Co-existing pericardial and pleural malignant mesothelioma responding well to nedaplatin and pemetrexed: a case report

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Background: Malignant mesothelioma (MM) is a rare cancer with poor prognosis. It is less common that two serosal cavities are involved when the patient seeks medical attention firstly. The current first-line chemotherapy for advanced MM is a combination with cisplatin and pemetrexed. However, nedaplatin, a second-generation platinum-based antitumor agent, has the similar therapeutic effects as cisplatin but lower toxicity and higher water solubility. To our knowledge, this is the first case of co-existing pericardial and pleural MM treated with nedaplatin and pemetrexed and responding well.

Case Description: A 33-year-old woman, who had worked in a kiln for more than 10 years, suffered from dyspnea and chest tightness for 6 days. Chest computed tomography (CT) showed a massive pericardial effusion. She was diagnosed tuberculous pericarditis and received 6 months antituberculosis treatment (rifampicin, isoniazide, pyrazinamide, ethambutol). But it was ineffective and she was re hospitalized again due to massive pleural effusion and pericardial effusion. She was diagnosed with co-existing pericardial and pleural MM finally based on pleural biopsy and cytology of pericardial effusion. She was responding well excitedly to chemotherapy with nedaplatin and pemetrexed with high tolerance. Bone marrow toxicity or recurrent massive pericardial or pleural effusion were not observed during chemotherapy. However, she gave up chemotherapy and has survived for 22 months, from the onset symptoms.

Conclusions: In terms of clinical tolerance and less adverse reactions, we suggest that chemotherapy of nedaplatin with pemetrexed may be a more appropriate treatment in advanced MM. Further clinical trials are warrant.

Keywords: Malignant pericardial mesothelioma; malignant pleural mesothelioma; chemotherapy; nedaplatin; case report

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Introduction

Background

Malignant mesothelioma (MM) is a rare cancer with a dismal prognosis that arises from mesothelial cells of the pleura (65–70%), peritoneum (10–20%), pericardium (1%) or tunica vaginalis (1%) (1,2). The insidious and nonspecific initial presentations with the low sensitivity of diagnostic methods make it hard to diagnose promptly and result in very poor prognosis. It is less common that two serosal cavities are both involved when the patient seeks medical attention firstly.

Rationale and knowledge gap

The current first-line chemotherapy for advanced MM is a combination with cisplatin and pemetrexed (3,4). However, cisplatin may cause some serious adverse effects, such as severe gastrointestinal side effects, renal toxic effects and so on, which always force patients to discontinue chemotherapy (5-7). Several clinical trials have found out that nedaplatin, a second-generation platinum-based antitumor agent, has the similar therapeutic effects as cisplatin but higher water solubility and lower toxicity (lower gastrointestinal toxicity and nephrotoxicity compared with cisplatin), which may be a more appropriate choice and used increasingly in chemotherapy of lung cancer (7,8). Moreover, the same clinical findings could be also confirmed in other carcinoma like nasopharyngeal carcinoma and esophageal cancer, in comparison between nedaplatin-based and cisplatin-based chemotherapy (9,10).

Highlight box

Key findings

- This is the first case of co-existing pericardial and pleural malignant mesothelioma (MM) treated with nedaplatin and pemetrexed and responding well.

What is known and what is new?

- The current first-line chemotherapy for advanced MM is a combination with cisplatin and pemetrexed. However, nedaplatin is confirmed that it has the similar therapeutic effects as cisplatin but lower toxicity and higher water solubility in several carcinoma.
- Our case report provides evidence for the effective treatment of MM with nedaplatin and pemetrexed.

What is the implication, and what should change now?

- We suggest that chemotherapy combined nedaplatin with pemetrexed may be a more appropriate treatment in advanced MM. Further clinical trials which focus on the comparison of efficacy and toxicity between nedaplatin and cisplatin in treating MM are warrant.

Objective

To our knowledge, there is no report of co-existing pericardial and pleural MM treated with nedaplatin and pemetrexed. Here, we report a 33-year-old woman diagnosed with co-existing pericardial and pleural MM is responding well to chemotherapy with nedaplatin and pemetrexed. We present this case in accordance with the CARE reporting checklist (available at https://acr.amegroups.com/article/view/10.21037/acr-22-102/rc).

Case presentation

The case timeline and treatment were summarized in *Figure 1A*. The whole dynamic changes in chest computed tomography (CT) imaging were shown in *Figure 1B*. A 33-year-old previously healthy woman who suffered from dyspnea and chest tightness for 6 days was hospitalized in Department of Cardiology in March 2020. She had worked in a kiln for more than 10 years which showed a history of occupational exposure to asbestos. Physical examination revealed a blood pressure of 123/87 mmHg, distended right jugular vein and both pulmonary rales. Chest CT showed a massive pericardial effusion, little pleural effusion and irregular interlobular fissure thickening (*Figure 1B*, panel I). Echocardiography showed no definite pericardial thickening or heart failure (ejection fraction 66%). Laboratory tests showed mild inflammation (C-reactive protein: 17.5 mg/L, procalcitonin: 0.061 ng/mL) and elevated concentration of cytokeratin fraction 21-1 (CYFRA 21-1; 5.11 ng/mL, baseline 3.3 ng/mL) and carbohydrate antigen-125 (CA125; 224.9 U/mL, baseline 35 U/mL) but not carcinoembryonic antigen (CEA). Emergency pericardiocentesis was performed and 1,860 mL of fluid was drained. Pericardial fluid was bloody and exudate with elevated lactate dehydrogenase (LDH; 6,954 U/L). The acid-fast bacilli stain was negative. Pericardial tuberculosis infection T cell spot test (T-SPOT.TB) was positive [the ratio of TB-specific antigen (TBAg) to phytohaemagglutinin (PHA), TBAg/PHA ratio: 0.11], but T-SPOT.TB in peripheral blood was negative. Cytological examination showed moderate mesothelial hyperplasia, but was negative for malignancy. Further positron-emission tomography (PET) revealed partial inflammation responses as the only manifestation.

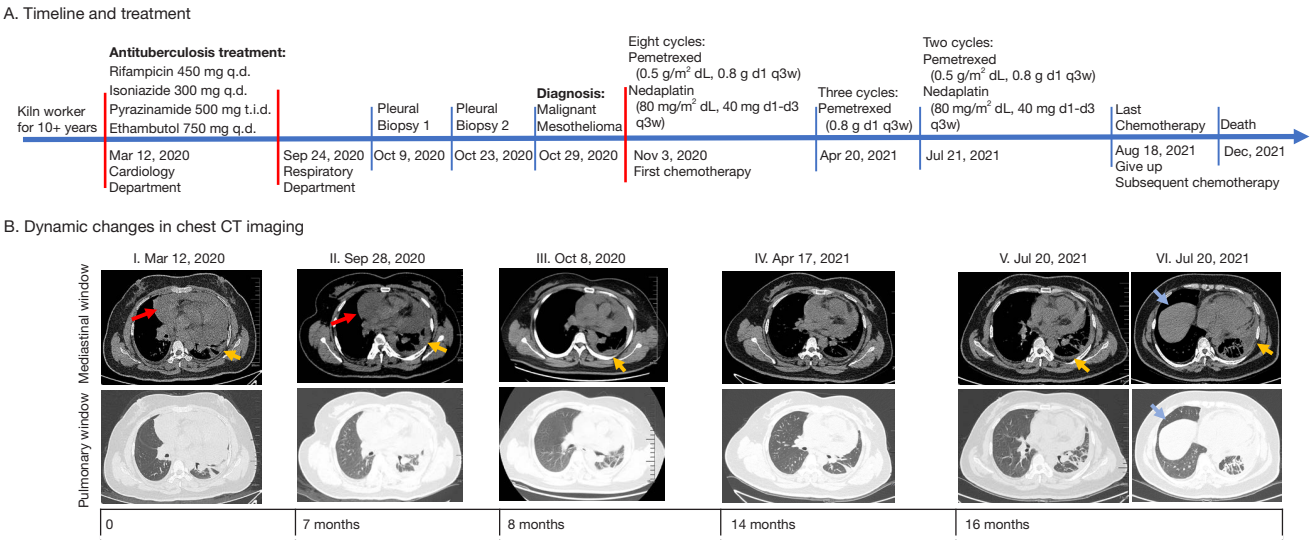

Figure 1 Treatment timeline. (A) Timeline and treatment. Illustration of the treatment received by the patient. (B) Dynamic changes in chest CT imaging at different time-points. Yellow arrow: pleura; red arrow: pericardium; blue arrow: liver. CT, computed tomography.

Thus, the patient was treated for suspected tuberculous pericarditis and received 6 months antituberculosis treatment (rifampicin 450 mg q.d., isoniazide 300 mg q.d., pyrazinamide 500 mg t.i.d., ethambutol 750 mg q.d.).

In September 2020, she was readmitted to respiratory apartment with 14 days history of cough, expectoration, dyspnea and chest tightness. Chest CT images showed massive pleural and pericardial effusion (*Figure 1B*, panel II). Thoracentesis and pericardiocentesis were performed. 3,300 mL of yellow pleural fluid and 1,910 mL of hemorrhagic pericardial fluid were drained. LDH was found to be elevated in both fluids, 5,372 U/L in pleural fluid and 1,818 U/L in pericardial fluid respectively. Both fluids showed marked mesothelial proliferation (*Figure 2A*). The mesothelial cells in pericardial fluid were strongly positive for calretinin, hector battifora mesothelial-1 (HBME-1), cytokeratin (CK) 5/6 but negative for thyroid transcription factor-1 (TTF-1), MOC31 immunohistochemically (*Figure 2B,2C*). Blood laboratory examination showed a normal concentration of CEA but up-regulated level of CYFRA 21-1 (31.84 ng/mL) and CA125 (299.3 U/mL). Second chest CT revealed an uneven left pleural thickening and thus twice left pleural biopsy were done (*Figure 1B*, panel III). Hematoxylin and eosin (H&E)-stained sections of the pleura showed a neoplasm characterized by a predominantly diffuse growth pattern and monomorphic epithelioid cells with eccentric, hyperchromatic nuclei (*Figure 2D*). The neoplastic cells were positive for calretinin, HBME-1, pan-cytokeratin (pan-CK), and vimentin (*Figure 2E,2F*). Immunostains for glucose transporter-1 (GLUT-1), Desmin, S100, Myogenin, cluster of differentiation (CD)34, B-cell lymphoma (BcL)-2 and Signal Transducer and Activator of Transcription-6 (STAT-6) were negative. She disagreed pericardial biopsy for its high risk.

MM (T4N2Mx, grade IV) in pericardium and pleural was diagnosed according to International Mesothelioma Interest Group (IMIG) staging system, based on the summarized results: (I) a long history of occupational exposure to asbestos; (II) clinical manifestation: cough, expectoration, dyspnea and chest tightness; (III) imaging results: recurrent pleural and pericardial effusion, pleural thickening; (IV) laboratory results: exudative effusion with significantly elevated LDH and marked mesothelial proliferation; high level of CYFRA 21-1 and CA125 but not CEA. (V) Immunohistochemical results: positive for calretinin, HBME-1, pan-CK, CK5/6, but negative for TTF-1, GLUT-1, Desmin, S100, Myogenin, CD34, BcL-2 and STAT-6. Because of the advanced carcinoma, palliative chemotherapy was chosen as the initial treatment. After 8 cycles of pemetrexed (0.5 g/m^2 dL, 0.8 g d1 q3w) and nedaplatin (80 mg/m^2 dL, 40 mg d1–d3 q3w) during 6 months, the clinical manifestations such as cough, expectoration, dyspnea and chest tightness were all alleviated significantly and the malignancy had been improved gradually without

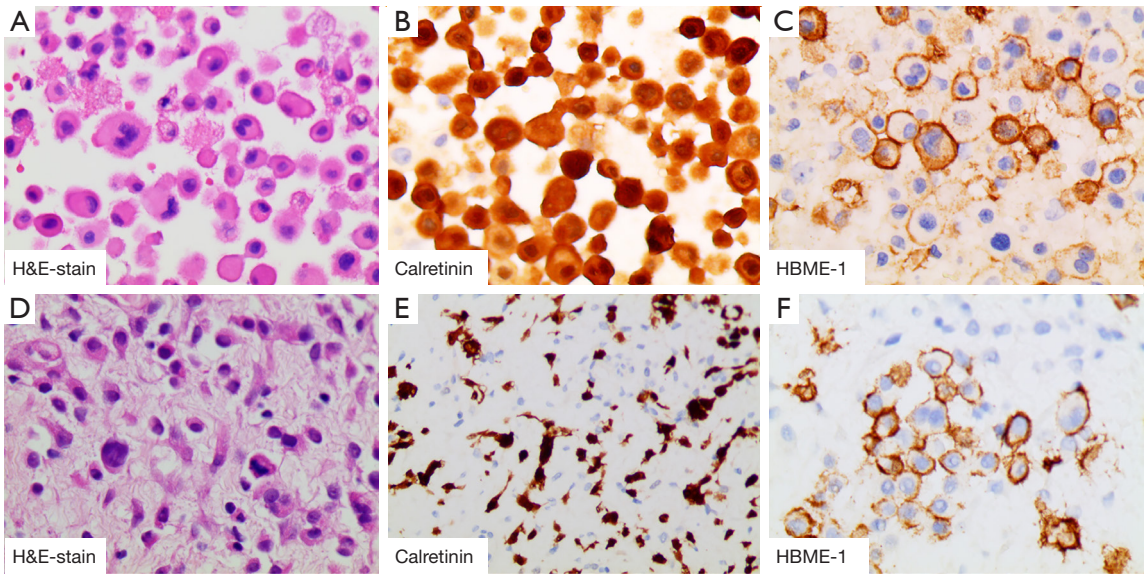

Figure 2 Epithelioid malignant mesothelioma of the left pleura and pericardium. (A) Pericardial fluids cytology showed marked mesothelial proliferation. The mesothelial cells in pericardial fluid were strongly positive for calretinin (B) and HBME-1 (C) immunohistochemically. (D) H&E-stained sections of the left pleura showed a neoplasm characterized by a predominantly diffuse growth pattern and monomorphic epithelioid cells with eccentric, hyperchromatic nuclei. The neoplastic cells were positive for calretinin (E) and HBME-1 (F) immunohistochemically. (A-C,F) Magnification: ×400. (D,E) Magnification: ×200. H&E, hematoxylin and eosin; HBME-1, hector battifora mesothelial-1.

bone marrow toxicity, and maintained clinical stabilization based on non-recurrent massive pericardial or pleural effusion (*Figure 1B*, panel IV). Pemetrexed (0.8 g d1 q3w) was selected for subsequent maintenance therapy. However, the pleural thickening and pleural or pericardial fluid was increased after 3 cycles of pemetrexed (*Figure 1B*, panels V and VI). With another 2 cycles of pemetrexed and nedaplatin, she gave up chemotherapy due to the poor economic condition in August and died at home in December 2021. From the onset symptoms, the patient has survived for 22 months.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent for publication of this case report and accompanying images was not obtained from the patient or the relatives after all possible attempts were made.

Discussion

Key findings

To our knowledge, this is the first report of co-existing pericardial and pleural MM treated with nedaplatin and pemetrexed.

Strengths and limitations

In our case, although the patient refused subsequent chemotherapy because of poor economics, she responded well to nedaplatin and pemetrexed without bone marrow toxicity and didn't have recurrent massive pericardial or pleural effusion again during chemotherapy. She had a total survival of 22 months after first clinical manifestation. However, the case report had a major limitation that we failed to obtain pericardial pathology because the patient disagreed pericardial biopsy for its high risk, although pericardial effusion cytology and pleural biopsy were all suggestive of MM.

Comparison with similar researches and explanations of findings

Pleural MM is the most common primary MM. Disease progression is seen usually by invading local contiguous tissue such as lung, whereas in rare instances pericardium

and myocardium. Its common images show pleural effusion, diffuse pleural thickening, pulmonary nodules, lung encasement, mediastinal shift and elevation of hemidiaphragm (11). Primary pericardial MM is extremely infrequent tumor with the prevalence of 0.001–0.007% among cardiac tumors (12). Metastases to heart and pericardium are much more frequent than primary malignancy (13). Pericardial MM always presents with pericardial effusion, constrictive pericarditis, cardiac tamponade and heart failure (14). The diagnostic methods include cytology, biopsy, CT, magnetic resonance imaging (MRI), PET and ultrasonography. It is known that the diagnostic sensitivity of cytology is very low as only 20% (15). PET is often difficult to have positive manifestations in the early stage of MM and generally used to evaluate the metastatic extent and treatment efficacy assessment (16). Together with the insidious and nonspecific initial presentations, the low sensitivity of diagnostic methods makes it hard to diagnose promptly and results in very poor prognosis. Interestingly, in our case, both pericardium and pleura appeared to involved by mesothelioma. At the first medical visit, mild irregular interlobular fissure thickening with little pleural effusion and pericardial effusion without pericardial thickening were both presented synchronously, although PET didn't reveal significant strong uptake which suggesting malignancy. Regrettably, a pleural or pericardial biopsy was not performed at that time. At the second visit after 6 months, pericardial effusion cytology and pleural biopsy were all suggestive of MM. The major limitation was that we failed to obtain pericardial pathology because the patient disagreed pericardial biopsy for its high risk. There was no clinical evidence of which malignancy was the primary one because it was hard to distinguish based on molecular marker. In terms of incidence, the greatest possibility is suspected primary pleural MM with pericardial metastasis. In rarer cases, primary MM coexisting in the pericardium and pleura might be suspected because the patient had long history of occupational asbestos exposure. Therefore, unresolving recurrent pleural and pericardial effusion should raise suspicion for MM.

The treatments of MM include surgical therapy, chemotherapy and radiotherapy (17). Surgical therapy is useful for localized disease, tumor reduction and preventing fatal tumor complications such as cardiac tamponade. However, when diagnosed, MM is often locally progressive or distant metastatic which is unavailable for surgery and should be administered by chemotherapy. No reliable large clinical trials for chemotherapy have been conducted. Therefore, a standard chemotherapeutic guideline has not yet been established. The current first-line chemotherapy is a combination with pemetrexed and cisplatin, which was confirmed to lead to longer survival times than cisplatin monotherapy (3,4). However, cisplatin and carboplatin may cause some serious adverse effects, such as myelosuppression, neurotoxicity and gastrointestinal reactions, which limit their clinical use and force to discontinue cisplatin-based chemotherapy (5-7). Nedaplatin, a second-generation platinum-based antitumor agent, has the similar therapeutic effects as cisplatin but higher water solubility, lower gastrointestinal toxicity and lower nephrotoxicity compared with cisplatin in lung cancer, nasopharyngeal carcinoma and esophageal cancer (7,9,10,18). Lin *et al.* and Zhong *et al.* reported that the efficacy of nedaplatin was similar as cisplatin but nedaplatin had higher tolerance and less toxicity, in treating advanced lung adenocarcinoma or cancer-induced pleural effusion (19,20).

Implications and actions needed

In terms of clinical tolerance and less adverse reactions, we suggest that chemotherapy of nedaplatin with pemetrexed may be a more appropriate treatment in advanced MM. Nevertheless, since it is only a case report, further clinical trials are warrant to analyze the efficacy, safety, dose and cycle required for maximal response and minimal toxicity, progressive-free survival and overall survival of nedaplatin plus pemetrexed in advanced MM.

Conclusions

MM is a rare cancer and a huge socioeconomic burden. Early recognition, staging and response evaluation are very critical to determine treatment. Chemotherapy combined nedaplatin with pemetrexed is effective for advanced MM with low toxicity and high tolerance. However, further clinical trials are warrant.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://acr.amegroups.com/article/view/10.21037/acr-22-102/rc

Peer Review File: Available at https://acr.amegroups.com/article/view/10.21037/acr-22-102/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://acr.amegroups.com/article/view/10.21037/acr-22-102/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent for publication of this case report and accompanying images was not obtained from the patient or the relatives after all possible attempts were made.

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