



# A Rare Case of Peritoneal Mesothelioma with Complete Pathological Response after Treatment with Pemetrexed/ Cisplatin and Cytoreductive Surgery with HIPEC

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## Abstract

Malignant peritoneal mesothelioma is a rare malignancy with a generally poor prognosis. For patients with resectable disease, cytoreductive surgery with hyperthermic intraperitoneal chemotherapy offers the best chance of overall survival. However, in patients with initially unresectable disease, chemotherapy with pemetrexed and cisplatin remains the only treatment option. In some cases, up-front chemotherapy will enhance a patient's resectability, making the patient a surgical candidate. Complete pathological response is an extremely rare outcome with only a handful of cases reported in recent literature. We report a case of a 44-year-old male patient with initially unresectable malignant peritoneal mesothelioma who received pemetrexed and cisplatin with good response and then underwent cytoreductive surgery with hyperthermic intraperitoneal chemotherapy, demonstrating complete pathologic response on final pathology. This is a rare case that may provide helpful insight into the successful treatment of initially unresectable malignant peritoneal mesothelioma.

**Keywords:** Malignant peritoneal mesothelioma; Cytoreductive surgery; Hyperthermic intraperitoneal chemotherapy; Complete pathologic response

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## Abbreviations

CRS: Cytoreductive Surgery; HIPEC: Hyperthermic Intraperitoneal Chemotherapy; MPM: Malignant Peritoneal Mesothelioma

## Background

Malignant Peritoneal Mesothelioma (MPM) is a rare malignancy in the United States (500 to 800 incident cases per year) and worldwide (1 to 2 incident cases per million per year) [1,2]. Overall, only 25% to 33% of all diagnosed mesothelioma cases are of peritoneal origin [2]. Despite the fact that treatment algorithms have historically followed those for the more common pleural mesothelioma, the pathogenesis and pathophysiology are more distinct than previously realized, and in the last decade an abundance of research has been focused on optimal treatment strategies for MPM [1,3].

If deemed resectable, current consensus guidelines indicate that Cytoreductive Surgery (CRS) with Hyperthermic Intraperitoneal Chemotherapy (HIPEC) offered at a specialized center is the standard of care with the best expected prognosis. If initially resectable, neoadjuvant chemotherapy is typically not offered [1]. In fact, recent data indicates that MPM demonstrates one of the highest resectability rates of all the diseases that present with peritoneal carcinomatosis with 87% of patients being resectable at initial, index operation [4]. However, median survival for unresectable disease unfortunately only ranges from 6 months to 9 months [5].

For patients who are not candidates for upfront surgery, chemotherapy, namely pemetrexed and cisplatin, remains the only treatment option for patients fit enough to tolerate it. Approved for treatment of MPM since 2004, this regimen has been the standard of care since it demonstrated longer survival compared to cisplatin alone in a large, phase III trial including patients with malignant pleural mesothelioma [3,6]. In the years that closely followed, these positive findings were echoed in specifically MPM populations, but outcomes still remained generally poor with overall response rates of 20% to 25% and one year survival of 57% [3,7]. Outcomes have only somewhat improved over the years; more recent data including larger study populations demonstrate overall

response rates of 33% to 46% and median overall survival times of 13.1 months to 15.8 months [8-10]. Thus, the outcomes of patients with unresectable MPM unfortunately still remain poor.

In some patients, treatment with chemotherapy ultimately enhances resectability and enables surgical candidacy for CRS and HIPEC. If this occurs, Complete Pathological Response (CPR) has been very rarely observed in a limited number of case studies and small-scale retrospective reviews. While these rates range from 0% to 33% in the published literature, they average only about 12% [3,7,9-12]. Below, we report one such case a patient with initially unresectable MPM who received pemetrexed and cisplatin, became an operative candidate, underwent CRS with HIPEC, and demonstrated CPR on final pathology.

## Case Presentation

The patient was a 44-year-old male with a childhood history of leukemia requiring bone marrow transplant as well as chronic dysphagia who initially presented with three months of fatigue, anorexia, early satiety, weight loss, and increasing abdominal girth. When a CT scan demonstrated ascites and evidence of peritoneal nodules, he was referred for paracentesis which demonstrated atypical mesothelial cells. He subsequently underwent omental biopsy which demonstrated epithelioid MPM. He was referred to a surgical oncologist to determine resectability. At the time of his initial presentation he was deemed unresectable due to both significant volume of disease especially affecting his omentum and pelvis as well as very poor nutritional status (albumin 2.4 g/dL). He was referred to medical oncology for consideration of chemotherapy. He completed three cycles of pemetrexed and cisplatin over a three month period while also receiving total parenteral nutrition to improve his nutritional status. At the time of re-evaluation, CT scan demonstrated a significant improvement in both ascites and volume of disease, his nutritional state had improved (albumin 3.3 g/dL), and his symptoms had improved rather dramatically. He was re-evaluated by the surgical oncologist at that time and was offered surgery. He was taken to the operating room for a diagnostic laparoscopy which demonstrated multiple peritoneal adhesions between the small intestine, large intestine, and colon as well as peritoneal and omental nodules. About a week later, he returned to the operating room and underwent exploratory laparotomy, CRS including a total omentectomy, appendectomy, cholecystectomy, and peritonectomy, HIPEC with 30 mg mitomycin C for 90 minutes, and feeding jejunostomy tube placement (placed due to ongoing workup for chronic dysphagia thought to be unrelated to his MPM). He recovered well without complications and was discharged on post-operative day 11. His final pathology demonstrated CPR. At one month follow up, he was doing well save for his chronic dysphagia. CT scan did not demonstrate any evidence of disease progression. It was agreed that he would return in 3 months for another CT scan. Unfortunately, 2 months later, he was admitted to the ICU at an outside hospital with sepsis of unknown origin and passed away when comfort care measures were chosen by his family.

## Discussion and Conclusion

MPM is a rare disease, and all aspects of its management present challenges to the multidisciplinary treatment team. Even though our patient had a CPR after chemotherapy and surgery, he unfortunately passed away without a chance for long-term follow-up. His case does, however, highlight the important aspects of management including

timely diagnosis and determination of resectability, definitive surgical treatment with CRS and HIPEC, and the use of chemotherapy.

Diagnosis of MPM is often delayed owing to its insidious presentation. Many times, peritoneal disease is discovered incidentally during abdominal operations, or patients present, as ours did, with vague and non-specific signs and symptoms that can include increasing abdominal girth, ascites, anorexia, early satiety, and failure to thrive [1]. Regardless of how the diagnosis is made, prompt surgical consultation to determine resectability and candidacy for CRS and HIPEC are vital to give the patient the greatest chance of survival [1,13].

In patients with unresectable disease, overall prognosis is worse, but numerous studies indicate that chemotherapy with pemetrexed and cisplatin is well-tolerated and may improve overall survival in a meaningful way [3,7,8-10,12,13]. Additionally, recent data indicates that in patients with initially unresectable disease, systemic chemotherapy may help them to become resectable candidates for CRS and HIPEC. In 2017, Le Roy et al. [14] demonstrated a statistically significant decrease in Peritoneal Carcinomatosis Index (PCI) and a 50% chance of undergoing complete CRS and HIPEC in 20 initially unresectable patients through the use of up-front, bidirectional (systemic as well as intraperitoneal) chemotherapy. The study further confirmed the beneficial role of surgery as 83% of the surgical patients achieved 2 year overall survival compared to only 44% in the patients who remained unresectable [14]. Although our patient received systemic rather than bidirectional up-front treatment, chemotherapy is what ultimately helped him to become a surgical candidate. More research into MPM biology may help determine which patients might benefit from up-front chemotherapy. Still more research is required to determine if any of these factors might predict CPR.

Another question to be answered involves the optimal timing of chemotherapy in relation to CRS and HIPEC for initially resectable patients who undergo up-front surgery. Varying results have been described in the recent literature. In 2013, Deraco et al. [15] found no statistically significant difference in short and long-term overall survival between resectable MPM patients who received neoadjuvant versus adjuvant systemic chemotherapy. Additionally, neither the completeness of cytoreduction nor the post-operative complication rate was influenced by neoadjuvant chemotherapy [15]. In contrast, in 2016, Kepenekian et al. [13] demonstrated a 40% 5-year survival in initially resectable MPM patients who underwent neoadjuvant therapy compared to a 67% 5-year survival in those who underwent adjuvant therapy. The rate of post-operative complications was not significantly different between the groups; the decrease in survival in the neoadjuvant group was attributed to possibility of disease progression during the "waiting period" prior to surgery. This data would suggest that upfront CRS and HIPEC, when feasible, followed by adjuvant chemotherapy offer the best overall outcome for patients with MPM [13]. Clearly, more data is necessary to answer this difficult clinical question.

Although chemotherapy is the only treatment option for a patient with unresectable MPM, we report a case of a patient who initially presented with unresectable MPM but ultimately achieved a CPR after treatment with pemetrexed/cisplatin and CRS/HIPEC. CPR is a very rare entity with only a handful of cases published in the recent literature. This case highlights the important principles of management of this difficult disease and helps raise important questions regarding the use of chemotherapy in both initially

resectable and unresectable MPM.

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