Peritoneal Mesothelioma Associated with Polyclonal Hyperimmunoglobulinemia

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ONODERA, S., INABA, R., NIIKAWA, K., OIKAWA, K. and YOSHINAGA, K. *Peritoneal Mesothelioma Associated with Polyclonal Hyperimmunoglobulinemia.* Tohoku J. exp. Med., 1974, 114 (3), 195-203—This patient had marked polyclonal hyperimmunoglobulinemia associated with mesothelioma in the right subphrenic space. Histopathologically the lymph nodes around the mesothelioma showed marked plasma cell proliferation intermingled with infiltration of mesothelioma cells. The plasma cell proliferation was observed even in distant lymph nodes not infiltrated by the tumor cells. The review of the literature disclosed rather frequent occurrences of hyperimmunoglobulinemia in mesothelioma and significance of this association should be stressed. ——— peritoneal mesothelioma; polyclonal hyperimmunoglobulinemia

It is well known that polyclonal hyperimmunoglobulinemia occurs in various diseases, such as chronic infections (Fahey 1965; Buchley and Dorsey 1970), collagen diseases (Barnett and MacDonald 1970), liver diseases (Fahey 1965) and some carcinomatous conditions (Fenoglio et al. 1973). The presence of polyclonal hyperimmunoglobulinemia probably reflects the proliferation of lymphoreticular system stimulated by some antigenic substance, but in majority of cases of polyclonal hyperimmunoglobulinemia it is extremely difficult to determine what the exact antigen responsible may be.

We have recently experienced a case of puzzling persistent polyclonal hyperimmunoglobulinemia. Extensive diagnostic approaches failed to disclose its underlying disease, but the autopsy disclosed the presence of mesothelioma in the subphrenic area. The histopathological findings suggest that this polyclonal hyperimmunoglobulinemia was closely related to metastasis of mesothelioma cells to the neighboring lymph nodes.

CASE REPORT

This 20 year-old Japanese male clerk was admitted to Tohoku University Hospital on May 29, 1972, because of fever and upper abdominal pain. He had been operated upon for acute appendicitis in 1969. In June, 1971 exploratory laparotomy was performed in a local hospital for the diffuse abdominal discomfort

TABLE 1. Laboratory data on admission

Urinalysis	Protein (+), sugar (-), urobilinogen (+), Bence-Jones protein (-)	Actual pH Actual P _{CO} ₂ Base excess	7.428 33.2 mmHg - 1.9 mEq/liter blood
		Standard bicarbonate	22.6 mEq/liter plasma
RBC	2.96 × 10 ⁶ /mm ³	Icterus index	10 units
Hb	7.1 g/100 ml	Serum total bilirubin	0.4 mg/100 ml
Reticulocytes	20 %	Serum indirect bilirubin	0.2 mg/100 ml
WBC	10,100/mm ³ (Band 21, Seg 51, Baso 1, Mono 17, Lymph 10%)	SGOT	14 units
Platelets	211,000/mm ³	SGPT	12 units
Prothrombin time	50% (one stage)	Serum alkaline phosphatase	13.4 units (King-Armstrong)
Bleeding time	5'30" (Duke)	ESR 1 hr	152 mm
Coagulation time	8' (Lee-White)	RA-test	(-)
Fibrinogen	736.8 mg/100 ml	CRP	(+5)
Serum iron	51 γ/100 ml	ASLO titer	833
UIBC	183 γ/100 ml	LE cell	(-)
Serum sodium	139 mEq/liter	Antinuclear factors	(-)
Serum potassium	4.1 mEq/liter	Coombs' test direct	(+)
Serum chloride	96 mEq/liter	indirect	(-)
Serum calcium	8.0 mg/100 ml	Paul-Bunnell test titer	448
Serum phosphorus	4.3 mg/100 ml	IgG	3850 mg/100 ml
Total cholesterol	80 mg/100 ml	IgA	420 mg/100 ml
Fasting blood glucose	104 mg/100 ml	IgM	110 mg/100 ml
Serum uric acid	2.6 mg/100 ml	IgD	5.6 mg/100 ml
Blood urea nitrogen	10 mg/100 ml	IgE	160 units/ml
Glomerular filtration rate	65.2 ml/min

Fig. 1. Plasma cells proliferating in the bone marrow in October, 1972.

he began to complain of, but no remarkable finding was observed except for the presence of some ascitic fluid. In October, 1971 the abdominal pain with distention gradually increased and fever, fatigue, anorexia and anemia developed. Under the

Fig. 2. Electrophoretic pattern on cellulose-acetate at the time of admission. Total protein 8.3 g/100 ml. Albumin 20.7%, α_1 -globulin 4.1%, α_2 -globulin 11.4%, β -globulin 9.8%, γ -globulin 53.9%.

for 3 months with no improvement.

His family history reveals no significant illness among the family. He has no history of exposure to asbestos.

Physical examination at the time of admission revealed an emaciated man who appeared pale. Temperature 38.5°C. Pulse rate 110/min. BP 130/180 mm Hg. Multiple small-finger-tip size lymph nodes were palpable in both cervical, axillar and inguinal areas. The lungs were clear. No heart murmurs were audible. The abdomen was slightly distended and shifting dullness was present. There was some tenderness over the epigastric and rt. hypochondriac area. The liver, spleen and kidneys were not palpable. No pedal edema was detected.

The laboratory examinations at the time of admission are shown in Table 1. Hypochromic anemia was present with decrease of serum iron. The liver functions were not extremely deranged. ESR was increased to 152 mm in one hour. The test for rheumatoid factors was negative, while ASLO titer was increased to 833. LE cells were not demonstrated and antinuclear factors were not present. Direct Coombs' test was positive, but subsequent studies employing an elution technique disclosed that this was due to non-specific binding of γ -globulin to the surface of red cells. Sternal bone marrow aspiration revealed that the marrow contained 174,000 nucleated cells per cubic millimeter with 3 per cent plasma cells, no abnormal cell being detected. Subsequent bone marrow studies, however, showed gradual increase in plasma cell percentage as shown in Fig. 1. The level of serum total protein was 8.3 g/100 ml with 53.9% of γ -globulin, its electrophoretic pattern on cellulose-acetate membrane being shown in Fig. 2. This marked elevation of γ -globulin was persistent and gradually increased, reaching 68.9% of total serum protein which became 12.4 g/100 ml. Fig. 3 shows the results of immunoelectrophoretic analysis, determining ultimately the polyclonal nature of the hypergammaglobulinemia suggested by the broad pattern of γ -globulin increase in cellulose acetate membrane. The results of quantitation of various immunoglobulins are shown in Table 1. Fig. 4 demonstrates the pattern of ultracentrifugal analysis of the patient's serum, revealing that the increased protein consisted mainly of 7S globulin.

The course after admission is shown in Fig. 5. Since the various antibiotics

Fig. 3. The results of immunoelectrophoresis. P, patient's serum; N, normal serum; AWH, anti-whole human serum; AG, anti-IgG serum; AA, anti-IgA serum; AM, anti-IgM serum; AD, Anti-IgD serum; AK, anti- κ light chain serum; AL, anti- λ light chain serum.

Fig. 4. Ultracentrifugal analysis of patient's serum. Photos were taken every 15 minutes. 60,000 rpm.

probable diagnosis of tuberculous peritonitis he received anti-tuberculous agents failed to suppress the temperature elevation, adrenal corticosteroid and indomethacine were employed with some response to fever. There was no improvement,

Fig. 5. Course after admission to Tohoku University Hospital. PAS, *p*-aminosalicylic acid; CER, Cephaloridine; INH, Isoniazid; APC, Ampicillin; SM, Streptomycin; RFP, Rifampicin.

Fig. 6. Lymphangiographic picture of retroperitoneal lymph nodes.

Fig. 7. Chest X-ray demonstrating pleural effusion in the right side.

however, in ESR acceleration and in hypergammaglobulinemia. As hyperglycemia became excessive, reaching to glucose level of 314 mg/100 ml, the adrenal corticosteroid was decreased and then stopped. Meanwhile cervical lymph node biopsy, laparoscopy, and examination of ascitic fluid were performed with no significant information. The lymphangiographic picture is shown in Fig. 6, revealing some granular pattern of the retroperitoneal lymph nodes. His condition deteriorated

Fig. 8. Tumors of mesothelioma under the right diaphragm.

Fig. 9. Histological view of the section of mesothelioma.

gradually with increase of abdominal pain and ascites. In October, 1972 pleural effusion also was noted as demonstrated roentgenologically in Fig. 7. The analysis of the pleural fluid revealed the increase of protein, but no abnormal cell was detected. The culture of the fluid gave no growth of bacteria. In spite of the readministration of adrenal corticosteroid and antituberculous agents, no recovery was seen. Towards the end of his course increase of BUN and serum creatinine was observed, jaundice, hepatomegaly and dyspnea becoming prominent. On December 13, 1972 he expired.

Fig. 10. Histological picture of a distant lymph node.

Fig. 11. Histological picture of the liver at the time of autopsy.

Upon autopsy the most remarkable feature was the presence of numerous confluent coarsely granular tumors in the right subphrenic space as is shown in Fig. 8. Histologically the mesothelioma cells showed papillary proliferation, covering in one layer the surface of connective tissue which contained abundant capillaries, as shown in Fig. 9, and was classified as mesothelioma of epithelial type. The tumor cells were cuboidal and showed no atypia, but metastases to the neighboring lymph nodes were definitely recognized. Metastases to distant lymph nodes and other

organs were not demonstrated. Generalized distant lymph nodes, however, showed plasma cell proliferation as shown in Fig. 10.

Other prominent pathological findings were fibrinous pericarditis and enlarged liver with dark red tone. Histological picture of the liver is shown in Fig. 11 which demonstrated the destruction of basic liver structure. This was regarded as toxic hepatitis which appeared shortly before death.

DISCUSSION

Malignant mesothelial tumors are relatively rare and present difficult diagnostic problems (Smith et al. 1968; Roberts and Irvine 1970). It was reported that confidence in the diagnosis of diffuse mesothelioma during an autopsy rested on the ability to exclude other tumors (McCaughy 1965). In one report, however, 30 cases of mesothelioma were studied histopathologically (Churg et al. 1965). The association of the mesothelioma occurrence to asbestos exposure has been suggested (Hourihane 1965; Vigliani et al. 1965; McDonald et al. 1970), and it is reported that the elevated level of acid mucopolysaccharide in serous effusion may be useful for the diagnosis of mesothelioma (Thompson et al. 1969).

Although no characteristic clinical pattern has been summarized, since reviews on mesothelioma seem to have been mainly on histopathology (Churg et al. 1965; McCaughy 1965) it may be regarded that gradual increase of abdominal discomfort, ascites and emaciation are seen in peritoneal mesothelioma (Smith et al. 1968; Roberts and Irvine 1970), and pleural effusion and dyspnea occur in pleural mesothelioma (Persaud et al. 1970; September and Villet 1972). Differentiation from tuberculous peritonitis, collagen diseases and other malignant diseases may be extremely difficult as observed in the present case, unless mesothelioma be suspected.

The most prominent feature in the present case was the persistent and increasing hyperimmunoglobulinemia which took a chronic course. Although liver failure appeared terminally, we regard that this was due to administration of various drugs. Most case histories concerning mesotheliomas reported so far lacked in the descriptions of the detailed serum protein analysis, but we could accumulate 3 additional cases of mesothelioma with hypergammaglobulinemia from the world literature. Baran et al. (1972) reported a case of hyperglobulinemia associated with pleural mesothelioma and stated that it was not certain whether this hyperglobulinemia was related to mesothelioma or not. September and Villet (1970) also reported a case of monoclonal gammopathy associated with malignant mesothelioma and mentioned that the bone marrow of this patient showed diffuse plasma cell infiltration. However, since the immunoelectrophoretic pattern was not shown in this case, we wonder if this hypergammaglobulinemia was really monoclonal instead of polyclonal. Furthermore, as early as in 1954, Jallut (1954) reported a case of pleural mesothelioma associated with multiple myeloma. Although it may occasionally be difficult to differentiate between multiple myeloma and reactive plasmacytosis, it would not be denied that his case resembled our case. Our case, in addition to the 3 cases mentioned above may suggest that mesothelioma cell infiltration can cause

the proliferation of plasma cells in the lymphoreticular system and lead to excessive production of immunoglobulins. Although this phenomenon may be seen in other malignancies (Fenoglio et al. 1973), the peculiar character of mesothelioma cell invasion might be more prone to cause plasma cell proliferation than other malignant cells such as carcinoma cells. However, what the precise mechanism of this plasma cell proliferation is, and whether it is related to some antigenic stimulus or mere mechanical stimulation await further studies.

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References

- 1) Baran, E., Vacariu, O., Dobre, D. & Dorescu, G. (1972) Polyglobulia and pleural mesothelioma. *Rev. Med. Chir. Soc. Med. Nat. Iasi*, **16**, 763-766.
- 2) Barnett, L.J. & MacDonald, N.S. (1970) Altered immunoglobulin metabolism in systemic lupus erythematosus and rheumatoid arthritis. *J. clin. Invest.*, **49**, 708-715.
- 3) Buchley, C.E. & Dorsey, F.C. (1970) A comparison of serum immunoglobulin concentrations in sarcoidosis and tuberculosis. *Ann. intern. Med.*, **72**, 37-42.
- 4) Churg, J., Rosen, S.H. & Moolten, S. (1965) Histological characteristics of mesothelioma associated with asbestos. *Ann. N.Y. Acad. Sci.*, **132**, 614-622.
- 5) Fahey, J.L. (1965) Antibodies and immunoglobulins. II. Normal development and changes in diseases. *J. Amer. med. Ass.*, **194**, 255-258.
- 6) Fenoglio, C., Ferenczy, A., Isobe, T. & Osseman, E.F. (1973) Hepatoma associated with marked plasmacytosis and polyclonal hypergammaglobulinemia. *Amer. J. Med.*, **55**, 111-115.
- 7) Hourihane, D.O'B. (1965) A biopsy series of mesotheliomata, and attempts to identify asbestos within some of the tumors. *Ann. N.Y. Acad. Sci.*, **132**, 647-673.
- 8) Jallut, O. (1954) Reaction plasmocytaire ou myelome vrais dans un cas de mesotheliome pleural. *Schweiz. med. Wschr.*, **84**, 1110-1112.
- 9) McCaughey, W.F.E. (1965) Criteria for diagnosis of diffuse mesothelial tumors. *Ann. N.Y. Acad. Sci.*, **132**, 603-613.
- 10) McDonald, A.D., Harper, A., El Attar, O.A. & McDonald, J.C. (1970) Epidemiology of primary malignant mesothelial tumors in Canada. *Cancer*, **26**, 914-919.
- 11) Onodera, S. (1966) Quantitative determination of serum immunoglobulins in various diseases. *Tohoku J. exp. Med.*, **89**, 279-292.
- 12) Persaud, V., Bateson, E.M. & Bankay, C.D. (1970) Pleural mesothelioma associated with massive hepatic calcification and unusual metastases. *Cancer*, **26**, 920-928.
- 13) Roberts, G.H. & Irvine, R.W. (1970) Peritoneal mesothelioma. A report of 4 cases. *Brit. J. Surg.*, **57**, 645-650.
- 14) September, B.A. & Villet, W.T. (1972) Monoclonal gammopathy associated with malignant mesothelioma: case report. *South Afri. med. J.*, **46**, 545-549.
- 15) Smith, P.G., Higgins, P. McR. & Park, W.D. (1968) Peritoneal mesothelioma presenting surgically. *Brit. J. Surg.*, **55**, 681-685.
- 16) Thompson, M.E., Bromberg, P.A. & Amenta, J.S. (1969) Acid mucopolysaccharide determination. A useful adjunct for the diagnosis of malignant mesothelioma with effusion. *Amer. J. clin. Path.*, **52**, 335-339.
- 17) Vigliani, E.C., Mottura, G. & Maranzana, P. (1965) Association of pulmonary tumors with asbestosis in Piedmont and Lombardy. *Ann. N.Y. Acad. Sci.*, **132**, 558-576.