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CASE REPORT

Production of granulocyte colony-stimulating factor by malignant mesothelioma

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ABSTRACT: We present the case of a male patient, aged 45 yrs, with malignant mesothelioma producing granulocyte colony-stimulating factor (G-CSF). The diagnosis was established by histopathological examination of the autopsied pleural tissues. Production of G-CSF was confirmed by immunoperoxidase staining, using a specific monoclonal antibody against recombinant G-CSF (rhG-CSF).

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Granulocyte colony-stimulating factor (G-CSF) is produced by normal monocytes, macrophages, endothelial cells, fibroblasts and neutrophils. It is also known that some malignant tumours produce G-CSF [1, 2]. However, production of G-CSF by mesothelioma has not previously been reported. We present the first case of G-CSF producing mesothelioma.

Case Report

A 45 year old male plasterer was admitted to our university hospital because of general fatigue and chest pain. Chest roentgenogram (fig. 1) and computed tomographic (CT) scan disclosed a massive effusion in the right pleural cavity, and an ipsilateral pleural thickening. There was no apparent mass lesion in the lung field.

Peripheral blood analysis revealed a marked leucocytosis of 51×10^9 cells·mm^{-3}, 93% of the cells being matured neutrophils, slight anaemia (Hb 12.3 g·dl^{-1}), and a normal thrombocyte count of 341×10^9 cells·mm^{-3}. Blood chemistry demonstrated elevated serum levels of lactate dehydrogenase (LDH), 3,830 U·*l*$^{-1}$, (normal range (N)100~4000 U·*l*$^{-1}$), alkaline phosphate (ALP), 18.8 U·*l*$^{-1}$ (N<10 U·*l*$^{-1}$) and creatine phosphate (CRP) 19.6 mg·dl^{-1} (N<1 mg·dl^{-1}). Other hepatic and renal function indicators and tumour markers in the serum remained within normal ranges. Examination of the pleural exudate disclosed an increase in amounts of tumour markers; squamous cell carcinoma related antigen (SCC) 18.2 mg·ml^{-1} (N<1.5 mg·ml^{-1}), tissue polypeptide antigen (TPA) 669×10^3 U·ml^{-1} (<1.10 U·ml^{-1}), and adenosine deaminase (ADA) 79.2 IU·*l*$^{-1}$ (<50 IU·*l*$^{-1}$).

A tentative diagnosis of tuberculous pleurisy was made on the basis of the slightly elevated level of ADA (although the tuberculin skin test was negative), and the patient received antituberculous agents. More detailed examination shortly after the start of antituberculous chemotherapy disclosed marked increases in the amounts of hyaluronic acid and G-CSF in the pleural effusion, as compared with those in the serum (33.0 *vs* 0.05 μg·ml^{-1} and 11,300 *vs* 49.7 pg·ml^{-1}, respectively). Granulocyte-macrophage colony-stimulating factor (GM-CSF) was not detected in the serum or in the pleural effusion. The patient underwent right thoracotomy and biopsy of the pleural tumour. Microscopic examination of the tissue strongly suggested poorly differentiated malignant mesothelioma, leaving a possibility of large cell carcinoma. Despite intensive antineoplastic chemotherapy, the pleural tumour rapidly increased in size and spread widely over the surface of the pleura. The patient died four weeks after admission.

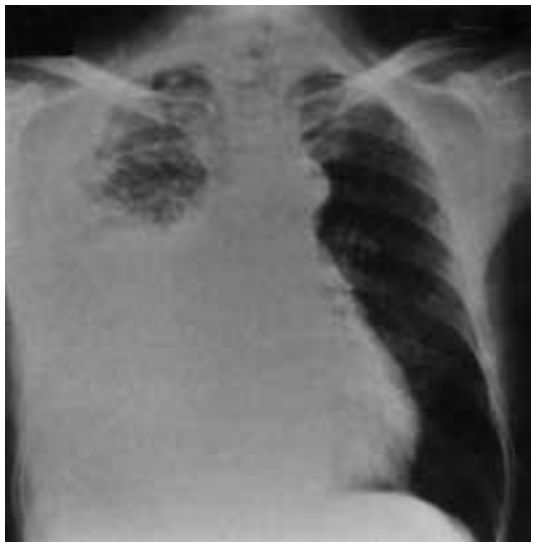

Fig. 1. – Chest roentgenogram on admission showing right pleural effusion.

Autopsy confirmed the absence of primary bronchogenic carcinoma and the replacement of the entire right

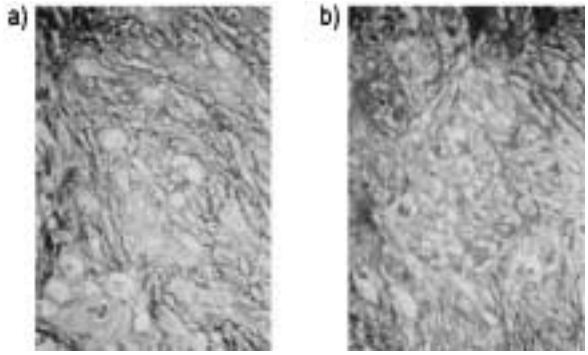

Fig. 2. – a) Hyaluronic acid stained with iron colloid stain, and b) digested by hyaluronidase (scale bar=20 μm).

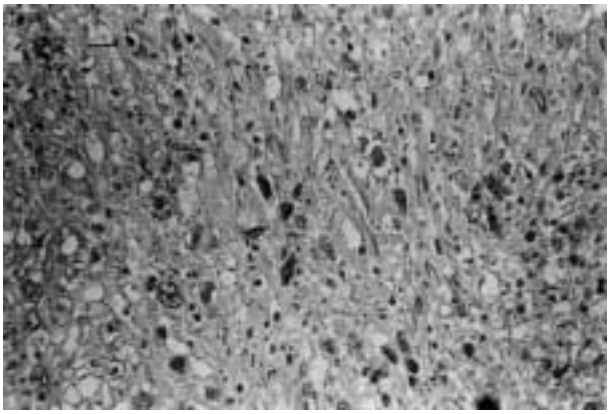

Fig. 3. – Immunoperoxidase stain using specific monoclonal antibodies against recombinant granulocyte colony-stimulating factor (rhG-CSF) showed positive staining in the tumour cells. (scale bar=20 μm).

pleura by tumour. Micrometastases were found in both lungs, the liver and pancreas. In the autopsied pleural tissues, the deposition of large amounts of hyaluronic acid, which was digested by treatment with hyaluronidase (fig. 2b), was demonstrated by staining the tissues with iron colloid stain (fig. 2a), but not by staining with periodic-acid-Schiff (PAS). Thus, a definite diagnosis of malignant mesothelioma (epithelial type), at Stage IV according to Butchart's pathological staging classification [3], was established. Immunohistochemistry using a specific monoclonal antibody against recombinant G-CSF (rhG-CSF) conjugated with peroxidase [4], clearly demonstrated that the tumour produced a considerable amount of G-CSF (fig. 3).

Discussion

Colony-stimulating factors (CSFs) include G-CSF, GM-CSF macrophage colony-stimulating factor (M-CSF) and interleukin 3 (IL-3) multi-CSF. Among them, G-CSF induces colony-forming unit-granulocyte/macrophage (CFU-GM) to differentiate into the mature granulocyte, and then to be activated. During the last few years, rhG-CSF has been used for the treatment of neutropaenia due to antitumour chemotherapy. GM-CSF has also been used for this purpose.

In 1977, ASANO *et al.* [1], first reported a case of G-CSF production in lung cancer. Since then, there have been several reports of G-CSF production by bronchogenic carcinomas, especially large cell and squamous cell carcinomas [2, 5, 6].

Tumour progression has usually been rapid, as observed in our patient. The production of G-CSF may be contributory. WOLFGANG *et al.* [7] reported that human haematopoietic growth factors stimulate clonal growth of nonhaematopoietic tumour cells. Such effects are, however, likely to be less important when CSFs are used for therapeutic purposes, since rhG-CSF disappears rapidly after intravenous or subcutaneous administration [8]. In contrast, persistent high levels were observed in our patient.

To our knowledge, there has not been any clinical report on G-CSF production by mesothelioma, although both normal human mesothelial cells and established human malignant mesothelioma cell lines in culture are known to produce haematopoietic colony-stimulating factors, including G-CSF [9, 10].

Dominant clinical manifestations in the present case were fever, and chest pain with pleural effusion, accompanied by marked neutrophilia both in peripheral blood and pleural exudate. These features led to a diagnosis of purulent pleurisy, and later to that of tuberculous pleurisy on the basis of a moderately elevated ADA level in the exudate, before a definite diagnosis of G-CSF production by mesothelioma was established. Care must be taken in similar cases to differentiate malignant effusions from bacterial or tuberculous pleurisy

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