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CASE REPORT

Metastatic thymic-enteric adenocarcinoma responding to chemoradiation plus anti-angiogenic therapy: A case report

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Abstract

BACKGROUND

Thymic-enteric adenocarcinoma with positive expression of CDX2 and CK20 is rare in adults, with only 16 reported cases. However, standard treatment options for this type of thymic adenocarcinoma has not yet been established. Therefore, we report a case of stage IV thymic-enteric adenocarcinoma treated with radiotherapy, chemotherapy, and anti-angiogenesis therapy.

CASE SUMMARY

We report a case of thymic-enteric adenocarcinoma occurring in a 44-year-old woman. The tumor was considered unresectable owing to its invasiveness. The patient was treated with six cycles of oxaliplatin (130 mg/m², day 1) and capecitabine (1000 mg/m² BID, days 1-14). During the first three cycles of chemotherapy, concurrent radiotherapy (60 Gy/30 fractions) and anti-angiogenic therapy using apatinib were recommended. The primary tumor achieved partial remission based on the Response Evaluation Criteria in Solid Tumors. During follow-up, there was no evidence of disease relapse, except a high serum CA19-9 level. The patient is alive and regularly followed. Based on the previous literature and the present case, we believe that early diagnosis of thymic-enteric adenocarcinoma is important.

CONCLUSION

XELOX (capecitabine plus oxaliplatin) combined with radiotherapy is an optional therapy for inoperable thymic-enteric adenocarcinoma.

Key Words: Radiotherapy; Chemotherapy; Case report; Thymic adenocarcinoma; Antiangiogenic therapy; Thymic-enteric adenocarcinoma

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Core Tip: This report introduces the diagnosis and treatment of a metastatic thymicenteric adenocarcinoma with positive expression of CDX2 and CK20. For the first time, radiotherapy and chemotherapy combined with anti-angiogenesis therapy were used. The tumor was partially remitted, and there was no sign of recurrence. XELOX (capecitabine plus oxaliplatin) combined with radiotherapy is an alternative treatment for inoperable metastatic thymic-enteric adenocarcinoma.

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INTRODUCTION

Thymic cancer is rare, accounting for only 0.06% of all thymic neoplasms^[1]. It may be asymptomatic or associated with an intermittent cough, chest pain, or dyspnea. According to the 2015 World Health Organization thymic cancer classification, its histological types include squamous cell carcinoma, lymphoid epithelioid carcinoma, or basal-like carcinoma. However, the enteric type was first identified in 2003^[2]. To date, a total of 16 cases of thymic adenocarcinoma with positive expression of CDX2 and CK20 have been reported (Table 1). However, standard treatment options for this type of thymic adenocarcinoma have not yet been established. We report a case of stage IV thymic-enteric adenocarcinoma treated with radiotherapy, chemotherapy, and anti-angiogenesis therapy. Our primary result demonstrated the effectiveness of a comprehensive approach.

CASE PRESENTATION

Chief complaints

A 44-year-old woman was admitted to our hospital for dyspnea with chest pain in April 2018.

History of present illness

The patient had no history of present illness.

History of past illness

The patient had no history of past illness.

Personal and family history

The patient had no personal and family history.

Physical examination

No obvious abnormalities were found on physical examination.

Laboratory examinations

Laboratory tests showed elevated levels of several serum tumor markers (CA19-9, 483.98 U/mL; CA125, 111.44 IU/mL; CA242, 138.50 IU/mL; cytokeratin-19 fragment, 5.34 ng/mL; and carcinoembryonic antigen, 20.07 ng/mL). Liver and kidney function tests were normal. The pericardial effusion was bloody, and tumor cells were detected. Mediastinal mass biopsy showed pathological adenocarcinoma infiltration (Figure 1A). Immunohistochemical staining showed that the tumor cells were positive for CK20 (Figure 1B), CDX2 (Figure 1C), villin, and EGFR; partially positive for CA15-3; and negative for lung cancer markers, including CK7, TTF-1, and Napsin A. The Ki-67 index was 70%. Moreover, wild types of KRAS, NRAS, and BRAF were detected. The pathological results suggested intestinal metastatic adenocarcinoma. However, no other primary tumor was found on systemic examination.



Table 1 Clinicopathologic features of 16 patients with thymic adenocarcinoma as reported in the literature

Case No.	Age	Gender	Ki-67	Treatment	Outcome	Ref.
1	70	Male	20%- 30%	Surgery	AWD, 7 mo	[2]
2	59	Female	NA	Surgery + chemoradiotherapy + radiotherapy	Alive with disease, 11 mo (bone and lung metastasis)	[8]
3	41	Female	90%	Surgery	AWD, 18 mo	[9]
4	39	Female	NA	Surgery	AWD, 159 mo (recurrence +)	[9]
5	28	Female	NA	Surgery + chemotherapy (GEMOX) + radiotherapy	AWD, 30 mo (2 times recurrence)	[10]
6	55	Male	NA	Surgery + radiotherapy	AWD, 14 mo	[11]
7	36	Female	NA	Surgery + chemotherapy (Taxol/CDDP) + radiotherapy	DOD, 15 mo	[<mark>12</mark>]
8	66	Female	NA	Surgery	AWD, 5 yr	[13]
9	NA	NA	NA	Surgery	NA	[14]
10	52	Female	NA	Surgery + chemotherapy (cisplatin + etoposide/carboplatin + paclitaxel) + radiotherapy	Alive with disease, 11 mo (lung and lymph node metastasis)	[15]
11	38	Male	NA	Surgery + radiotherapy + chemotherapy (carboplatin + docetaxel)	DOD, 12 mo (bone metastasis)	[15]
12	55	Male	NA	Surgery + chemotherapy (carboplatin + docetaxel/paclitaxel)	DOD, 24 mo (bone, liver, lung, adrenal gland metastases)	[15]
13	41	Male	NA	Surgery	AWD, 43 mo (lung metastasis+)	[<mark>16</mark>]
14	34	Male	NA	Surgery + chemotherapy (carboplatin, Adriamycin, cyclophosphamide, and vincristine) + radiotherapy	DOD, 20 mo	[17]
15	15	Male	NA	Surgery + radiotherapy	DOD, 26 mo	[18]
16	29	Female	NA	Surgery	AWD, 8 mo	[19]
Present case	44	Female	70%	Concurrent chemoradiotherapy + antiangiogenic therapy	AWD	

AWD: Alive without disease; DOD: Died of disease; NA: Not available; NOS: Not otherwise specified.

Imaging examinations

Whole-body positron emission computed tomography (CT) (Figure 2A) showed an anterior calcified mediastinal mass measuring approximately 43 mm × 38 mm with an increased edge radioactivity uptake [maximum standardized uptake value (SUV) of 6.4; CT value of 41.8 HU]; increased pericardial radioactive uptake and a fluid density shadow; and increased sternal spot-like radioactivity uptake (maximum SUV value of 3.4).

FINAL DIAGNOSIS

After consultation with histopathologists in our institution, the tumor was diagnosed as a thymic adenocarcinoma (enteric type T4N0M1b stage IVb) with pericardial and sternal metastases according to the American Joint Committee on Cancer Staging Manual Eight Edition (2017).

TREATMENT

A comprehensive therapeutic regimen was administered. First, the patient underwent six cycles of oxaliplatin (130 mg/m², day 1) and capecitabine (1000 mg/m², BID, days 1-14) therapy. During the first three cycles of chemotherapy, concurrent radiotherapy (60 Gy/30 fractions) targeting the thymic mass was planned. Meanwhile, antiangiogenic therapy using apatinib, a VEGFR2 inhibitor (Jiangsu Hengrui Pharmaceutical Company Limited, Jiangsu Province, China), was omitted. This

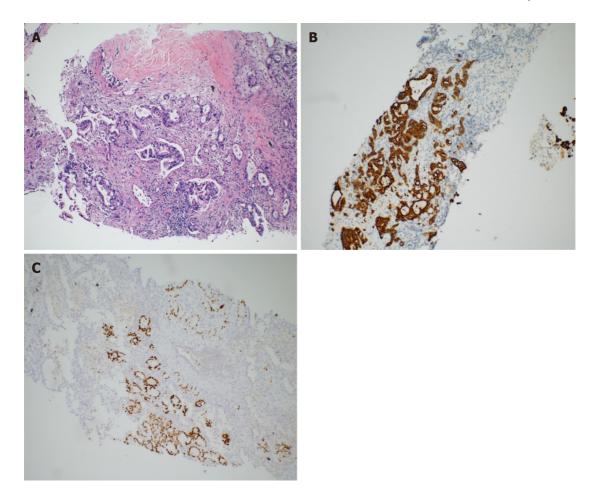


Figure 1 Pathological and immunohistochemical features of puncture tissue of the mediastinal tumor (× 100). A: The tissue was infiltrated by adenocarcinoma cells; B: Neoplastic cells were positive for cytokeratin; C: CDX-2 20 (× 100).

elicited grade II myelosuppression and grade II radioactive esophagitis during the concurrent chemoradiotherapy.

OUTCOME AND FOLLOW-UP

The patient's chest pain and dyspnea were significantly relieved after chemoradiotherapy. The thymus mass size was reduced after radiotherapy (30 Gy/15 fractions), but the patient occasionally experienced tachycardia. To reduce heart toxicity, we narrowed the irradiation field. During treatment, the tumor continued to shrink, as shown in Figure 2B and C. After six cycles of XELOX, chest CT showed that the tumor was approximately 37 mm × 20 mm (Figure 2D). Laboratory tests showed that only one serum tumor marker (CA19-9, 60.70 U/mL) remained elevated. The patient refused physical examination during her long-term follow-up; however, she was alive without recurrence for 16 mo when this paper was written.

DISCUSSION

During embryogenesis, the thymus and gut originate from the same arch endoderm. Intriguingly, tuft cells were found to be present in the adult thymus^[3]. In fact, tuft cells are functional intestinal epithelial cells^[3]. Moreover, mutations in tuft cells elicit gut carcinogenesis in humans. In this regard, thymic tuft cells' role as potential sources for thymic carcinogenesis should be investigated.

To the best of our knowledge, there is no standard of care for the thymic-enteric adenocarcinoma. Previously, patients were mainly treated surgically because the disease was localized. In this case, tumor resection was challenging because of pericardial involvement. Initially, the Ki-67 index was 70%, suggesting that the tumor



Li M et al. A case of metastatic thymic-enteric adenocarcinoma

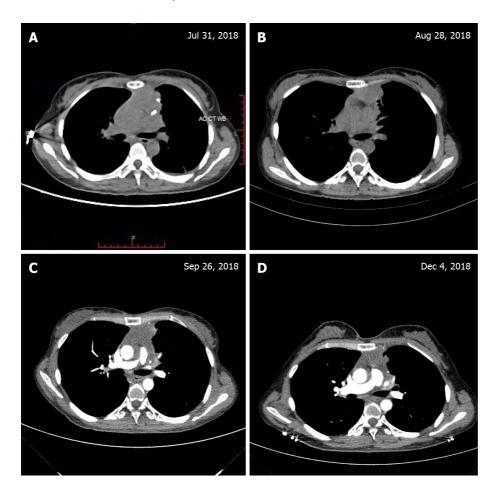


Figure 2 Serial high-resolution computed tomography scans of the chest. A: The computed tomography (CT) scan on July 31, 2018 showing an anterior mediastinal mass with calcification; B: The CT scan on August 28, 2018 showing that the anterior mediastinal mass was improved during the treatment; C: The CT scan on September 26, 2018 showing that the anterior mediastinal mass decreased during the treatment; D: The CT scan on December 4, 2018 showing that the anterior mediastinal mass was stable after treatment.

cells expanded in number. Proliferative cells are sensitive to ionizing irradiation^[4]. Therefore, we chose radiotherapy for controlling the primary tumor, thereby alleviating the patient's symptoms. Meanwhile, systematic chemotherapy plus antiangiogenic therapy was used as the main treatment. Based on the similarities between thymic-enteric adenocarcinoma and colorectal cancer in histologic phenotype, the XELOX regimen was selected. Capecitabine inhibits DNA synthesis^[5], while oxaliplatin induces immunogenic cell death. Moreover, angiogenic factors such as VEGF were detected in the malignant effusion^[6]. Secreted by tumor cells, VEGF is a potent inducer of angiogenesis^[6]. In this process, VEGF can significantly increase vascular permeability. Inhibition of angiogenesis in tumors limits pericardial effusion^[7]. Thus, apatinib was selected for this patient.

CONCLUSION

In this case, the primary tumor achieved partial remission according to the Response Evaluation Criteria in Solid Tumors, and there was no evidence of relapse during follow-up, except for high serum CA19-9 levels. In addition, treatment-related toxicity was manageable. Only grade II myelosuppression and grade II radioactive esophagitis occurred during treatment, thus demonstrating that our treatment was effective in this patient.

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