


CASE REPORT

Paraneoplastic leukemoid reaction in a patient with metastatic adenocarcinoma of the lung

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Abstract

Paraneoplastic syndromes in lung malignancies can lead to leukemoid reaction with an elevation of eosinophils, neutrophils, and monocytes. The elevation of these three lineages together due to paraneoplastic syndromes has not been described in literature yet.

KEYWORDS

leukemoid reaction, paraneoplastic syndrome

1 | INTRODUCTION

Lung cancer is considered to be the most common fatal cancer in both sexes in the United States.¹ It is not uncommon for lung cancer to be associated with mild leukocytosis. However, this should be distinguished from a leukemoid reaction, which is characterized by extreme nonleukemic leukocytosis, greater than 50 000 cells/ μ L, with a marked mature neutrophilia and a left shift (increased myelocytes, metamyelocytes, and bands). Isaacson and Rapoport were the first to describe the correlation between eosinophilia and neoplasms in 1946.² Since then, there has been an acknowledged association between eosinophilia and neoplasms. Eosinophilia, which can be mild (350-1500 cells/ μ L), moderate (1500-5000 cells/ μ L) or severe (>5000 cells/ μ L), is defined as an increase in peripheral blood eosinophils. Monocytosis, which is defined as an increase in monocyte count above 1000 cells/ μ L, is also a common finding in malignancies but is considered to be extremely nonspecific. However, a case of the elevated triad of eosinophils,

neutrophils, and monocytes in a patient with lung cancer has not been described in the literature yet.

2 | CASE

A 57-year-old woman known to have metastatic adenocarcinoma of the lung with pleural, liver, and osseous metastases as well as pelvic carcinomatosis, presented to the emergency department with acute confusion of one-day duration. Patient had previously received multiple lines of treatment including Carboplatin in combination with Pemetrexed and Pembrolizumab, docetaxel, phase I study utilizing the glutaminase inhibitor CB-839 in combination with nivolumab, phase I study of mitogen-activated protein kinase (MAPK)—interacting serine/threonine-protein kinase 1 (MNK1) and 2 (MNK2) inhibitor, phase I study using TAK-659 (spleen tyrosine kinase) in combination with nivolumab, and most recently phase I study of SEA-CD40 (nonfucosylated, humanized IgG1 monoclonal antibody, which binds CD40, an

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immune-activating TNF receptor). Her last Oncologic treatment was two months prior to her presentation.

Upon evaluation, initial complete blood count revealed neutrophils of 38 400 /mm³, eosinophils of 27100/mm³, and monocytes of 1700/mm³ (Figure 1). Peripheral blood smear showed numerous vacuolated neutrophils, eosinophils, and monocytes. (Figure 2). There were very few myelocytes and promyelocytes seen in the peripheral blood smear. Patient's brain MRI showed no signs of metastasis that could explain her confusion. Extensive infectious workup was negative. A reverse transcription Polymerase chain reaction (RT-PCR) for BCR-ABL1 gene fusion was negative, which ruled out a rare variant of Chronic Myeloid Leukemia that could result in similar leukemoid reaction presentation. An extensive workup was done, and the patient's leukemoid reaction was determined to be due to paraneoplastic syndrome related to the lung adenocarcinoma secreting macrophage colony-stimulating factor (GM-CSF).

3 | DISCUSSION

Leukemoid reaction can develop due to a variety of causes making its diagnosis somewhat challenging. Several infections such as Tuberculosis and Clostridium Difficile, drugs such as corticosteroids, ethylene glycol intoxication, acute hemolysis, and miscellaneous etiologies have been associated with the development of a leukemoid reaction.³ In our case, the patient had no clear reason to develop this leukemoid reaction as both her urine and blood cultures were negative; the chest X-ray did not reveal any signs of pneumonia, and no blood products were transfused to her, nor did she take glucocorticoids.

Malignancy-induced extreme leukocytosis also known as paraneoplastic leukemoid reaction (PLR) still represents a diagnostic dilemma due to the need to rule out a multitude of secondary causes. Thus, PLR remains a diagnosis of exclusion.⁴ Extreme leukocytosis has been reported in most types of solid tumors.^{3,5,6} However, its frequency in nonhematologic cancer remains unclear, with a reported range of 1% to 4% in several small case series.^{5,7} Numerous scientists tried to explain the reason behind this reaction in malignancies. Asano et al published the first report of colony-stimulating factor (CSF) producing lung cancer associated with the

development of extreme neutrophilia.⁸ Further investigations demonstrated elevated serum concentrations of hematopoietic growth factors granulocyte (G)-CSF, granulocyte monocyte (GM)-CSF, and interleukin-6 (IL-6) in patients with lung cancer and extreme neutrophilia.^{9,10} These cytokines tend to promote tumor growth in a paracrine manner.^{8,11} Neutrophilia driven by leukogenic cytokines produced by tumor cells was also observed in nude mice upon tumor cells transplantation.^{12,13}

Eosinophilia can be a manifestation of a myriad of causes such as infections, drug reactions allergic, and autoimmune processes. Eosinophils are derived from pluripotent stem cells of the bone marrow through the eosinophil lineage stimulated by cytokines and growth factors. Several cytokines and growth factors have been associated with the production and maturation of eosinophils, with the main cytokines being IL-3 and IL-5 and the main growth factors being GM-CSF.¹⁴ Isaacson and Rapoport presented in 1946 a study of 34 cases of eosinophilia associated with neoplasm.² Since then, numerous reports of malignancies associated with eosinophilia have been reported.

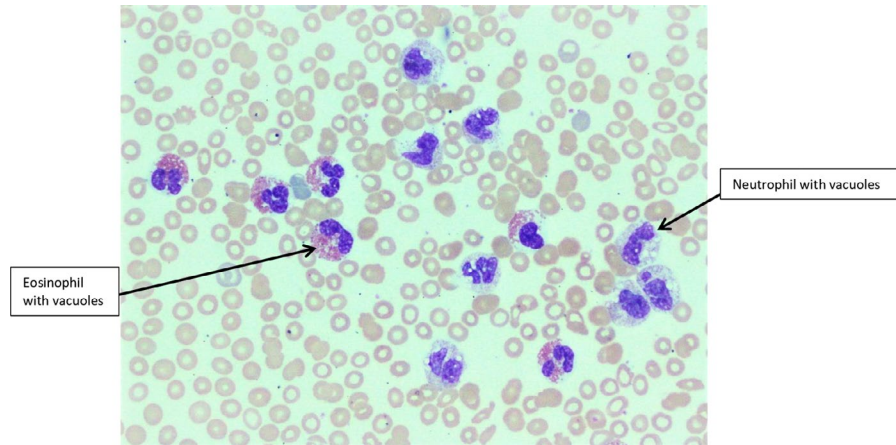
Several hypotheses have been suggested regarding the etiology behind the observed eosinophilia. These include protein material released from tumor-induced necrosis causing an eosinophilic response, tumor cells release of eosinophilic chemotactic factors, metastatic tumor cells seeding the bone marrow causing production of eosinophils, and tumor cell eosinophilic factors stimulating eosinophils production by the bone marrow cells.¹⁵ However, when it comes to eosinophilia as a prognostic sign, several reports have demonstrated both positive and negative significance in patients with malignancy-associated eosinophilia.¹⁶ On the other hand, Kaminska et al reported a positive correlation between IL-6 levels and tumor size in patients with nonsmall-cell lung carcinoma.¹⁷ Thus, to date, no final conclusion can be made regarding the role of eosinophilia as a prognostic factor in malignancy. However, tissue eosinophilia has been associated with a better prognosis than peripheral eosinophilia.¹⁸

Finally, monocytosis is extremely nonspecific and most cases will prove to be reactive in nature. It is common with infections, connective tissue disorders such as systemic lupus erythematosus, and rheumatoid arthritis, obesity, recovery from myelosuppression such as chemotherapy, as well as malignancy.¹⁹ This patient's history lacked any evidence for

Blood	Date	7/9/18	7/11/18	7/12/18
White blood cells		87.3	91.4	96.7
Absolute Lymphocyte count		3.5	-	1
Absolute Monocyte count		1.7	1.8	1.9
Absolute Eosinophilic count		27.1	40.2	13.5
Absolute Neutrophilic count		47.1	38.4	53.2

FIGURE 1 The variation of cell count ($\times 10^3/L$) throughout hospital stay

FIGURE 2 Peripheral blood smear shows numerous neutrophils and many eosinophils, both with vacuoles



connective tissue disease, as well as infection was ruled out by the diagnostic workup previously mentioned. Moreover, the patient's last chemotherapy was several months prior to developing this unique leukemoid reaction. Monocytosis has been also described in myeloproliferative disorders most likely chronic myelocytic leukemia, which has also been ruled out with a negative RT-PCR for BCR-ABL1 gene fusion.


4 | CONCLUSION

An increased level of white blood cells is often observed in patients due to multiple causes such as infection, glucocorticoids, growth factors, and cancer. Thus, multiple secondary causes need to be ruled out before the diagnosis of PLR is established. Most previous reported cases in the literature described cancer-associated leukemoid reaction with or without eosinophilia. We reported here the first case of leukemoid reaction in lung cancer with a combined triad of neutrophilia, eosinophilia, and monocytosis.

AUTHOR CONTRIBUTIONS

CB: is a practicing oncologist at Karmanos Cancer Institute/Wayne State University where the present case report took place and is the primary investigator of the case report. MNA: is the hematology-oncology fellow at Karmanos Cancer Institute/Wayne State University that examined the patient and helped shape the manuscript. AK/OC/EK: are residents at Wayne state/DMC that examined and followed up the patient as well as assisted in writing the case report. CM: is currently a first-year intern at St Elizabeth Medical Center who wrote the manuscript with support from the names mentioned above.

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