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CASE REPORT

# Granulocyte-colony stimulating factor (G-CSF) producing malignant pleural mesothelioma: Report of a case

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## Abstract

This report presents a case of malignant pleural mesothelioma (MPM) producing granulocyte colony-stimulating factor (G-CSF) that was treated by tumor resection. A 76-year-old male presented with a huge right-side chest wall tumor, along with a slight fever and chest wall pain. Laboratory findings showed an increased white blood cell count (64600 cells/μL) and C-reactive protein level (20.57 mg/dL). The patient underwent surgical removal of the tumor along with tissue from the chest wall and histopathological analysis led to a diagnosis of sarcomatous type of MPM. Immunohistochemical findings for both anti-human G-CSF and interleukin-6 monoclonal antibodies were positive. Although the general condition of the patient quickly improved after surgery, local recurrence occurred two months later and he died of respiratory failure seven months after the operation, though surgery provided symptom relief. G-CSF-producing MPMs usually show a poor prognosis, though less-invasive surgery may be considered for relief of symptoms.

## Introduction

Granulocyte colony-stimulating factor (G-CSF) is found in hematopoietic progenitor cells and neutrophil granulocytes, which are generally produced by marrow cells and cells with a hematopoietic origin. Some neoplasms, usually epithelial tumors, also produce G-CSF, while a G-CSF-producing malignant pleural mesothelioma (MPM) is extremely rare, with only six cases reported in English literature. Here, we report a rare case of a G-CSF-producing MPM treated by tumor resection.

## Case report

A previously healthy 76-year-old male was admitted for treatment of a huge right-side chest wall tumor. He had a slight fever, and reported chest wall pain and recent weight loss. The patient had been smoking one pack of cigarettes per day for 55 years and worked as an auto mechanic for 60 years, suggesting the possibility of asbestos exposure. Chest computed tomographic (CT) findings revealed a chest wall tumor 11 cm in size that had destroyed the fourth and fifth costal bones, and invaded the lung parenchyma (Fig 1a). A laboratory investigation showed an increased white blood cell (WBC) count of 64600 cells/μL (94.6% neutrophils) and increased C-reactive protein (CRP; 20.57 mg/dL). Major tumor markers in serum were within normal ranges. An 18F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) revealed increased uptake in the tumor with a maximum standardized uptake value (SUVmax) of 18.7 and diffuse high FDG uptake in bone marrow (Fig 1b). The serum concentration of G-CSF was 71.8 pg/mL (normal range, 5.8–27.5) and that of interleukin (IL)-6 was 40.5 pg/mL (<4.0).

Palliative surgery was planned for the purpose of making a diagnosis and eliminating chest wall pain. The patient underwent surgical removal of the tumor with a portion of the chest wall and partial resection of the right lung. The chest wall defect, 15 cm in size, was reconstructed using a double synthetic woven mesh and latissimus dorsi muscle flap. Histopathological analysis of the resected specimen revealed large diffusely proliferated spindle-shaped cells (Fig 1c). Immunohistochemistry findings showed the tumor to be positive for calretinin, D2-40 (Fig 1d), and epithelial membrane antigen (EMA), and negative for carcinoembryonic

  

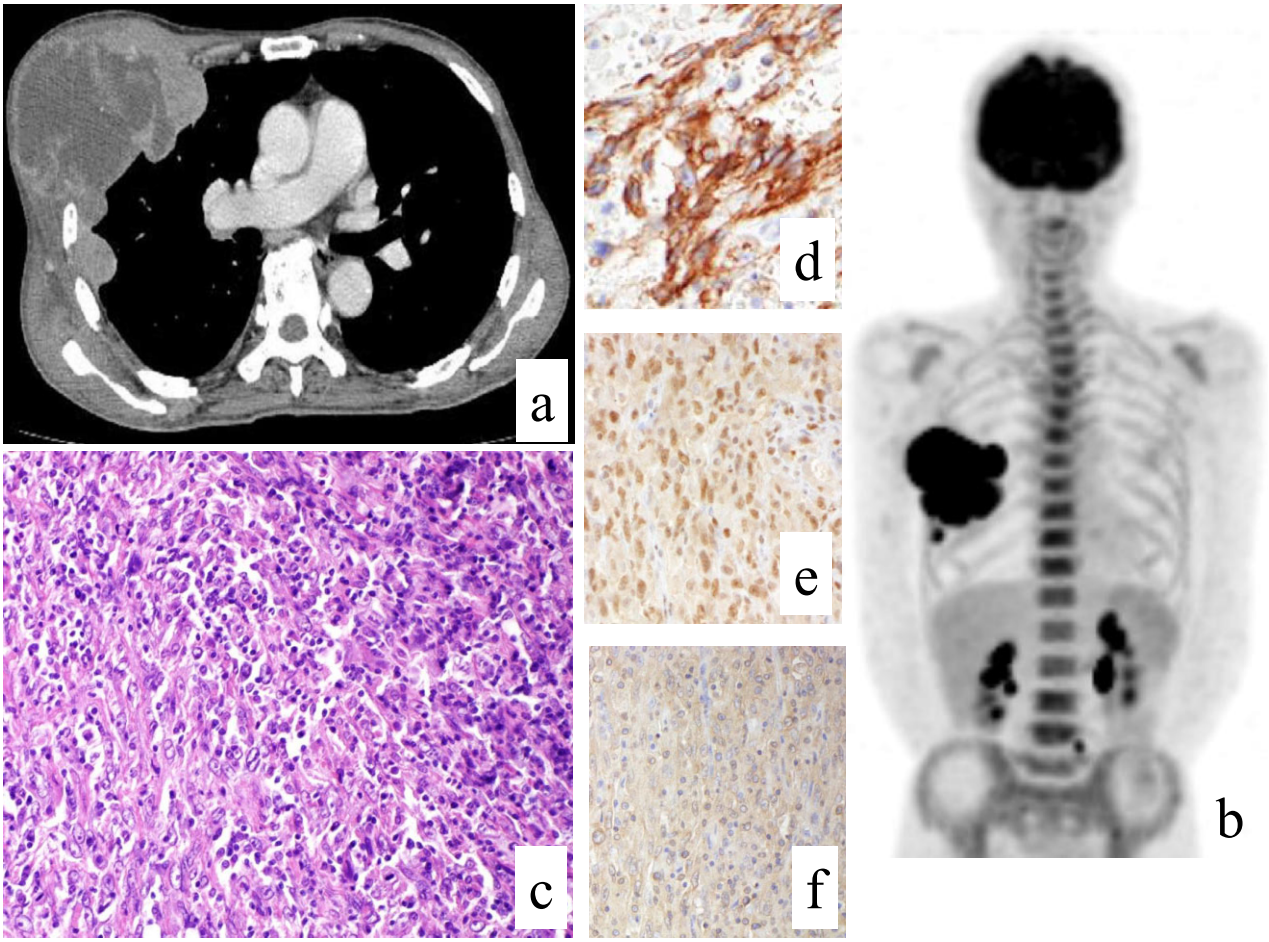


**Figure 1** (**a**) Chest computed tomography (CT) image showing a huge mass in the right chest wall that had destroyed the fourth and fifth costal bones, and invaded the lung parenchyma. (**b**) Positron emission tomography (PET)/CT image showed increased uptake in the tumor at 18.7, along with diffuse high fluorodeoxyglucose (FDG) uptake in bone marrow. (**c**) Photomicrograph of the tumor. Large spindle-shaped cells are seen diffusely proliferating. Hematoxylin and eosin (HE), magnification 100×. (**d**) Immunohistochemical analysis for D2-40. The tumor was diagnosed as a malignant pleural mesothelioma. Magnification 100×. (**e**,**f**) Immunohistochemical analysis for anti-human granulocyte colony-stimulating factor (G-CSF) monoclonal antibody (**e**) and anti-human interleukin (IL)-6 monoclonal antibody (f) in the resected specimen were both positive. Magnification 100×.

antigen (CEA) and thyroid transcription factor 1 (TTF-1). These results indicated the tumor was a sarcomatous type of MPM. Immunohistochemical analysis showed that both the anti-human G-CSF monoclonal and anti-human IL-6 monoclonal antibodies were positive (Fig 1e,f). Soon after surgery, the WBC and CRP decreased to a normal level, while the serum concentration of G-CSF also decreased to 8.22 pg/mL. Body temperature also stabilized to within a normal range and the chest wall pain was resolved.

Two months after surgery, chest CT and PET/CT scanning revealed local recurrence in the pleural cavity without distant metastasis. A laboratory investigation showed that WBC, neutrophil, and CRP levels were again increased, while the serum concentration of G-CSF was elevated to 69.0 pg/mL. Concurrent radiotherapy and chemotherapy with cisplatin (CDDP) and pemetrexed (PEM) were immediately planned. Radiotherapy at a dose of 60 Gy was performed, while chemotherapy was discontinued after two courses because of tumor progression. Despite rapid disease progression with the tumor occupying a substantial portion of the right chest cavity, the general condition of our patient remained stable after surgery. Seven months after surgery, he was admitted on an emergency basis for hemoptysis and later died of respiratory failure. The clinical course including diagnosis and treatment is shown in Figure 2.

## Discussion

Robinson described the first G-CSF producing tumor in 1974.[1] G-CSF producing malignancies have since been reported in various organs, usually in epithelial tumors. In autopsy study, the most frequent primary sites were the lung

 

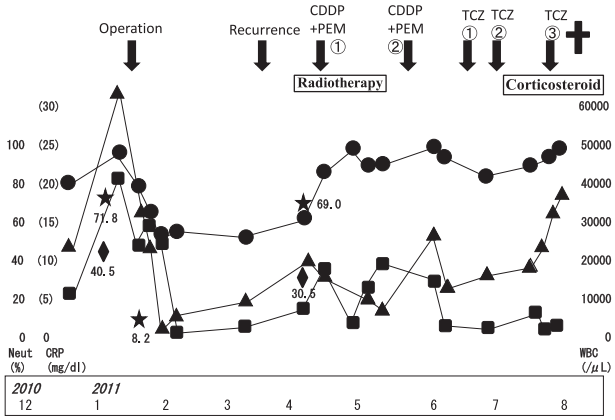


**Figure 2** Clinical course including diagnosis and treatment. ■ C-reactive protein (CRP), ▲ White blood cell (WBC) count, ● Neutrophil sequestration, ★ Granulocyte colony-stimulating factor (G-CSF), ◆ interleukin (IL)-6. CDDP: cisplatin, PEM: pemetrexed.

(50%), followed by the liver (7.6%), and stomach (6.0%).[2] The majority are undifferentiated carcinomas.[3] The prognosis of patients with G-CSF producing tumors is usually very poor, regardless of the primary organs; the longest survival period is 14 months.[4,5] There are some possible explanations for the poor prognosis: (i) G-CSF itself has an effect on tumor cell growth; and (ii) G-CSF induces a microenvironment that promotes tumor progression by modulating the tumor stroma.[6]

A G-CSF producing mesothelioma is extremely rare. Only six cases have been reported in English literature (Table 1). All patients were male, with a mean age of 57.6 years (range, 45–76). The most common symptoms were pleural effusion or pleural thickening, such as that seen in common MPM patients, though the proportion of sarcomatous or biphasic histological type was relatively high in G-CSF producing MPM patients.

Four of the seven reported patients, including our case, with a G-CSF-producing MPM received only chemotherapy or supportive care because of advanced stage. Two patients that underwent an extrapleural pneumonectomy (EPP) relapsed soon after surgery and no additional treatment was possible because of their poor general condition. The median survival of the six previously reported G-CSF-producing MPM patients was only 2.7 months after WBC elevation, which was significantly worse than other cases of G-CSF-producing malignancy or common MPM. Our patient received chemoradiotherapy after the initial operation, lived longer than the median term, and showed a generally good condition until just before death. Although novel therapeutic modalities have been recently tested in clinical trials, such as biologic and molecular targeted drug therapies, those treatments are not widely employed. Furthermore, our patient required immediate therapy for the fast growing tumor and

**Table 1** Summary of the reported cases of granulocyte colony-stimulating factor (G-CSF) producing malignant pleural mesothelioma

| No | Age/Gender | Exposure to asbestos | Symptoms | Max. leukocytes (cells/μL) | Max. neutrophils (cells/μL) | Max. CRP (mg/dL) | Max. Serum G-CSF level (pg/mL) | Histology | Treatment | Survival (weeks) | Reference/Year |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 45/M | Yes | Pleural effusion<br>Pleural thickening | 51000 | 93.0 | 19.6 | 50 | Por epithelial | Chemotherapy | 4 | Rikimaru *et al*. 1995[7] |
| 2 | 48/M | Yes | Pleural effusion<br>Pleural thickening | 33100 | 85.0 | Unknown | 138 | Desmoplastic | Chemotherapy | 6/42† | Kasuga *et al*. 2001[8] |
| 3 | 49/M | Yes | Pleural effusion<br>Pleural thickening | 50000 | 89.0 | 16.4 | 130 | Biphasic | Surgery | 11 | Usami *et al*. 2007[9] |
| 4 | 59/M | Yes | Pleural effusion<br>Pleural thickening | 147000 | 96.2 | Unknown | 77 | Sarcomatous | Surgery | 4 | Nishimura *et al*. 2006[10] |
| 5 | 61/M | No | Pleural effusion<br>Pleural thickening | 85100 | 95.0 | 16.6 | 67 | Mixed | BSC | 29 | Ohbayashi *et al*. 1999[11] |
| 6 | 65/M | No | Pleural effusion<br>Pleural thickening<br>Small nodules | 53600 | 93.0 | 27.1 | 36 | Spindle-cell fibrous | Chemotherapy | 28/89† | Yoshimoto *et al*. 2005[12] |
| 7 | 76/M | Yes | Chest wall tumor | 64600 | 97.8 | 20.57 | 71.8 | Sarcomatous | Surgery<br>Chemotherapy<br>Radiation | 28 | Present case 2014 |

†The anterior is the number of weeks after white blood cell elevation, and the posterior is the number of weeks from the patients first visit. BSC, best supporting care; CRP, C-reactive protein; G-CSF, granulocyte colony-stimulating factor; Por, poorly-differentiated.

relief of severe associated symptoms. We also considered that radiotherapy and chemotherapy were not indicated, as the tumor was quite large and biopsy results did not lead to a diagnosis.

Some malignant tumors including MPM secrete IL-6, a multifunctional cytokine[13] that may play a crucial role in resistance to chemotherapy or hormonal therapy,[14] as it might be involved in angiogenesis via expression of vascular endothelial growth factor (VEGF), promote establishment of metastatic tumors,[15] and cause cachexia.[16]

In the present case, both G-CSF and IL-6 were elevated, and the trend of fluctuation was in line with disease progression. Interestingly, there may be a relationship between G-CSF and IL-6, as Shannon *et al*. reported that IL-6 might be a promoter of G-CSF.[17] Meanwhile, G-CSF may induce IL-6 production because it stimulates the production of cytokines. Therefore, tumor growth might be accelerated by the interaction of these cytokines, in addition to their individual actions. Inhibition of the functions of these cytokines may contribute to effective treatment for G-CSF-producing MPM. Furthermore, Tachibana *et al*. reported that the anti-G-CSF antibody inhibited cultured cells from a transitional cell carcinoma of the bladder that had been stimulated by G-CSF.[18] Recently, two new drugs were developed to inhibit IL-6 activity,[19,20] which may improve treatment options for G-CSF- or IL-6-producing malignancies, though further studies are needed.

## Conclusion

We encountered a rare case of a G-CSF-producing MPM that was treated by a tumorectomy. The patient had early recurrence and died seven months after surgery, demonstrating the degree of malignancy of such a neoplasm. Interestingly, the general condition of our patient was stable for a relatively long period after the operation. Although novel therapeutic modalities are currently being tested and encouraging results are expected, less-invasive surgery may be considered to both prolong survival and maintain patient quality of life, depending on prognosis.

## Disclosure

No authors report any conflict of interest.

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