A Case of Pulmonary Hyalinizing Granuloma

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Exp. Med., 1992, 167 (1), 39-45 — A case of pulmonary hyalinizing granuloma
was presented. The patient was a 37-year-old male who was found to have
abnormal chest roentgenograms showing multiple pulmonary nodules taken at the
annual chest mass survey in October 1989. The largest nodule measured 35 mm in
diameter. He was asymptomatic. No definite diagnosis was established either by
brushing cytology, biopsy through bronchoscopy or percutaneous needle biopsy.
No abnormalities were found in the GI tract, the urogenital system or the bone.
Brain CT indicated an iso-density area surrounded by low density in the left
fronto-parietal region. Two nodules of the lingula removed by open lung biopsy
revealed a homogeneous cut surface. Histological diagnosis was pulmonary
hyalinizing granuloma, consisting of hyalinized collagen fibers and bundles
infiltrated with chronic inflammatory cells. No therapeutic effect was recognized
with prednisolone. Craniotomy was performed and the brain lesion was removed.
Anaplastic astrocytoma was the diagnosis. The brain lesion had no etiological
correlation with pulmonary hyalinizing granuloma. Pulmonary hyalinizing
granuloma itself is a rare benign disease with no specific therapy and is important
in the differential diagnosis of lung diseases showing multiple pulmonary nodules.
——— benign pulmonary nodules; multiple pulmonary nodules; pulmonary
hyalinizing granuloma

In 1977 Engleman et al. described pulmonary hyalinizing granuloma (PHG).
Since then only one case has been reported in Japan (Kuramochi et al. 1985) and
about 50 cases in other countries (Engleman et al. 1977; Drasin et al. 1979;
Schlosnagle et al. 1982; Dent et al. 1983; Chalaoui et al. 1984; Guccion et al.
1984; Macedo and Adolph 1985; Maijub et al. 1985; Yousem and Hochholzer
1987; Gans et al. 1988). An immune response to the antigenic stimulus by
infection or an auto-immune process has been postulated in the pathogenesis but
the true etiology yet remains to be obscure. In this report we present a case report
of a patient with PHG complicated with malignant brain tumor.

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CASE REPORT

A 37-year-old male was admitted to the hospital of The Research Institute for Tuberculosis and Cancer, Tohoku University on December 1, 1989 because of abnormal chest roentgenograms showing multiple nodular shadows. Either his past history or family history was non-contributory. He smoked 20 cigarettes a day for 20 years. He was

TABLE 1. *Laboratory findings on admission*

Hemogram							Serology	
WBC	7,300/mm ³						CRP	—
Ba	Eo	St	Seg	Ly	Mo	RA	—	
2.0	1.0	19.5	39.5	32.5	5.5 (%)	ASLO	50U	
RBC	476×10 ⁴ /mm ³						Wa-R	—
Hb	15.0 g/100 ml						Immunological test	
Ht	44.5%						IgG	1,726 mg/100 ml
Plt	31.1×10 ⁴ /mm ³						IgA	312 mg/100 ml
ESR	18 mm (1°) 40 mm (2°)						IgM	168 mg/100 ml
Urinalysis							IgE	190 IU/ml
protein	(—)						CD4	42.7 (%)
sugar	(—)						CD8	41.5 (%)
Blood chemistry							CD4/8	1.03
T-Bil	0.57 mg/100 ml						anti-DNA antibody	<1.0 IU/ml
GOT	15 U						ANA	negative
GPT	28 U						CH50	42.5 U/ml
LDH	247 U						PPD	$\frac{0 \times 0 \text{ mm}}{8 \times 6 \text{ mm}}$
ALP	132 U						Tumor marker	
T-Cho	192 mg/100 ml						CEA	0.7 ng/ml
TG	230 mg/100 ml						NSE	5.2 ng/ml
Amy	121 IU/liter						SCC	<0.5 ng/ml
BUN	12 mg/100 ml						CA19-9	<6 U/ml
Cr	0.7 mg/100 ml						Elastase	1,220 ng/100 ml
Na	145.2 mEq/liter						Arterial blood gas analysis	
K	4.4 mEq/liter						pH	7.379
Cl	107.4 mEq/liter						PO ₂	73.4 torr
Ca	10.0 mg/100 ml						PCO ₂	44.8 torr
P	3.4 mg/100 ml						HCO ₃ ⁻	26.1 mEq/liter
TP	7.0 g/100 ml						Pulmonary function test	
Alb	65.9 %						VC	3,950 ml
α ₁ -gl	3.0 %						(100% of the predicted)	
α ₂ -gl	9.1 %						FEV _{1.0}	3,560 ml
β-gl	8.8 %						MMF	6.70 liter/sec
γ-gl	13.3 %						D _{LCO}	23.83 ml/min/mmHg
ACE	19.4 IU/liter/37°C							

asymptomatic. The annual chest roentgenogram in 1987 was within normal limits. He did not take the annual examination of the chest in 1988.

He was 167.5 cm in height and 80 kg in weight. His temperature was 35.5°C, pulse, 60/min; and blood pressure, 110/65 mmHg. Physical examination was essentially within normal limits; no conjunctival anemia nor jaundice, no palpable lymph nodes, no cyanosis of the lips or the nails, normal breath and heart sounds without arrhythmia, soft and flat abdomen without palpable liver, spleen or kidneys. Neither motor nor sensory disturbances were noted.

Laboratory findings are shown in Table 1. White blood cells (WBC) were 7,300/mm³ with some shift to the left. Erythrocyte sedimentation rate (ESR) was 18 mm/hr. Arterial blood gases at room air showed that pH was 7.379, Po₂, 73.4 torr and Pco₂, 44.8 torr. Pulmonary function test was normal. PPD skin reaction was 8×6 mm. Tumor markers were within normal range. Immunoglobulins, CD4 and CD8 were within normal range. Antinuclear antibody (ANA) and anti-DNA antibody were normal. CH50 was 42.5 U/ml and slightly elevated (normal <40 U/ml). Cryptococcal and echinococcal antibodies were negative. Microbiological examinations of sputum including acid fast bacilli were negative. Cytology of sputum revealed class II.

Plain chest roentgenograms on admission revealed multiple nodular shadows in both lungs (Fig. 1). The lesions were sharply circumscribed and homogeneous in density and the largest nodule measured 35 mm in diameter. CT scan of the thorax confirmed the x-ray findings (Fig. 2). No mediastinal lymphadenopathy was noted.

From the above findings metastatic lung cancer was most suspicious. Brushing cytology and biopsy through bronchoscopy and percutaneous needle biopsy were not diagnostic of malignancy. We investigated the GI tract, the urogenital and skeletal systems to search for a primary lesion if any, but no abnormalities were found. Brain computed tomography (CT) was also performed. Against our expectation brain CT indicated an iso-density area surrounded by low density in the left fronto-parietal region that was compatible with brain

Fig. 1. Chest roentgenogram on admission (Dec. 1, 1989), showing multiple nodular densities in both lungs.

Fig. 2. CT scan of the thorax, showing multiple well circumscribed nodules.

metastasis. On February 27, 1990 he underwent an open lung biopsy and two nodules in the left lingula (S4) were removed. The nodules were well defined and cartilaginous hard. The cut surface was gray-white in color and homogeneous. Portions of the nodules were sent for microbiological, fungal and acid-fast stain and culture. All tests were negative.

Histopathological examinations revealed as follows; the margin of the nodule was sharply demarcated. Lamellar, thick collagen bundles or hyalinized fibrous materials with a few inflammatory cells could be seen in the central part of the lesion (Fig. 3). Chronic inflammatory cells consisting of lymphocytes were seen forming germinal centers, and the plasma cells and histiocytes infiltrated in the periphery of the nodule (Fig. 4). The histopathological diagnosis was compatible with pulmonary hyalinizing granuloma. It took almost one month and a half to reach the diagnosis.

He began to complain of a mild headache in March, 1990. He was given 40 mg of oral prednisolone from April 20, 1990 over 4 months' period with tapering dose. There were neither changes on chest roentgenograms nor improvement in the mild headache. The brain lesion appeared slightly increased in size on subsequent brain CT scans. If it had something to do with the lung lesions, it should not grow in size in the time interval of several months. An exploratory craniotomy was performed on August 13, 1990; the brain lesion was removed. Histopathological diagnosis was anaplastic astrocytoma. After surgery 54 Gy of radiation to the whole brain and 4 courses of chemotherapy with nimustine (ACNU) were given in combination. At present (as of April 1992) he remains asymptomatic and no radiological changes on chest roentgenograms have been noticed.

DISCUSSION

The chest roentgenograms of PHG frequently reveal multiple and bilateral pulmonary nodules. Radiographic differential diagnoses include metastatic lung cancer, rheumatoid nodules, plasma cell granuloma, Wegener's granulomatosis,

Fig. 3. Microphotograph of a pulmonary nodule, showing haphazard arrangement of hyalinized collagen fibers with chronic inflammatory cell infiltration. (E-M stain, $\times 50$)

Fig. 4. Microphotograph of an interface between pulmonary hyalinizing granuloma (asterisk) and pulmonary tissue. Note the dense aggregate of chronic inflammatory cells consisting mainly of lymphocytes forming a germinal center (arrow). (E-M stain, $\times 10$)

multinodular sarcoidosis, nodular amyloidosis, histoplasmosis, echinococcosis and tuberculosis. All these lesions should be differentiated by their clinical, biological, bacteriological, radiological and histopathological characteristics (Kalifa et al. 1976; Engleman et al. 1977; Chalaoui et al. 1984).

Diagnosis of PHG can be made only by histopathological examination. PHG have unique histologic features. The lesions are well-circumscribed nodules. The center of the nodule is occupied by lamellae of hyalinized collagen. The deposition pattern of lamellar collagen is diagnostic of this disease and characterized by rosy whorled collagen bundles separated by clear spaces. The collagen is frequently arranged in parallel lamellae or in a coarse storiform pattern. Necrosis, calcification or ossification is rare. Electronmicroscopically the hyaline lamellae are consisted of an electron-dense, compact, homogeneous, amorphous material (Guccion et al. 1984). Blood vessels in the nodule are surrounded by the hyalinized collagen fibers and have intimal fibroelastosis and medial hyalinization. Toward the periphery of the nodule, the spaces between the lamellae are occupied by flattened, compressed fibroblasts and a sprinkling of mononuclear inflammatory cells, creating a distinct gradient of cellularity from the center to the periphery of the nodule. At the interface between the pulmonary parenchyma and the hyalinized nodule there are occasional aggregates of non-specific chronic inflammatory cells consisting mainly of lymphocytes forming germinal centers, and rarely of plasma cells and histiocytes (Maijoub et al. 1985; Yousem and Hochholzer 1987).

PHG is usually radiologically characterized by multiple and bilateral nodules without preferential localization. Commonly the lesions are well defined and homogeneous. Calcifications or cavity formation is rare. Diameter of the nodules is variable from a few millimeters to 15 cm. Patients with PHG are asymptomatic or present with mild symptoms of cough, fever, dyspnea and fatigue. The mean age of PHG is 45 years. There is no sex or race predilection (Engleman et al. 1977).

The etiology of PHG is unknown. The nodules probably represent an immune response to the antigenic stimulus by infection or an auto-immune process. Sometimes sclerosing mediastinitis or retroperitonitis is complicated with PHG (Engleman et al. 1977; Dent et al. 1983). The former has a microscopic picture much like that of PHG, and can be caused by granulomatous diseases like histoplasmosis or tuberculosis (Chalaoui et al. 1984). Previous exposures to fungal or mycobacterial diseases have been reported in some of patients with PHG (Engleman et al. 1977; Yousem and Hochholzer 1987). Guccion et al. (1984) and Schlosnagle et al. (1982) have reported immunologic abnormalities, including elevated ANA, rheumatoid factor and circulating immune complexes in their patients. Yousem and Hochholzer (1987) reported auto-immune phenomena indicated by positive ANA, positive rheumatoid factor, or Coombs-positive hemolytic anemia. Drasin et al. (1979) reported a case of

PHG complicated with malignant lymphoma who developed multiple myeloma and systemic amyloidosis nine years later. In our case only serum complement titer was slightly elevated. No other immunologic abnormalities could be detected and no previous infection seemed responsible for the present illness. Chest roentgenograms two years previous to the present episode were within normal limits.

The prognosis of PHG is generally favorable. Normal longevity is common. Usually the nodules tend to grow slowly, but spontaneous regression and a status quo are also described (Macedo and Adolph 1985). No specific therapy for PHG has been described. Schlosnagle et al. (1982) reported a case that nodules did not change after treating with prednisolone. We also administered prednisolone to our patient in vain. The brain lesion in the present case did not seem to have any etiological correlation with PHG.

PHG should be remembered in the differential diagnosis of lung diseases showing multiple pulmonary nodules.

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