Nivolumab for Pediatric Malignant Peritoneal Mesothelioma

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Abstract

Mesothelioma is a rare and aggressive tumor originating from the serosal lining of the pleural, peritoneal and pericardial cavities. There are very few cases diagnosed with malignant peritoneal mesothelioma reported in childhood. Thanks to the developments in the field of immunotherapy, the prognosis of the disease has improved with the addition of the immune check point inhibitor, an anti-programmed death-1 monoclonal antibody, nivolumab to the treatment of MPM. In the treatment of our case who was diagnosed with diffuse malignant peritoneal mesothelioma at a very early age; cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, platinum and pemetrexed combination chemotherapy and nivolumab were used. Our patient, who has been on nivolumab therapy for 14 months and has been followed up for 20 months since her diagnosis, is still in remission. This case supports the utility of nivolumab in pediatric MPM.

Introduction

Mesothelioma is a rare and aggressive tumor that originates from the serosal lining of the pleural, peritoneal and pericardial cavities. Although pediatric mesotheliomas are more frequently located in the pleura than in the peritoneum, the incidence of peritoneal mesotheliomas are proportionally higher in children than in adults [1].

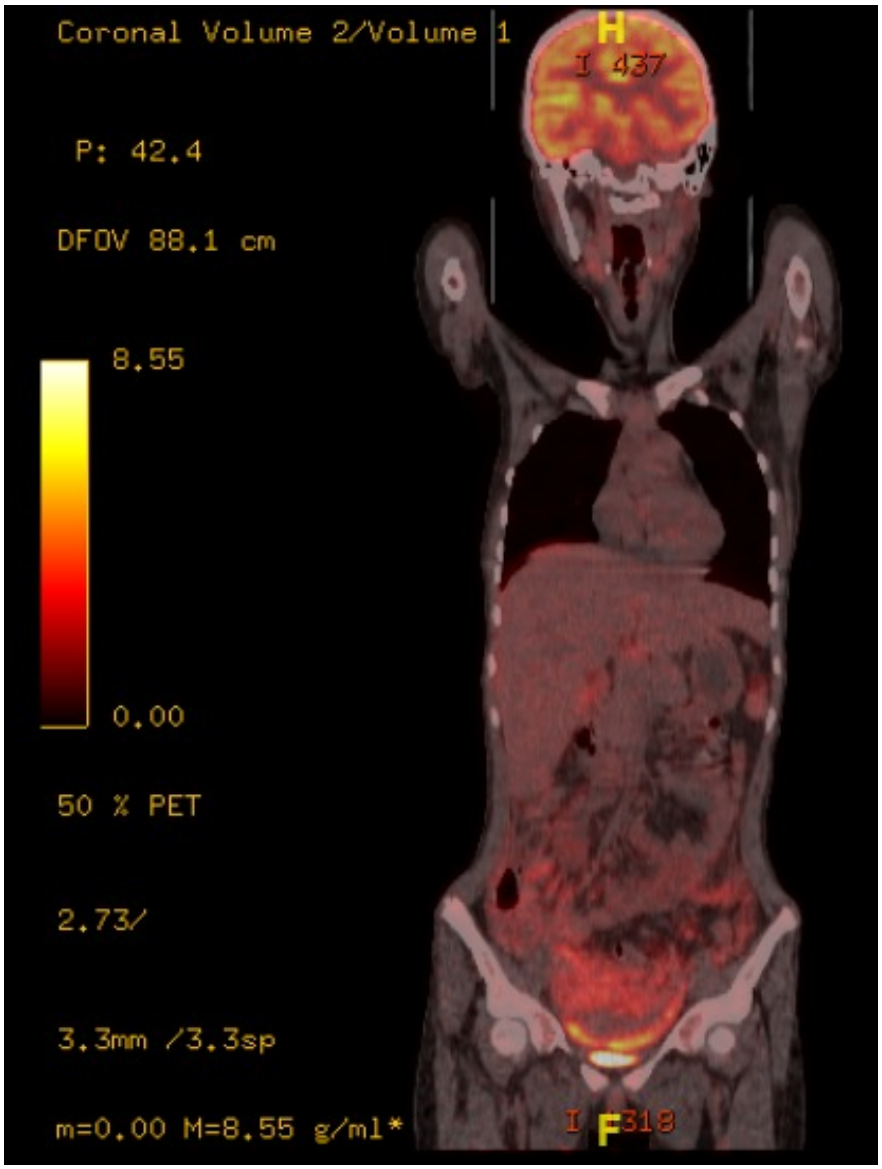
It is often associated with asbestos exposure but prior exposure to asbestos cannot be demonstrated in all patients diagnosed with malignant mesothelioma [2-4]. Although the pathogenesis of mesothelioma has not been clearly elucidated, there are genetic and epigenetic mechanisms as well as environmental factors. Environmental and genetic factors influence the inflammatory tumor microenvironment. Two of the most frequently mutated tumor suppressor genes in mesothelioma are neurofibromatosis type 2 and BRCA1-associated protein-1 genes. Alterations in DNA methylation patterns (especially in E-cadherin, fragile histidine triad, retinoic acid receptor and wnt inhibitory factor-1 and dysregulation of microRNA expression may also contribute to the development of mesothelioma [2].

The diagnosis and treatment of with diffuse malignant peritoneal mesothelioma (DMPM) in children is challenging due to the rarity of the disease and lack of the specific guidelines. The treatment choice for mesothelioma in children is extrapolated from studies in adult patients. The use of combination of cytoreductive surgery (CRS), hyperthermic intraperitoneal chemotherapy (HIPEC), and conventional chemotherapy has been reported with favorable outcomes [3, 5, 6]. Recently, the introduction of immune checkpoint inhibitors (ICI) in the therapeutic strategy of DMPM has shed a new light of hope for this orphan disease, especially in the first-line setting.

Here, we report 13-year-old girl diagnosed with DMPM patient. In the treatment of our case CRS, HIPEC, platinum and pemetrexed-based conventional chemotherapy and immune checkpoint inhibitor nivolumab were used. To our best knowledge, this is the first pediatric case report of the nivolumab combined with CRS, HIPEC and conventional chemotherapy for treatment of DMPM.

Case Report

A 13-year-old female patient, who was previously healthy, applied with the complaints of fatigue and fever. On her physical examination, there was tenderness in the abdomen. The patient's laboratory tests revealed elevations of the liver enzyme tests (Grade1-2, CTCAE v5). In the abdominal ultrasonography, omental thickening near the pelvic region, soft tissue appearance and dense fluid related to the parametrial areas were observed. Contrast-enhanced abdominal magnetic resonance imaging revealed soft tissue with diffusion restriction and contrast enhancement in the pelvic region, thickening of the peritoneal surface and omentum around the liver, and enlargement of the pelvic lymph nodes. The differential diagnosis included tuberculosis, peritoneal carcinomatosis, and lymphoma-like involvement. Laparoscopy was performed to investigate the etiology of fever of unknown origin and an abdominal mass. In the laparoscopy procedure, lymph node excision and biopsy, appendectomy (perforated appendicitis), omentectomy, peritoneal washing and debridement were performed. The pathology result was epithelioid type malignant mesothelioma. It was detected that the tumor infiltrated the appendix serosa and wall, peritoneal tissue, omental tissue and lymph nodes. Widespread positivity was detected with CK5, CK6, CK 7, mesothelin and calretinin in tumor cells. Mild to moderate positivity was observed with D2-40. Multifocal cytoplasmic positivity was detected with epithelial membrane antigen. Other markers were found negative. To determine the extent of the tumor, the first positron emission tomography (PET/CT) was obtained. Except for the normal physiological accumulation sites of the given radiopharmaceutical, diffuse pathological activity accumulation (maximum standard uptake value, SUVmax: 9.0) was observed on the peritoneal surface, prominently in the pelvis and in the pericapsular area of the liver periphery (Figure 1a).



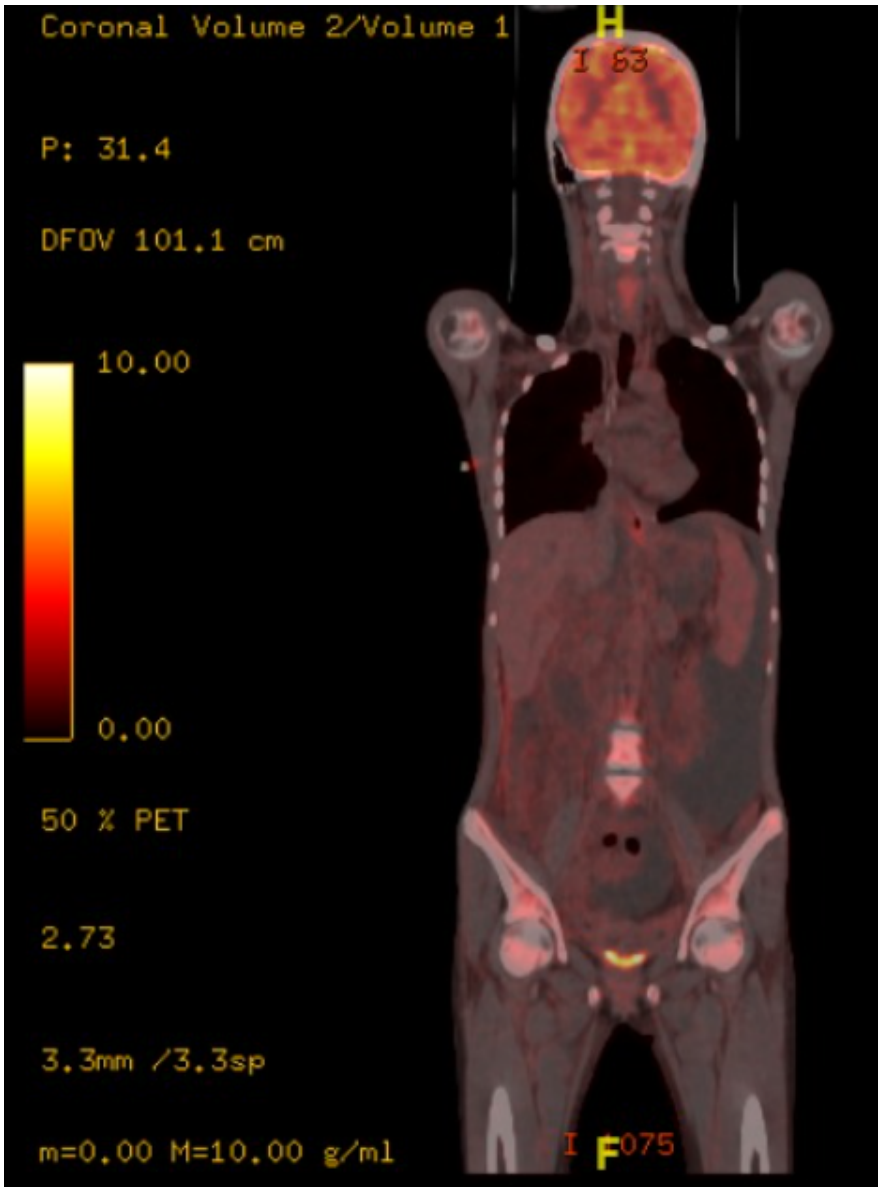


Figure 1a Figure 1b

Positron emission tomography, diagnosis; blue arrows show increased uptake of 18F-Fluorodeoxyglucose in the peritoneal surface, prominently in the pelvis and in the pericapsular area of the liver periphery, SUVmax: 9.0 (F1a), 10 months later, no pathological involvement was detected (F1b).

The patient underwent 2 cycles of intravenous chemotherapy with cisplatin and pemetrexed (Pemetrexed 500 mg/m2/day in each cycle on days 1 and 21, Cisplatin 75 mg/m^2/day on days 1 and day 21 in each cycle, totally 6 cycles were given). After 2 cycles of IV chemotherapy, CRS and HIPEC with cisplatin were applied in purpose of local disease control and to prevent relapse. Follow-up was done with serial abdominal magnetic resonance imaging, they showed regression in the disease findings. Because of a positive for Programmed Death Ligand 1 status, we started nivolumab at the 5th month of the chemotherapy. Nivolumab treatment was given as 3 mg/kg/dose, every 2 weeks by IV infusion over 1 hour. No disease activity was detected in the PET/CT imaging performed 10 months after the diagnosis.

At the time of diagnosis and in the follow up, hepatic transaminase level elevation (Grade1-2, CTCAE v5) observed in laboratory examinations. In the 4th month of nivolumab, an increase in serum creatinine value (Grade2, CTCAE v5) and hypertension (Grade3, CTCAE v5) were detected. Considering the nephrotoxic effect of nivolumab, the drug dose was reduced by 25%. After nivolumab dose reduction, kidney functions, blood pressure monitoring and urine output turned back to normal.

The patient was administered 32 courses of nivolumab without disease relapse. The patient had been progression free for 20 months.

Discussion

The presented case highlights the difficulties in diagnosis and treatment of DMPM. Malignant peritoneal mesothelioma is an extremely rare malignancy of the peritoneum in children and has a poor prognosis. As in our case, the presence of non-specific clinical symptoms such as abdominal discomfort, ascites, and weight loss can contribute to the delay in diagnosis [4].

Pediatric mesothelioma is not associated with asbestos exposure as much as the adult disease is. In this case, asbestos exposure was not documented in the patient or his direct relatives. Additionally, she also had no family history of cancer.

Without aggressive treatments, DMPM is rapidly fatal. In the past, DPMM was treated in most cancer centers with a combination of systemic chemotherapy and palliative surgery. However, the median survival before year 2000 was 1 year and patients did not appear to be responding to these treatments [3]. DMPM mostly remains localized in the abdominopelvic space throughout its course. The combination of CRS and HIPEC, applied for regional treatment, resulted significant improvement in treatment results [7-10]. This approach involves optimal operative tumor cytoreduction to improve efficacy of perioperative HIPEC as the penetration of HIPEC into peritoneal nodules is generally limited to [?] 3 mm [8].

The extremely low incidence of DMPM makes it nearly impossible to conduct randomized trials for the most effective chemotherapy regimen. Until recent years platinum agents plus folate antimetabolites, such as pemetrexed, have been the only approved first-line treatment regimens for DMPM. Pemetrexed/cisplatin combination has not been changed as a standart treatment since 2004. However, long-term survival outcomes with chemotherapy remained poor. In adults, Checkmate 743 randomized, phase 3 trial showed clinically significant improvement in overall survival with immunotherapy added to pemetrexed and platinum in the first-line treatment of unresectable DMPM. Then, In October 2020, the US Food and Drug Administration approved nivolumab plus ipilimumab for this patient population [2, 11]. In the present case, neoadjuvant systemic chemotherapy with cisplatin plus pemetrexed, CRS, and HIPEC therapy showed beneficial responses of reducing the right lower abdominal mass, improving the peritoneal thickening, and clearing the ascites. Then, we performed nivolumab maintenance therapy, which also showed a favorable response for about 14 months. We think that this report demonstrates the need of immunotherapy in pediatric cases as well as adult cases, because it can reverse the course of a potentially fatal disease.

ICI initiate antitumor immunity. However, these agents can cause immune-related side effects that can affect various organs [12, 13]. Renal immune related side effects most commonly present with asymptomatic acute kidney injury, which is often detected by routine laboratory testing. The severity of acute kidney injury ranges from mild to severe. As this group of patients have several reasons to have acute kidney injury, it can be challenging to diagnose [13]. In our case, the baseline creatinine level was normal at the time of diagnosis and before nivolumab treatment was started. At the 4th month of nivolumab treatment, serum creatinine elevation (Grade2, CTCAE v5) and hypertension (Grade3, CTCAE v5) were observed. No other factor was found to explain the nephrotoxicity. After reducing the dose of nivolumab by 25 percent, renal functions and blood pressure monitoring remained normal. Patients using ICI should be closely monitored for immune related side effects throughout their follow-up. Especially in terms of renal immune related side effects, renal functions and blood pressure monitoring should be followed closely even if there are no symptoms.

We herein report a child with DMPM, a rare and aggressive tumor. She responded well to chemotherapy with

cisplatin plus pemetrexed, CRS, HIPEC and maintenance nivolumab. The meaningful and durable clinical response to nivolumab in the current case of DMPM suggests the utility of immunotherapy in children with DMPM. To our best knowledge, we are the first to describe a successful treatment with nivolumab in a pediatric patient with DMPM. However, a well-designed multicenter clinical trial is needed to examine whether nivolumab should be considered as a new treatment option for pediatric DMPM. Additionally, collaborative research between pediatric oncologists and adult experts should be reinforced and supported to develop pediatric targeted therapies, especially for adult type cancers occurring in children.

Acknowledgments

None.

Conflict of Interest

The authors declare that there is no conflict of interest.

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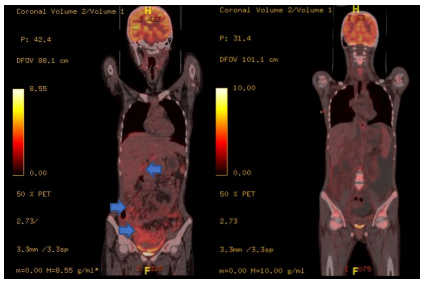

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