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Eosinophilia as a presenting symptom of the metastatic lung adenocarcinoma with an unknown primary localization

Case Report

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Abstract: Apparent hematological symptoms rarely dominate the clinical picture of an underlying non-hematological malignancy. Malignancy-associated eosinophilia can result from clonal or non-clonal proliferation of eosinophils. Here, we report the case of a 59-year-old man with metastatic adenocarcinoma of the lung with an unknown primary tumor site, which presented as hypereosinophilia, anemia, lymphadenopathy, weight loss, and malaise. Bone marrow biopsy disclosed metastatic adenocarcinoma positive in immunohistochemistry for cytokeratin 7. Further assessment of specimens obtained from the bronchoalveolar lavage and biopsy of the mediastinal lymph nodes confirmed the diagnosis of the metastatic lung cancer, although the primary tumor site remained undiscovered. This case underlines that eosinophilia may represent a rare primary manifestation of an undetected malignancy, and it is thus important to consider this as part of the differential diagnosis in patients presenting with unexplained eosinophilia.

Keywords: *Eosinophilia • Malignancy • Lung cancer • Adenocarcinoma*

1. Introduction

Blood eosinophilia depends on either a cytokine-mediated secondary phenomenon or primary eosinophilic disorders known as hypereosinophilic syndromes [1]. Underlying conditions that can cause eosinophilia range from allergic reactions, parasitic infections, connective tissue disorders, or adverse drug reactions (e.g., anticonvulsants, sulpha drugs, allopurinol), to malignancies [2,3]. Allergic disorders including drug hypersensitivity reactions are the most common etiology of secondary eosinophilia in industrial countries while parasitic infections are in developing countries. Malignancy-associated eosinophilia can result from clonal proliferation of eosinophils (i.e. myeloid or lymphoid neoplasms with distinct genetic abnormalities and eosinophilia) or non-clonal proliferation associated with lymphomas (i.e. Hodgkin lymphoma, T-cell lymphoma) and metastatic or necrotizing carcinomas [2,4].

Although it is generally advised that malignancy should be taken into consideration in the diagnostic work-up of eosinophilia, some have argued against extensive investigation, their reasoning being that most tumor-associated eosinophilia is accompanied by an advanced and clinically obvious metastatic disease [3,5]. However, in rare instances eosinophilia due to a paraneoplastic process can be the presenting symptom of an as yet unknown primary malignancy [6]. Here, we report the case of an adult patient with metastatic adenocarcinoma of the lung with an unknown primary tumor site, which presented with dominant hematological symptoms including hypereosinophilia.

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2. Case report

A 59-year-old Swedish male was admitted to hospital with a 2-month history of chest pain, effort dyspnea, malaise, and weight loss of 11kg. His past medical history was significant for ischemic stroke (12 years before), myocardial infarction (3 years before), hypertension and gastritis. He had been a heavy smoker for 30 years, although had reported to limit his smoking (≤5 cigarettes/day) since the myocardial infarction. Physical examination was non-contributory. Whole blood analysis showed a hemoglobin concentration of 101 g/L (control range 134–170), a white blood cell count of 12.1 × 10^9/L (control range 3.5–8.8) with the presence of apparent eosinophilia 3.75 × 10^9/L (control range 0.1–0.6) and slight basophilia 0.24 × 10^9/L (control range ≤0.1) and a platelet count of 123 × 10^9/L (control range 145–348). Peripheral blood smear demonstrating eosinophilia is shown in Figure 1. Further laboratory analyses revealed normal alanine transaminase, slightly elevated alkaline phosphatase (2.2 µkat/L; control range 0.6–1.8), elevated INR (1.4; control range 0.9–1.2), slightly prolonged APTT (44 sec; control range 28–42), elevated C-reactive protein (56 mg/L; normal value <5), and elevated lactate dehydrogenase (9.5 µkat/L; control range 1.8–3.4). Serum electrophoresis showed moderate inflammatory reaction but no M-protein. Renal function was normal.

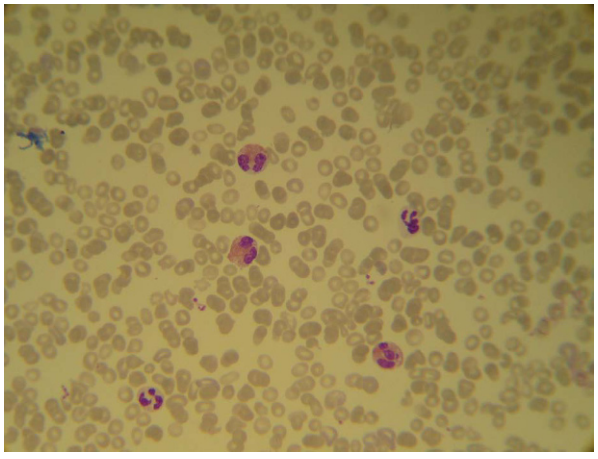

Figure 1. May-Grünwald-Giemsa stain of peripheral blood smears (x400). Three eosinophilic and two neutrophilic granulocytes are present in one microscopic field of vision.

Upon investigation of chest pain, a new acute coronary syndrome was excluded based on a normal result of electrocardiography and normal levels of cardiac markers (troponin-T, creatine kinase MB). Spiral computed tomography (CT) of the chest was performed. Pulmonary embolism was ruled out, however, it revealed mediastinal lymphadenopathy (Figure 2), with the largest lymph node measuring 3.5 × 2.5 cm, as well as non-recent compression fractures of the lower thoracic spine (Th10–12). Abdominal and pelvic CTs were non-contributory. Magnetic resonance imaging of the vertebral column disclosed the aberrant signal in the entire thoracic and lumbar spine area, suspicious of malignancy involvement.

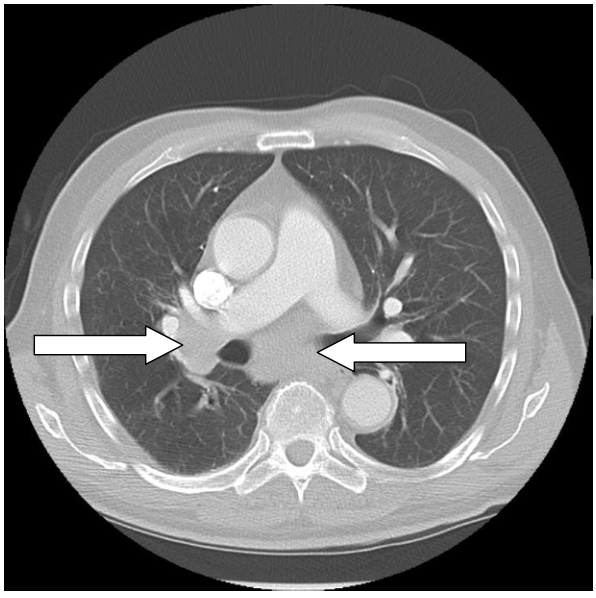

Figure 2. Horizontal CT scan of the chest. A moderate mediastinal lymphadenopathy (arrows) is present without a visible primary site of lung cancer.

The patient was referred to the hematology department with the working hypothesis of a hematological malignancy, based on symptoms of malaise, weight loss, anemia, leukocytosis with eosinophilia, and mediastinal lymphadenopathy. Fine needle bone marrow (BM) aspiration and trephine biopsy were performed. The aspiration was difficult to perform ('dry-tap') and therefore diluted with peripheral blood. Nevertheless, BM smears disclosed clusters of large non-hematopoietic cells with irregular nuclei and basophilic cytoplasm (Figure 3). Furthermore, BM biopsy disclosed metastatic adenocarcinoma immunohistochemically positive for cytokeratin 7, but negative for CK20, prostate specific antigen (PSA), thyroid transcription factor-1 (TTF-1) and thyroglobulin. Cells of similar morphologic presentation and phenotype were later found in transbronchial fine needle aspiration from mediastinal lymph nodes, and in cytological specimens from bronchoalveolar lavage. Bronchoscopy failed to demonstrate a primary tumor.

However, based on the aforementioned investigation results, the diagnosis of lung adenocarcinoma with bone metastases was established, and the patient was referred to a pulmonologist for further treatment.

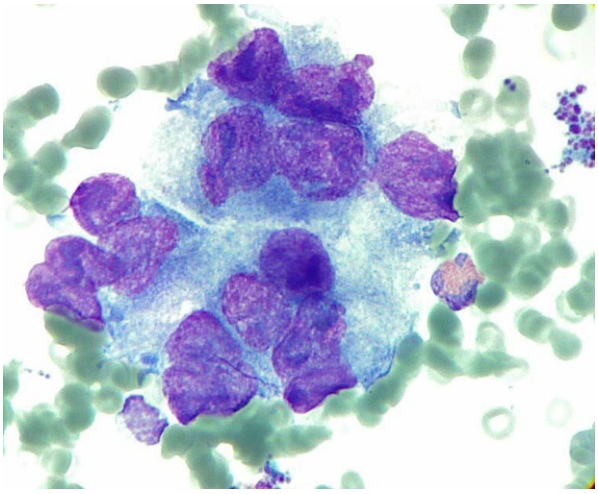

Figure 3. May-Grünwald-Giemsa stain of bone marrow aspirate smears (x1000). The centrally placed large cell conglomerate consists of adenocarcinoma cells with ample basophilic cytoplasm and irregular nuclei. A single eosinophil is present nearby.

3. Discussion

Eosinophilia refers to an increased number of eosinophils (eosinophilic granulocytes) >0.7 × 10^9/L in peripheral blood if calculated from the total leukocyte differential count, and >0.45 × 10^9/L if determined by absolute counting methods [4]. The term hypereosinophilia is used when the eosinophil count exceeds 1.5 × 10^9/L [3,4]. Non-malignant hematological conditions in which eosinophilia is a common finding are pernicious anemia and post-splenectomy status.

Malignancy-associated eosinophilia is a well-recognized but unusual symptom in different malignancies, in which the pathogenesis seems to be related to an increased production and secretion of cytokines and growth factors, especially interleukin(IL)-3, IL-5 and granulocyte-macrophage colony-stimulating factor (GM-CSF); either by the malignant cells themselves or by reactive CD4 positive T-helper type 2 lymphocytes [2–4,7,8]. Hematological malignancies presenting with eosinophilia include classical myeloproliferative disorders (i.e. chronic myeloid leukemia, polycythemia vera, myelofibrosis) or neoplasms with distinct genetic abnormalities (i.e. mutations in *PDGFRA*, *PDGFRB* or *FGFR1* genes) as well as Hodgkin lymphoma [4,8]. In contrast, only a few cases of eosinophilia were reported in acute lymphoblastic leukemia or non-Hodgkin lymphoma [4]. Solid tumors causing eosinophilia include carcinoma of the ovaries, thyroid, uterus, kidney, colon, pancreas, liver and lung, as well as mesothelioma and melanoma [2,4,6,9–11].

However, eosinophilia as a presenting symptom of cancer without an apparent primary tumor is a rare finding. Abali et al. reported a case of metastatic anaplastic carcinoma of unknown primary, detected three years after noticing blood eosinophilia [6]. In a large retrospective study by Xiao et al. [12] where 10,112 BM biopsy specimens were analyzed, it was determined that in only 101 (1%) patients, the biopsies revealed metastases from a previously unknown non-hematological malignancy (lung, stomach, breast cancer, etc.). The clinical indications for BM biopsy were most commonly hematological (i.e. anemia, pancytopenia) or related to skeletal metastases (i.e. skeletal pain, bone destruction). Apparent hematological symptoms can, albeit rarely, dominate the clinical picture of an underlying non-hematological malignancy. Of note, out of the 101 patients with previously unknown primary cancers reported by Xiao et al. to have been diagnosed by BM metastases, only 3 patients showed leukocytosis [12].

4. Conclusions

Although awareness of malignancy-associated eosinophilia is indispensable for each physician, this phenomenon has seldom been reported in medical literature in the last few years. The presented case underlines and points out the fact that eosinophilia may represent a rare, yet an important primary manifestation of an undetected malignancy and it is thus important to consider this possibility as part of the differential diagnosis in patients presenting with unexplained eosinophilia.

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Conflict of interest

The authors report no conflict of interest.

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