

## Significant Clinical Benefit of Pemetrexed-based Chemotherapy for Advanced Diffuse Malignant Peritoneal Mesothelioma: A Case Presentation

### Abstract

Diffuse malignant peritoneal mesothelioma (DMPM) is generally an understudied disease, largely because most molecular and clinical studies of mesothelioma have been conducted in patients with the more common malignant pleural mesothelioma. We present the case of a 45-year-old male that initially presented with abdominal discomfort and ascites. Diagnostic workup revealed advanced DMPM. Bimodal treatment was started with cytoreductive surgery and hyperthermic intraperitoneal perfusion with chemotherapy procedure, followed by pemetrexed systemic monotherapy. After the disease progression, and because of a very good previous treatment response to pemetrexed, we decided to rechallenge systemic pemetrexed, along with the introduction of cisplatin. Although the intent behind systemic treatment was at first solely palliative, overall survival after the initial diagnosis was 50 months. Treatment based on rechallenging pemetrexed with or without cisplatin in patients with advanced DMPM can result in a quite satisfactory disease control and symptom management.

**Keywords:** Diffuse malignant peritoneal mesothelioma, pemetrexed rechallenging, treatment options

### Introduction

Mesothelioma is usually considered to be an aggressive and lethal neoplasm arising from the mesothelial cells lining of pleura, peritoneum, pericardium, and tunica vaginalis testis.<sup>[1]</sup> Most frequent localization of mesothelioma is in the pleura, which accounts for about 70% of all mesotheliomas.<sup>[2]</sup> Therefore, the majority of literature focuses on the pleural variety of mesothelioma while diffuse malignant peritoneal mesothelioma (DMPM) has been evaluated to a far lesser extent, mainly because it accounts for only 10%–15% of all malignant mesotheliomas.<sup>[3]</sup> To put those percentages into perspective, it should be mentioned that incidence rates for DMPM in industrialized countries vary between 0.2 and 3 cases per million.<sup>[4]</sup> Due to the rarity of this entity, most of the available clinical information about DMPM treatment is derived from retrospective single-center series, which have inherent selection bases.<sup>[5]</sup> So far, DMPM has been poorly described with case reports being very few and far between.<sup>[6–18]</sup> That leads us to the fact that currently, there is no broad

consensus as to what the optimal treatment for advanced stage DMPM is or should be, especially not in the form of official treatment guidelines.

### Case Report

In September of 2009, a 45-year-old male patient was hospitalized complaining of periodical constipation and lower abdominal pain and presenting with a clinical syndrome of debilitating ascites. Patient was otherwise healthy, without serious illnesses in medical history, and was not taking any medications. Initial workup consisted of physical examination, routine clinical laboratory tests, echocardiography, chest X-ray, and abdominal ultrasound. Laboratory tests revealed only elevated C-reactive protein levels (101, range 0–5 mg/L). Abdominal ultrasound revealed ascites, with flank bulging and shifting dullness. Diagnostic paracentesis was conclusive for metastatic carcinoma with nonspecific cytological features. Tumor markers: Elevated CA-125-174 kIU/L (range 0–35 kIU/L), while carcinoembryonic antigen, CA 19-9, beta human chorionic gonadotropin,

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### Access this article online

Website: [www.ijmpo.org](http://www.ijmpo.org)

DOI: 10.4103/0971-5851.203495

### Quick Response Code:



**How to cite this article:** Peitl M, Seiwert S, Bašić-Koretić M, Šantek F. Significant clinical benefit of pemetrexed-based chemotherapy for advanced diffuse malignant peritoneal mesothelioma: A case presentation. *Indian J Med Paediatr Oncol* 2017;38:73-7.

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and alpha-fetoprotein were within normal range. Chest multislice computed tomography (MSCT) showed no evidence of intrathoracic involvement, whereas abdominal MSCT revealed a focal, localized lesion in the lower part of left kidney, peritoneal carcinomatosis, and omental cake form in the anterior abdominal wall, with a predominance of ascites. Other diagnostic procedures were also performed (abdominal X-ray, upper gastrointestinal tract endoscopy, and colonoscopy), but findings remained inconclusive. Explorative laparotomy was performed with probatory excision which discovered pelvic tumor mass infiltrating adjacent structures. Histopathology and immunochemistry staining was as follows: Calretinin and CK 5/6 were positive, whereas CD15 and BerEP4 were negative. Findings such as these are consistent with the diagnosis of a diffuse malignant peritoneal monomorphic epithelioid mesothelioma [Figures 1-5].

The patient denied any previous exposure to asbestos. Incomplete cytoreductive surgery (CRS) following hyperthermic intraperitoneal perfusion with chemotherapy (HIPEC) was performed. At our institution, we use mitomycin C which was dosed at 40 mg/m<sup>2</sup>, warmed at 40°C, and then circulated true the peritoneal cavity for 90 min by perfusor.

After a relatively slow 5-month postoperative recovery period (18), fludeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) restaging was performed. New locus with increased metabolic activity was found in anterior mediastinum, measuring 1.4 cm × 3.2 cm × 2.3 cm, highly suspicious for malignancy. Furthermore, we discovered a newly formed solitary metastasis on the splenic basal surface, along with multiple intrasplenic lesions. Cytological analysis of anterior mediastinal lesion was strongly suggestive for metastatic peritoneal malignant mesothelioma, which in turn confirmed intrathoracic involvement. Such involvement within only 5 months from initial diagnosis is very rare and highly indicative of a very aggressive type of the tumor. Initial systemic treatment approach consisted of six cycles of mono pemetrexed (500 mg/m<sup>2</sup>) with supplementation of folic acid and vitamin B<sub>12</sub> due to the state of the patient. Chemotherapy was administered in 3-week intervals, on an outpatient basis, and was generally very well tolerated. Posttreatment PET-CT evaluation showed complete mediastinal response with partial abdominal response of the nodal lesion at splenic basal surface. Routine follow-up during the next 12 months was performed in 3-month intervals. During

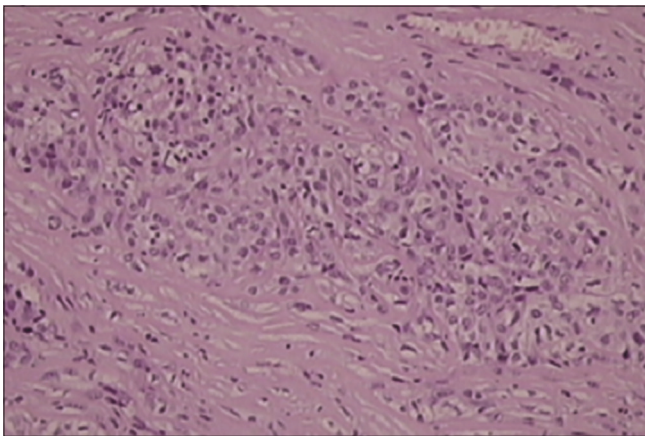


Figure 1: Histopathology showing monomorphic epithelioid peritoneal mesothelioma, (H and E, ×100)

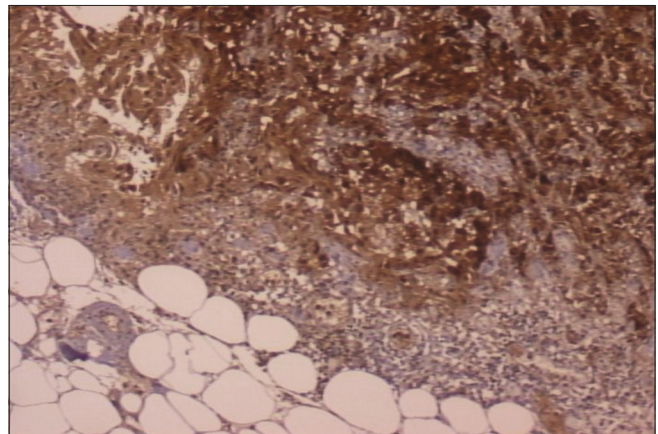


Figure 2: Calretinin-positive staining

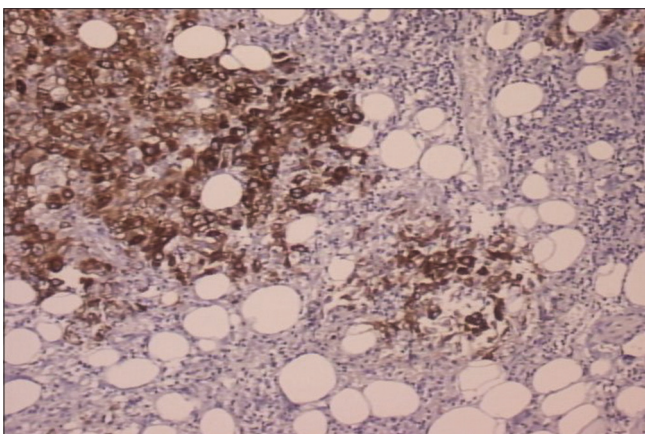


Figure 3: CK5/6 positive staining

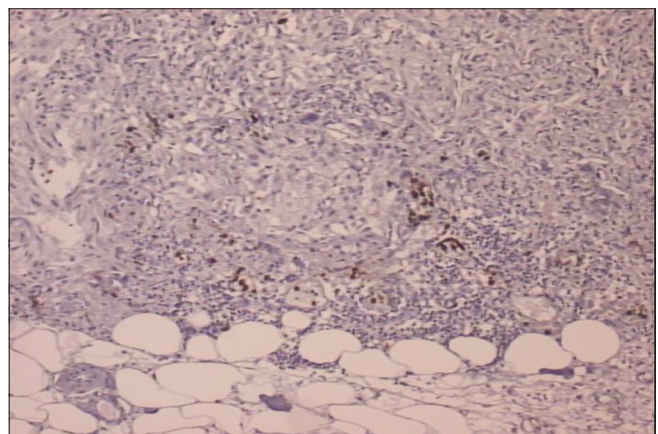


Figure 4: CD15 negative staining



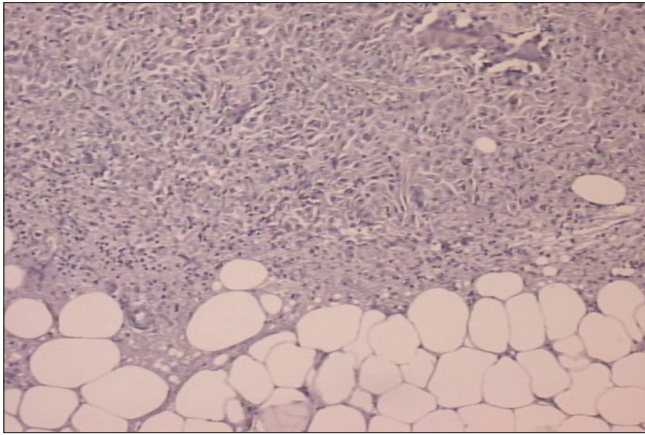


Figure 5: BerEP4 negative staining

that period, two postchemotherapy PET-CT scans were performed as the only means of evaluating DMPM progression. First follow-up scan, performed 6 months after first-line chemotherapy, showed stable intrathoracic and intra-abdominal disease [Figure 6a-d]. The patient presented with a good Karnofsky performance status (KPS >90). Second follow-up scan, 12 months after first-line chemotherapy, showed disease progression. New locus of high (18) FDG uptake was detected in the right internal mammary lymph node with bilateral pleural nodal lesions. New intrahepatic and intrasplenic metastases, along with numerous intra-abdominal and intrapelvic nodal-like lesions were found, while the preexisting solitary metastases showed morphological progression. As the patient was physically stable and of a satisfying KPS score (>80), due to the disease progression, we decided for a systemic therapy consisting of rechallenging pemetrexed (500 mg/m<sup>2</sup> with cisplatin (75 mg/m<sup>2</sup>) as a second-line chemotherapy means. Previously, described chemotherapy schedule was also administered in 3-week intervals on an outpatient basis. Main adverse events, according to common toxicity criteria, were hematologic toxic effects: Grade 2–3 neutropenia and Grade 2–3 anemia. Both were successfully treated with supportive treatment protocols. Given the fact that patient's clinical status was satisfactory and KPS only slightly decreased (KPS >70), chemotherapy was continued up to eight cycles. Control MSCT scans showed already known pleural nodal lesions, without significant change in their size and number compared to previous scans, which suggested stable intrathoracic disease. On the other hand, partial regression of intra-abdominal and intrapelvic secondary nodal lesions was evident. There was no evidence of lymphadenopathy or free fluid in the abdomen. Further follow-up was ambulatory as disease was deemed stable and in partial regression.

Last performed follow-up MSCT scan was 6 months after the completion of second-line chemotherapy (October 2013). Unfortunately, intra-abdominal secondary

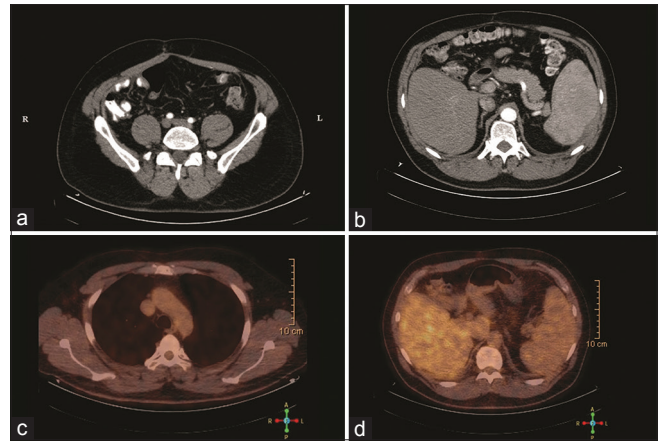


Figure 6: Radiological evaluation of diffuse malignant peritoneal mesothelioma with 18 (fludeoxyglucose) positron emission tomography-computed tomography scan performed 6 months after first-line chemotherapy. (a) Axial pelvic follow-up computed tomography demonstrates only fibrotic changes scattered throughout small bowel. (b) Axial abdominal follow-up computed tomography scan (intestine opacified with amidotrizoate) showing enlarged spleen, with smooth parietal peritoneal thickening. (c) Positron emission tomography-fused axial chest computed tomography scan without signs of increased (18) fludeoxyglucose uptake in thoracic cavity. (d) Positron emission tomography-fused axial abdominal computed tomography scan without detectable (18) fludeoxyglucose peritoneal uptakes

lesions further progressed. At that time, there were no available reports regarding treatment modalities for advanced DMPM, especially in the case following two lines of chemotherapy. Systemic treatment options were exhausted (due to the fact that the patient declined further gemcitabine and carboplatin treatment options that were still available), surgical treatment was not a feasible option, and radiotherapy produces questionable results due to the diffuse nature of the disease itself, while in this specific case, it was not applicable due to the location and size of DMPMs intra-abdominal deposits. Further medical approach was therefore based on best supportive care.

## Discussion

Clinical and radiological presentation of early stage mesotheliomas is nonspecific. That is why most DMPMs are diagnosed in their advanced stages, with a considerable amount of time passing before reaching the correct diagnosis.<sup>[19]</sup> Pathogenesis of DMPM is still unclear, and relationship between asbestos exposure and DMPM is not nearly as straightforward as is the case with malignant pleural mesothelioma.

In a not so distant past, patients such as presented here would be considered preterminal and therefore treated only palliatively and supportively, with quite a short life expectancy. Nowadays, treatment of choice for complete cytoreduction is CRS/HIPEC. On the other hand, guidelines for systemic therapy are not that straightforward. Available scientific data support pemetrexed in combination with

cisplatin as a first-line treatment option, while gemcitabine, carboplatin, and cisplatin are often considered as possible second-line treatments.<sup>[3,11,20]</sup> Due to the fragile postoperative state of the patient and because DMPM was deemed advanced at the time, single-agent pemetrexed as a palliative chemotherapy was an appropriate initial approach, even though current treatment recommendations suggest pemetrexed combined with cisplatin. Six cycles of first-line pemetrexed chemotherapy were followed by a 1-year chemotherapy-free period, as the optimal duration of chemotherapy for DMPM patients is still not established. Therefore, in this specific case of a patient with minimal burden of disease, we decided to observe for eventual disease progression. At that point, main goals were to minimize treatment toxicity and optimize patient's quality of life. After the disease progression was established, second-line chemotherapy was selected as a treatment of choice due to the satisfactory medical condition of the patient. As we already stated, data regarding the treatment of DMPM are scarce. However, Gilani *et al.* published a case report following their experience in the second-line treatment of advanced DMPM where they suggested that rechallenging pemetrexed with cisplatin may be a reasonable treatment option for patients who responded to the same drugs in the first line of chemotherapy.<sup>[21]</sup> In light of those facts, we sought a somewhat unconventional treatment approach, as we based second-line chemotherapy on rechallenging pemetrexed with the addition of cisplatin. Eight cycles of pemetrexed with cisplatin were applied, which lead to slower disease progression, prolonged overall survival, and better quality of life. Time to progression calculated from first- to second-line chemotherapy treatment was 12 months and overall survival after re-treatment was 7 months. Despite a highly unfavorable prognosis, patient lived for more than 50 months after the initial diagnosis. Nevertheless, it needs to be stressed out that complete recovery or even cure was never considered to be a reasonable expectation. According to the available medical reports, progression-free survival and median overall survival (OS) seem to be highly variable, with median overall survival ranging from 13.1 to 92 months.<sup>[11,22]</sup> Those periods seem to be influenced by the extent of disease at presentation, ability to surgically resect gross disease, gender, or intensity of treatment.<sup>[11,22]</sup> Physicians dealing with such a rare entity as DMPM have to bear in mind that the prognosis and overall survival of patients suffering from peritoneal mesothelioma has changed considerably during the last decade, even for the advanced stages, and that treatment of such patients should not only consist of symptomatic or palliative care.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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