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CASE REPORT

Organizing pneumonia after pancreatic cancer treatment with nab-paclitaxel and gemcitabine: a case report

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ABSTRACT

The incidence of pancreatic cancer is increasing. Most patients have advanced disease at diagnosis, and therapeutics is limited in this setting. Gemcitabine and nab-paclitaxel combination is indicated as first-line treatment in patients with metastatic cancer of pancreas. The most common adverse events of Grade 3 or higher gemcitabine and nab-paclitaxel combination are neutropenia, fatigue and neuropathy. In this report, we describe a rare case of organizing pneumonia associated with the use of nab-paclitaxel and gemcitabine in metastatic pancreatic cancer. A 68-year-old female underwent total splenopancreatectomy for ductal adenocarcinoma of the neck of the pancreas, followed by adjuvant chemoradiation therapy. Afterwards she relapsed and received first-line chemotherapy with gemcitabine plus nab-paclitaxel combination for 12 cycles. Following the administration of the 12th cycle of gemcitabine plus nab-paclitaxel, the patient experienced low-grade pyrexia, effort dyspnoea, persistent non-productive cough and malaise. High-resolution CT scan of chest revealed new-onset bilateral peripheral ground-glass opacities, smooth interlobular septal thickening and patchy subpleural consolidation areas, findings consistent with organizing pneumonia. A thorough microbiological workup was negative. Treatment with steroids resulted in prompt clinical and radiological improvement. Organizing pneumonia closely mimics infection or progressive disease and can be difficult to diagnose in the setting of malignancy. Correct diagnosis is of primary importance since delay in treatment can result in significantly adverse patient outcomes.

BACKGROUND

Pancreatic cancer is one of the most challenging human malignancies and ranks as the fourth leading cause of cancer-related mortality in the United States and Europe,¹ with a 5-year survival rate of 7 to 8% among all disease stages.^{2–4} Surgery offers the only curative treatment for pancreatic cancer; however, in the large majority of cases, diagnosis is made at an advanced stage, when patients already have metastases or locoregional extension precluding curative surgical resection.⁵ Therapeutic options in this setting remain limited. During the past 5 years, two Phase III studies demonstrated that the FOLFIRINOX regimen (oxaliplatin, irinotecan, fluorouracil and leucovorin) and then the gemcitabine plus nab-paclitaxel regimen significantly improve survival in patients with metastatic adenocarcinoma of the pancreas.^{6,7} Both regimens are currently considered standards of care for first-line treatment in patients with advanced pancreatic cancer and

good general condition [performance status (PS) Eastern Cooperative Oncology Group (ECOG) 0–1 for FOLFIRINOX and PS ECOG 0–2 for gemcitabine plus nab-paclitaxel].

Nab-paclitaxel (nanoparticle albumin-bound paclitaxel) is a solvent-free, albumin-coupled formulation of paclitaxel, indicated for the treatment of breast cancer, non-small cell lung cancer (NSCLC) and pancreatic cancer.

Gemcitabine is a pyrimidine antimetabolite and incorporates its active metabolite into the DNA, resulting in inhibition of DNA synthesis. It is used for the adjuvant and metastatic treatment of a wide variety of malignancies including breast, ovary, pancreas, bladder and NSCLC.

The most common adverse events of Grade 3 or higher, according to the Common Terminology Criteria for

Adverse Events (CTCAE) v4.0, gemcitabine and nab-paclitaxel combination are neutropenia, fatigue and neuropathy. The Phase 3 study MPACT reported significantly increased pneumonitis rates with the combination of gemcitabine and nab-paclitaxel compared to gemcitabine alone (4 vs 1%, respectively).⁷

Here, we present a rare case of organizing pneumonia (OP) following long-term treatment with nab-paclitaxel and gemcitabine for metastatic pancreatic cancer.

CASE PRESENTATION

A Caucasian 68-year-old non-smoker female, without a significant medical history except for hypertension and family history of pancreatic cancer, underwent total splenopancreatectomy for ductal adenocarcinoma associated with branch-duct intraductal papillary mucinous neoplasm (BD-IPMN) of the neck of the pancreas. Since May to September 2014 she received adjuvant treatment in another hospital: 3 cycles of weekly gemcitabine (1000 mg m⁻²) followed by chemoradiation with gemcitabine (50.4 Gy in 28 fr). A thoracoabdominopelvic computer-assisted tomography (TAP-CT) performed in March 2015 showed the presence of cancer recurrence locally, in retroperitoneal lymph nodes and in lungs. A positron emission tomography with 18-fluoro-deoxyglucose was also performed in order to confirm the diagnosis of relapse. Since April 2015 the patient received first-line chemotherapy at our oncology department. We administered gemcitabine plus nab-paclitaxel combination (gemcitabine 1000 mg m⁻² and nab-paclitaxel 125 mg m⁻² on days 1, 8 and 15 every 4 weeks) for 12 cycles. The CT scans performed every two cycles showed stable disease, while a metabolic response was seen on positron emission tomography with 18-fluoro-deoxyglucose.

Following the administration of cycle 12, day 15 of gemcitabine plus nab-paclitaxel, the patient experienced low-grade pyrexia, effort dyspnoea, persistent non-productive cough and malaise. She was empirically treated with a 5-day course of levofloxacin as outpatient, without any beneficial effects, and for the worsening of the symptoms she was eventually hospitalized. On admission, blood examination revealed moderate anaemia (haemoglobin 9.3 g dl⁻¹) and an increased level of C-reactive protein (8.2 mg dl⁻¹), whereas white cell differential count, electrolytes and

glucose levels and renal and liver function were within normal limits. A chest X-ray showed diffuse reduction of normal lung lucency, both perihilar and peripheral. High-resolution computed tomography (HRCT) scan showed new-onset bilateral peripheral ground-glass opacities, smooth interlobular septal thickening and patchy subpleural consolidation areas. These findings were consistent with OP (Figure 1).

Blood cultures were negative, as well as urine was negative for Legionella and Pneumococcal antigens. Serology tests for Mycoplasma, Legionella, cytomegalovirus, Epstein–Barr virus, adenovirus, influenza, parainfluenza and respiratory syncytial virus were negative, as was the Quantiferon-TB gold In-tube. The patient underwent bronchoscopy for bronchoalveolar lavage, and cytopathological and microbiological analyses were negative for infectious causes; the cell findings in bronchoalveolar lavage fluid were total cell count 271,000 ml⁻¹; macrophages 60%; lymphocytes 30%; neutrophils 10%; eosinophils 0%; no neoplastic cells. Chronic medications at diagnosis consisted in pancreatic enzyme supplements, insulin, amlodipine, pantoprazole and furosemide.

Suspecting chemotherapy-induced pneumonitis, nab-paclitaxel and gemcitabine were discontinued; the patient was started on treatment with prednisone 1 mg kg⁻¹ day⁻¹, which led to rapid clinical improvement. HRCT scan performed after 2 months showed disappearance of alveolar infiltrates and complete resolution of consolidation (Figure 2).

DISCUSSION

OP or bronchiolitis obliterans OP is a known manifestation of drug-induced lung injury. It is a histopathological reaction to a nonspecific inflammatory insult and can occur after exposure to a number of drugs including many antineoplastic agents.⁸

Patients with OP typically present with a subacute illness of relatively short duration (median, less than 3 months) with low-grade fever and variable degrees of dyspnoea and non-productive cough. HRCT characteristically shows patchy and often migratory consolidation in a subpleural, peribronchial or band-like pattern, commonly associated with ground-glass opacities. Perilobular opacities and reversed halo sign may be helpful in

Figure 1. (a) Coronal and (b) axial images from thorax CT at diagnosis. Bilateral peripheral ground-glass opacities, smooth interlobular septal thickening and patchy subpleural consolidation areas in upper lobes interspersed between known pulmonary metastasis.

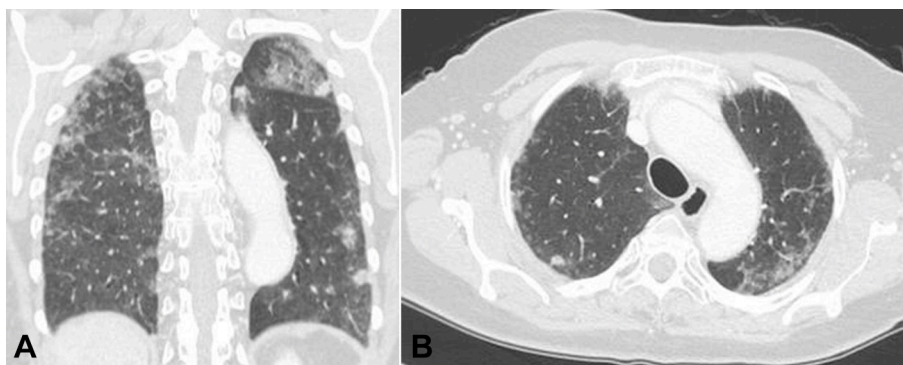
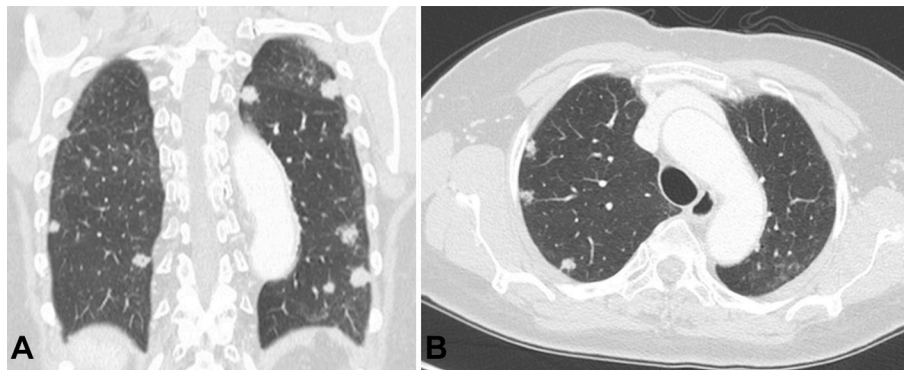


Figure 2. (a) Coronal and (b) axial images from thorax CT performed after 2 months of steroid treatment. Complete resolution of the diffuse and bilateral ground-glass opacities and of the consolidation areas, with an increase in the size of the nodules, known as lung metastases.



suggesting the diagnosis. In 10–30% of patients, small unilateral or bilateral pleural effusion may occur.⁹ The radiographic differential diagnosis of OP includes alveolar cell carcinoma, lymphoma, vasculitis, sarcoidosis and infection (particularly tuberculosis or atypical mycobacterial infection). When the consolidation is subpleural, the diagnosis of chronic eosinophilic pneumonia should also be considered.¹⁰

The pathology of OP is inflammatory fibrin filling the alveoli and spreading to the alveolar ducts and terminal bronchioles, with peculiar endoluminal buds of granulation tissue; an interstitial inflammatory infiltrate can be associated with these abnormalities. However, histological diagnosis, in the same way as in other interstitial lung disease, is no longer deemed to be the gold standard. Analysis of all available data in a multidisciplinary meeting should be performed in order to define the settings where biopsy is more informative than HRCT and those where biopsy is not needed.

The majority of patients recover completely with oral corticosteroids, with the symptoms resolving within days or weeks. However, sporadic reports have identified a subgroup of patients

with OP that does not completely resolve in spite of prolonged treatment. Some of these cases show residual or progressive interstitial fibrosis, often with recurrent episodes of OP.^{9,10}

Some cases of gemcitabine-induced OP have been reported to date (Table 1). Among those, two patients received single-agent gemcitabine treatment for pancreatic cancer, while the other three cases describe OP occurring in patients affected by lung cancer receiving a gemcitabine-containing doublet chemotherapy.^{11–15} A case of OP has also been described in a patient on treatment with trastuzumab and nab-paclitaxel for metastatic breast cancer, as well as fatal interstitial pneumonitis in a patient with refractory small cell lung cancer after two cycles of single-agent nab-paclitaxel.^{16,17}

Gemcitabine is generally a well-tolerated chemotherapeutic agent; however, a wide spectrum of lung toxicities have been reported with its use. Gemcitabine-related pneumonitis has been documented in patients with varied cancers in sites such as lung, ovary, breast, gallbladder and pancreas and is a potentially fatal complication that may cause significant morbidity and, rarely, mortality.^{18–22} The incidence of gemcitabine-induced

Table 1. Reports of gemcitabine organizing pneumonia

References	Primary diagnosis	Chemotherapeutic agents	Treatment (type and dosage)	Outcomes
Shaib et al ¹¹	Pancreatic cancer	Gemcitabine alone	Steroids (not reported)	Clinical and CT improvement
Kawsar et al ¹²	Non-small cell lung cancer	Carboplatin, gemcitabine	Steroids (not reported)	Clinical and CT improvement
Cobo Dols et al ¹³	Non-small cell lung cancer	Docetaxel, gemcitabine	Steroids (methylprednisone, 160 mg day ⁻¹)	Clinical and CT improvement
Aguiar Bujanda D et al ¹⁴	Non-small cell lung cancer	Paclitaxel, carboplatin, gemcitabine	Steroids (not reported)	Rapid clinical improvement within 24 h and chest X-ray improvement after 3 weeks
Hiraya et al ¹⁵	Pancreatic cancer	Gemcitabine alone	Steroids (methylprednisone 500 mg day ⁻¹ for 3 days and afterwards tapered off)	Rapid clinical improvement and CT improvement after 3 weeks

pneumonitis has been reported in different studies at rates ranging from 0.06 to 2.15%,^{23,24} and several clinical trials report a higher rate of pneumonitis in treatment that combines gemcitabine with other agents such as nab-paclitaxel and erlotinib.^{7,25}

Paclitaxel is also known to cause pneumonitis with an incidence ranging from 1 to 4%, increasing when paclitaxel is combined with other cytotoxic drugs or radiation therapy.²⁶

When considering risk factors of pulmonary toxicity one might hypothesize that combination chemotherapy, pre-existing pulmonary disease such as pulmonary metastatic disease and prior or concurrent radiation therapy play a role.²⁷

Regarding our patient's risk factors, she did have pulmonary metastases and received combination chemotherapy.

Patients receiving antineoplastic treatment who develop new respiratory symptoms or have abnormal chest radiographs are frequently encountered. Typically, the first concern is either progressive disease or an infectious process. These conditions are not easily differentiated on the basis of clinical presentation and radiographic findings. Moreover, as patients usually receive multiple antineoplastic agents, it is usually problematic to identify the culprit agent. Regardless of these difficulties, clinicians should consider this diagnosis when evaluating a patient receiving chemotherapeutic agents with a new pulmonary process. Discontinuation of the implicated causative agent and treatment with systemic corticosteroids may result in an excellent outcome.

To our knowledge, this is a rare case report of OP in a patient treated with gemcitabine and nab-paclitaxel for pancreatic cancer. This case report highlights the necessity of a high level of alertness for emerging respiratory symptoms for early intervention and management of a potential diagnosis of pneumonitis during gemcitabine and nab-paclitaxel therapy, which is now a commonly used first-line standard therapy for patients with metastatic pancreatic adenocarcinoma.

LEARNING POINTS

1. OP is a distinct disorder of lungs that can clinically present with subacute illness with low-grade fever and variable degrees of non-productive cough and dyspnoea.
2. OP diagnosis is mainly radiological. HRCT shows patchy and often migratory consolidation in a subpleural, peribronchial, or band-like pattern, commonly associated with ground-glass opacity.
3. OP is a rare, but possible consequence of treatment with nab-paclitaxel and gemcitabine. To confirm an association between a drug and OP, other causes, especially infectious, must be ruled out.
4. Once the diagnosis of OP is confirmed, early intervention including withdrawal of the chemotherapeutic agent and prompt use of corticosteroids is recommended.

CONSENT

Written informed consent for the case to be published (including images, case history and data) was obtained from the patient(s) for publication of this case report, including accompanying images.

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