Tumor Associated Blood Eosinophilia and Eosinophilic Pleural Effusion: Case Report and Review of the Literature

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Citation

Abstract
ABSTRACT
An 83 year old swiss female was admitted for fever, increasing dyspnea at rest, cough with purulent secretions, and a left sided pleural effusion. The work-up revealed a large left sided pleural effusion with a white cell count of 1600/ml and 65% eosinophils, an infiltration of the left lung with eosinophils, a right sided cystic, fluid filled structure in the region of the right kidney, interpreted as hydronephrosis, and a marked blood neutrophilia and eosinophilia. Despite extensive investigation with pleural tap, bronchoscopy and transbronchial biopsies, fine needle aspiration of the suspected hydropnephrosis, multiple radiographic examinations, and multiple cultures for various microorganisms, the cause of the eosinophilic effusion could not be found. An insertion of a catheter into the renal cyst drained necrotic material and cells of a transitional cell carcinoma. The patient was sent to the operating room for nephrectomy with removal of all the necrotic material. Intraoperatively a large tumor was found infiltrating the perirenal tissue and the inferior vena cava which was injured during the operation with nearly fatal hemorrhage. The patient died soon after the operation. The post mortem examination revealed a large transitional cell carcinoma arising from the renal pelvis infiltrating the inferior vena cava, a left sided pleural carcinomatosis, and lymphangitic spread to the lung. The significance of peripheral blood eosinophilia and eosinophilic pleural effusion in malignancy is reviewed.

Pleural fluid eosinophilia is commonly viewed to represent a benign and self-limited condition like air or blood in the pleural space, asbestos pleurisy, infection and drug induced 1-2. Although recently questioned 3, malignancy is considered to be a rare finding. The mechanisms involved in eosinophil recruitment into the pleural space are still unclear. However, locally produced IL-5 and probably other cytokines have been shown to attract these cells 4. Tumor induced pleural fluid eosinophilia has the potential to regress with antitumor treatment 5.

Similar mechanisms seem to be involved in stromal and blood eosinophilia in malignancy. IL-3, GM-CSF, and other factors have been suggested to be produced by tumor cells and be responsible for the stimulation and attraction of eosinophils 6-10. While stromal invasion by eosinophils usually purports a good prognosis 11-13, peripheral blood eosinophilia is believed to be a sign of widespread disease with dismal outcome 14-15.

CASE PRESENTATION
The 83-year old white female native from Switzerland was admitted for fever, dyspnea at rest, productive cough with purulent sputum, and left sided pleural effusion.

Three weeks before admission she developed fever up to 38.5ø C (101.3ø F), productive cough with colored phlegm, and slowly increasing shortness of breath. Treatment with Clarithromycin did not improve her symptoms. After tachycardic atrial fibrillation and left sided pleural effusion had been detected the patient was admitted to our hospital.

In her past medical history she had had a mastectomy four years before admission due to invasive ductal carcinoma with tumor-negative lymph nodes.
Three months before admission she was on a cruise on the Mediterranean Sea visiting northern Africa, the Middle East, and Turkey.

She complained about increasing weakness, night sweats and weight loss of 5 kg (10 lbs.) over the last year. Allergies were not known. She was a lifetime non-smoker and took Diltiazem for hypertension, nitroglycerin for suspected coronary artery disease, and clarithromycin for presumed pneumonia.

On admission she was febrile (37.8°C, 100°F), tachypneic at rest with a respiratory rate of 36. The blood pressure was 130/80, the heart rate 120, arrhythmic, the neck veins were dilated, and she had mild ankle edema. Examination of the lungs revealed dullness over the entire left side with absent breath sound. The abdomen, lymph nodes, and the scar from the right mastectomy were unremarkable.

An X-ray of the chest revealed a large left sided pleural effusion with normal right lung and mediastinum. The abdominal ultrasound showed a cystic, fluid filled structure in the region of the right renal pelvis interpreted as hydronephrosis. Liver and spleen were normal. On the CT scan of the abdomen no new findings were detected except for an enlarged right iliac lymph node and a calcified left hilar lymph node.

The laboratory examination of the blood showed an erythrocyte sedimentation rate (ESR) of 105 mm, a white blood count of 30.4 x 10^9/L with 46% bands, 14.5% eosinophils (absolute count 4.408 x 10^9/L), a hemoglobin concentration of 117 g/L, and a platelet count of 446 x 10^9/L. The neutrophils contained toxic granules and vacuoles. The C-reactive protein (CRP) was 140 mg/L (normal:<10 mg/L), the creatinin 114 mmol/L (1.3 mg/dL), and the serum glucose 12.7 mmol/L (230 mg/dL). The other laboratory results were within normal limits.

The pleural tap yielded yellowish, slightly turbid serous fluid with 1600 cells/ml with a cell differential of 61.5% eosinophils, 32% lymphocytes, and 5% neutrophils.

Cultures for bacteria and mycobacteria were sent and remained negative. The urinalysis showed signs of an infection with markedly increased neutrophils and red blood cells and many gram-negative microorganisms. Cultures remained negative.

At this time the cause of the blood and pleural fluid eosinophilia was unclear. Because the patient had a history of pneumonia and signs of an ongoing inflammatory disease she was started on Ceftriaxone 2 g qd and Clarithromycin 500 mg bid after drawing two sets of blood cultures.

Over the next days her condition deteriorated. The infiltrate...
in the left lung increased in size. The patient remained febrile with temperatures around 38.3°C (101°F) and developed a right sided foot drop and generalized weakness.

A fiberoptic bronchoscopy with bronchoalveolar lavage and transbronchial biopsies was performed. She had slightly increased purulent secretions and acute inflammatory changes. In the broncho-alveolar lavage fluid and the transbronchial biopsies eosinophils were markedly increased. No malignant cells were found. The aspiration of the bone marrow revealed a striking eosinophilia, toxic changes with a left shift, and increased plasma cells. Multiple examinations of the stool did not reveal parasites. Repeated blood cultures, serologic exams for parasites, and multiple acid fast smears were negative.

In the meantime her white blood count had risen to 65 x 10⁹/L with 32% bands, 23% neutrophils and 40% eosinophils (absolute number of eosinophils 26.24 x 10⁹/L). The CRP was 103 mg/L and the ESR 75 mm. An immunoelectrophoresis of the serum showed an α-2-peak with increased gammaglobulins. The antinuclear antibodies were 1:20, anti-DNA-antibodies, rheumatoid factor, circulating immunocomplexes, Hepatitis B antigen, anti Hepatitis C antibodies, and ANCA’s were all negative. Complements C3 and C4 were within normal limits. A sural nerve biopsy was refused by the patient.

Due to the rapidly deteriorating course with increasing eosinophils a therapy with corticosteroids (3 mg per kg of prednison), albendazol, and ciprofloxacin was instituted. However, neither the condition of the patient nor the eosinophil count improved.

Because the patient still had the untreated hydronephrosis with signs of infection it was reasoned that the undrained pus in the renal pelvis might cause the fever and the systemic inflammatory reaction. It was decided to drain the pus and a catheter was inserted. Surprisingly no fluid could be aspirated. After repeated instillations of normal saline some necrotic material was aspirated. Stains for bacteria and mycobacteria were negative. A cytologic exam raised the suspicion of a transitional cell carcinoma.

After surgical consultation the patient was brought to the operating room for nephrectomy. The intraoperative course was complicated by an injury of the inferior vena cava. The patient lost a massive amount of blood and barely could be kept alive. Hours after the operation she died in the intensive care unit.

The postmortem examination revealed a large transitional cell carcinoma with infiltration of the perirenal tissue and the inferior vena cava. The left lung had a pneumonic infiltrate with abundant neutrophils and eosinophils and lymphangitic spread. The pleura was seeded with small metastases. The right lung was normal.

**DISCUSSION**

This interesting case presented with blood and bone marrow neutrophilia and eosinophilia and pleural fluid eosinophilia. The underlying cause was a transitional cell carcinoma of the right renal pelvis with infiltration of the inferior vena cava and lymphangitic spread to the left lung. The eosinophilia was resistant to treatment with systemic corticosteroids. Absence of any kind of infection suggested a paraneoplastic syndrome.

Blood and bone marrow eosinophilia in malignant tumors is well known and generally considered to be an ominous sign reflecting dissemination and poor prognosis 14,15. It occurs in about 0.5% to 1.7% of patients with malignant tumors 6. Bronchogenic, pancreatic, cervical, liver, breast, kidney and thyroid malignancies are usually involved 6,10. Hematological cancers like lymphomas and T-cell-leukemias 16,17, as well as peritoneal mesothelioma 18 and liposarcoma 19 are also known to cause eosinophilia. With treatment of the malignancy the eosinophilia often resolves and reoccurs with relapse of the tumor 5,16.

The exact causes of the blood and bone marrow eosinophilia are not known. GM-CSF, IL-3, IL-5, and other cytokines are likely to be involved 4,6. Antibodies to GM-CSF and IL-3 are able to inhibit the stimulatory effect of serum and tumor tissue extracts from patients with blood and bone marrow eosinophilia secondary to malignant disease on human granulocyte, macrophage, and eosinophil colonies 6.
Proteins could be extracted from lung, thyroid, and carcinomas, lymphomas, and pancreatic and cervical carcinomas, that had granulopoietic and eosinophilopoietic activities. These proteins were structurally different and therefore it must be concluded that tumors secrete a variety of proteins with eosinophilotactic activity.

Eosinophilia in conjunction with Hodgkin’s lymphoma and acute lymphoblastic lymphoma has been well described. The mechanism is not entirely clear. T-cells are normally involved in activation of eosinophils and it is possible that malignant lymphocytes begin to produce factors with stimulatory activity on eosinophils.

Cells like neutrophils are sometimes also activated. This supports a role of factors like GM-CSF and IL-3. Release of substances from necrotic tumor tissue has also been suggested to be involved.

Stromal invasion of the peritumoral tissue and the tumor itself is seen in cases with blood eosinophilia but can occur independently as well. Cervical cancer is the most common malignancy causing tissue invasion by eosinophils. It has been described also in adenocarcinomas of the gastrointestinal or urogenital tract as well as in all the tumors causing blood eosinophilia. Contrary to the blood eosinophilia stromal invasion is generally believed to be a sign of good prognosis. This is supported by findings in cervical cancer and in adenocarcinomas of the stomach.

A review of patients with cervical cancer from Malawi studying 460 patients detected 13 cases (3%) with marked eosinophil invasion around and in the tumor. These tumors seemed to be histologically different from malignancies without eosinophil infiltration. Another study confirmed this observation, indicating that eosinophilia is a specific reaction to some tumors. It is not known if viral infection plays a role.

Eosinophilotactic factors have also been found in lung malignancies. Peritumoral invasion of eosinophils may be related to these factors. In malignant pleural effusions eosinophils have been found to form rosettes around tumor cells.

Tissue eosinophilia may represent the host's specific response to the tumor. In mice growth of implanted tumors is inhibited in regions where eosinophils invade the tissue and damage to tumor cells has been reported. On the other hand locally produced eosinophilotactic factors and cytokines are assumed to be involved in stromal invasion.

Our patient also had an eosinophilic pleural effusion secondary to lymphangitic spread. 10% or more eosinophils occur in about 8% of exudative pleural effusions. It is commonly stated that eosinophils denote a favorable prognosis. They are considered to represent a benign and self-limited condition like air or blood in the pleural space, asbestos pleurisy, infection or drug-induced. Malignancy is usually not related to eosinophilic pleural effusion. This has recently been questioned. In a study containing 476 patients with pleural effusion, an equal proportion of malignancy was found whether or not eosinophils were present. The mechanisms involved in recruiting eosinophils into the pleural space are not clear. In traumatic effusion lymphocytes produce locally IL-5 with secondary recruitment of eosinophils. Other cytokines like GM-CSF, IL-5, and IL-3 are likely to contribute to eosinophil proliferation and survival in pleural effusion. Malignant effusions with increased eosinophils possibly purport a better prognosis.

References
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Internet Scientific Publications