Case Report

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Response of a Patient with Pleural and Peritoneal Mesothelioma after Second-Line Chemotherapy with Lipoplatin and Gemcitabine

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Key Words
Lipoplatin · Gemcitabine · Mesothelioma · Second-line chemotherapy · Thoracoscopy · Cisplatin · Vinorelbine

Abstract
We report the case of a 56-year-old patient with malignant pleural mesothelioma of epithelial type, who responded to second-line chemotherapy with lipoplatin plus gemcitabine. Diagnosis and staging of the disease was done by medical thoracoscopy with biopsies of the right pleura in December 2003, when he was treated with talc pleurodesis. Eighteen months later, he presented with pleural effusion of the left side and underwent first-line chemotherapy with cisplatin plus vinorelbine. After 8 cycles, the patient presented renal toxicity limiting further cisplatinum chemotherapy and disease progression with peritoneal invasion of the tumor and ascites. Treatment with lipoplatin-gemcitabine was decided ~~on~~ in November 2006, and the patient showed important improvement in the clinical status and peritoneal effusion. He survived for 36 weeks, with symptom-free survival of 34 weeks.

Introduction

Malignant pleural mesothelioma (MPM) is a neoplasm with increasing incidence and poor prognosis. In the United States, MPM occurs in about 2,500 individuals every year, while 72,000 cases are expected to occur in the next 20 years. In Western Europe, 5,000 patients die of the disease each year [1]. In the last decade, patients with MPM underwent pleurodesis to palliate clinical symptoms and improve quality of life, since it was generally believed that no therapy was able to prolong survival. However, recent promising data seem to arise in the treatment of MPM. Studies suggest that chemotherapy may prolong survival [2] and improve quality of life [3].

We present the case of a 56-year-old man with MPM, who responded to a second-line regimen of lipoplatin-gemcitabine, after showing peritoneal progress of the tumor and renal-limiting toxicity after initial treatment with cisplatin-vinorelbine.

Case Report

A 56-year-old male, non-smoker, presented in December 2003 with important right pleural effusion. The patient's history had started approximately 1 year before admission with progressively worsening symptoms such as cough, dyspnea, pleuritic chest pain

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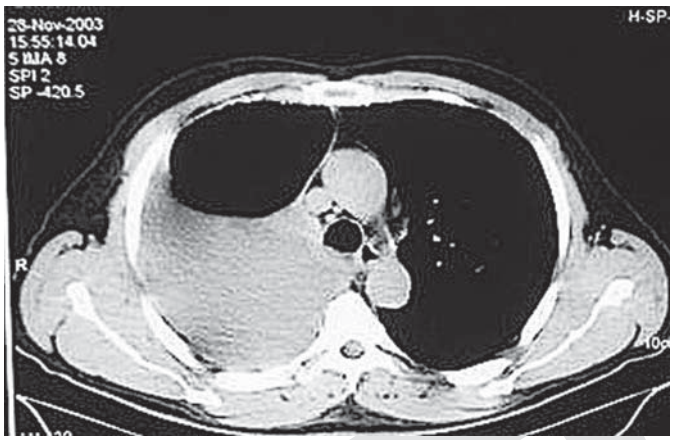

Fig. 1. Patient's chest computed tomography upon diagnosis in November 2003.

and weight loss. He used to work in the metal industry and on construction sites for 15 years in Germany.

On admission, radiological evaluation revealed an important pleural effusion on the chest X-ray, with pleural thickening of the upper right hemithorax on chest computed tomography (fig. 1), whereas analysis of the pleural fluid showed an exudative, lymphocytic effusion. The patient underwent medical thoracoscopy, during which, and after the evacuation of 3.2 liters of pleural fluid, pleural thickening was noted with diffuse nodules forming islets on thoracic, diaphragmatic and visceral pleura. Large biopsies were taken. Light microscopy and immunohistochemistry revealed the presence of epithelioid-type pleural mesothelioma (fig. 2). The patient underwent talc pleurodesis during a second procedure and after denial of any further therapy with the exception of external radiation therapy, including thoracoscopy and pleural punctures. He was discharged without complications and complete right lung re-expansion with no relapse of the pleural effusion and no other metastatic site after complete evaluation.

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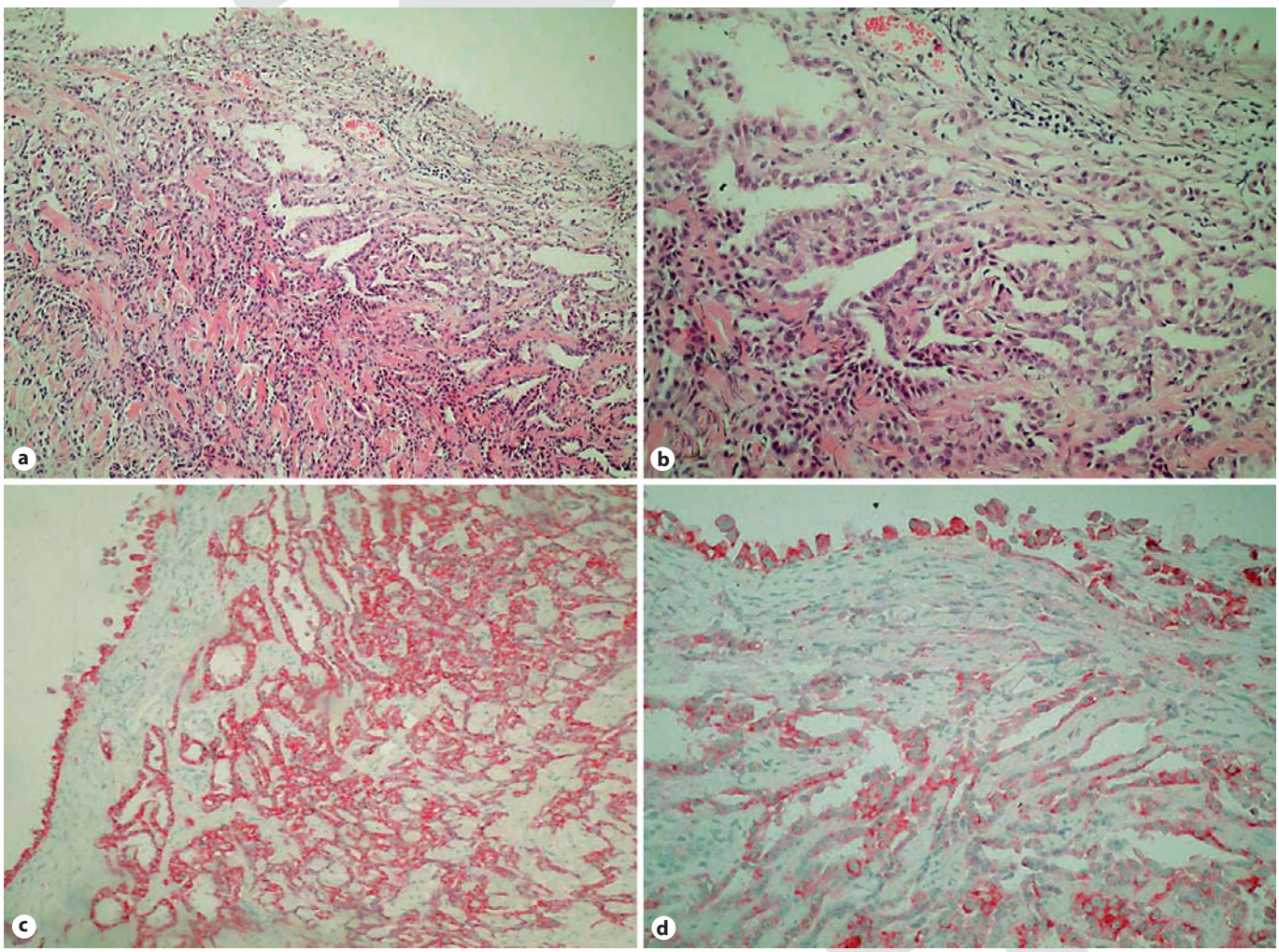

Fig. 2. Tissue section from thoracoscopic material reveals epithelioid neoplasm with immunohistochemical features consistent with epithelioid mesothelioma. **a** H&E. ×100. **b** H&E. ×200. **c** Pan-cytokeratin stain. ×200. **d** Calretinin stain. ×200.

The patient was regularly followed with clinical examinations, chest X-ray and chest computed tomography. He was free of symptoms, with no relapse of the right pleural effusion until June 2005, when he complained of cough and dyspnea. The new assessment showed a left-sided pleural effusion associated with tumor progression. After discussion with the patient, he accepted to initiate a first-line chemotherapy with cisplatinum 80 mg/m^2 on day 1 and vinorelbine 30 mg/m^2 on days 1 and 8, every 3 weeks. His condition improved after 3 courses, and he continued chemotherapy after evaluation showing an improvement in radiological findings.

However, an increase in the creatinine levels after chemotherapy significantly limited the accurate therapy by spacing treatment, and finally, after 8 regimens, in November 2006, the patient presented an important deterioration in the performance status. He also had ascites necessitating a peritoneal fluid removal of 18.2 liters within 2 weeks. The abdominal computed tomography showed invasion of the diaphragm and the peritoneum associated with massive ascites (fig. 3) and left-sided pleural effusion.

We decided to undertake a second-line chemotherapy combining lipoplatin and gemcitabine. The chemotherapy schedule included 120 mg/m^2 of lipoplatin and 1,000 mg/m^2 of gemcitabine, both on days 1 and 8 every 3 weeks [4]. The patient's condition significantly improved, and so did the computed tomography findings (fig. 4), with normalization of the serum creatinine levels. The patient continued symptom-free for 34 weeks, when his condition rapidly deteriorated and he died 2 weeks later.

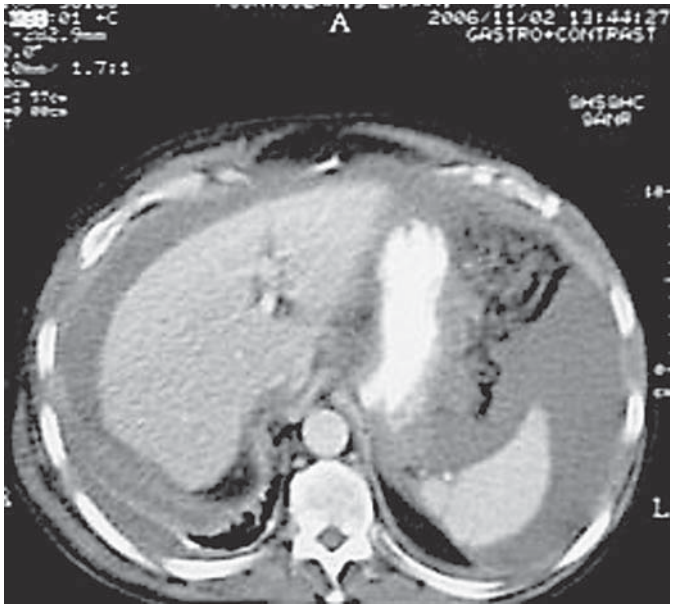

Fig. 3. Patient's abdominal computed tomography in November 2006, showing massive ascites.

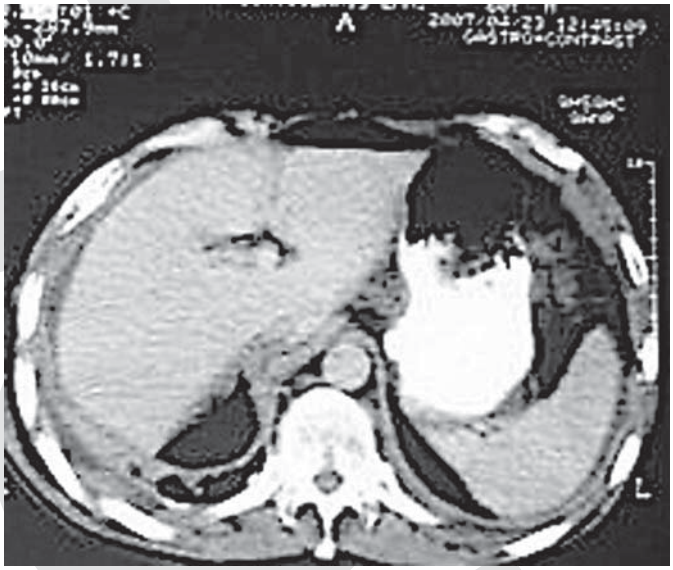

Fig. 4. Patient's abdominal computed tomography in April 2007, showing important improvement in the ascites.

Discussion

This case is the first report, to our knowledge, on the use of a combination of lipoplatin and gemcitabine as second-line treatment in a patient with MPM. The result is promising, since the regiment significantly improved the patient's symptoms and offered a symptom-free survival time of 34 weeks and an overall survival of 36 weeks, without any significant toxicity.

Lipoplatin (Lipoplatin™, Regulon Inc., Mountain View, Calif., USA) is a liposomal formulation of cisplatin developed in order to reduce the systemic toxicity of cisplatin, while simultaneously improving the efficacy of the drug on tumor cells [5]. Studies on lipoplatin showed a low toxicity profile, an ability to concentrate in tumors and to escape immune cells and macrophages, a slow clearance rate from the kidneys, long circulation properties in body fluids, a half-life of 36 h in the blood, and promising therapeutic efficacy [6].

Our patient was initially treated with a platinum-based therapy, which was stopped after development of severe nephrotoxicity leading to spacing treatment cycles and finally to tumor progression. Nephrotoxicity following cisplatin treatment is common and may manifest after a single dose with acute renal failure, or may present with a chronic syndrome of renal electrolyte wasting [7]. Despite this previously developed toxicity with platinum therapy, treatment with lipoplatin plus gemcitabine at the relapse of the disease was very well tolerated, as normal levels of creatinine were obtained during the second-line

treatment. Indeed, lower levels of total platinum have been observed in kidneys after liposoluble platinum infusion, compared with those after cisplatin administration [8]. It seems that the lipid capsule offers protection in kidney cells by rendering the drug active inside the tumor cell, where its cytotoxic effect is needed [8].

MPM was considered an aggressive tumor with unsatisfactory therapeutic success. The median survival from presentation is 9–12 months [9]. Many cytotoxic agents have been used either as monotherapy or in combination regimens, with poor rates of tumor regression (10–30%) and no significant prolongation of median survival [10]. Actually, pemetrexed plus cisplatin is considered to be the standard of care as first-line chemotherapy, since in a phase III trial, it showed significantly better response rates (41.3 vs. 16.7%), median time to progression (5.7 vs. 3.9 months) and median survival (12.1 vs. 9.7 months) compared with cisplatin alone [2]. However, prospective phase III trials comparing this regimen with best supportive care (talc pleurodesis) with accurate disease staging are lacking; thus, firm conclusions about the possible benefit of chemotherapy on survival cannot be drawn [11].

To date, there is no standardized therapy being used as second-line treatment. Manegold et al. [12] presented the results of a retrospective analysis of patients who did or did not receive post-study treatment (PST) with a variety of drugs, such as cisplatin, gemcitabin, doxurubicin, following their participation in the phase III trial, which compared ~~premetexed~~ pemetrexed plus cisplatin with cisplatin alone. According to this analysis, the PST subgroup had a longer survival than the subgroup without PST, but Manegold et al. [12] note that it is not certain whether this difference can be attributed to the PST. Furthermore, several phase II studies have been conducted for the role of second-line chemotherapy in which partial responses were achieved in 5–10% of the patients with various agents [12]. Pemetrexed also seems to be promising as second-line treatment [13]. It seems that randomized trials could be conducted to estimate the role of second-line treatment in MPM. Accordingly, we have conducted a phase I study of lipoplatin-gemcitabine in patients with non-small cell lung carcinoma refractory/resistant to platinum combination first-line chemotherapy [4]. Our results confirm the low toxicity of the combination associated with an acceptable overall response rate (23%) [4].

The case of our patient provides a promising future for the combination of lipoplatin-gemcitabine as a second-line treatment even in patients who had previously received platinum-based therapy. This combination is worthwhile testing in a further study as second-line treatment in patients with MPM.

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