

Rapidly progressive squamous lung cancer with peripheral blood eosinophilia in a 25-year-old woman: A case report

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Received June 30, 2025; Accepted December 1, 2025

DOI: 10.3892/ol.2026.15568

Abstract. Solid tumors combined with eosinophilia are a rare clinical presentation. The present study reports a case of squamous carcinoma of the lung with peripheral blood eosinophilia that developed concurrent with a period of rapid deterioration, without any obvious clinical symptoms of eosinophilia, in a 25-year-old female patient. To the best of our knowledge, this is the first report in such a young patient. The current case favored the diagnosis of paraneoplastic eosinophilia after excluding multiple secondary and non-cancerous factors. However, the lack of bone marrow aspiration results to rule out leukemia posed a clinical diagnostic challenge. The application of glucocorticoids in combination with antineoplastic agents led to a marked decrease in peripheral blood eosinophils. The present case report emphasizes the importance of early recognition of the potential role of eosinophils in squamous lung cancer. The current report aims to provide a reference for the clinical management of similar cases.

Introduction

Peripheral blood eosinophilia is a rare condition in patients with solid tumors, with an overall incidence of only 0.5-1.0% (1). The condition occurs predominantly in colorectal, breast, ovarian, oral cavity and Hodgkin's lymphomas (2), and has rarely been reported in lung cancers, especially squamous lung cancer. Eosinophils are non-differentiated leukocytes derived from hematopoietic stem cells in the bone marrow, which serve roles in immunomodulation, mediating tissue repair, maintaining the stability of the internal environment and killing parasites (3). High levels of eosinophils in lung

cancer are closely associated with decreased survival time and increase the risk of the metastasis of lung cancer (4). Typically, eosinophilia of a paraneoplastic nature can be diagnosed by excluding non-cancerous factors, such as allergies and parasitic infections. Most patients do not exhibit obvious clinical manifestations; however, the persistent elevation of eosinophil levels is likely to lead to eventual multi-organ damage.

Treatment of eosinophilia of a paraneoplastic nature usually involves tumor resection, chemotherapy or corticosteroids. The present report describes a case of eosinophilia in a 25-year-old female patient with squamous lung cancer. The lung cancer suddenly deteriorated with a sudden rise in peripheral blood eosinophil levels that did not cause significant clinical symptoms. Glucocorticosteroids in combination with antitumor drugs were administered to counteract the condition and prevent target organ damage, and the peripheral blood eosinophil levels showed marked improvement. The present report discusses the various factors that trigger eosinophilia and the potential role of eosinophils in solid tumors to provide a reference for the early diagnosis and treatment of solid tumors associated with eosinophilia in the future.

Case report

A 25-year-old woman who presented with a cough and bloody sputum without obvious triggers was admitted to The First Affiliated Hospital of Hebei University of Traditional Chinese Medicine (Shijiazhuang, China) in December 2023. Poorly differentiated squamous cell carcinoma of the lower lobe of the right lung was diagnosed after a biopsy was obtained by bronchoscopy. The lung histology showed a large number of abnormally proliferated squamous cells with large and oval nuclei, deeply stained nuclear chromatin, prominent nucleoli and keratinization (Fig. 1; Data S1). Immunohistochemistry (Data S1) revealed the following results: Thyroid transcription factor 1(-), NapsinA(-), AE1/AE3(+), Vimentin(-), p40(+), cytokeratin 5/6(+), CD56(-), Synaptophysin(-), Chromogranin A(-), CD99(+) and CD117(-) (data not shown). Next-generation sequencing (NGS) (Data S1) was performed on Illumina NextSeq550/NovaSeq6000 platform, and the reference genome was GRCh37/hg19. The detection targets include 10 core genes related to lung cancer, including single nucleotide variation, small fragment insertion or deletion, copy number

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Key words: lung squamous carcinoma, eosinophilia, malignant tumor, case report

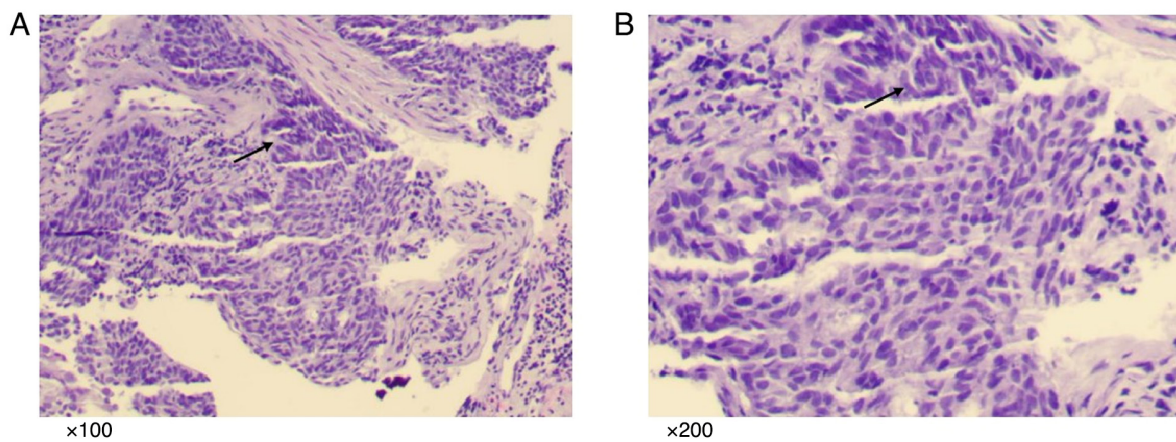


Figure 1. Hematoxylin and eosin-stained section of the patient's lung histopathology. Lung histology showed (A) a large number of abnormally proliferated squamous cells and (B) large and oval nuclei, deeply stained nuclear chromatin, prominent nucleoli and keratinization. The black arrow points to the typical cell morphology.

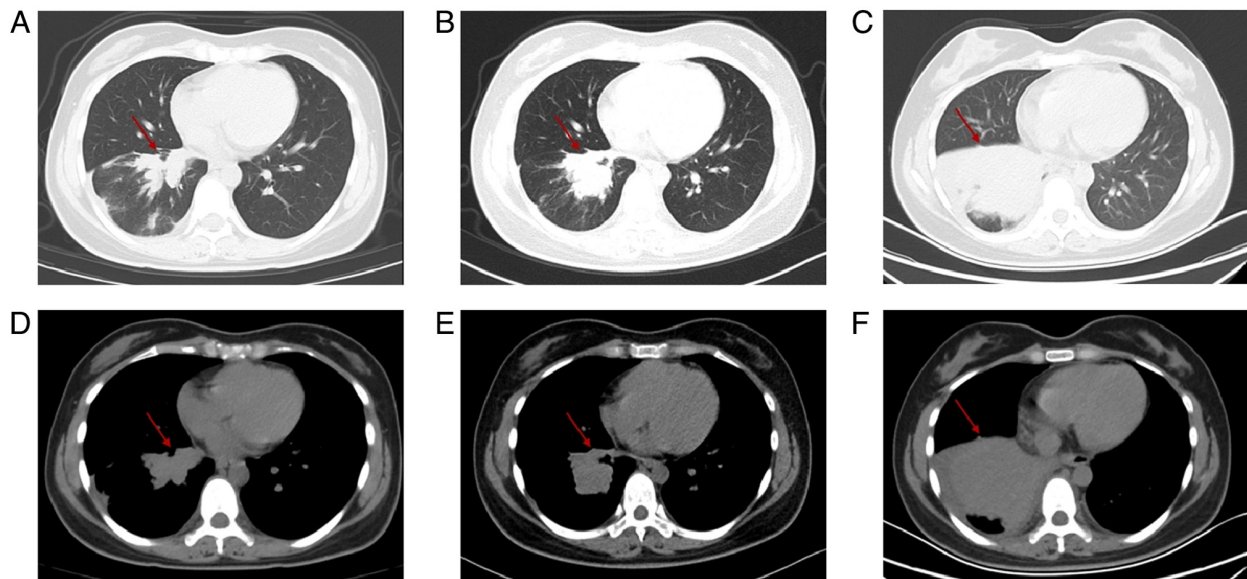


Figure 2. Successive chest CT scans. (A and D) In January 2024, a soft tissue mass was detected in the lower lobe of the right lung (size, 3.2x2.5 cm) [(A) lung window; (D) mediastinal window]. (B and E) In October 2024, the tumor in the lower lobe of the right lung was found to be slightly enlarged compared with that in the previous CT scan (size, 5.2x3.5 cm) [(B) lung window; (D) mediastinal window]. (C and F) In December 2024, occupation in the lower lobe of the right lung was found to be markedly enlarged compared with that in the previous CT scan (size, 10x8.4x5.6 cm) [(C) lung window; (F) mediastinal window]. The red arrows point to the lesion.

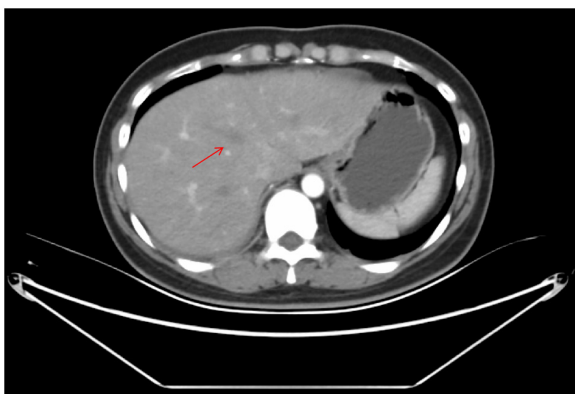


Figure 3. CT scan of the patient's abdomen. A round low-density shadow was seen in the liver, which was a new lesion, and a metastatic tumor was considered. The red arrow points to one of the lesions.

variation and gene fusion of ERBB2 and other genes, which can be used to assist prognosis evaluation and predict the efficacy of targeted drugs. The results showed that the patient had a c.2369C>T (p.T790M) mutation in the EGFR gene, and the mutation frequency was 53.51%. Lymph nodes and distant metastases were not detected at that time. The patient had no previous underlying diseases, and had no history of allergies, blood transfusions or contact with infected water, as well as no known family genetic history. Following the detailed evaluation of the disease by the doctor and the development of a treatment plan, the patient received immunotherapy combined with chemotherapy for a total of 6 cycles (0.2 g tislelizumab on day 1 + 0.2 g nab-paclitaxel on day 2 + 0.3 g carboplatin on day 2, every cycle of 21 days) at The First Affiliated Hospital of Hebei University of Traditional Chinese Medicine between

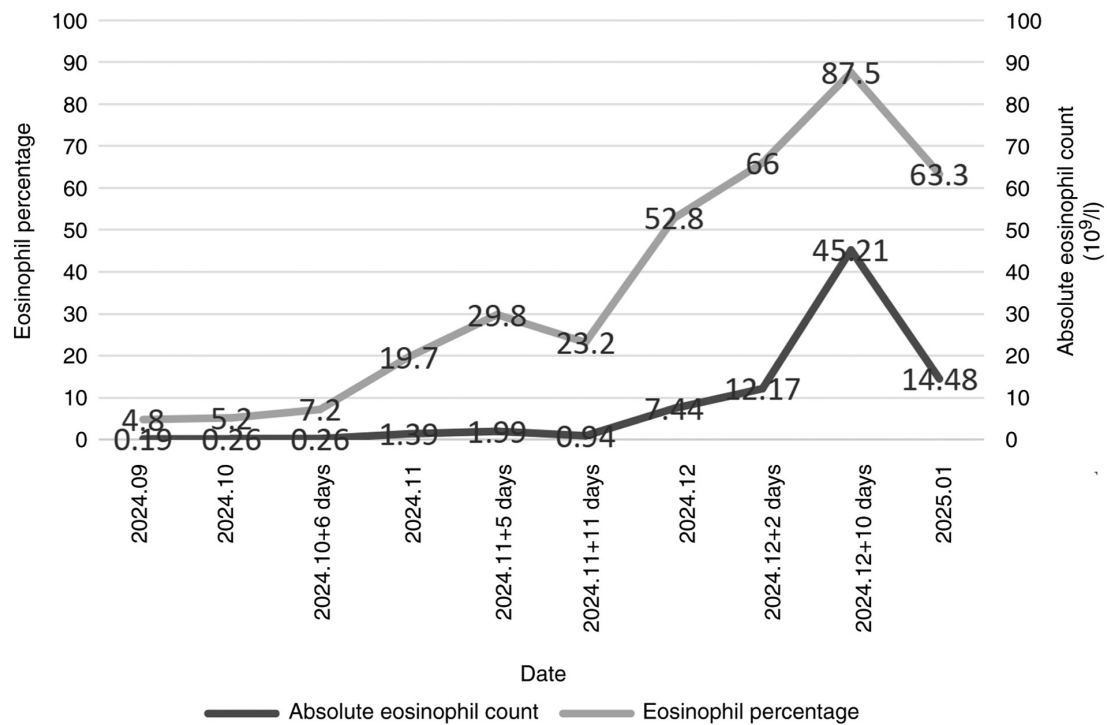


Figure 4. Peripheral blood eosinophil test results. Eosinophil levels showed an increasing trend but decreased markedly after the application of methylprednisolone sodium succinate.

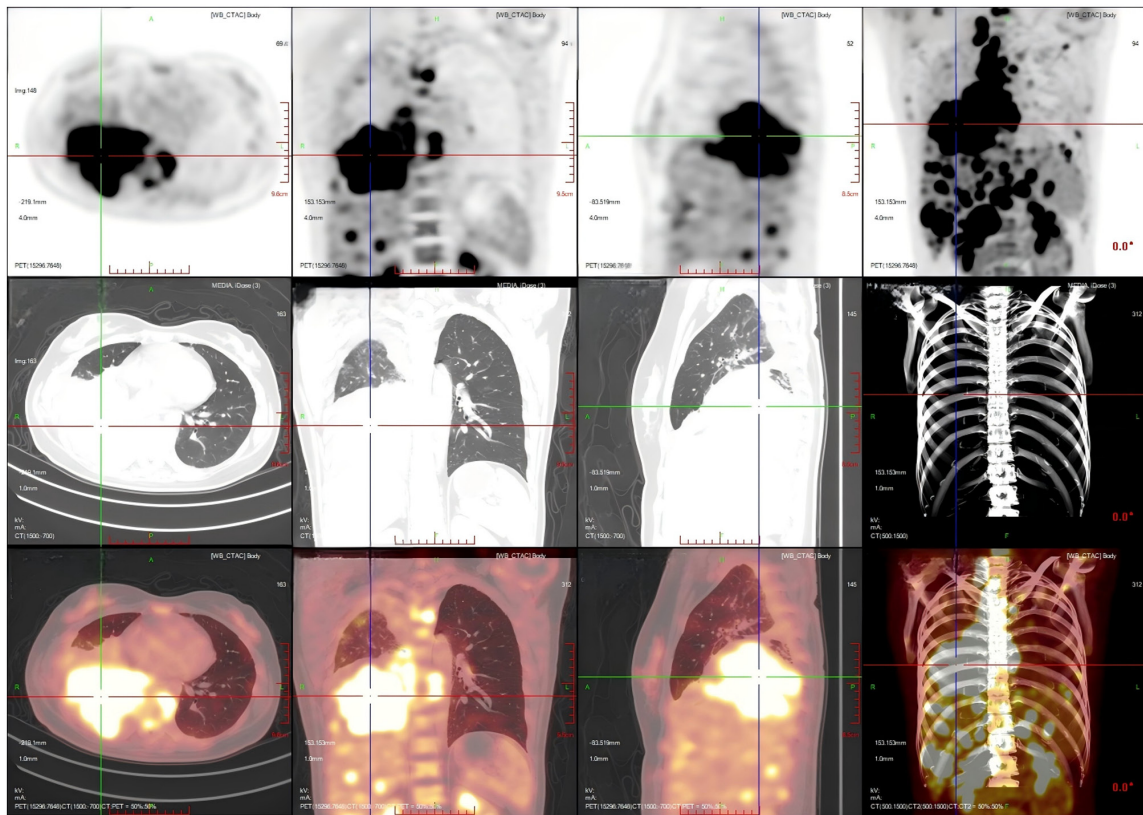


Figure 5. Multiplanar 18F-FDG PET/CT imaging of the patient's hypermetabolic mass lesion in the right lung. An irregular mass-like hyperdense shadow was detected in the right lung hilar and the middle and lower lobes of the right lung; no normal lung tissue was seen, the lesion crossed the interlobular pleura and invaded the upper lobe of the right lung, and the corresponding area on positron emission tomography showed a mass-like radiolucency focus with a SUV_{max} of 25.8. Imaging modalities: PET (top row); CT (middle row); PET/CT fusion imaging (bottom row). Imaging planes: Axial plane (first column) showing cross-sectional views, with transaxial details of the right pulmonary lesion. Coronal plane (second column): Frontal views displaying craniocaudal extension of the lesion across right lung lobes. Sagittal plane (third column): Lateral views illustrating anteroposterior localization of the lesion relative to the hilum. Volume-rendered CT (fourth column, middle row); a 3D reconstructed thoracic CT scan depicting the bony thorax and spatial context of the pulmonary lesion. CT, computed tomography; PET, positron emission tomography.

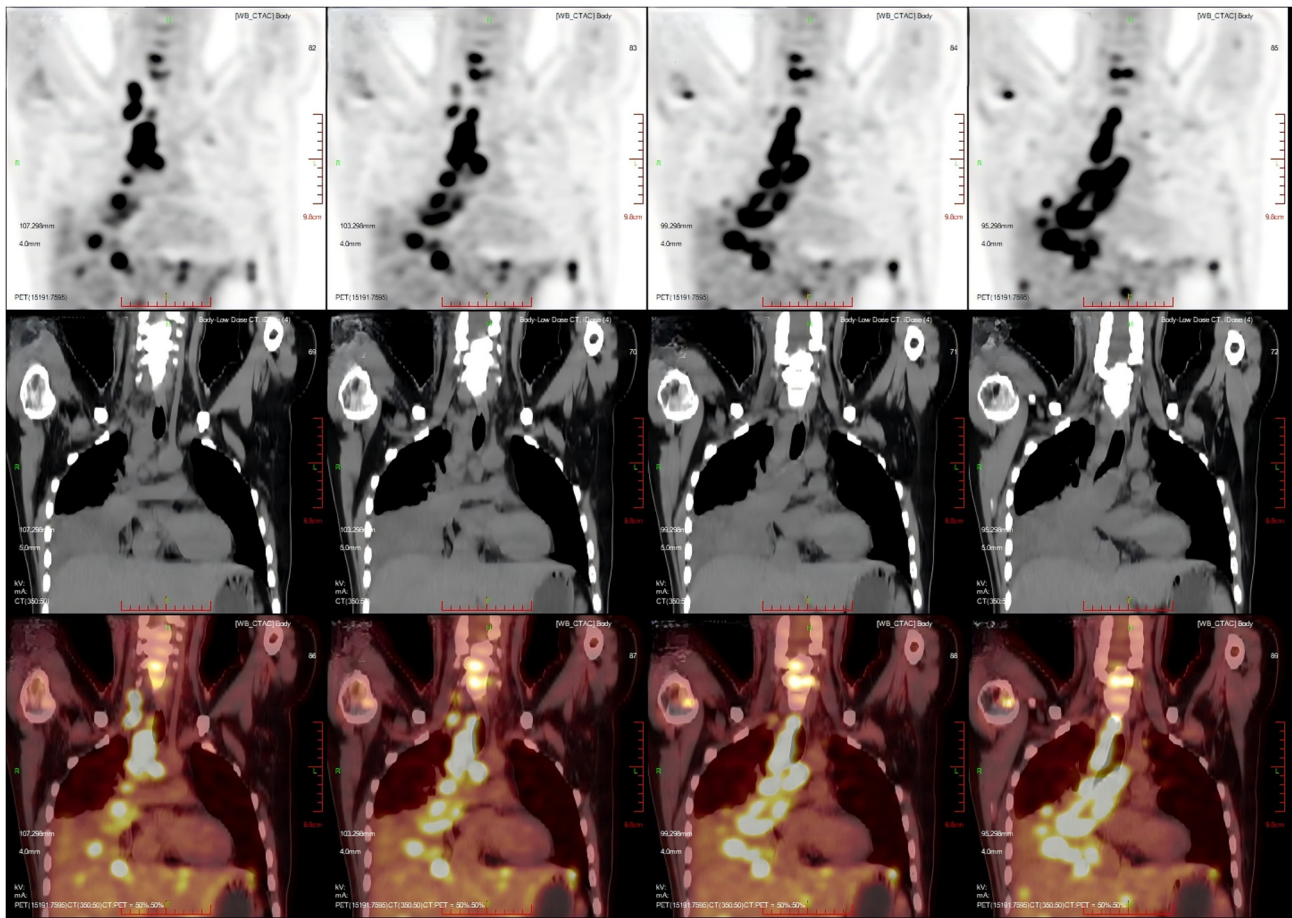


Figure 6. Multiplanar 18F-FDG PET/CT imaging of the patient's chest with diffuse hypermetabolic lymph nodes and right pleural effusion. Multiple enlarged and swollen lymph nodes were detected in the mediastinum, bilateral pulmonary hilar region, bilateral diaphragmatic pedicle and right cardiogenic angle area, partially fused in the form of a mass. PET showed a mass of radiolucent foci in the corresponding areas, and the SUV_{max} of the hypermetabolic area under the bronchus was measured to be 21.4. Thickening of the right pleura was observed, an arcuate fluid density shadow was seen in the thoracic cavity and mild radiolucant uptake was visible in the area of pleural effusion on the right side of the chest cavity. Imaging modalities: PET (top row); CT (middle row); PET/CT fusion imaging (bottom row). Imaging planes: All panels present coronal plane views, consisting of serial craniocaudal coronal sections (progressing from right to left across this panel series). These views illustrate the spatial distribution of hypermetabolic lymphadenopathy across mediastinal/hilar compartments, as well as the anatomical relationship between the nodal lesions and right pleural effusion. CT, computed tomography; PET, positron emission tomography.

January and April 2024. The condition of the patient was deemed stable in May 2024, and the regimen was adjusted to a total of three cycles of treatment with 0.2 g tislelizumab and 0.5 g carboplatin. In August 2024, an evaluation of disease progression revealed the need for additional chemotherapy. Nab-paclitaxel (0.2 g) were added for a total of two cycles. In October 2024, the regimen consisted of 0.2 g tislelizumab, 30 mg cisplatin, and 0.2 g nab-paclitaxel, administered for one cycle. In November 2024, treatment was continued with 200 mg tislelizumab + 1.4 g gemcitabine + 400 mg carboplatin for one cycle.

In mid-December 2024, the patient was readmitted to the hospital due to complaints of marked posterior back pain, generalized weakness and a dry cough. Laboratory tests after admission showed varying degrees of elevation of tumor markers as follows: Carcinoembryonic antigen, 14.80 ng/ml (normal value, <3.4 ng/ml); ferritin, 215.00 ng/ml (normal value, 13-150 ng/ml); glycan antigen 125, 65.70 U/ml (normal value, <35 U/ml); neuron-specific enolase, 20.70 ng/ml (normal value, <16.3 ng/ml); and cytokeratin 19 fragment, 14.30 ng/ml (normal value, <3.3 ng/ml). The blood routine showed a white

blood cell count of $14.10 \times 10^9/l$ (normal value, $3.50-9.50 \times 10^9/l$), an eosinophil percentage (EOS%) of 52.8% (normal value, 0.4-8.0%), an absolute eosinophil value of $7.44 \times 10^9/l$ (normal value, $0.02-0.52 \times 10^9/l$), a platelet count of $508 \times 10^9/l$ (normal value, $125-350 \times 10^9/l$), a quantitative D-dimer level of $1,195 \mu g/l$ (normal value, $\leq 243 \mu g/l$) and an alkaline phosphatase level of 120 U/l (normal value, 35-100 U/l). No abnormalities were observed in the fecal routine.

As early as the chest CT scan in January 2024, a soft-tissue mass measuring 3.2×2.5 cm was detected in the lower lobe of the right lung (Fig. 2A and D). However, CT scans of the chest in December 2024 (size, $10 \times 8.4 \times 5.6$ cm; Fig. 2C and F) showed that the malignant space in the lower lobe of the right lung was markedly enlarged compared with the previous scan in October 2024 (size, 5.2×3.5 cm; Fig. 2B and E), with multiple ground-glass density nodules of varying sizes in both lungs (the largest diameter of which was ~ 1.1 cm), multiple enlarged lymph nodes in the right hilar and mediastinal regions, and occlusion of the right lower lung bronchus with obstructive inflammation, as well as thickening of the right lower pleural membrane. Bone destruction of the seventh thoracic vertebra

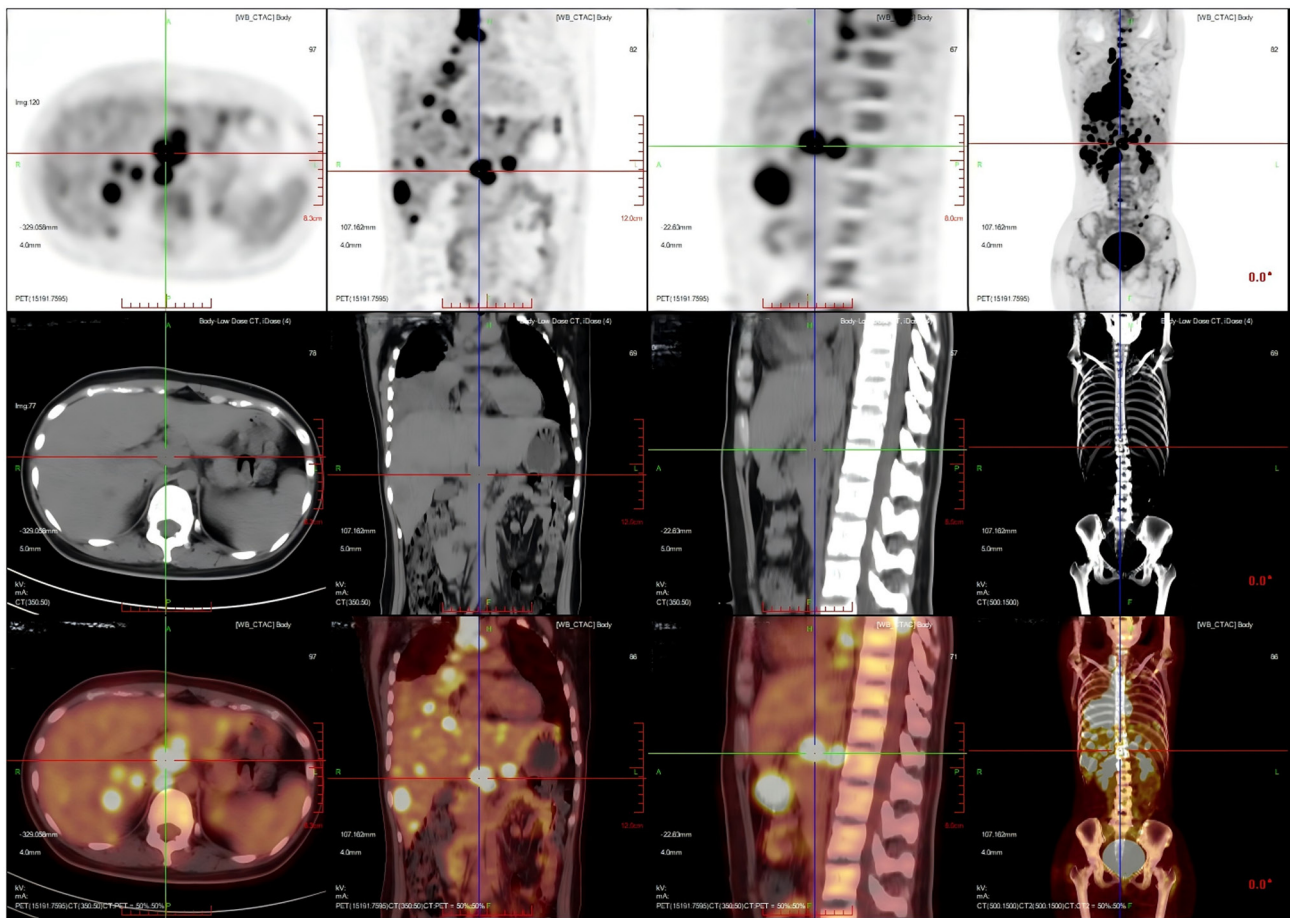


Figure 7. Multiplanar 18F-FDG PET/CT imaging of the patient's hilar hypermetabolic confluent lymph nodes. The liver was full, with diffuse low-density nodules and masses of varying sizes in the liver, and PET showed nodular and mass-like radioactivity uptake in the corresponding areas. The low-density mass in the S4 segment of the liver was measured to be $\sim 5.0 \times 4.4$ cm in size, with a SUV_{max} value of 20.0. Several enlarged lymph nodes were observed in the portal region of the liver, which had fused to form a mass. PET scans showed mass-like radioactivity uptake in the corresponding areas, with a SUV_{max} value of 20.2. Imaging modalities: PET (top row); CT (middle row); PET/CT fusion imaging (bottom row). Imaging planes: Axial Plane (first column): Cross-sectional views depicting transaxial details of the hepatic hilar coalescent lymph nodes. Coronal plane (second column) showing frontal views, illustrating the craniocaudal distribution of the hepatic hilar lesions. Sagittal plane (third column): Lateral views showing anteroposterior localization of the hypermetabolic lymphadenopathy in the hepatic hilum. Volume-rendered CT (fourth column, middle row): 3D reconstructed whole-body CT, visualizing the spatial relationship between the hepatic hilar lesions and thoracic/pelvic bony structures. CT, computed tomography; PET, positron emission tomography.

with pathological fracture suggested bone metastasis. CT scans of the abdomen cavity (Fig. 3) showed multiple new lesions in the liver (the largest of which was ~ 2.7 cm in diameter), suggesting metastases. The imaging suggested that the condition of the patient was in a deteriorating state.

In response to the severe pain caused by bone metastases in the back of the patient, ibandronate injection (5 mg intravenously) was administered to counteract the bone metastases. However, 10 days after admission, peripheral blood eosinophil levels were markedly elevated, with an EOS% of 87.5% and an absolute eosinophil value of $45.21 \times 10^9/l$. A blood smear revealed 87% eosinophils, with these cells readily visible (data not shown). An immediate review of previous test results showed that the peripheral blood eosinophil count had fluctuated between 1.39 and $45.21 \times 10^9/l$ during the last 2 months, with an overall increasing trend (Fig. 4). Based on the aforementioned observations, a joint consultation with the Departments of Respiratory Medicine and Rheumatology was immediately conducted, and measurements of immunoglobulin E (IgE), rheumatoid factor, cytomegalovirus antibody, antinuclear antibody (ANA) and antibody against systemic vasculitis were

performed, which did not show any significant abnormalities. However, the serum total IgE level was high (79.61 IU/ml; normal value, 0-60 IU/ml). The patient was advised to undergo a bone marrow aspiration to rule out hematological diseases. The patient's family refused to allow this invasive operation in consideration of the physical tolerance of the patient, and thus, evidence of leukemia could not be obtained for the time being.

In order to avoid organ damage caused by eosinophilia, intravenous methylprednisolone sodium succinate (20 mg; injection time, 30 min) was immediately administered for anti-inflammatory treatment. After evaluating the condition and tolerance of the patient, the patient was also administered nab-paclitaxel (0.2 g) chemotherapy to treat the tumor, diphenhydramine hydrochloride injection (20 mg) to prevent allergic reactions before chemotherapy and tropisetron hydrochloride injection (5 mg) as an antiemetic. Electrocardiogram, blood pressure and blood oxygen test results were closely monitored. During the past almost 1 year of treatment, the tumor control of the patient had been relatively stable, but the chest CT showed that the tumor was rapidly deteriorating. Coincidentally, the stage of the peripheral blood eosinophilia elevation coincided

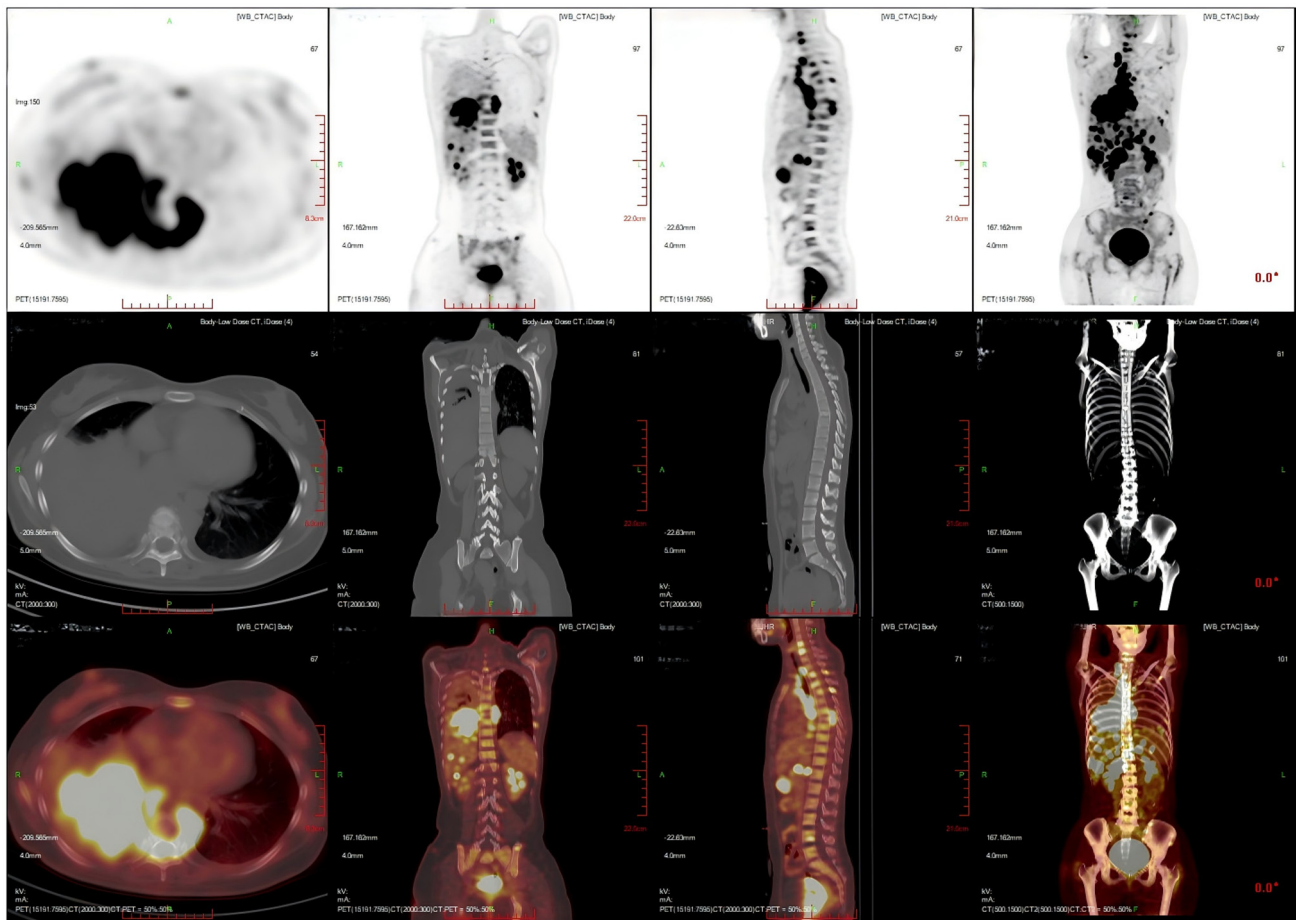


Figure 8. Multiplanar 18F-FDG PET/CT imaging of the patient's multifocal hypermetabolic bone lesions with corresponding skeletal structural abnormalities. Multiple nodular and striated radiographic uptake of the right humeral head, multiple parts of the sternum, bilateral scapulae, cervical, thoracic and lumbar vertebral bodies, part of the accessory bones, the two flanks of the sacrum, multiple parts of the pelvic bone and the proximal segment of the left femur. CT demonstrated an inhomogeneous increase in the density of the bone at the corresponding sites, discontinuity of the cortex in some of the neighboring bones, flattening of the seventh thoracic vertebral body, morphological disorders and an increase in the peripheral soft-tissue shadows. A high metabolic area was measured in the seventh thoracic vertebral body, with a SUV_{max} of 20.4. Imaging modalities: PET (top row); CT (middle row); PET/CT Fusion Imaging (bottom row). Imaging planes: Axial Plane (leftmost column): Cross-sectional views (perpendicular to the body's long axis), depicting transaxial details of focal osseous lesions. Coronal Plane (second column): Frontal views (parallel to the body's coronal axis), illustrating the craniocaudal distribution of multifocal osseous lesions across the skeleton. Sagittal Plane (third column): Lateral views (parallel to the body's sagittal axis), showing anteroposterior localization of vertebral lesions. 3D Volume-Rendered CT (rightmost column, middle row); a 3D reconstructed whole-body CT scan visualizing the spatial relationship of widespread osseous lesions within the global skeletal framework.

with the time of tumor deterioration (October-December 2024), and it was hypothesized that eosinophilia was involved in the progression of the lung cancer.

After 1 month, the patient developed numbness and discomfort below the waist, weakness of both lower limbs and limitations to lifting. To clarify the changes in the condition of the patient, positron emission tomography/CT (PET/CT) was performed. PET/CT images showed that an irregular mass-like hyperdense shadow was detected in the right lung hilar and the middle and lower lobes of the right lung; no normal lung tissue was seen, the lesion crossed the interlobular pleura and invaded the upper lobe of the right lung, and the corresponding area on PET showed a mass-like radiolucency focus with an maximum standardized uptake value (SUV_{max}) of 25.8 (Fig. 5). Multiple enlarged and swollen lymph nodes were detected in the mediastinum, bilateral pulmonary hilar region, bilateral diaphragmatic pedicle and right cardiogenic angle area, partially fused in the form of a mass. PET showed a mass of radiolucent foci in the corresponding areas, and the SUV_{max} of

the hypermetabolic area under the bronchus was measured to be 21.4. Thickening of the right pleura was observed, an arcuate fluid density shadow was seen in the thoracic cavity and mild radiolucent uptake was visible in the area of pleural effusion on the right side of the chest cavity (Fig. 6). The liver was full, with diffuse low-density nodules and masses of varying sizes within it, and PET showed nodular and mass-like radioactivity uptake in the corresponding areas. The low-density mass in the S4 segment of the liver was measured to be $\sim 5.0 \times 4.4$ cm in size, with an SUV_{max} of 20.0. Several enlarged lymph nodes were observed in the portal region of the liver, which had fused to form a mass. PET scans showed mass-like radioactivity uptake in the corresponding areas, with a SUV_{max} of 20.2 (Fig. 7). Multiple nodular and striated radiographic uptake of the right humeral head, multiple parts of the sternum, bilateral scapulae, cervical, thoracic and lumbar vertebral bodies, part of the accessory bones, the two flanks of the sacrum, multiple parts of the pelvic bone and the proximal segment of the left femur were noted. CT demonstrated an inhomogeneous

increase in the density of the bone at the corresponding sites, discontinuity of the cortex in some of the neighboring bones, flattening of the seventh thoracic vertebral body, morphological disorders and an increase in the peripheral soft-tissue shadows. A high metabolic area was measured in the seventh thoracic vertebral body, with an SUV_{max} of 20.4 (Fig. 8).

The peripheral blood eosinophil level was markedly but transiently decreased (EOS%, 63.3%; absolute eosinophil count, $14.48 \times 10^9/l$), but still higher than the normal range. In response to the rapidly deteriorating condition, the situation was explained to the family of the patient, and the treatment regimen was changed to oral target therapy with erlotinib capsules (12 mg, for 2 consecutive weeks, once a day). In addition, morphine hydrochloride extended-release tablets (30 mg, once a day) were administered orally to alleviate the pain of bone metastasis. Lactulose oral liquid (20 ml, once a day) was administered orally, and glycerine enema (20 ml, once a day) and multivitamins (5 ml, once a day) were provided for nutritional support. The patient was discharged from the hospital after symptomatic relief. During one of the semimonthly outpatient follow-up appointments in February 2025, it was observed that the patient was unable to walk upright due to severe bone metastases. In June 2025, the patient succumbed to complications from the tumor.

Discussion

Eosinophils are multifunctional immune cells that circulate in the peripheral blood and are distributed throughout tissues. At present, eosinophils are generally considered to serve a pleiotropic and bifacial role in the tumor microenvironment. On the one hand, eosinophils stimulate malignant plasma cells through an IL-6-independent mechanism, and form a synergistic support with stromal cells (5). On the other hand, eosinophils promote CD8⁺ T cell-mediated antitumor immunity and significantly delay tumor progression (6). Although the prognosis of patients with eosinophilic pleural effusion due to lung cancer has been reported to be improved compared with that of patients with non-eosinophilic malignant pleural effusion (7), in individual cases of lung adenocarcinoma combined with eosinophilia, this paraneoplastic syndrome is likely to reflect the aggressiveness and progression of the lesion (8). The present report describes a rare case of peripheral blood eosinophilia in a young woman with squamous lung cancer during the same period as rapid tumor progression. After treatment with glucocorticoids in combination with antitumor agents, the peripheral blood eosinophil levels decreased markedly. We hypothesize that the eosinophils served an important role in promoting tumor progression.

The current diagnostic classification for eosinophilia is mild ($0.5-1.5 \times 10^9/l$), moderate ($1.5-5 \times 10^9/l$) and severe ($>5 \times 10^9/l$) (9). Patients who are asymptomatic and have only mild to moderate eosinophilia may be temporarily excluded from further testing (10). With systemic symptoms or persistent eosinophilia ($>1.5 \times 10^9/l$) with or without suspected organ damage, the examination should be refined to identify or exclude secondary causes (10,11). Among secondary factors, allergic diseases are the most common, followed by parasitic infections (12). Solid tumors or lymphomas may also be associated with reactive eosinophilia (13). Drug reactions,

immunodeficiency disorders and certain skin diseases should also be taken into consideration. The clinical history should focus on a history of allergies, a rash or cardiopulmonary and gastrointestinal symptoms. To consider allergic factors, serum IgE measurements may be performed. To rule out parasitic infections, including fecal parasites and eggs, microscopy may be performed. Considering gastrointestinal causes, gastrointestinal endoscopy or serological testing for serum amylase and celiac-related autoantibodies is indicated. Imaging tests (such as chest CT scans) and fiberoptic bronchoscopy can help rule out respiratory diseases. Rheumatologic antibody-related tests, such as ANA or anti-double-stranded DNA antibody analysis, should be performed in individuals predisposed to connective tissue disease. Serological testing for antineutrophil cytoplasmic antibodies, cytomegalovirus and human parvovirus B19 may also be performed to rule out factors associated with vasculitis. Eosinophilia caused by solid tumors usually has no obvious clinical manifestations or has overlap with tumor-induced associated symptoms, making the diagnosis challenging (10,12). After ruling out non-cancer factors, attention may be paid to whether the period of eosinophilia overlaps with the period of tumor progression. Additionally, if there is suspected organ damage due to eosinophilia (for example, to the heart, lungs, liver, spleen, skin and nervous system), evaluation of the affected organs should be performed (11).

Primary eosinophilia usually refers to hematological disorders (14). In cases where no secondary cause has been identified and eosinophilia ($>1.5 \times 10^9/l$) is present, a primary cause should be considered, especially eosinophilic leukemia (15). Eosinophilic leukemia is a rare type of leukemia characterized by abnormal eosinophilia in the peripheral blood and bone marrow, with progressive anemia and thrombocytopenia, and a markedly elevated white blood cell count of up to $50-200 \times 10^9/l$ (16,17). The presence of naïve eosinophils in the blood and $>5\%$ of primitive cells in the bone marrow is also required (18). The acute form of eosinophilic leukemia is characterized by eosinophilic infiltration of multiple organs, with cardiac, pulmonary and central nervous system involvement, in addition to involvement of the liver, spleen and lymph nodes. Clinical manifestations include progressive heart failure, dyspnea, psychiatric disorders, delusions and ataxia. Erythema and papules may appear on the skin (19). The chronic type of eosinophilic leukemia has a slow onset, with a course of up to 2-8 years, and manifestations such as malaise, anemia, and enlargement of the liver, spleen and lymph nodes (20). The greatest diagnostic limitation in the current case was the failure to perform a bone marrow aspiration, which restricted the ability to rule out a hematological disorder (eosinophilic leukemia). When the patient presented with a rapid increase in blood eosinophils, the family of the patient was immediately informed of this notable phenomenon and the need for bone marrow aspiration was emphasized. However, the family members believed that the patient was in the end stage of cancer, and the quality of life of the patient was very low due to the long-term pain. They were not willing to allow the patient to undergo this additional invasive operation, and the main goal was to relieve the pain. In keeping with the concept of humanistic care for the patient and respect for the opinions of the family members, a bone marrow puncture was not insisted on. After this, some secondary factors were

excluded by serial examination. Although a bone marrow aspiration was not performed, there was insufficient evidence to diagnose eosinophilic leukemia when considering the routine blood results and the absence of apparent target organ damage and symptomatic manifestations.

Furthermore, the immunohistochemical results described in the manuscript are based on pathology reports rather than retrievable image files. This is also a major limitation of the diagnosis.

The diagnosis of eosinophilia is a diagnosis of exclusion. Based on the exclusion of primary etiology, understanding the clinical manifestations and laboratory tests of various secondary etiologies and correlating them with the progression of the disease is key for clinicians to diagnose paraneoplastic eosinophilia.

The most important mechanism by which malignant tumors lead to eosinophilia is the secretion of several cytokines, including IL-5, IL-3 and granulocyte-macrophage colony-stimulating factor, by tumor cells. Among them, IL-5 serves a key role in the production, activation and recruitment of eosinophils into the tumor microenvironment (21). Early study of *in vitro* models of non-small cell lung cancer have demonstrated the ability of lung cancer cells to produce IL-5-based type 2 cytokines to recruit eosinophils (22). Eosinophils directly interact with the tumor microenvironment, mainly via two mechanisms: First, release of cytokines and particulate contents that affect the tumor microenvironment and tumor cells. For example, eosinophils can directly kill tumor cells by releasing major basic protein (MBP), eosinophil peroxidase (EPO) and reactive oxygen species, or eosinophils can secrete TGF- β , IL-13 and other cytokines, which promote fibrosis, angiogenesis, immunosuppression and tumor metastasis (23). Second, eosinophil receptors bind to tumor cells, thereby altering the prognosis of tumors. Eosinophils can initiate direct contact with cancer cells and express natural killer group 2 member D, killer markers of natural killer cells and CD8⁺ T cells, thereby exerting direct antitumor effects (24,25). Eosinophilia may be a manifestation of a poor tumor prognosis. The coincidence of the rapid tumor progression stage and the timing of eosinophilia in the present case also confirmed the relationship of mutual promotion. In addition, local or systemic inflammatory reactions triggered by cancer, the abnormal bone marrow hematopoietic environment caused by tumor bone metastasis and other factors will also aggravate eosinophilia, forming a vicious circle.

Solid tumor-associated eosinophilia involves complex immune-tumor interactions. Eosinophils can modulate inflammatory allergic responses and interact with lymphocytes to modulate their function in immune defense. This could be either a positive signal of antitumor immunity or a pathological factor that promotes tumor progression. On the one hand, activated eosinophils cause an independent and synergistic antitumor effect of CD8⁺ T cells, which can improve the tumor microenvironment to enhance the immune response. An early study showed that eosinophils mediate tumor rejection by promoting tumor vascular normalization (reducing vascular leakage and alleviating hypoxia) and enhancing CD8⁺ T cell infiltration, and their survival in the tumor microenvironment may be prolonged (26). Furthermore, eosinophils can inhibit the apoptosis of CD8⁺ T cells to participate in the generation of

memory CD8⁺ T cells and enhance the immune defense (27). In addition, activated eosinophils can induce the polarization of M1 macrophages, thereby improving the immunosuppressive state in tumors. The aforementioned studies suggest that eosinophils have a tumor-killing effect, and may enhance and activate T cells in a type 1 immunity manner (26). This may be an active mechanism in tumor immunotherapy. However, on the other hand, eosinophils can promote tumor cell migration and metastasis by secreting C-C motif ligand 6 (4). Lee *et al* (28) suggested that tumor-associated tissue eosinophilia is associated with poor overall survival and that activated eosinophils promote tumor migration primarily through C-C motif ligand 2. Meanwhile, eosinophils can induce tumor angiogenesis, which is related to the immunosuppressive tumor microenvironment. Eosinophils may also promote epithelial-mesenchymal transition, thereby enhancing tumor invasiveness through the immunomodulatory pathway involving IL-13 and STAT6 (29). Such studies support the idea that eosinophils promote cancer, thus confirming the dual role of eosinophils in cancer from an immunomodulatory perspective.

One study found that eosinophilia was positively associated with the response to immunotherapy. However, some patients receiving immunotherapy were prone to peripheral blood and intra-tumor eosinophilia, which may be related to IL-5 secretion by CD4⁺ T lymphocytes and IL-33-mediated eosinophil recruitment (30). Therefore, the altered immune status of the patient needs to be taken into consideration. Although the current patient received tislelizumab immunotherapy, no abnormal eosinophil manifestations were observed in the peripheral blood during the past year of treatment. In conjunction with the stage of the eosinophil elevation of the patient, it was determined that pharmacogenetic factors were less likely to be involved.

Although the total serum IgE level of the patient was high, the patient had no history of food and drug allergies. The patient did not exhibit any allergic symptoms, such as dyspnea, rash, nasal congestion or a runny nose. Tumor-causing factors and tumor cells are alloantigens or sensitizers for the human body. The rapidly growing and spreading tumor foci of the patient stimulate the body to produce antibodies, including IgE antibodies, which can result in allergic reaction-like manifestations (31). In addition, both eosinophils and IgE are typical markers of the type 2 immune response, and the synergistic effect between them involves multiple cytokines and signaling pathways (32-34). It has been found that IL-4, IL-5 and IL-13 secreted by T helper 2 cells and type 2 natural lymphocytes in the tumor microenvironment not only stimulate bone marrow eosinophilia but also stimulate the conversion of B lymphocytes to plasma cells, which triggers the elevation of serum total IgE levels (35). The high-affinity IgE receptor on the surface of tumor-associated mast cells is capable of releasing eosinophil chemokines (such as Eotaxin-1/C-C motif chemokine ligand 11) upon binding to antigens (36), which directly recruits eosinophils to the tumor microenvironment. MBP and EPO secreted by eosinophils can further stimulate mast cell degranulation, forming a positive feedback loop (35). Therefore, it is possible that the elevated serum total IgE level in the current patient reflected the activation of type 2 immunity *in vivo* and was closely related to the eosinophilia.

It has been noted that ~10% of patients with solid tumors develop leukocytosis as a result of paraneoplastic leukemia-like reactions, while eosinophilia is even rarer (37). Zhu *et al* (38) reported the case of an 80-year-old man presenting with chest pain. Eosinophilia was found in the peripheral blood (absolute value, $2.15 \times 10^9/l$) and bronchial lavage fluid, accompanied by right pulmonary artery and main bronchus invasion, and adjacent bone destruction. A subsequent needle biopsy revealed squamous cell carcinoma of the lung. This report highlights that elevated eosinophil counts may be associated with metastasis and a poor prognosis in lung cancer. Ozaki *et al* (39) reported a case of cerebral infarction in a 67-year-old man with eosinophilia (eosinophil count, $13,600/\mu l$) due to metastasis of lung adenocarcinoma to the bone marrow, but the precise mechanism was unclear. In addition, Verstraeten *et al* (40) reported a case of non-small cell lung cancer associated with peripheral eosinophilia. The affected 65-year-old man received a diagnosis of paraneoplastic hypereosinophilia after ruling out anaphylaxis, leukemia, vasculitis and parasitic infection. This is similar to the present case. In the 8 previously reported cases of squamous cell carcinoma of the lung combined with peripheral blood eosinophilia, the mean age of the patients was 63 years, and only 1 case was in a female patient (41). In the present case, the female patient was only 25 years old, which is a notable indication of the specificity and rarity of the case. The severity of paraneoplastic eosinophilia can range from asymptomatic to life-threatening. In numerous cases, markedly elevated eosinophil counts may be accompanied by respiratory reactions and rashes, with some patients exhibiting specific symptoms such as shortness of breath, cognitive deficits, disorientation and speech disorganization (42). However, in the present case, there were no specific clinical manifestations, which made clinical detection and identification difficult, but also suggested that there was no apparent target organ damage.

A significant causal effect of eosinophilia, especially with the development of squamous lung cancer, has been found in East Asian populations. The risk of developing lung cancer in patients with eosinophilia may be increased 1.28-fold compared with that of patients with no eosinophilia (43). In lung squamous carcinoma biopsy tissues, an association has been observed between the level of tissue eosinophil infiltration and programmed cell death ligand 1 expression $\geq 50\%$ (44). The present patient had no history of smoking, blood transfusion or allergies, and no family genetic history. Considering that the likelihood of EGFR mutation is markedly higher in patients with these particular types of risk factor for squamous lung cancer (for example, female, non-smoker and Asian ethnicity), genetic testing was performed using next-generation sequencing analysis in the present case. A mutation in exon 20, p.T790M, of the EGFR gene (mutation frequency, 53.51%) was detected. Blood eosinophilia in patients with lung adenocarcinoma harboring the EGFR L858R mutation and mesenchymal-epithelial transition factor amplification has previously been reported to parallel disease progression. Blood eosinophilia has a negative effect on prognosis in driver-positive non-small cell lung cancer (45), suggesting that eosinophil counts and EGFR mutations may be associated.

Since absolute peripheral blood eosinophil counts are not necessarily positively associated with end-organ damage, there is no consensus on whether treatment is needed and when to start it in the absence of apparent organ involvement, dysfunction and clinical manifestations. Patients with paraneoplastic eosinophilia are typically asymptomatic, and treatment focuses on reducing eosinophil counts and preventing eosinophil-mediated organ damage. Resection of the tumor and chemotherapy can lead to a decrease in paraneoplastic eosinophils (46,47). Eosinophil counts can also be decreased by short-term use of low-dose corticosteroids and occasionally glucocorticoids (48). The combination of corticosteroids and hydroxyurea has been reported to enhance therapeutic effects (29). If eosinophilia is extreme, allopurinol should be administered concurrently (49). Glucocorticoid therapy must still be applied when eosinophilia is severely life-threatening, and a starting dose of 1 mg/kg/day is generally recommended, maintained for 1-2 weeks, and tapered off over 2-3 months. If the efficacy is not satisfactory, treatment with immunomodulators (interferon- α , cyclosporine or azathioprine) and hydroxyurea can be added (50,51). In the current case, nab-paclitaxel was applied in addition to the intravenous infusion of methylprednisolone sodium succinate to combat the primary tumor, resulting in a marked improvement in the peripheral blood eosinophil counts and preventing organ damage caused by further eosinophilia.

Current research suggests that the prognosis of eosinophilia is mainly dependent on the diagnosis of the disease, and that patients with eosinophilia in combination with most diseases have an improved prognosis if the diagnosis is recognized at an early stage and treated appropriately (52). However, in the current case, the exceptionally high eosinophil count and rapidly progressive malignant disease suggested a poor prognosis.

In conclusion, to the best of our knowledge, this is the first report of rapidly progressive squamous lung cancer with eosinophilia in a young woman. Eosinophilia is a paraneoplastic syndrome that can occur in the advanced stages of squamous lung cancer and becomes a potential risk factor promoting the proliferative progression of squamous lung cancer. This also suggests the importance of recognizing the role that paraneoplastic eosinophilia serves in the tumor and the need to take early steps to combat it. Clinical practice should also consider the possibility that the presence of eosinophilia in the blood may be associated with malignancy. Corticosteroids, in combination with anticancer drugs, should be used after early diagnosis to prevent organ damage caused by eosinophilia and to enhance the effectiveness of anticancer therapy to some extent. However, eosinophilia is complicated to diagnose in both the early and late stages, and it may also involve multiple organ systems or present with systemic manifestations. A multidisciplinary approach should be employed to optimize diagnosis and treatment when necessary.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study may be found in the National Center for Biotechnology Information under accession number PRJNA1348469 or at the following URL: <http://www.ncbi.nlm.nih.gov/bioproject/1348469>. The remaining data generated in the present study may be requested from the corresponding author.

Authors' contributions

MZ and HF designed the study. HF, CS, DL, and JG advised on patient treatment. MZ, DL, JG, and YH acquired the data. HF, DL, YH, and JC analyzed and interpreted data for the work. MZ, HF, CS, DL, JG, YH and JC confirm the authenticity of all the raw data. All authors agree to be accountable for all aspects of the work. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The Ethics Committee of The First Affiliated Hospital of the Hebei University of Chinese Medicine approved this study, which was conducted according to the 1964 Helsinki Declaration and its subsequent amendments, or comparable ethical standards. The patient provided written informed consent for the publication of their data prior to succumbing to the disease.

Patient consent for publication

The patient provided written informed consent for the publication of their data and associated images prior to succumbing to the disease.

Competing interests

The authors declare that they have no competing interests.

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