Lung Cancer with Eosinophilia in the Peripheral Blood and the Pleural Fluid

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A case of lung cancer associated with eosinophilia in the peripheral blood and pleural fluid is reported. A 55-year-old man with a tumor in the right lower lung lobe and right pleural effusion was admitted to Ehime University Hospital. Histology of specimens biopsied under a bronchoscope revealed that he had poorly differentiated squamous cell carcinoma. On admission, his peripheral blood leukocyte count was 11,500/ μ l with 7.8% eosinophils and the pleural fluid showed a high eosinophil count (60.5%). After chemotherapy, blood eosinophilia disappeared and the pleural effusion was decreased with the reduction of the tumor. The patient's serum had the activity to stimulate eosinophil proliferation in human bone marrow cell culture, suggesting that the tumor may have produced an eosinophil proliferating factor. (Internal Medicine 31: 525–529, 1992)

Key words: eosinophil proliferating factor, eosinophilic pleural effusion

Introduction

Among the patients with malignant tumor not associated with parasitic infestations, allergic diseases or certain skin diseases, some patients have eosinophilia. Numerous explanations have been proposed for this phenomenon. Tumor necrosis and extensive dissemination are reported to induce eosinophilia (1–3). In a few cases with lung cancer, eosinophil chemotactic factor has been demonstrated in tumor extracts (4, 5). Recent studies have suggested the existence of a tumor which produces an eosinophil proliferating factor or an eosinophil colony stimulating factor which in turn stimulates eosinophil colony formation (6–9).

Here we report a patient with lung cancer, in whom eosinophil count was increased in the peripheral blood and the pleural fluid, and stimulation of eosinophil proliferation by the patients's serum was observed in human bone marrow cell culture.

Case Report

A 55-year-old man was admitted to our hospital on January 30, 1986, because of cough, sputum and right chest pain. The patient had smoked 20 cigarettes a day for 30 years and had no allergic or skin disease in the past.

On admission, crepitant rale was heard in the right lower lung field, and percussion was dull at the same site. The chest X-ray revealed a nodular shadow at the right lower lung lobe and pleural effusion on the right side (Fig. 1A). Exfoliative cytology of the sputum showed no malignant cells. Histological examination of specimens biopsied under a bronchoscope revealed had poorly differentiated squamous cell carcinoma (Fig. 2).

The peripheral blood leukocyte count was 11,500/ μ l, of which 7.8% were mature eosinophils (Table 1). Bone marrow aspiration revealed hypocellularity with 52.4% granulocytes, 12% erythroblasts and 13.2% eosinophils (2.2% immature type and 11.0% mature type) without abnormal cells.

Sodium and chloride levels in the blood were found to be slightly low by electrolyte analysis. Serum enzymes, blood urea nitrogen and creatinine were within the normal range. Immunoglobulin E level and the tumor marker CEA were not elevated. Ova and parasites were negative in his stool. The pleural fluid was bloody and positive for Rivalta reaction. Cytological examination revealed no malignant cells, and differential leukocyte counts were 60.5% eosinophils, 5.0% lymphocytes, and 34.5% others (Fig. 3). Image diagnosis including abdominal echograph and CT scan showed no evidence of metastasis to the liver, pancreas or kidneys.

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Fig. 1. A) Chest X-ray on admission. A nodular shadow can be seen in the right lung S₆ region and pleural effusion on the right side. B) Chest X-ray after chemotherapy. There is shrinking of the tumor shadow and a decrease in the pleural fluid.

Fig. 2. Microscopic findings of the tumor cells (hematoxylin-eosin stain, $\times 400$).

Figure 4 shows the clinical course of the patient. After diagnosed as lung cancer (stage 1 by the international stage system), chemotherapy consisting of cisplatin (100 mg/body), vindesine (3 mg/body) and mitomycin-C (10 mg/body) without any steroid was administered, because he refused to have an operation. After two weeks the tumor shadow on the X-ray distinctly shrank and pleural effusion reduced (Fig. 1B). After the drug administration was started, both the peripheral leukocyte count and the ratio of eosinophils decreased. On March 7, the leukocyte count was $5,900/\mu\text{l}$ and the ratio of eosinophils was 3.0% indicating the return to a normal hematological picture. The patient refused the consecutive treatment in our hospital; he then went to a clinic in his neighborhood. Therefore, we could not observe his course thereafter.

The effect of patient's serum and pleural fluid on eosinophils in human bone marrow cell culture.

Non-adherent cells of human bone marrow taken from a healthy male volunteer were used as target cells, and the culture was performed by the liquid suspension method. To non-adherent bone marrow cells (5.0×10^5 cells/ml) in Iscove's modified Dulbecco's medium (IMDM) containing 20% fetal calf serum (FCS), either the patient's serum, the patient's pleural fluid or healthy human serum was added at 10% the final concentration, and cultures were performed under humidified air with 5% CO₂ at 37°C. After 14 days, the cell population in the culture was analyzed on May-Grunwald-Giemsa stained preparation. As shown in Table 2, the eosinophil number was markedly increased when the patient's serum was used (95.7×10^3 cells/ml compared to 5.0×10^3 cells/ml at the start of culture), whereas the increase in eosinophils was much less when the patient's pleural fluid or healthy human serum was used (9.8×10^3 cells/ml, patient's pleural fluid; 25.4×10^3 cells/ml, healthy human serum). The result showed that the patient's serum had activity to stimulate eosinophil proliferation.

Discussion

The increased blood eosinophil level in the present case was not associated with any disorders other than lung cancer, which may cause it; the level decreased concomitant with reduction of the tumor. In a human bone marrow cell culture, stimulation of eosinophil proliferation by the patient's serum was observed. However, isolation and characterization of eosinophil proliferating factor were not successful in this case.

The incidence of eosinophilia associated with malignant

Lung Cancer with Eosinophilia

Table 1. Laboratory Findings

ESR	75 mm/h	Mo	5.6%	AFP	2.9 ng/ml
		Ly	16.6%		
Urinalysis	normal	Plasma	0.4%	Immunoglobulin	
		Ebl	12.0%	IgE	256 U/ml
Stool study		M/E ratio	5.33		
occult blood	(-)			Sputum culture	
parasites and ova	(-)	Blood chemistries		α -Streptococcus	(+)
		Na	136 meq/l	Neisseria	(+)
Peripheral blood		K	5.0 meq/l	Candida albicans	($\pm$)
RBC	$391 \times 10^4/\mu\text{l}$	Cl	98 meq/l		
Hb	12.6 g/dl	GOT	9 IU/l	Sputum cytology	
Ht	36.8%	GPT	16 IU/l	cancer cells	(-)
WBC	11,500/ μl	LDH	66 IU/l		
Neutro	61.1%	AIP	128 IU/l	Pleural fluid findings	
Eo	7.8%	γ -GTP	9 IU/l	bloody	
Ba	1.7%	LAP	35 IU/l	Rivalta reaction	(+)
Mo	7.4%	T.protein	6.7 g/dl	CEA	2.4 ng/ml
Ly	22.0%	Alb.	50.5%	bacteria, fungi	(-)
Platelet	$53.4 \times 10^4/\mu\text{l}$	α 1-gl	5.5%	cytology	
		α 2-gl	17.9%	Neutro	11.5%
Bone marrow		β -gl	10.2%	Eo	60.5%
NCC	$5.1 \times 10^4/\mu\text{l}$	γ -gl	15.9%	Ba	1.0%
Mgk	30/ μl	BUN	16 mg/dl	Mo	22.0%
Mbl	1.0%	Creatinine	0.9 mg/dl	Ly	5.0%
Pro	2.4%	Uric acid	4.3 mg/dl	cancer cells	(-)
My	7.6%				
Met	1.4%	Serology		ECG	normal
St	17.4%	VDRL	(-)		
Seg	21.4%	TPHA	(-)	Abdominal CT, ultrasonography	
Eo	13.2%	CRP	3+	no evidence of metastasis	
Ba	0.6%	CEA	2.4 ng/ml		

Fig. 3. May-Giemsa stain of the pleural fluid. Many eosinophils can be seen ($\times 400$).

tumor has been reported to be 26.3% by Grewe and Schlitter (10), and 11.6% by Linke (11). Among the Japanese population, the ratio was reported as 0.8% by Asano and Ohsawa (12) and 4% by Kajiwarra (13). Isaacson and Rapoport (1) reported that malignant tumor accompanying eosinophilia generally occurs in the digestive system (stomach, colon, pancreas) with prominent metastasis and poor prognosis.

Various causes of tumor-associated eosinophilia have

been postulated. Some reports state that tumor necrosis (1, 2), extensive dissemination (1, 3), vagal reflexes (14), or local stimulation of connective tissue around the tumor (15) induce eosinophilia. Wassermann et al (4) extracted peptide which is preferentially chemotactic for eosinophils, from a large-cell anaplastic carcinoma of human lung; other similar studies have been reported (5, 16).

With regard to the production of eosinophil proliferating factor by the tumor, Slungaard et al in 1982 first reported a case of lung cancer (6). In 1984, Kodama et al demonstrated the presence of both eosinophil colony stimulating factor and eosinophil chemotactic factor in lung cancer tissues (8). Also, Kajiwarra reported that an eosinophil proliferating factor exists in the cytosol of gastric cancer and colon cancer cells (13). In this case, the fact that proliferative stimulation of eosinophils by the patient's serum was observed in a human bone marrow cell culture suggested the possibility of the production of an eosinophil proliferating factor by the tumor itself. Slungaard et al reported a glycoprotein produced by a tumor with a molecular weight of 45,000 which directly acted on bone marrow and caused eosinophilia (6).

In recent years, participation of various hematopoietic growth factors including colony stimulating factors (CSFs) on the proliferation and differentiation of hematopoietic

Fig. 4. Clinical course.

Table 2. Effect of Patient's Serum and Pleural Fluid on Healthy Human Marrow Cells in Liquid Suspension Culture

	Prior to culture	Medium	Patient's serum	Patient's pleural fluid	Healthy human serum
Cell count	$5.0 \times 10^5/\text{ml}$	$3.0 \times 10^5/\text{ml}$	$3.3 \times 10^5/\text{ml}$	$3.9 \times 10^5/\text{ml}$	$3.9 \times 10^5/\text{ml}$
Cell types					
Mbl	2.0%	0.0%	0.0%	0.0%	0.5%
Neutro	88.0%	82.5%	58.5%	72.0%	78.5%
Eo	1.0%	3.0%	29.0%	2.5%	6.5%
	($5.0 \times 10^3/\text{ml}$)	($9.0 \times 10^3/\text{ml}$)	($95.7 \times 10^3/\text{ml}$)	($9.8 \times 10^3/\text{ml}$)	($25.4 \times 10^3/\text{ml}$)
Ba	0.0%	0.5%	6.0%	3.5%	4.5%
Mo	2.5%	2.0%	5.5%	6.0%	6.0%
Ly	5.5%	9.5%	1.0%	16.0%	4.0%
Plasma	1.0%	2.5%	0.0%	0.0%	0.0%

Normal nonadherent bone marrow cells were incubated in media containing 20% FCS with 10% of supplement for 14 days. Absolute number of eosinophils is given in parentheses.

progenitor cells has become evident. Interleukin 3 (IL-3), interleukin 5 (IL-5) and granulocyte-macrophage CSF (GM-CSF) are known to act on colony-forming unit eosinophils (CFU-Eo). In human bone marrow cell culture, recombinant human IL-3 (17), murine IL-5 (18) and recombinant human GM-CSF (19) are reported to stimulate proliferation of the eosinophil colonies. In the present case, further cumulative studies are necessary to ascertain whether tumor-associated eosinophil proliferating factor is correlated to IL-3, IL-5 or GM-CSF.

In the present case, a large increase of eosinophils in the pleural fluid was observed, but no obvious sign of proliferative stimulation on eosinophils was found in the pleural fluid. The pathological condition with a great number of eosinophils in pleural fluid has been termed eosinophilic pleural effusion (EPE). It has been reported that EPE occurs concomitant with various background diseases, but malignant tumors are rarely involved

(20–23). The causes for EPE have not yet been clearly defined, however many speculations have been proposed: intrusion of air or erythrocytes into thoracic cavity, heterogeneous protein or its decomposition product, eosinophilic chemotactic factors including immune-complex and specific lymphokines (24–26). Since the ratio of eosinophils in the pleural fluid was higher than that in the peripheral blood in this case, it was considered that the eosinophils were mobilized from the peripheral blood to thoracic cavity. There is a possibility of the presence of tumor-associated eosinophil chemotactic factor in this case.

The significance of eosinophilia associated with malignant tumor and the mechanism of increase of eosinophils in thoracic cavity are not yet clarified; further studies on this mechanism will be necessary.

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