatment, the patient's body temperature stabilized, but the anemia intensified and platelet transfusions were ineffective. The mean corpuscular volume (MCV) gradually increased and blood agglutination tests were positive. Excluding the possibilities of a hepatitis outbreak, hemophagocytic syndrome, cryoagglutinin syndrome, cryoglobulinemia, and bone marrow infiltration, an enhanced MRI of the skull indicated intracranial metastasis. The patient was diagnosed with Evans syndrome [8], and responded well to steroid therapy, with a gradual normalization of the complete blood count. Post-treatment with anlotinib [9,10] for brain metastases from lung cancer, the patient's condition stabilized, and the complete blood count remained normal.

Our patient exhibited thrombocytopenia and progressively worsening anemia, prompting consideration of Evans syndrome, a condition characterized by concurrent or sequential autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP). Evans syndrome is classified as a paraneoplastic syndrome (PNS), with an incidence of up to 8 % reported among cancer patients [11]. The incidence of PNS in lung cancer is approximately 10 % [12], and secondary Evans syndrome represents a rare PNS in malignant solid tumors [13]. Putenparambil et al. [14] reported paraneoplastic hemolytic anemia in nine out of 52 cases of lung cancer, with all nine cases being non-small cell lung cancer and two-thirds involving warm antibodies. Krauth et al. [15] reported a third involving cold antibodies. Out of 68 solid tumors, 15 lung cancer patients developed ITP, four of whom had adenocarcinoma. Some PNS cases may be attributed to the long-term impact of tumors, such as ectopically produced bioactive factors (hormones, cytokines) by tumor cells or cross-reactivity between tumor cells and normal host tissues.

The patient is a middle-aged male with a history of smoking and a family history of lung cancer. He was hospitalized with severe thrombocytopenia and anemia following radiotherapy and chemotherapy, diagnosed during an admission for facial cellulitis. An investigation into the cause revealed tumor progression. Therefore, regardless of the presence of inflammation, transfusion, or tumor progression, further research is necessary. We believe that more laboratory studies on patients with paraneoplastic syndromes (PNS) could provide valuable insights into the biological behavior of malignant tumors. Specifically, the interaction between tumors and the immune system may offer clues for the immunotherapy of solid tumors.

4. Conclusions

We describe a lung cancer patient with Evans syndrome, who had poor results of red blood cell and platelet transfusion, improved anemia after hormone therapy, found neurological symptoms in the course of treatment, and then diagnosed brain metastasis of lung cancer, and then stabilized the disease after oral antitumor treatment with Anlotinib, and the blood was gradually returned to normal, and we expected that the emergence of Evans syndrome would be related to the progression of the disease, but the specific mechanism We expect that Evans syndrome is related to disease progression, but the specific mechanism needs more research.

CRediT authorship contribution statement

Shengru Yang: Writing – review & editing, Writing – original draft. **Xu Li:** Conceptualization. **Zhang Hui:** Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

HB: Hemoglobin concentration
MCV: Average red blood cell volume
PLT: platelet count
CRP: C-reactive protein
mg: milligram
mm: millimeter
cm: centimeter
NMRI: **N**uclear **M**agnetic **R**esonance **I**maging
PNS: Paraneoplastic syndromes
AIHA: Autoimmune hemolytic anemia