Case Report

Sustained response to FOLFOX and Bevacizumab in metastatic bronchial carcinoid – A case report and review of the literature

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Introduction

Bronchial carcinoids are neuroendocrine tumors of foregut origin typically considered benign. The WHO classifies the tumors as typical or atypical carcinoids. Bronchial carcinoids rarely metastasize to the liver. Metastatic carcinoids can be cured in some instances by hepatic resection however there is a significant rate of relapse following curative resection of neuroendocrine tumors at five years (1,2). In patients with midgut metastatic neuroendocrine carcinoma octreotide may provide an improvement in progression free survival (PFS) over placebo (3). The role of chemotherapy and antiangiogenic therapy in this disease is evolving. We present a patient with diffuse hepatic metastatic from bronchial carcinoid, who had a durable partial response to octreotide plus mFOLFOX6 and bevacizumab.

Case presentation

A 65-year-old male nonsmoker who in November 2000 underwent a right middle lobectomy with negative margins followed by adjuvant chemoradiation therapy with carboplatin, paclitaxel as radiation sensitizers at an outside facility for the diagnosis of atypical bronchial carcinoid. Post-surgery, the patient was disease free for over five years. In October 2006, surveillance Octreotide scans demonstrated increased activity in the left hepatic lobe, with non-specific activity in the right lung. CT scan revealed a hypodense mass in the left hepatic lobe and a biopsy of this mass was obtained. The biopsy was positive for metastatic neuroendocrine tumor and immunohistochemical studies were positive for chromogranin. The patient was treated with a combination of cisplatin and etoposide starting in December 2006, but developed progressive disease in the liver after four months. He was then switched to carboplatin and paclitaxel in April 2007 and following three cycles of this regimen he was evaluated in our institution for a second opinion.

On initial assessment, he had no chest tightness, productive cough, shortness of breath or palpitations. He also had no diarrhea, abdominal pain, nausea, vomiting or flushing. His past medical history was positive for hypertension controlled on Amlodipine 10mg daily. Physical examination: Eastern Cooperative Oncology Group (ECOG) performance status of one. He had an enlarged and palpable left hepatic lobe, with normal cardiopulmonary examination.

A computed tomography (CT) scan of the chest, abdomen and pelvis demonstrated a well-circumscribed mass occupying the bulk of the left hepatic lobe (7.7 x 9.0 cm) (Figure 1A and 1B). A biopsy specimen of the mass was consistent with metastatic neuroendocrine carcinoma. The chromogranin A level was 468 ng/mL (normal ≤ 36.4 ng/mL). The patient's case was reviewed in

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our multidisciplinary tumor board and he was considered potentially resectable. Subsequently, in August 2007, he underwent surgical resection of segments II and III of the liver and intraoperative examination revealed that the tumor was located in these two segments.

Pathologic examination of the specimen demonstrated an encapsulated, 8 x 8 x 6.5 cm well-differentiated neuroendocrine tumor morphologically consistent with metastatic carcinoid to liver. The resection margins were negative and lymphovascular invasion was identified. Immunohistochemical staining was positive for chromogranin and synaptophysin and negative for insulin, glucagon, serotonin, calcitonin, bombexin, TTF and CDX-2 (Figure 2). The Ki-67 immunostain showed a low proliferative activity. The patient had an uneventful post-operative course. Approximately 1 month after resection, his serum chromogranin A level was 19 ng/mL (normal ≤ 15 ng/mL) and repeat octreotide scan again demonstrated non-specific increased activity in the right lower lung. Seventeen months after the surgical resection, octreotide scan demonstrated increased activity in the right lobe of the liver, skull, humerus and ribs in addition to persistent uptake in the right lower lung. The CT scan demonstrated innumerable hypodense lesions in both hepatic lobes. Therapy was commenced with the long acting somatostatin analogue (Octreotide LAR) monthly with initial stable disease. After nine months of therapy with Octreotide LAR, he developed progressive disease, with rise in the serum chromogranin from 340 to 2980 (normal ≤ 36.4 ng/mL) and increased uptake of octreotide in the bones on Octreoscan in addition to progressive disease in the liver. (Figure 3A and 3B)

He was started on modified FOLFOX 6 (5-FU, 400 mg/m^2 bolus infusion, followed by Leucovorin 400 mg/m^2 and Oxaliplatin 85 mg/m^2 given in "Y" over 2 hours followed by 5 FU 2,400 mg/m^2 continuous infusion over 46 hours) plus bevacizumab in addition to Octreotide LAR and zolendronic acid in October 2009, with achievement of partial response by RECIST criteria, as noted on the CT scan obtained after 9 and 18 cycles of chemotherapy (Fig 4A and 4B respectively) The serum chromogranin A level decreased to 424 by December 2010. He received 26 cycles of mFOLFOX6 plus bevacizumab administered every 2 weeks over 16 months without dose reduction. The treatment was well tolerated, and he experienced NCI-CTC grade 2 tinnitus with sensorineural hearing impairment that did not require treatment; grade 2 mucositis, anemia and neutropenia. He also had grade 1 thrombocytopenia, proteinuria and peripheral sensory neuropathy. He had no grade 3 or 4 adverse events. Upon the development of grade 2 tinnitus, the treatment with modified FOLFOX 6 was delayed for two weeks to enable full audiology and otolaryngology evaluation. On occasion the patient had treatment delays for personal reasons. In February 2011 restaging imaging studies demonstrated progressive disease in the liver and bones and he was switched to everolimus.

Discussion

Bronchial carcinoid tumors are neuroendocrine neoplasms of foregut origin which are generally considered low grade neoplasms. These tumors usually present with respiratory symptoms such as cough, wheezing, hemoptysis, and recurrent pneumonias (3-5). Carcinoid tumors greater than 5mm in diameter are classified as typical or atypical based on the mitotic activity and necrosis. Typical features include mitotic activity in fewer than 2 cells per 10 HPF and absence of focal necrosis. Atypical features include greater mitotic activity and punctuate necrosis (3,5,6). Metastasis to regional lymph nodes occurs in less than 15% of typical bronchial carcinoids, but may be present in 30% to 50%

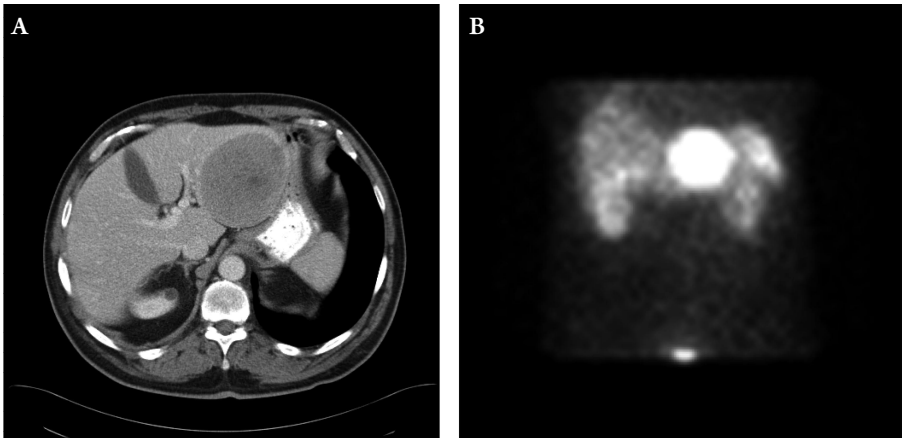

Figure 1A and 1B showing large left lobe liver metastases with increased activity on Octreoscan

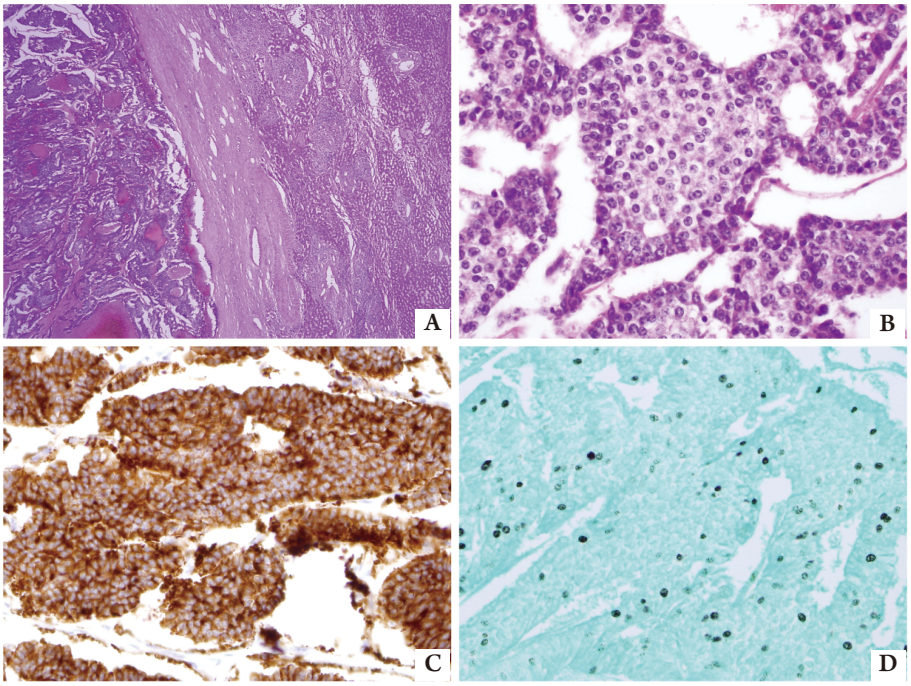

Figure 2 A. Well encapsulated tumor (H&E, 100x); B. The tumor is composed by uniform and polygonal cells with scant eosinophilic cytoplasm and coarsely granular chromatin (H&E, 400x); C. Tumor cells show diffuse and strong cytoplasmic immunoreactivity for synaptophysin (SYN, 400x); D. Ki67 immunostaining showing low proliferative activity (Ki67, 200x).

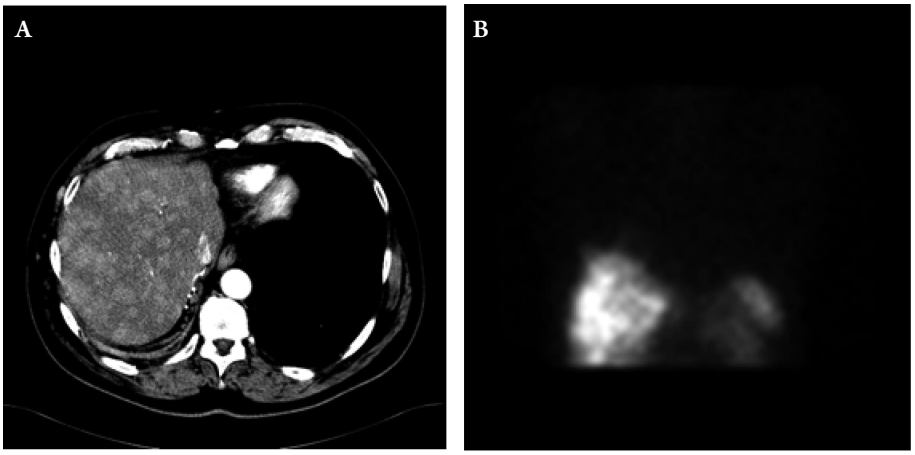

Figure 3A and 3B showing diffuse metastases in the liver with increased activity on Octreoscan

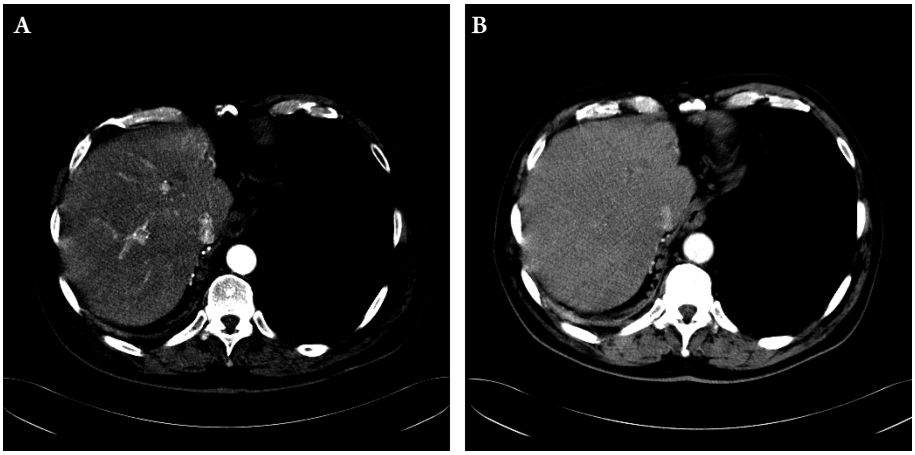

Figure 4A and 4B showing a sustained response in the liver after 9 and 18 cycles of FOLFOX + Bevacizumab

of atypical tumors (4,5). Certain features, like extension along the bronchial tree, may increase the risk of metastasis of typical bronchial carcinoids (7) Peripheral tumors with typical features are preferably removed with a large wedge or segmental resection, whereas more radical procedures, such as lobectomy with lymph node sampling, bi-lobectomy, sleeve resection, or pneumonectomy, are often chosen for central or atypical carcinoids. The long-term postoperative survival is 83% to 96% for typical carcinoids and 31% to 79% for atypical carcinoids (4-6).

Resection of metastasis may have a curative role in neuroendocrine cancers, however, about 90% of patients with liver metastases have bilateral and multifocal hepatic metastases and only 10-25% of patients have tumors that are sufficiently localized to allow for a curative resection (1,8). In selected patients with resectable liver metastases, surgery provides both a symptomatic relief and a potential survival benefit (5-year actuarial survival of 18% to 29% without surgery, increasing to 50% to 79% after resection) (8,9). Despite the multifocal and unresectable nature of many patients with liver metastases, the clinical course can be prolonged and debilitating with pain due to progressive increase in liver size and development of carcinoid syndrome in patients with hormonally active cancers (8). Debulking surgery with resection of greater than 90% of gross tumor in patients whose tumors cannot be completely excised provided both a palliative and a potential survival benefit (1,10).

Metastatic carcinoid tumors are relatively chemoresistant (4,11,12). However, oxaliplatin in combination with a fluoropyrimidine has demonstrated activity in metastatic neuroendocrine tumors (11,13,14). However, we are unaware of any reported case of a patient with metastatic bronchial carcinoid treated with FOLFOX or XELOX (capecitabine and oxaliplatin in combination). In patients with well differentiated neuroendocrine tumors of the gastro-entero-pancreatic region, the combination of capecitabine and oxaliplatin had a clinical benefit of 78% (30%PR and 48%SD) (15). Somatostatin analogues have been historically used in patients with NET for symptom palliation. However, antitumor effect was not demonstrated until recently. The PROMID study group demonstrated that Octreotide LAR significantly improved the PFS from 6.6 to 14.3 months over placebo in patients with functional and non-functional midgut NETs (16).

The hypervascular nature of neuroendocrine carcinomas makes them an interesting target for antiangiogenesis agents. In patients with well differentiated pancreatic neuroendocrine tumor, a recent phase 3 clinical trial with the antiangiogenesis agent sunitinib showed a significant improvement in PFS over placebo, from 5.5 to 11.3 months (17). In an earlier phase 2 trial, sunitinib demonstrated a clinical benefit of 85.4% (2.4% ORR and 83% SD) in patients with advanced carcinoid; however, the authors did not specify how many patients had stable disease at study entry and the ORR in carcinoids was less than the 16.7% observed in pancreatic NET (18). Bevacizumab with and without IFN has shown activity in neuroendocrine tumors (19,20). Preliminary data of a small Phase II clinical trial of FOLFOX and bevacizumab administered every 2 weeks in patients with advanced and progressive NETs including carcinoid tumors demonstrated promising clinical activity, with 20% PR and 80% SD in the patients with carcinoid (21). The patients received a median of 11 cycles (range 3 to 26) of chemotherapy with 30% Grade 3-4 neutropenia, 38% grade 3-4 fatigue and 23% grade 3-4 hypertension (21). Preliminary results presented at the 2010 ASCO annual meeting from another phase II clinical trial of XELOX plus bevacizumab in 31 patients with predominantly metastatic unresectable enteropancreatic NETs showed a clinical benefit ratio of 94% (23% PR and 71% SD). However, it is unclear if any of the patients enrolled in these studies of XELOX or FOLFOX with bevacizumab had metastatic bronchial carcinoid (20-22). The MTOR inhibitor everolimus has demonstrated activity in NETs; in phase II clinical trial involving patients with low to intermediate grade NET, everolimus achieved a PR of 17% and 27 % in carcinoid tumors and pancreatic NET respectively (23). A recent phase III clinical trial of everolimus compared to placebo in patients with progressive metastatic pancreatic NET demonstrated a statistically significant increase in PFS from 4.6 months to 11months in favor of everolimus (24). The result of the recent phase III clinical trial RADIANT-2 in patients with non-pancreatic NETs including bronchial carcinoids, showed that the combination of everolimus and octreotide led to a 5.1 month increase in PFS compared to octreotide plus placebo (16.4 vs. 11.3 months); however, this did not meet the predetermined statistical end point (25).

This is the first case of a patient with bronchial carcinoid treated with FOLFOX and bevacizumab. FOLFOX and XELOX with or without bevacizumab appear to be a very attractive chemotherapy regimen in metastatic neuroendocrine tumors. The response and clinical benefit of FOLFOX with bevacizumab in this case suggest that this treatment is active and should be further studied in patients with metastatic and unresectable bronchial carcinoid tumors. The emergence of new treatment options in NET is exciting; however the place of these agents in the treatment algorithm of NET remains to be better defined.

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