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MUCINOUS PLEURAL EFFUSION

An unusual case of alveolar-cell carcinoma of the lung

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Abstract—— A 52-year-old female patient with alveolar-cell carcinoma of the lung is presented. From the onset of her illness, very stringy pleural fluid was obtained at every pleural puncture all through the period of her hospitalization. Morbid anatomy revealed alveolar-cell carcinoma of the left lung and the section through the tumor disclosed several large mucin-containing cavities. Furthermore, with a view to analysing the constituents of glycoprotein, chemical analysis was carried out on the native pleural fluid and the partially purified mucin. Results proved that the mucin purified in the present stage was still contaminated with a relatively large amount of human serum albumin. The authors discussed the rarity of the case reported on here and the analytical approach to the mucin found in the alveolar-cell carcinoma of the lung.

Alveolar-cell carcinoma of the lung is not an extremely rare disorder, and may be accompanied by unilateral or bilateral pleurisy with serous or fibrinous exudate in a relatively high frequency[1], but no reports on the eidence of pleurisy with mucinous effusion have been available. This paper deals with a female patient with alveolar-cell carcinoma of the lung in whom mucinous pleural effusion was present over one year. Here we describe the clinical course of her illness, autopsy findings and the results obtained from the biochemical analysis on the pleural fluid.

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CASE REPORT

Patient K.F., a 52 year-old housewife, was admitted to the Naruwa General Hospital on July 13, 1966, because of dyspnea and general malaise. Her past history revealed that at the age of 16 years she had been treated for tuberculous pleurisy and 5 years before the admission had received an operation for oophoritis. Since then she had been in good health until 2 months prior to the admission, when she became ill with cough and sputum. Attempts to relieve it failed. Moreover, she developed additional symptoms of dyspnea and general malaise. On admission, a chest X ray disclosed pleural effusion in the left pleural cavity. Physical examinations showed a blood pressure 116/80mm Hg, the pulse was regular at 112, the temperature 36.8 C. Dullness and decreased breath sounds were heard on the left lung, and the right border of cardiac dullness extended to the right midclavicular line. Thoracentage was carried out, and straw colored slightly turbid but unusually stringy fluid was aspirated in which neither tubercle bacilli nor typical malignant cells were detectable. The significant laboratory data are shown in Table 1.

Table 1. Significant laboratory data obtained during the hospitalization at the Naruwa General Hospital.

Blood		Blood chemistry	
RBC, /mm³	458×10⁴	BUN, mg/100 ml	15
Hb, %	88	Cholesterol,	
WBC, /mm³	6,200	mg/100 ml	230
Differential	no abnormalities	Total serum protein, g/100 ml	7.6
ESR, mm	10/23	Albumin, %	55
ASLO, units	50	Alpha-globulin, %	10
CRP	negative	Beta-globulin, %	15
Enzymes		Gamma-globulin, %	20
LDH, units	950	Fibrinogen,	
SGOT, units	13	mg/100 ml	330
SGPT, units	26	Pleural fluid	
Liver function test		Rivalta's test	positive
BSP, %	20 (15 min)	Cell counts, /mm³	650
	54 (120 min)	TB	negative

She was thought to suffer from a nontuberculous pleurisy, but her treatment was started with intrapleural injection of adrenocortical steroid hormone, in addition to the treatment with major three tuberculostatic drugs, i.e. SM, PAS and INH. The sputum gradually diminished, but the pleural effusion remained unchanged. To relieve the distresses, it was necessary for her to remove the fluid once a month, but later once a week. At every pleural puncture about 1 liter of the fluid could be aspirated. She was transferred to the Department of Clinical Research, Cancer Research Institute,

because of persistent and refractory pleural effusion and its curious findings. On admission physical examination revealed a poorly nourished woman. The pulse was regular at 84, the temperature 36.2 C. Respirations were rapid, shallow and regular. She often coughed and could not lie on her back, because of dyspnea. The positive physical examinations were limited to the thorax. The left neck veins were distended. The left supraclavicular fossa was shallower than the right. The right border of cardiac dullness extended to the right midclavicular line, the left was undecided. The apical activity was not visible or palpable. The heart sounds were clear. Tactile fremitus was absent over the left thorax, with dullness and decreased breath sound. No rales were audible. A thumb size tumor was visible on the left anterior axillary line in the eighth intercostal space, where repeated thoracentage had been carried out. It was hard and painless. No pathological findings were found in the abdomen. Neurological examinations disclosed no abnormalities.

The RBC was 3.94 million/mm^3 with Hb 12.4 g/100 ml, the WBC 5,000, the differential was normal. The serum protein was 7.4 g/100ml. fractionation revealed 60.0% albumin, 2.5% alpha-1 globulin, 5.5% alpha-2 globulin, 11% beta globulin, 21% gamma grobulin. The uncorrected sedimentation rate was 22 mm/hr(Westergren). Urinanalyses revealed no abnormalities. The blood urea nitrogen was 21 mg/100 ml, fasting blood sugar 76 mg/100 ml, serum cholesterol 268 mg/100 ml, serum iron 100 μg/100 ml. The ASLO titer was under 100 Todd units, CRP was negative, Wa.R. negative, RA-test negative. The serum electrolytes were sodium 135, potassium 4.5, chloride 103, and calcium 4.7 mEq/liter. Cultures of sputum for tubercle bacilli were negative. ECG was within normal limit, except for low voltage in the chest leads. A chest X ray film showed a dense homogenous shadow all over the left lung field(Figure 1). Tomograms yielded no positive information in the left lung because of the abnormal density. Bronchography could not be carried out because of the severity of her distresses. Thoracentage was performed. Mucinous pleural fluid was obtained, its specific gravity measured by using a pycnometer was 1.019 at 13 C, nitrogen content was 0.49% (Kjeldahl's method). When the pleural fluid was dropped into the cold water slightly acidified with acetic acid in the same way the Rivalta's test was carried out, precipitate appeared in a form simulating a sea jelly, and slowly fell to the bottom(Figure 2). The pleural fluid was sterile, no acid-fast bacilli were found and cultured, and a cell block contained malignant cells. The tumor on the left chest wall was resected for histological examination. A diagnosis of metastatic adenocarcinoma was made. On the basis of the results above described we made a clinical diagnosis of carcinomatous pleurisy.

At first she was treated with intrapleural administration of adrenocortical steroid hormone and on the 17th day of her hospitalization intrapleural chromomycin A_3 once a week was added to the treatment above-mentioned. The severe productive cough remained unchanged. The sputum was characteristically thin, watery and white in color, and the amount very massive. She often suffered from dyspnea. Administration of oxygen and aspiration of the pleural fluid seemed to be the only treatment. We

could aspirate about half a liter of the fluid at every puncture. Two months later from the onset of the treatment with drugs above-mentioned the pleural fluid seemed to become thinner in both color and viscosity than before. But her appetite and body weight gradually decreased and emaciation became severer. Toward the end of July she was in a terminal condition, with tachycardia, tachypnea and confused mental condition. She died on the 26th July. Total volume of the pleural fluid aspirated during the period of hospitalization in the Cancer Research Institute was estimated to reach upward of five liters.

Autopsy revealed that the left thoracic cavity was almost completely occupied by a large tumor mass which adhered tightly to the parietal pleura and invaded the mediastinum. The tumor mass surrounded completely the entire lung in a form of thick cortex. The pleural space the capacity of which was diminished by the tumor invation remained beneath the left lateral chest wall, where the repeated pleural punctures had been carried out, and was filled with mucinous fluid mixed with necrotic debris to the brim. The volume of mucinous fluid obtained from the pleural space was about 500 ml. The tumor was white or pink in color, and slimy and gelatinous soft in consistency. Section through the tumor disclosed numerous cavities filled with clear pale brown mucinous fluid. Pressing and washing out the mucin from the tumor, it showed sponge like structure, that is, it composed of columns of cells arranged in a radial manner running from the outer layer of the lung to the pleura, as was seen in a pine apple cut in a round slice, and numerous cavities ranging in size from a pin head to walnut were found. The outer layer of the lung was affected by the tumor, and the visceral pleura was obscure, but most parts of the lung parenchym remained intact. The main bronchi were normal. The aorta, caval veins, trachea and esophagus were surrounded by the tumor, but the inner surface of these organs were saved from the tumor invasion. The pericardium was also effected by the tumor, but the pericardial fluid had a normal appearance. The heart was small in size but normal. The right lung was pressed but yielded no informations. No distant metastases were found in any other organs.

The tumor stroma was composed of the alveolar walls which were lined by tall cuboid or low columnar neoplastic cells in one or more layers. The cells were not ciliated. The nuclei were placed near the base, and oval and pale, with prominent pink nucleoli. In some fields there were papillary protrusions from the wall, and whole layers or sheets of lining cells became detached from the wall. In some alveoli mucus was observed, and in some areas where the alveolar walls fell into destruction large sacs filled with mucus were formed (Figure 3).

SPECIFIC ANALYSIS OF THE PLEURAL FLUID

Immediately after the aspiration the pleural fluid was stored in the refrigerator at −20 C until it was subjected to use. Prior to use the fluid was centrifuged for 30 minutes at 6,000 rev/min in order to remove the cellular elements.

Table 2. Chemical composition of the pleural fluid obtained from a patient with alveolar-cell carcinoma of the lung.

Constituent	Value mg/100 ml	Method	Reference
Total bound hexose	430	Weimer and Morshin	(2)
Mucoprotein hexose	353	ditto	
Total bound hexose	140	Winzler	(3)
Mucoprotein hexose	105	ditto	
Fucose	8–10	Dische and Shettles	(4)
Hexosamine	184	Elson and Morgan	(5)
Sialic acid	38.8	Ayala et al.	(6)
Hexuronic acid	+	Tracey	(7)

The trial of electrophoretic analysis, except for free electrophoresis failed to separate the constituents because of the high viscosity of the fluid, but the electrophoretic pattern obtained by free electrophoresis showed two peaks as shown in Figure 4. It is not yet decided which peak of the two corresponds to the mucinous substance itself.

Total hexose in the same specimen of the fluid was measured by means of the two different methods examined, that is, of Weimer and Morshin[2] and of Winzler[3]. Each value obtained by the two methods did not agree with each other. Also similar results were obtained about the values of mucoprotein hexose. Fucose, hexosamine, sialic acid and hexuronic acid were estimated by using specific methods for each substance. The data obtained were shown in Table 2.

An attempt to purify the mucin contained in the fluid was made by us. The pleural fluid was dropped into a large amount of cold water which was slightly acidified with acetic acid and pH of which was adjusted to about 5.0. Mucin clot

Table 3. Chemical composition of the mucin twice precipitated with acetic acid from the mucinous pleural fluid.

Constituent	Value %	Method
Nitrogen	10.2	Kjeldahl
Hexose	3.1	Weimer and Morshin
Fucose	0.07	Dische and Shettles
Hexosamine	7.2	Elson and Morgan
Sialic acid	3.2	Ayala et al.
Hexuronic acid	—	Fishman et al. (8)
Total sugar	13.6	

thus formed was collected and dissolved in as small an amount as possible of 1% solution of sodium carbonate. Mucin clot was again made from the solution of mucin and redissolved in the same way as described above. One volume of the solution of the mucin twice precipitated was added slowly into 9 volumes of ethanol-ether mixture (1:1, vol/vol) under gentle stirring. The precipitate formed was collected and dried in vacuo. The pulverized mucin was subjected to chemical analysis with a view to the constituents of glycoprotein. The results were given in Table 3. Double diffusion test by using Ouchterlony's method[9] disclosed that the mucin obtained here was still contaminated with a relatively large amount of human serum albumin.

DISCUSSION

In our case the fact that an abnormal homogenous density all over the left lung field at the roentgenological examination made it difficult to know changes occurring in the lung, and that pleural fluid could be easily aspirated, and moreover the fact that the severity of her distresses made it difficult to perform additional examinations led us to make a diagnosis of carcinomatous pleurisy.

Of the primary malignancies of the lung, the alveolar-cell carcinoma is believed to be rare. The incidence of the disease is reported ranging from 0.1% to 4.0% as shown in Teble 4. This disease does not resemble any other growth. It appears grossly in two forms, a multiple nodular form and a diffuse form, and both forms may occur at the same time. In our case the tumor is thought to be a nodular form in which nodules fused completely into one and formed a large mass. In both forms the tumor produces mucin which can be commonly observed macro- and microscopically. The tumor may be of soft and mucinous consistency. The mucin can be scraped from the cut surface and its production is confirmed at the microscopical examination, that is, the secretion of mucin is observed in the involved alveoli, or the spaces lined by tumor cells, as was observed in many cases[17-24]. But in very rare cases it is observed macro-

Table 4. The incidence of alveolar-cell carcinoma of the lung.

Author (Reference)	Year	Primary bronchial and lung cancer	Alveolar cell carcinoma	Per cent
Ikeda(10)	1945	206	8	4.0
Swan(11)	1949	900	9	1.0
Good et al.(12)	1950	275	7	2.5
Langer and Willmann (13)	1954	1,000	1	0.1
Fanconi(14)	1956	1,095	11	1.0
Josef(15)	1956	450	1	0.2
Walther and Heuck (16)	1962	521	3	0.6

scopically as a mucin-containing cavity. In a case reported by Löhlein[25] the size of the largest mucin-containing cavity was 8 mm in diameter, and Sochosky[26] found in his case a large cavity which was filled with mucin, though no detailed informations on its size are available. The cavity formation in the alveolar-cell carcinoma is recognized to be extremely rare[27], but pleurisy may sometimes occur[28], though more frequently not. Pleural fluid, as reported by Decker[27] in his review, is observed in 10% of cases, ranging in quantity from a small amount to a chest full, and serous or fibrinous in nature. No cases, however, ever been noted in which mucinous pleural fluid was observed. In what a manner did the pleurisy with mucinous effusion develop in this case? The alveolar-cell carcinoma having an extremely marked tendency to produce mucin might secrete a large amount of mucin which accumulated in a form of small cavities between the tumor tissue, and some cavities formed fuse into ones and thus large cavities be formed. On the other hand mucin secreted from the tumor might burst through the spaces from the framework of the tumor tissue, into the pleural space and offer a feature of pleurisy. Or, from the onset of her illness the tumor might invade the pleura, develop there and secrete a large amount of mucin to give a feature of pleurisy. The latter possibility seems to be reasonable for us.

Mucin production in the alveolar-cell carcinoma has attracted much attention, but strikingly little information about the chemical composition of the mucin has been published. Perhaps this evidence may be due to the rarity of the disease and the difficulty in the purification of epithelial mucin. It is so with the mucin originated from respiratory organs; nevertheless, mucinous sputum is commonly observed in various respiratory diseases. Werner[29] stated his observation about the chemical composition of the mucin of sputum obtained from a patient with acute bronchitis, but his analytical studies were performed on the merely dried not purified sputum. According to his study, sputum contained 12.9% of nitrogen, 8.3% hexosamine, 3.6% hexose, 3.0% fucose, 3.8% sialic acid. Bourrillon[30] reported on detailed investigations on the chemical and physical properties of the pleuromucoid. But this glycoprotein is not epithelial mucin but alpha-1 glycoprotein. Our investigation reported here was limited to the chemical analysis performed on the native pleural fluid and on the mucin partially purified in which a relatively large amount of human serum albumin still remained, as was estimated in the Ouchterlony's test. The results of our studies have not yet reached discussing the chemical properties of the mucin originated from the alveolar-cell carcinoma of the lung. But fortunately, we have been able to collect a large amount of the native pleural fluid during the clinical course of the patient, and have stored it. We shall have an opportunity to present the results of further studies in the near future.

SUMMARY

A case of what is believed to be a hitherto undescribed variant of alveolar-cell carcinoma of the lung is described. A 52 year-old woman became ill with productive

cough, and her chest roentgenogram simulated a pleurisy with a chest full amount of effusion, and pleural puncture gave mucinous fluid. After a year period of hospitalization she died of gradually increasing dyspnea and general emaciation. Morbid anatomy revealed a nodular form of alveolar-cell carcinoma of the lung. About 500 ml of mucinous fluid was present in the pleural cavity, and moreover, section through the tumor disclosed several large cavites filled with mucin. Attempts were made to analyse the native pleural fluid and the mucin partially purified. Furthermore, we briefly discussed the way in which the mucinous pleurisy developed, and the chemical composition of the mucin obtained from the alveolar-cell carcinoma of the lung.

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Fig. 1. A chest roentgenogram showing a dense homogenous shadow all over the left lung field.

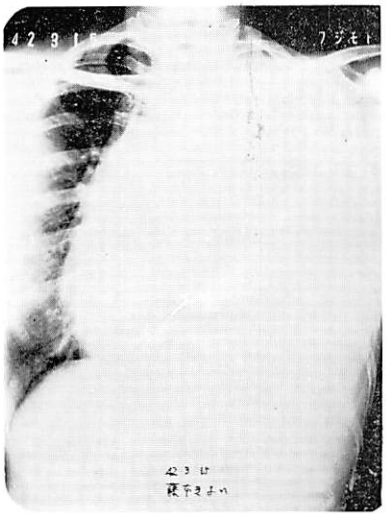


Fig. 2. The Rivalta's test giving a sea jelly-like coagulum.

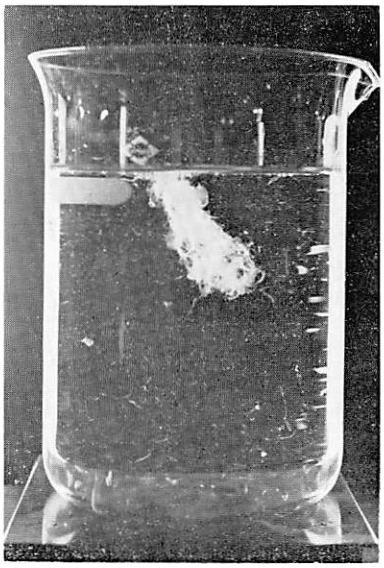
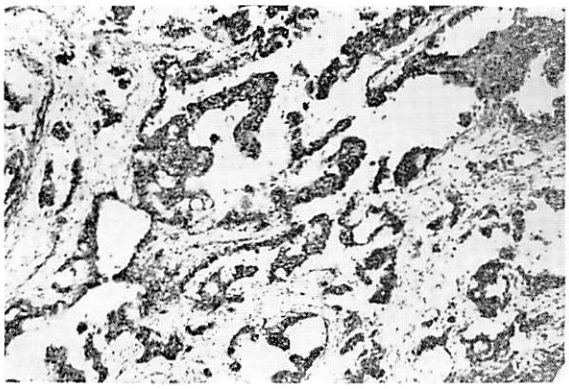


Fig. 3. Microscopic findings of the alveolar-cell tumor of the lung. A) Tumor tissue showing the diffuse involvement of the lung alveoli. B) Papilla-like projections enclosing spaces filled with mucin.

A)



B)

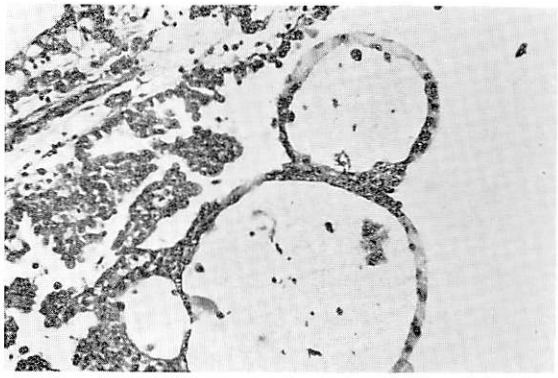
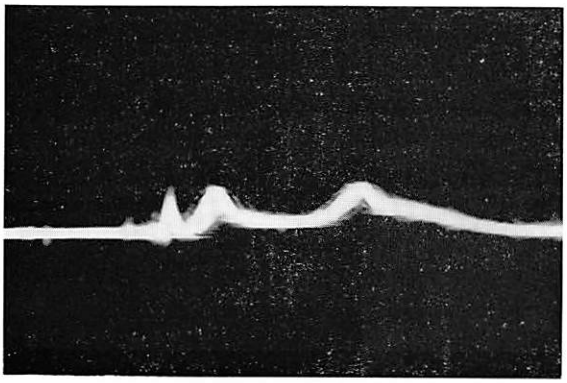


Fig. 4. Free electrophoretic pattern showing two peaks in the ascending side.



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