Favorable response to pemetrexed, cisplatin and bevacizumab in invasive mucinous adenocarcinoma: A case report and literature review

XIAN WEN SUN[1*], YONG JIE DING[1*], YU YAN ZHANG[1,2*], PEI LI CHEN[1], YA RU YAN[1], JI MIN SHEN[1] and QING YUN LI[1]

[1]Department of Respiratory Medicine and Critical Care Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200025; [2]Department of Respiratory Medicine, Zhongwei People's Hospital, Ningxia Hui Autonomous Region 751700, P.R. China

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Abstract. Invasive mucinous adenocarcinoma (IMA) was formerly referred to as mucinous bronchioloalveolar carcinoma. The lack of effective chemotherapy and comprehensive treatment for this type of tumor poses a great challenge in clinical practice. We herein report the case of a male patient with IMA who was treated with a combination of pemetrexed (500 mg/m^2), cisplatin (75 mg/m^2) and bevacizumab (15 mg/kg) as first-line chemotherapy. The patient achieved significant radiological improvement with 6 courses of this regimen. After the tumor progressed, the patient again achieved marked improvement with an additional 4 courses of the same regimen. The patient survived for a total of 30 months after the first chemotherapy. Therefore, bevacizumab in combination with pemetrexed/cisplatin may be an effective strategy for the treatment of IMA. The available literature on this chemotherapy regimen was also reviewed and discussed in the present study.

Introduction

Invasive mucinous adenocarcinoma (IMA), formerly referred to as mucinous bronchioloalveolar carcinoma (BAC), accounts for ~3-4% of all lung cancers and exhibits an increasing tendency annually (1). Due to the lack of specific clinical manifestations, the majority of the early cases were misdiagnosed as pneumonia, tuberculosis, and other diffuse pulmonary diseases. Furthermore, the pathogenesis, classification of subtypes and, particularly, the treatment protocols of IMA, have not yet been fully elucidated. In recent years, the platinum-based regimen with pemetrexed (PEM; a folic acid metabolism antagonist) and bevacizumab (BEV) was reported as an effective choice for patients with IMA (2,3). We herein present the case of a patient with IMA who achieved a rapid and stable response to an initial 6-cycle course and a subsequent 4-cycle course of combination chemotherapy with bevacizumab and pemetrexed/cisplatin. In addition, a review of the relevant literature on the treatment of IMA is presented.

Case report

A 42-year-old man, who was a current smoker (Brinkman index: 500; his father had died of lung cancer), presented with a sore throat and productive cough, night sweats, but no fever. A chest computed tomography (CT) scan revealed exudation and a cavity in the upper lobe of the right lung (URL), with enlarged mediastinal lymph nodes. No relief of the symptoms was achieved by a 2-week treatment with antibiotics. With obvious progression on imaging, the patient was diagnosed with pulmonary tuberculosis (Fig. 1A) and received diagnostic anti-tuberculosis therapy including pyrazinamide and ethambutol. One week later, the patient developed chest pain and dyspnea. Fibrotic bronchoscopy identified swelling and voluminous secretions in the URL, without any readily evident neoplasms. Adenocarcinoma cells were found in the bronchoalveolar lavage fluid. A positron emission tomography/CT scan demonstrated that the wall of the cavity was thick and the metabolic activity was increased [standardized uptake value (SUV)=6.3]; the right hilar lymph nodes were also enlarged (SUV=3.9). Following CT-guided percutaneous transthoracic needle biopsy in April 29, 2014, and subsequent histological analysis, the patient was diagnosed with IMA (Fig. 2A). An immunohistochemical analysis was positive for carcinoembryonic antigen, cytokeratin (CK)7, CK20 and

Correspondence to: Dr Qing Yun Li, Department of Respiratory Medicine and Critical Care Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, No. 197 Rui Jin Er Road, Shanghai 200025, P.R. China
E-mail: liqingyun68@hotmail.com

*Contributed equally

Abbreviations: BEV, bevacizumab; DDP, cisplatin; IMA, invasive mucinous adenocarcinoma; PEM, pemetrexed

Key words: invasive mucinous adenocarcinoma, chemotherapy, bevacizumab, pemetrexed, cisplatin

Table I. Response to systemic chemotherapy in patients with IMA.

Year	Authors	n	Pathological type (cases)	Treatment (no. of cases)	Response	(Refs.)
2005	West *et al*	58	BAC (58)	PTX (27)	ORR 14%; PFS 5 months; OS 12 months	(11)
2005	Scagliotti *et al*	19	BAC (19)	PTX (19)	ORR 11.1%; DCR 54%; PFS 2.2 months; OS 8.6 months	(10)
2007	Dziadziuszko *et al*	1	BAC (1)	WN (1)	Sx. improved; CR 6 months	(12)
2013	Dirican *et al*	44	BAC (44)	Platinum-based (21)	ORR 33.3% (4 PR, 3 CR); SD 42.8%; PD 23.8%	(13)
2016	Luo *et al*	3,681	Pure IMA (97) Mixed IMA (48) Ade. (3,536)	Platinum-based (78/36/2,753)	DFS (P=0.003); OS (P=0.514)	(14)
2013	Lau *et al*	27	Pure BAC (6) Mixed BAC (18)	PEM (24)	ORR 23%; PFS 6 months; OS 25 months	(17)
2011	Okuda *et al*	1	BAC (1)	PEM (1)	Sx. improved; CR-SD 12 months	(16)
2012	Duruisseaux *et al*	88	BAC (88)	TAX-based (29) GEM-based (12) PEM (2) Bortezomib (3) Erlotinib (1)	ORR 21%; DCR 56%; PFS 3 months	(19)
2010	Manson *et al*	1	BAC (1)	PEM (1)	Sx. improved; CR-SD 12.6 months	(18)
2013	Koma *et al*	2	IMA (2)	DDP/PEM/BEV (2)	Sx. improved; CR-SD 6.1 months	(2)
2013	Yamakawa *et al*	2	IMA (2)	DDP/PEM/BEV (2)	Sx. improved; CR-SD 4.7 months; CR-SD 7.2 months	(3)

Ade, adenocarcinoma; BAC, bronchioloalveolar carcinoma; IMA, invasive mucinous adenocarcinoma; PTX, paclitaxel; PEM, pemetrexed; DDP, cisplatin; BEV, bevacizumab; TAX, taxanes; GEM, gemcitabine; CBP, carboplatin; WN, vinflunine; Sx, symptom; S, tumor size; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; DCR, disease control rate; DFS, disease-free survival; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RR, response rate.

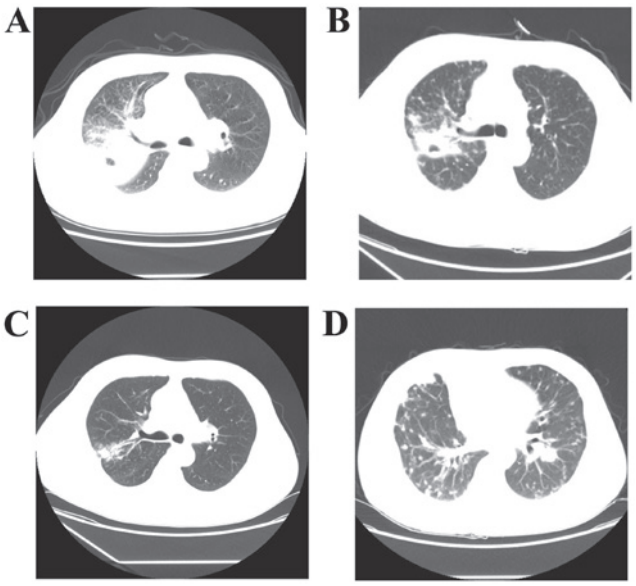

Figure 1. Chest CT performed on initial presentation revealed (A) diffuse exudation and a cavity in the URL; after 6 cycles of chemotherapy (B) partial exudation was seen in the URL, and the cavity was absorbed; (C) radiological deterioration was observed, with a thick-walled cavity in the URL; (D) bilateral multiple nodules of different densities were identified. CT, computed tomography; URL, upper lobe of the right lung.

epithelial membrane antigen, and negative for thyroid transcription factor-1. Brain magnetic resonance imaging and bone scintigraphy revealed no evidence of extrathoracic metastasis. Thus, the clinical stage was IIIb (cT4N2M0).

Table II. Response to EGFR-TKI in patients with IMA.

Year	Authors	n	Pathological type (no. of cases)	Treatment (no. of cases)	Evaluation	Response	(Refs.)
2003	Yano *et al*	2	BAC (2)	ZD1839 (2)	Sx., S	Sx. improved; Sputum cytology (-); CR 8-13 months	(24)
2003	Chang *et al*	2	BAC (2)	ZD1839 (2)	Sx., S	Sx. improved; CR 2 weeks - 2 months	(23)
2004	Bayle *et al*	1	BAC (1)	Gefitinib (1)	Sx., S	PR 12 months	(25)
2005	Milton *et al*	2	BAC (2)	Gefitinib (2)	Sx., S	Sx. improved; CR 4-7 weeks	(27)
2005	Kitazaki *et al*	2	BAC (2)	Gefitinib (1)	Sx., S	Sx. improved; CR 2 -2.7 weeks	(26)
2005	Taja-Chayeb *et al*	1	BAC (1)	Gefitinib (1)	Sx., S	Sx. improved; CR 4 weeks	(28)
2006	West *et al*	136	BAC (136)	Gefitinib (136)	ORR, CRs, OS	ORR 17%; CRs 6% (untreated), 9% (pretreated); OS 13 months	(29)
2007	Kijima *et al*	1	BAC (1)	Gefitinib (1)	Sx., S, OS	Sx. improved; CR-SD 8.5 months; OS 26 months	(30)
2009	Cadranel *et al*	88	BAC (88)	Gefitinib (88)	DCR, PFS, OS	DCR 29.4%; PR 12.9%; SD 16.4%; PFS 2.9 months; OS 13.2 months	(31)
2012	Popat *et al*	1	BAC (1)	Gefitinib (1)	Sx.	Sx. improved	(32)
2008	Miller *et al*	101	BAC (12) Ade. (89)	Erlotinib (101)	ORR, OS, PFS	ORR 22%; OS 4 months (BAC), 19 months (Ade); PFS 4 months.	(33)
2012	Yuyama *et al*	1	BAC (1)	Erlotinib (1)	Sx.	Sx. improved	(34)
2014	Sanz Rubiales *et al*	1	BAC (1)	Erlotinib (1)	S	PR 8 months	(35)

Ade, adenocarcinoma; BAC, bronchioloalveolar carcinoma; Sx, symptom; S, tumor size; CR, complete response; PR, partial response; SD, stable disease; PD; progressive disease; DCR, disease control rate; DFS, disease-free survival; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RR, response rate.

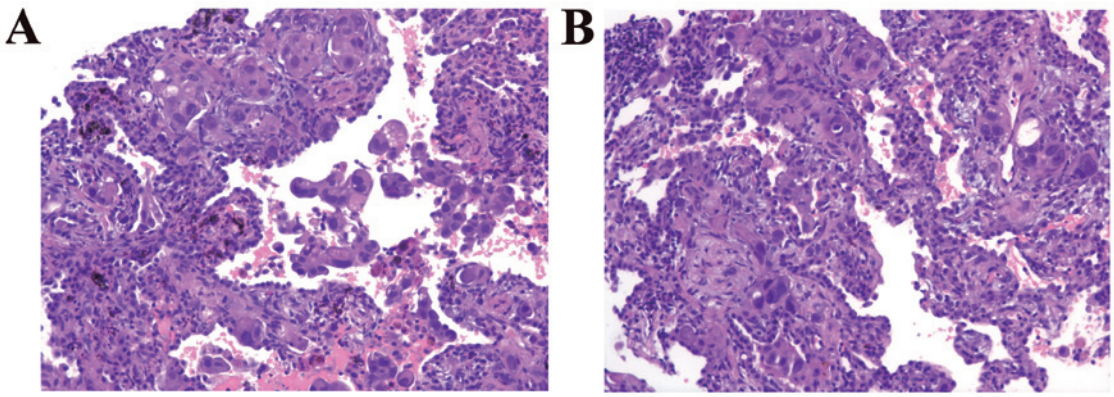

Figure 2. Histopathological evaluation (hematoxylin-eosin; magnification, x100). Thickened alveolar walls and pulmonary fibrous tissue proliferation were observed. Tumor cells were (A) scattered as single cells, with large nuclei and abundant mucin in cytoplasm or (B) arranged in nests or forming papillae along the alveolar wall.

Thereafter, the patient underwent first-line treatment with PEM (500 mg/m^2), cisplatin (DDP; 75 mg/m^2) and BEV (15 mg/kg) starting on day 1 every 21-day cycle, along with folic acid and vitamin B12 supplementation. The patient was evaluated for partial response (PR) after 6 cycles, with favorable radiological improvement (Fig. 1B). During follow-up, he exhibited radiological progression after 2 months (Fig. 1C) and he received 2 cycles of gemcitabine plus carboplatin, and 2 cycles of paclitaxel plus DDP (d1) combined with Conmana [icotinib; an epidermal growth factor receptor tyrosine kinase

(EGFR-TKI) (d8-d21)]. However, multiple metastatic lung nodules were identified on CT examination, indicating disease progression (Fig. 1D).

The second biopsy was also diagnosed as adenocarcinoma (Fig. 2B) with *KRAS* gene mutation. The patient was then administered another 4 cycles of PEM + DDP + BEV and again achieved stable disease. After the disease progressed again, vinorelbine and oxaliplatin combined with BEV were selected as the chemotherapy regimen. However, the patient did not respond to treatment, and succumbed to the disease in October 2016.

Discussion

We herein report that IMA may present as pneumonia mimicking pulmonary tuberculosis. Based on the unique radiological, morphological and genetic characteristics, BAC was renamed as IMA and classified as a new distinct category of lung cancer (4). The imaging findings are as follows (5): The solitary nodule type displays the characteristics of peripheral adenocarcinoma, which is lobulated or has scalloped margins, with heterogeneous density on CT scans, located subpleurally. The segmental type comprises multisegmental or multilobular lesions on bronchiolography, located in the lower lung. Finally, the diffuse type includes bilateral diffuse nodules of various sizes and distributions. In the present case, diffuse patchy shadows and a cavity in the URL were identified on chest CT, which displayed all the radiological characteristics mentioned above.

As regards the treatment of IMA, surgery remains the first choice for patients diagnosed as stage I or II (6,7). A wide variety of chemotherapeutic options are available for advanced BAC or IMA (8,9), but with a poor sensitivity rate. According to the results of 30 relevant studies, including 19 case reports and 11 clinical trials on IMA treatment (Table I), IMA exhibits a poor response to traditional chemotherapy, such as paclitaxel (10,11), navebine (12) and platinum-based chemotherapy (13,14), with a median progression-free survival (PFS) ranging from 2.2 to 5 months, and an overall survival (OS) ranging from 13 to 23 months.

PEM is a new member of the antifolate class that acts by inhibiting thymidylate synthesis, dihydrofolate reductase and glycinamide ribonucleotide formyltransferase, promoting S phase arrest of tumor cells (15). The response of IMA to PEM has been reported to be good, with fewer side effects (16,17), even in patients insensitive to gefitinib and/or erlotinib (18,19). BEV, a recombinant humanized monoclonal antibody developed against vascular endothelial growth factor that may prevent receptor binding and inhibit endothelial cell proliferation and vessel formation, has been used as a molecular-targeted treatment for malignant tumors in recent years (20,21). As a cell stabilizer, BEV exerts a synergistic effect with PEM. To a certain extent, PEM + BEV as second-line therapy for non-small-cell lung cancer (NSCLC) appears promising, with a PFS of 4 months and an OS of 8.6 months (22). The present case demonstrated the clinical efficacy and survival benefit of PEM/DDP and BEV in the treatment of IMA. The initial 6 cycles of treatment were effective and well-tolerated. The benefit of this combination therapy was consistent with that of an additional 4 cases reported in Japan (2,3).

Over the last decades, selective EGFR-TKIs achieved excellent results in the treatment of NSCLC (Table II). Gefitinib (23-32) and erlotinib (33-35), as first-generation EGFR-TKIs, significantly prolonged the OS to 13.2-23 months, although the PFS remained at 2.9-13 months. However, IMA derived from metaplasia of bronchiolar epithelia, is strongly associated with *KRAS* mutations and absence of *EGFR* mutations (36,37), indicating that EGFR-TKIs would not be beneficial for this patient.

Finally, this patient with IMA had a better prognosis, with a 10-month PFS and 30-month OS, compared with 4 cases reporting a 12.6-month OS (2,3). Therefore, early treatment with BEV combined with PEM and DDP may be beneficial in terms of prolonged IMA survival.

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Availability of data and materials

Not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of this case report and the accompanying images that have been submitted together with this manuscript.

Authors' contributions

XS, YD and YZ carried out the design and coordination of the study, PC, YY and JS performed the data and statistical analysis. XS and QL drafted the manuscript. All the authors have read and approved the final version of this manuscript.

Competing interests

The authors declare that they have no competing interests.

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