Malignant peritoneal mesothelioma. Is there a new treatment?

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Abstract

The authors report a novel, alternative approach to treat malignant peritoneal mesothelioma (MPeM) targeting, vascular endothelial growth factor (VEGF) using anti-VEGF (bevacizumab) chemotherapy combination.

Case Report

In June 2008, a 60-year-old Jordanian man presented with abdominal distension and para umbilical hernia. His medical history was significant for hypertension, diabetes mellitus and hyperlipidemia and the patient was receiving regular treatment. The patient underwent hernia repair and the hernia sac sent for histopathologic examination. Histopathologic findings showed atypical mesothelial cells with prominent nucleoli and occasional mieotic figures as well as areas of focal necrosis, psammomatous calcification and tumor cells showed encroachment on the adipose tissue illustrated by microscopic appearance (resolution 200X) of the tumor showing papillary structures on one side and sheets of malignant tumor on the other side, as shown in Figure 1. Immunoperoxidase stain for mesothelioma markers was positive for calretinin, AE1, AE3, HBME-1, cytokeratin 5/6 (CK 5/6), FMA, and negative for Vimentin, CEA, CD15 and Ber-FP4 providing a conclusive diagnosis of MPeM.

Figure 2 shows microscopic appearance (resolution 200X) of positive immunostaining of neoplastic cells by HRP conjugated Cytokeratin 5/6 antibody. Cytological examination of ascitic fluid showed mesothelial cells with features of malignancy, CEA was 2.3 IU/L, AFP was 9.4 IU/L. Complete blood picture, renal and liver function tests were normal. CT scan of chest and abdomen showed gross ascites, multiple mediastinal and abdominal lymph nodes enlargement, diffused nodular mass in the omentum and peritoneal lining central and right side of the abdomen, as revealed in Figure 3 CT scan image taken in October 2008 showing peritoneum thickening and ascites.

The patient was treated with cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2 i.v every three weeks after draining about 10 liters of ascitic fluid. Although repeated CT scan showed some resolution of the enlarged lymph nodes, omental and peritoneal nodes, the patient required aspiration of nearly 6-8 liters of ascitic fluid with each cycle. With other chemotherapy regimens including gemcitabine + pemetrexed for 2 cycles and intraperitoneal cisplatin the patient continued to have re-accumulation of the ascitic fluid.

In January 2009 the patient started with combination of gemcitabine 1250 mg/m^2 plus bevacizumab 5 mg/kg every 2 weeks. The patient responded clinically with no requirement of aspiration from the very first cycle of treatment and received 6 cycles of treatment providing strong evidence of clinical response and improvement in quality of life. Side effects like epistaxis were observed which was mild and managed by local pressure.

MPeM is a cancer of extremely rare occurrence and arises from the mesothelial cells of the peritoneum. It accounts for only 10% of all mesotheliomas with majority arising from pleura and the role of asbestos exposure in the etiology compared to pleural mesothelioma is not well defined.[1,2] The clinical manifestations of this disease are usually abdominal pain, increasing abdominal girth, weight loss and abdominal masses with or without ascites. Though it can occur in any age group, the most affected is the 50 to 69 year age group.[2,3] The aggressive nature of the disease is evident with rapid spread within the confines of the abdominal cavity involving most accessible peritoneal and omental surfaces and requires aggressive treatment. Mortality and morbidity are associated with the spread of the disease rather than the metastasis and without aggressive treatment the neoplasm is rapidly fatal.[2,4,5]

Studies that have reported patients with peritoneal mesothelioma are few and treatment of MPeM have largely extrapolated from the treatment of pleural disease.[6] Currently, no standard treatment for this disease has been established and management involves an intensive loco-regional treatment strategy including cytoreductive surgery, intraoperative and/or perioperative intraperitoneal chemotherapy using doxorubicin, cisplatin, and interferon gamma with or without abdominal radiation and cytoreductive surgery along with hyperthermic intraperitoneal chemotherapy using mitomycin and cisplatin followed by whole body irradiation.[1,5] Several studies demonstrated an improved overall survival with these regimes as compared to historic controls, treated with systemic chemotherapy and palliative surgery in which the median survival was uniformly less than 1 year.[4] However, extensive intraperitoneal disease precludes the possibility of cytoreductive surgery always and these multimodality therapeutic strategies are associated with significant morbidity.[1]

A number of chemotherapeutic agents either single or in combination with other drugs have shown promise in the treatment of

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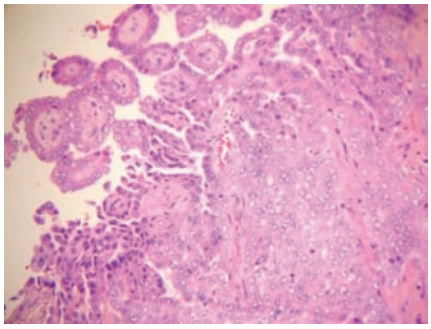

Figure 1. Micro-scopic appearance of the tumor showing papillary structures on one side and sheets of mali-gnant tumor on the other side.

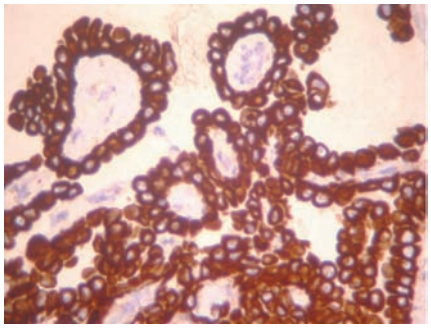

Figure 2. Positive immunostaining of neoplastic cells by HRP conjugated cytokeratin 5/6 antibody (resolution 200X).

MPeM. Nevertheless, the low incidence of the disease and clinical heterogeneity precludes Phase II efforts to define conclusively the benefit of systemic chemotherapy and other treatment options. The Expanded Access Program (EAP) conducted both in the US and internationally provided access to 109 patients with MPeM including chemo-naive or previously treated patients with MPeM not amenable to curative surgery. This study showed that median survival for pemetrexed (antifolates) was 10.3 months, and 1-year survival rates for pemetrexed with cisplatin and pemetrexed alone were 57.4% (95% CI: 10.3, 100) and 41.5% (95% CI 4.6, 78.4), respectively. The disease control rate was 71.2% in MPeM patients, establishing the value of this treatment regime in improving survival in patients with unresectable MPeM.[6-8]

For patients who cannot tolerate a platinum-based regimen a Phase II trial (20 patients) provided an alternative regimen with gemcitabine and pemetrexed documenting a disease control rate (DCR) of 50%, median TTPD (time to progressive disease) and OS of 10.4 months and 26.8 months, respectively.[1]

In addition, a Phase III trial where 456 patients was assigned randomly to cisplatin 75 mg/m^2 alone or with pemetrexed 500 mg/m^2 indicated that supplementation with folic acid and vitamin B12 resulted in improved survival time, TTPD, response rates and significantly reduced treatment related toxicity when compared to non-supplemented patients.[7]

VEGF plays key role in MPeM biology and in a Phase II trial anti VEGF antibody (bevacizumab 15 mg/kg) was added to gemcitabine 1250 mg/m^2 plus cisplatin 75 mg/m^2 regimen, improvement in overall survival with bevacizumab combination was not demonstrated in this study.[9]

This patient presented with abdominal distension, which is a presenting symptom in majority of cases. CT scan findings of mesothelioma are nonspecific but are useful for detection, characterization and staging. It is also useful for guiding biopsy of peritoneal masses. Definitive diagnosis is based on histological and immunohistochemical examination.

Cytologic sampling of ascitic fluid and Immunohistochemical expression of tumor markers (calretinin and cytokeratin 5/6) provides a diagnosis of MPeM in approximately 80% of the cases. Since pemetrexed in combination with cisplatin showed survival improvements, the patient started with this regime. Failure to show clinical response as evidenced by repeated aspirations of 6-8 liters, the treatment was changed to gemcitabine plus pemetrexed and cisplatin was not included in the regime as the patient failed to respond to intraperitoneal cisplatin. The constant non-response of the patient to this regime, led to

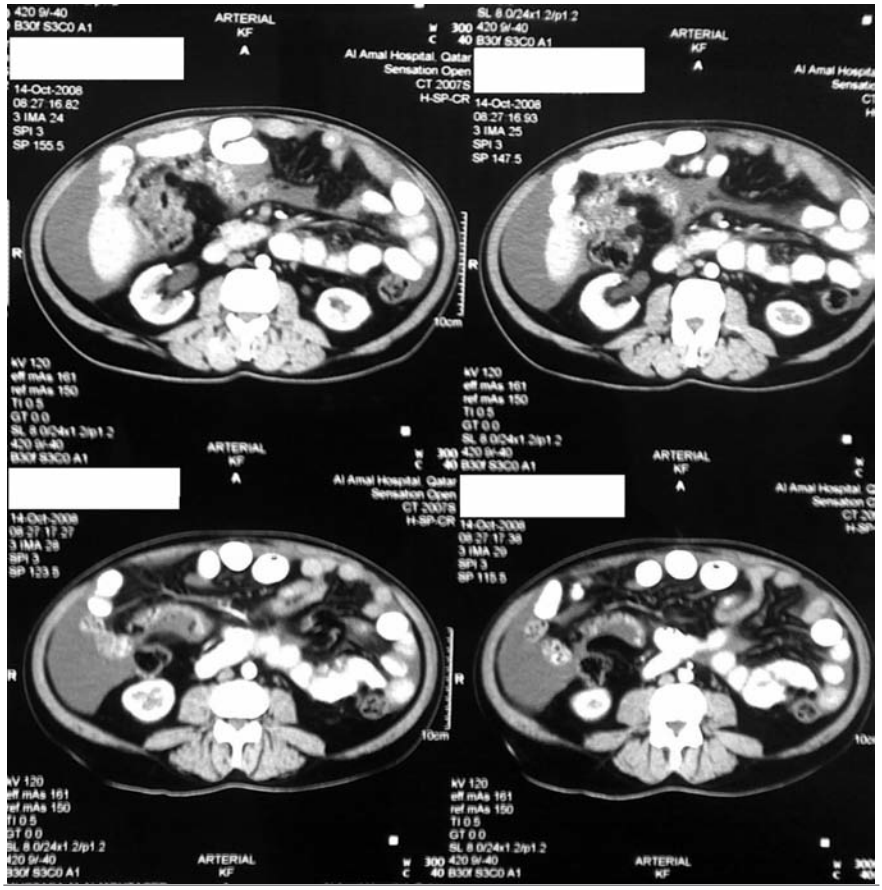

Figure 3. CT scan in October 2008 showed peritoneal thickening and ascites.

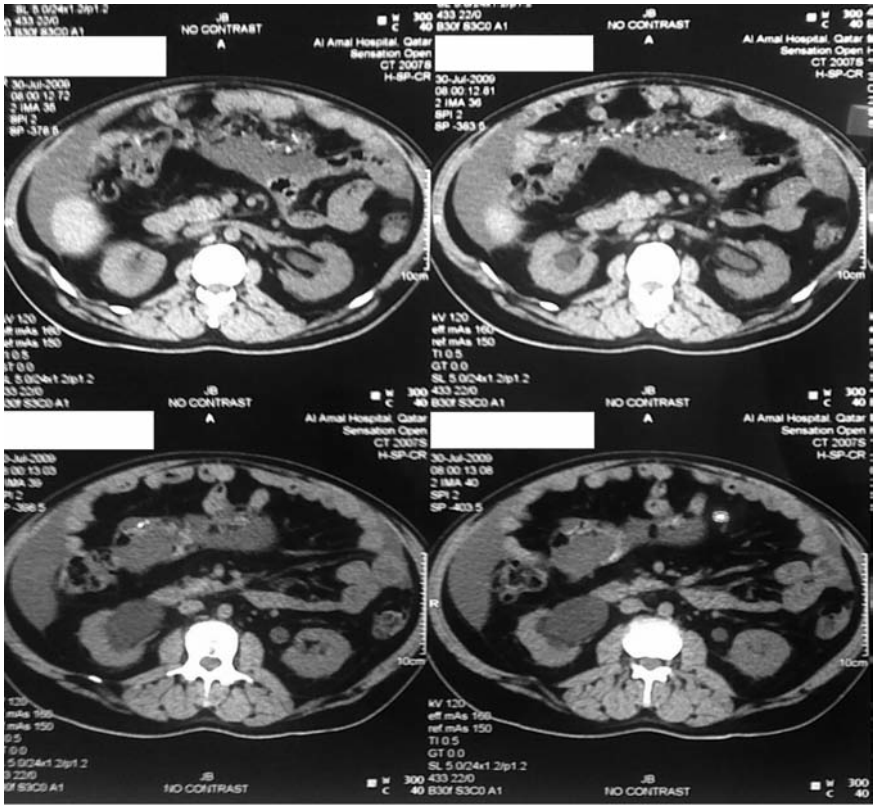

Figure 4. CT scan in July 2009 showed resolution of the peritoneal thickening and hydronephrosis of right kidney.

change in treatment and the patient was continued to be treated with bevacizumab and gemcitabine due to a strong evidence of improvement in clinical response and quality of life. This was observed by no requirement of aspiration of ascitic fluid until August 2009 (7 months post treatment) and the patient was working and maintained his job during this period. Figure 4 showed CT scan image taken in July 2009 showed resolution of the peritoneal thickening as depicted in the anterior and hydronephrosis of the right kidney at the posterior. This case demonstrates that bevacizumab in combination chemotherapy could be an effective alternative treatment in patients who are non-responsive to other proven agents and highlights the need for further clinical studies to establish the role of bevacizumab in the treatment of MPeM to improve progression free survival and overall survival.

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