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Case Report

DRAMATIC TUMOUR RESPONSE TO PEMETREXED THERAPY IN MALIGN MESOTHELIOMA IN AN OLD PATIENT

Abstract

Malignant mesothelioma is a highly aggressive kind of tumour with a poor prognosis and a limited response to chemotherapy. Pemetrexed disodium, a multi-targeted antimetabolite inhibiting folate pathway, has demonstrated promising clinical activity in a wide variety of solid tumours including mesothelioma. An 81-year-old female patient was admitted to our hospital because of cough and dyspnea. Unilateral right-sided massive pleural effusion and multiple pleural nodules were determined by thorax CT. Mesothelioma was diagnosed by an open lung biopsy. As chemotherapy could be toxic for an elderly patient, radiotherapy was administered. After an asymptomatic follow-up period of 18 months, a new TCT revealed multiple pleural nodules, massive pleural effusion, mediastinal lymph nodes with pathological sizes and a subcutaneous mass, which was interpreted as progression of the primary tumour. We decided to administer chemotherapy containing pemetrexed and cisplatin at tolerable doses. After the chemotherapy, the patient was evaluated with TCT, which revealed that, subcutaneous mass had disappeared and mediastinal lymph nodes and pleural nodules had dramatically regressed. As is known, studies on chemotherapy for treatment of malign mesothelioma are not very promising. This case, with a dramatic tumour response is presented to show that pemetrexed can be an effective and favorable chemotherapeutic agent for mesothelioma treatment, even in elderly patients.

Key Words: Mesothelioma/drug therapy; Pemetrexed; Cisplatin; Aged; Treatment outcome.

Olgu Sunumu

MALİGN MEZOTELYOMA TANILI YAŞLI BİR HASTADA PEMETREKSET TEDAVİSİ İLE DRAMATİK TÜMÖR YANITI

Öz

Malign mezotelyoma, kötü prognoz ve kemoterapiye sınırlı yanıtla seyreden agresif bir tümördür. Pemetrexed disodium ise, folat metabolizmasını inhibe edebilen ve mezotelyoma dahil özellikle solid tümörlerde, giderek artan klinik etkinliği gösterilmekte olan bir antimetabolittir. 81 yaşında bayan hasta kliniğimize öksürük ve nefes darlığı yakınmaları ile başvurdu. Toraks bilgisayarlı tomografisinde masif sağ plevral effüzyon ve multipl plevral nodüller saptanan hastaya ilerleyen tetkiklerde açık akciğer biyopsisi ile mezotelyoma tanısı konuldu. Yaşlı hastada kemoterapinin toksik olabileceği düşünülerek hastada radyoterapi planlandı. Ardından 18 aylık semptomsuz izlem sonrasında efor dispnesinde artma yakınmasıyla yeniden kliniğimize başvurdu. Yeni toraks tomografisinde, sağ hemitoraksta mevcut masif plevral effüzyon ve multipl plevral nodüllerin yanında, patolojik boyutlarda mediastinal lenf nodları ve önceki biyopsi alanında cilt altı kitle tespit edildi; bu durum primer tümörün progresyonu olarak yorumlandı. Hastaya, tolere edebileceği dozlarda, pemetrexed ve cisplatin kombine kemoterapisi uygulanmasına karar verildi. Kemoterapi sonrası çekilen toraks tomografisinde, derialtı kitlenin tamamen kaybolduğu ve mediastinal lenf nodları ile plevral nodüllerde belirgin regresyon olduğu gözlendi. Bilindiği üzere, malign mezotelyomada kemoterapi tedavisi ile ilgili umut verici çalışmalar bulunmamaktadır. Bu olguyla birlikte, pemetrexed kemoterapisinin, yaşlı hastalar da dahil olmak üzere, mezotelyoma tedavisinde yüz güldürücü sonuçlar oluşturabileceği ve efektif bir kemoterapi ajanı olarak kullanılabileceği öngörülmektedir.

Anahtar Sözcükler: Mezotelyoma/ilaç tedavisi; Pemetrekset; Sisplatin; Yaşlı; Tedavi çıktısı.

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Introduction

Malignant mesothelioma is a rare and highly aggressive kind of tumour with a poor prognosis which primarily arises from the surface serosal cells of the pleural, peritoneal, and pericardial cavities (1). The most important risk factor for mesothelioma is known to be asbestos exposure (2). Characteristic thoracic computed tomography (TCT) findings are pulmonary nodules, pleural plaques, thickening, masses and lymphadenopathy; however the definitive diagnosis of mesothelioma requires histopathological evidence obtained from biopsy samples.

Currently, there is no gold standard treatment for mesothelioma, the treatment options being surgery, chemotherapy and radiotherapy. Surgical resection is possible only in a minority of patients and approximately 15% of them live beyond 5 years (3,4). Radiotherapy has limited benefits in decreasing the tumour volume, and is also toxic to the surrounding normal tissue (5). However, chemotherapy may improve the symptoms and may decrease the size of the tumour. Various chemotherapy regimens (either as a single agent or in combination) are used for treatment of malignant mesothelioma and although they are not curative, they may prolong survival in selected patients (6).

Effectiveness of chemotherapy with single agents is limited (7,8). Although response rates up to 48% (9,10) were observed with combination chemotherapy regimens, neither single agents nor combination chemotherapy regimens were shown to improve survival. In addition, the toxicity profile of chemotherapeutic agents may be a major problem especially in older patients, and may increase mortality and morbidity.

Pemetrexed disodium (Alimta), a multi-targeted antimetabolite agent inhibiting the folate pathway, has demonstrated promising clinical activity in a wide variety of solid tumours. In recent years, pemetrexed disodium is being used for chemotherapy treatment in unresectable malignant pleural mesothelioma.

We present a case with a perfect response to pemetrexed disodium chemotherapy showing that pemetrexed may be an effective chemotherapeutic agent in malignant mesothelioma treatment.

Case Presentation

A 81-year old female patient was admitted to our hospital because of cough and dyspnea. She was a housewife and she had a history of direct exposure to asbestos. She had a smoking history of 5 packs a year. She had no medical history of comorbid diseases or operations.

Posterior-anterior chest X-ray revealed a right-sided pleural effusion with loss of volume and possible pleural thickening (Figure 1A). A massive unilateral pleural effusion and multiple pleural nodules were determined by a TCT (Figure 1B). Pleural effusion aspirated by thorasynthesis contained mostly lymphocytes, and was not diagnostic. A pleural biopsy

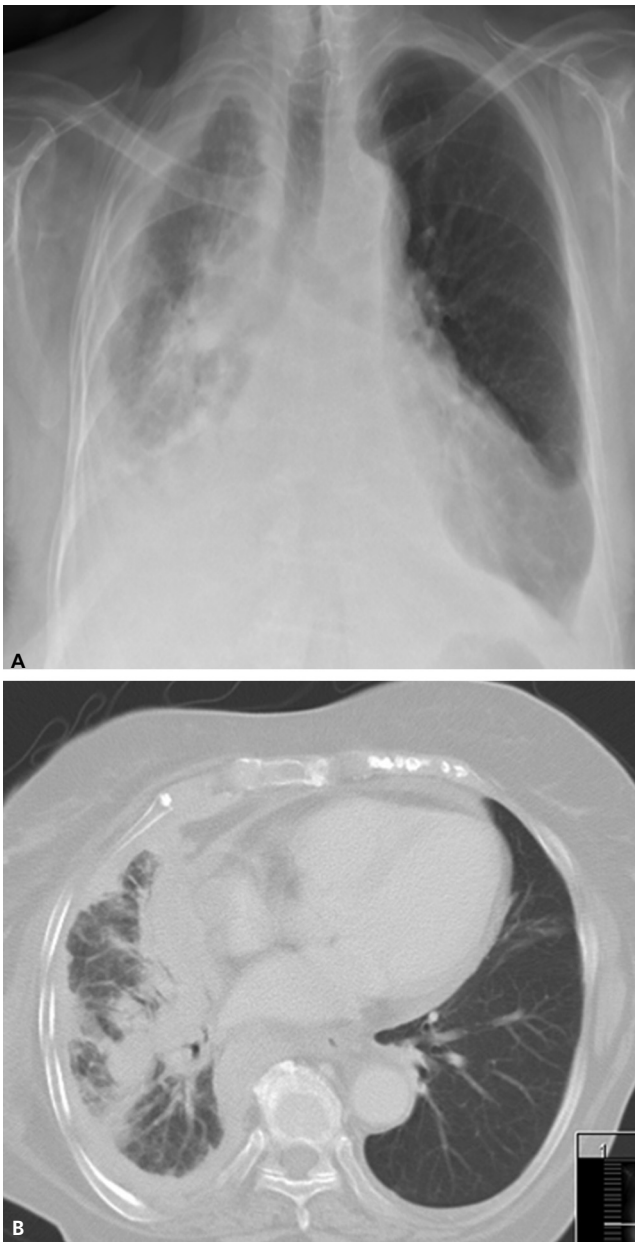

Figure 1— A right-sided pleural effusion and pleural thickening in posterior-anterior chest X-ray (**A**) and a massive pleural effusion with multiple pleural nodules in thorax CT (**B**).

was performed by video-assisted thoracoscopic surgery for diagnosis. Histopathological analysis showed malignant neoplasms with a tumour lesion with irregular tubuloglandular structures, irregular solid areas settled in desmoplastic stroma, and cells with nuclear pleomorphism and atypical mitosis. Immunohistochemical analysis revealed positive staining of tumour cells for D-PAS, vimentin and calretinin; and was negative for carcinoembryonic antigen (CEA), transcription termination factor (TTF-1) and mucicarmin.

The patient was diagnosed with malign epithelial mesothelioma using this histopathological analysis and we decided to apply radiotherapy for her primary tumour considering her age, as chemotherapy could be more toxic for elderly patients. After radiotherapy, she was followed up without any symptoms for 18 months until she had a new complaint of effort dyspnea. In the new TCT, there were multiple pleural nodules, massive pleural effusion in the right hemithorax, mediastinal lymph nodes with pathological sizes and a subcutaneous mass localized at the previous biopsy region; which was interpreted as progression of the primary tumour (Figure 2A,B). We decided to apply chemotherapy containing pemetrexed (Alimta) and cisplatin. After the first two cycles, a clinical improvement was observed and chemotherapy was well tolerated without any toxicity, therefore four cycles were completed. Following the last cycle, the patient was evaluated with a TCT which showed that her subcutaneous mass had disappeared and her mediastinal lymph nodes and pleural nodules had dramatically regressed (Figure 3A,B). Also, she had no complaints in this period, with an increase in her Karnofsky Performance Status.

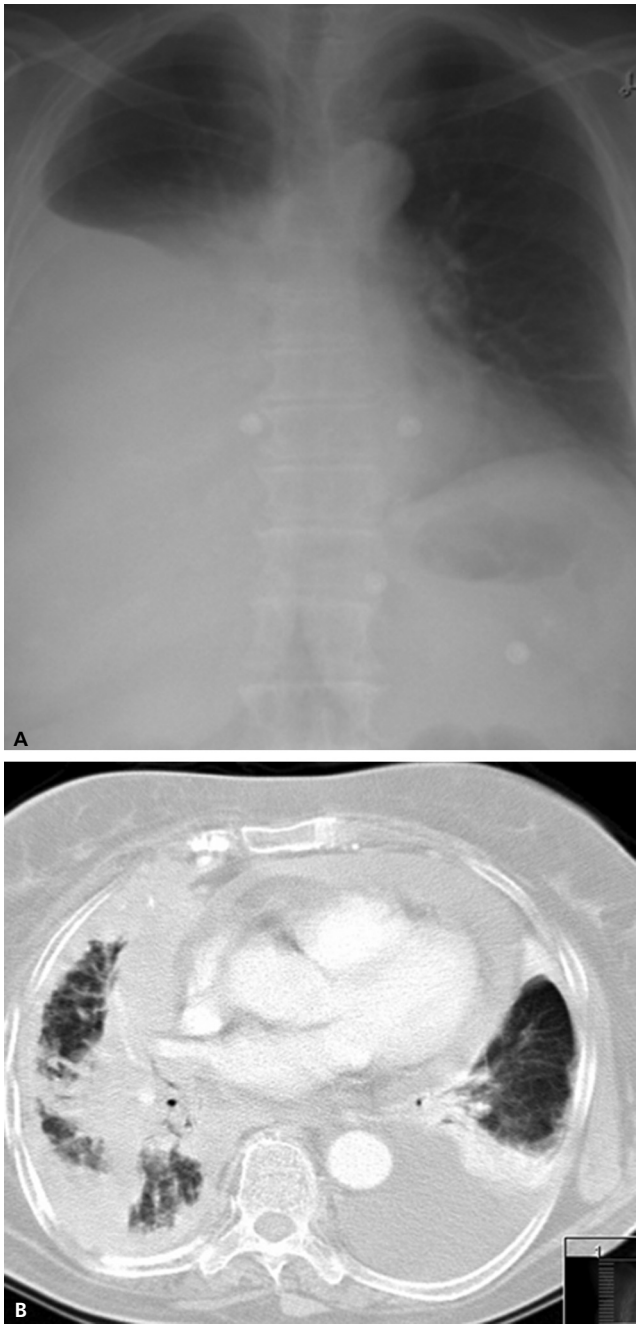

Figure 2— (**A** and **B**) Multiple pleural nodules, massive pleural effusion in the right hemithorax and mediastinal lymph nodes in figures; interpreted as progression of primary tumour.

CONCLUSION

Malignant pleural mesothelioma (MPM) is a disease with a poor prognosis and limited response to chemotherapy (7,8). The survival time without any treatment is approximately 4-12 months (11), therefore, a number of treatment options may be tried to extend it. Although most cytotoxic agents have been evaluated for treatment of mesothelioma, response rates observed were above 20% with only a few single agents (12). In general, chemotherapy regimens (single agent/combination) are not curative but they may prolong survival in selected patients (6).

A few chemotherapeutic agents have been used for treatment of mesothelioma. Antimetabolites, like metotrexate, are known to be the most active drugs against mesothelioma; and one of the most effective members of this group is antifolate drugs (12). Pemetrexed (Alimta) is a multitargeted and newer antifolate drug and has been used both as a single agent and as a part of a combination regimen with a tolerable toxicity profile and high activity in a variety of solid tumours, including MPM (13,14). In addition, it is considered as a favorab-

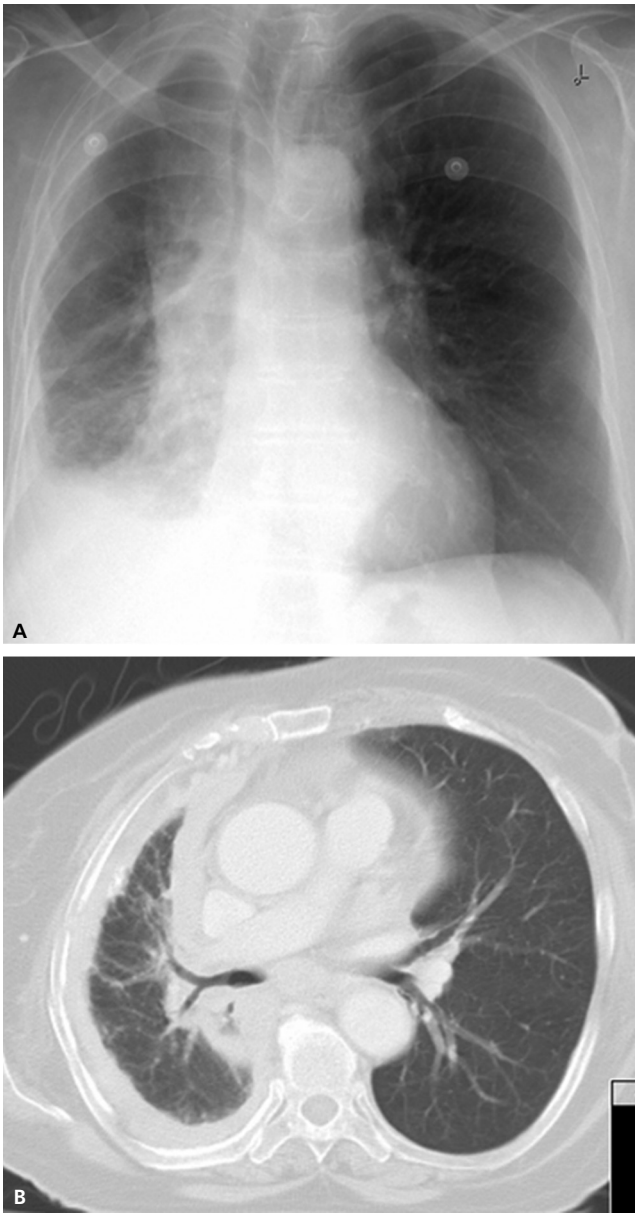

Figure 3— (**A** and **B**) Posterior-anterior chest X-ray and TCT showing regression of mediastinal lymph nodes and pleural nodules after chemotherapy containing pemetrexed.

le treatment option in exclusively selected elderly patients and in patients unfit for a platinum based chemotherapy (15).

Pemetrexed cisplatin combination was shown to prolong survival significantly when compared to cisplatin alone and the combination was also found to be superior in terms of quality of life, response rates, pulmonary functions and clinical benefit (12,13,16). In an analysis of 456 patients randomized to combination therapy or single-agent cisplatin, median survival times were found to be 12.1 and 9.3 months, and the response rates were found to be 41.3% and 16.7% respectively (1). As the most common adverse events like dehydration, nausea and vomiting were clinically manageable and tolerable, pemetrexed was considered to have a good safety profile (15). Vogelzang et al. recommended that pemetrexed-cisplatin combination should be regarded as the standard therapy for the first-line treatment of MPM (17).

Age is generally considered as a risk factor for increased toxicity and poor tolerance to chemotherapy. An age-dependent increase in toxicity due to chemotherapy was observed in elderly cancer patients (18), however, pemetrexed was demonstrated to be a good alternative in this age group. Kulkarni et al. found similar response rates in older and younger patients with pemetrexed therapy, as a single-agent or in combination and pemetrexed was also well tolerated in the elderly population (19).

Pemetrexed (Alimta) seems to be a useful treatment option with a good efficacy and a favourable toxicity profile in malign mesothelioma, however further studies with larger samples are required to confirm this result. Due to observation of a dramatical tumour response to pemetrexed-cisplatin combination in our case, we would like to affirm that pemetrexed should be considered as an effective chemotherapeutic agent in MPM, even in elderly patients.

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