Monoclonal Gammopathy Associated with Malignant Mesothelioma: Case Report

BARBARA A. SEPTEMBER, M.B., CH.B. (NATAL) AND W. T. VILLET, M.B., CH.B. (CAPE TOWN), Department of Pathology, Faculty of Medicine, University of Natal, Durban

SUMMARY

The association of a monoclonal gammopathy with mesothelioma of the pleura is sufficiently rare to warrant the reporting of such a case. Interpretation of the possible cause of the monoclonal gammopathy as being due to myelomatosis is made on the bone marrow examination, serum electrophoresis and radial immunodiffusion studies.

The relationship between asbestos exposure and pleural mesothelioma is briefly discussed.


CASE REPORT

A 57-year-old Bantu male, was admitted to King Edward VIII Hospital on 21 January 1970 complaining of backache and 'blackouts' for one month, with dyspnoea on exertion for 10 days. Clinical examination showed a right basal pneumonia, raised jugular venous pressure, decreased chest movements, 4-finger hepatomegaly and marked intercostal tenderness on the right, associated with sharp abdominal pain.

During a previous admission in July 1968, following a 2-week illness, left upper lobe pneumonia and hepatomegaly had been found in this patient. Laboratory findings on this occasion were haemoglobin level 13.4 g/100 ml, leucocyte count 8000/mm³ and ESR 47 mm/hour. The pneumonia responded to therapy and the patient was discharged after 5 days, without investigation of the hepatomegaly.

The patient’s progress during the second admission simulated an intrathoracic malignancy. Within a few days splenomegaly, lymphadenopathy in both axillae and neck, and a space-occupying lesion in the right chest were observed. Ascites, abdominal varices and bilateral superior mediastinal obstruction had developed by the second month. During the following 2 weeks nodules appeared on the right chest wall and the right breast became enlarged.

The patient succumbed on 25 May 1970, following a steadily downhill course during which he became progressively more dyspnoeic and developed inferior venacaval obstruction.

Treatment during the last 2 months consisted of nitrogen mustard (0.5 mg/kg in 2-3 divided doses at 1-2-day intervals).

CLINICAL INVESTIGATIONS

Blood count. Haemoglobin was 13.4 g/100 ml on admission, dropped to 6.8 g/100 ml, and rose to 11.1 g/100 ml after transfusion. Leucocyte count ranged from 8000 to 15 000/mm³ with 1% plasma cells on 2 occasions. Platelets were 500 000/mm³. ESR varied between 23 and 66 mm/hour. Rouleaux formation was present on 2 occasions.

Bone marrow showed numerous large myeloma cells with eccentrically placed nuclei, each with a nucleolus. Occasional mitoses were noted. The abundant granular, basophilic cytoplasm showed vacuolation and a perinuclear clear area. Binucleate cells were frequent (Fig. 1).

Fig. 1. Bone marrow aspirate consistent with myelomatosis (Giemsa × 960).
The protein electrophoretic pattern showed a high level of paraprotein and loss of the normal immunoglobulins (Fig. 2). The radial immunodiffusion results were IgG 4400 mg/100 ml, IgM 65 mg/100 ml, and IgA 232 mg/100 ml. Bence-Jones protein was not detected.

**PROTEIN ELECTROPHORESIS**

<table>
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<th>Component</th>
<th>Value</th>
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<tbody>
<tr>
<td>ALBUMIN</td>
<td>2.3%</td>
</tr>
<tr>
<td>GLOBULINS:</td>
<td></td>
</tr>
<tr>
<td>Alpha 1</td>
<td>0.5%</td>
</tr>
<tr>
<td>Alpha 2</td>
<td>1.5%</td>
</tr>
<tr>
<td>Beta</td>
<td>1.2%</td>
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<tr>
<td>Gamma</td>
<td>3.3%</td>
</tr>
<tr>
<td>TOTAL PROTEIN</td>
<td>8.8%</td>
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Sputum. Large numbers of asbestos bodies were present.

**Histology.** Examination of an axillary node (10 February 1970) showed a poorly differentiated tumour. On 2 occasions (20 March 1970, before nitrogen-mustard therapy, and on 10 April 1970) liver biopsy showed large numbers of plasma cells in the sinusoids and centrilobular regions. In addition, the second biopsy showed centrilobular venous congestion (possibly from inferior vena-caval obstruction) and siderosis. Pleural biopsy was unsuccessful. Biopsy of a skin nodule consisted of undifferentiated cells with reticulin formation and some mucin production.

**Radiological examination** in 1968 showed only the left upper lobe pneumonia. Between January and April 1970 the radiological changes progressed from consolidation and effusion at the right base to massive obliteration of the right lower zone, with a right-sided apical effusion, mediastinal shift and hilar masses, and later spread of the right basal opacity towards the apex with an effusion at the left base (Fig. 3).

**Autopsy Findings**

At postmortem the body weighed 55 kg and showed marked wasting. There was a firm mass about 3 cm in diameter beneath the right nipple. Similar subcutaneous nodules of varying size were noted on the anterior and posterior aspects of the right chest wall. A healed incision in the right axilla marked the site of biopsy of the axillary
node. There was a midline surgical scar in the upper abdomen through which the umbilical vein had been catheterized for a venoportogram.

The right lung, which was compressed and showed a suppurative bronchopneumonia, was completely enveloped by thick (2.5 cm) fleshy, mucinous, white tumour tissue, adherent to both the lung surface and the chest wall and growing along the interlobar fissures. Small pockets of mucinous material were found within this tissue.

There was contiguous spread of this tumour tissue to the mediastinum with compression of the great vessels; to the intercostal and pectoral muscles, the right breast and right axilla, and to the posterior wall of the oesophagus 5 cm below the tracheal bifurcation. There was no mucosal ulceration of the oesophagus (Fig. 4).

The left parietal pleura had numerous thick fibrous plaques. Tumour nodules (2 - 3 mm) were present in the parenchyma of both lungs (Fig. 4).

Continuous spread was noted in lymph nodes around the porta hepatis, those along the pancreas, and in the para-aortic nodes to about 3 cm below the renal arteries. Small nodules (less than 1 cm) were found in the liver, ileum (pedunculated) and myocardium. Both kidneys had numerous small secondaries. An adrenal metastasis was found on histological examination. There were no other noteworthy morbid anatomical findings.

**Histopathology**

The pleural tumour showed mainly a tubulo-papillary pattern in which the cells had vesicular nuclei with prominent eosinophilic nucleoli, and varied from cuboidal to flattened types. There was little tendency to a sheet-like pattern. The profuse fibrocellular tissue element was more active and the cells more pleomorphic than one would expect with a carcinoma. Clefts in the collagen were lined by tumour cells. Some areas showed cystic spaces. Mitoses were infrequent (Fig. 5). Cellular regularity was a feature of the tumour.

Asbestos fibres and asbestos bodies with their white, colourless centres were present in the cellular collagenous matrix (Fig. 6). Asbestos bodies were noted also in the unaffected lung tissue. There was no associated fibrosis to enable the diagnosis of asbestosis to be made.

In the area of the epithelial component, periodic-acid Schiff stain was negative. The metachromasia with tolui-
3. Obvious intrathoracic malignancy.

Our case fulfils the currently acceptable criteria for diagnosis:

(a) no other demonstrable primary that can conceivably cause serosal spread;
(b) the gross appearance of the tumour is that of a superficial growth along the serosal planes with only shallow invasion of the underlying organs;
(c) metastases, if any, are by and large limited to regional lymph nodes.

Fig. 7. Intra-alveolar spread involving left lung (H. and E. × 150).

In addition to the small metastatic deposits in the liver there were large numbers of plasma cells in and around the central vein and in the sinusoids. Occasional plasma cells were present in the portal tracts (Fig. 8).

Secondary spread of the mesothelioma was confirmed in the kidneys, adrenal, ileum, para-aortic lymph nodes and myocardium.

**DISCUSSION**

A case of diffuse malignant mesothelioma is presented in which the clinical features and progress are consistent with the 3 stages described by Sleggs, Marchand and Wagner.1

1. Pleurisy and bronchitis diagnosed as viral or pyogenic pneumonitis and treated with antibiotics.
2. Pleural effusion with thickening, where a differential diagnosis of tuberculosis, malignancy, asbestosis, etc. is entertained.

Further characteristics of the mesothelioma are the cellular regularity and histological variability which we noted in our case.2 Reports3,4 have been published of diffuse mesotheliomas occasionally spreading to the upper abdominal structures (liver, lung, kidneys, adrenals and para-aortic nodes), the skin and peritoneum. Therefore the presence of metastases in our patient does not provide a reason for rejecting the diagnosis, since the other characteristics of the tumour are typical. Distant metastases have also been reported in the pericardium and brachial plexus.3,4
Haematogenous spread is unusual. There is a right-sided preponderance and the mesothelioma is initially unilateral.\(^1\) Implantation in biopsy scars and aspiration sites is known to occur. The radiological changes described in our case correspond with those noted by Helier et al.\(^2\).

Asbestososis of the lung is characterized by the exposure to asbestos fibres with the subsequent development of asbestos bodies and pleural and pulmonary fibrosis. It has been stated\(^3\) that the average interval between exposure and the development of pulmonary asbestosis is about 15 years.

In our patient asbestosis bodies with white colourless centres\(^4\) were present in the lung, but no diffuse pulmonary fibrosis was demonstrated. Unfortunately we were unable to obtain the history regarding exposure to asbestos.

The association between mesotheliomas and asbestosis has long been disputed. It has been shown that the mesothelioma need not be accompanied by asbestosis. An explanation for this has been postulated by Thomson,\(^5\) and Thomson et al.\(^6\) who reported a limited basal asbestosis forming a carcinogenic focus, resulting in a mesothelioma without generalized asbestosis. This basal asbestosis, they stated, does not result in pulmonary disease or disability, but appears to be of aetiological significance in mesothelioma of the pleura and peritoneum. Patients with asbestosis may die of pulmonary insufficiency long before the development of a mesothelioma.\(^7\)

The unusual feature of this case was the associated monoclonal gammopathy as evidenced by the bone marrow finding of a diffuse plasma cell infiltration,\(^8\) the serum protein electrophoretic pattern,\(^9\) the serum immunoglobulin values and the plasma cell infiltration of the liver. These findings alone would justify a diagnosis of myelomatosis despite the absence of lytic bone lesions.

Whether the dual pathology in this case, i.e. the mesothelioma and the gammopathy, is interrelated or whether this represents merely a chance association, is an interesting question. Apart from myeloma and Waldenström's macroglobulinaemia, monoclonal gammopathy has been reported in association with a variety of conditions,\(^10\), both benign and malignant, including lymphoma, carcino-

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**REFERENCES**