

World Journal of *Clinical Cases*

World J Clin Cases 2022 April 26; 10(12): 3639-3968



EVIDENCE REVIEW

- 3639** Tilt and decentration with various intraocular lenses: A narrative review
Chen XY, Wang YC, Zhao TY, Wang ZZ, Wang W

REVIEW

- 3647** Role of zonula occludens in gastrointestinal and liver cancers
Ram AK, Vairappan B

MINIREVIEWS

- 3662** Pathophysiological mechanisms of hepatic stellate cells activation in liver fibrosis
Garbuzenko DV

ORIGINAL ARTICLE

Retrospective Cohort Study

- 3677** Predictors of unfavorable outcome at 90 days in basilar artery occlusion patients
Chiu YC, Yang JL, Wang WC, Huang HY, Chen WL, Yen PS, Tseng YL, Chen HH, Tsai ST

Retrospective Study

- 3686** Role of multidetector computed tomography in patients with acute infectious colitis
Yu SJ, Heo JH, Choi EJ, Kim JH, Lee HS, Kim SY, Lim JH
- 3698** Efficacy and prognostic factors of neoadjuvant chemotherapy for triple-negative breast cancer
Ding F, Chen RY, Hou J, Guo J, Dong TY
- 3709** Relationship between subgroups of central and lateral lymph node metastasis in clinically node-negative papillary thyroid carcinoma
Zhou J, Li DX, Gao H, Su XL
- 3720** Nomogram to predict postoperative complications in elderly with total hip replacement
Tan XJ, Gu XX, Ge FM, Li ZY, Zhang LQ
- 3729** Flap failure prediction in microvascular tissue reconstruction using machine learning algorithms
Shi YC, Li J, Li SJ, Li ZP, Zhang HJ, Wu ZY, Wu ZY

Observational Study

- 3739** Surgery in platinum-resistant recurrent epithelial ovarian carcinoma
Zhao LQ, Gao W, Zhang P, Zhang YL, Fang CY, Shou HF

- 3754** Anorectal dysfunction in patients with mid-low rectal cancer after surgery: A pilot study with three-dimensional high-resolution manometry

Pi YN, Xiao Y, Wang ZF, Lin GL, Qiu HZ, Fang XC

Randomized Controlled Trial

- 3764** Effect of wrist-ankle acupuncture on propofol dosage during painless colonoscopy: A randomized controlled prospective study

He T, Liu C, Lu ZX, Kong LL, Li Y, Xu Z, Dong YJ, Hao W

META-ANALYSIS

- 3773** Melatonin intervention to prevent delirium in hospitalized patients: A meta-analysis

You W, Fan XY, Lei C, Nie CC, Chen Y, Wang XL

- 3787** Risk factors for hospital readmissions in pneumonia patients: A systematic review and meta-analysis

Fang YY, Ni JC, Wang Y, Yu JH, Fu LL

CASE REPORT

- 3801** Anti-programmed death 1 antibody in the treatment of coexistent *Mycobacterium fortuitum* and lung cancer: A case report

Zhang CC, Chen P

- 3808** Acute pancreatitis-induced thrombotic thrombocytopenic purpura: A case report

Wang CH, Jin HF, Liu WG, Guo Y, Liu Z

- 3814** Successful management of life-threatening aortoesophageal fistula: A case report and review of the literature

Zhong XQ, Li GX

- 3822** Isolated coagulopathy without classic CRAB symptoms as the initial manifestation of multiple myeloma: A case report

Zhang Y, Xu F, Wen JJ, Shi L, Zhou QL

- 3828** Evaluation of intracoronary function after reduction of ventricular rate by esmolol in severe stenotic myocardial bridge: A case report

Sun LJ, Yan DG, Huang SW

- 3834** Pediatric living donor liver transplantation using liver allograft after *ex vivo* backtable resection of hemangioma: A case report

Li SX, Tang HN, Lv GY, Chen X

- 3842** Kimura's disease in soft palate with clinical and histopathological presentation: A case report

Li W

- 3849** Combined targeted therapy and immunotherapy in anaplastic thyroid carcinoma with distant metastasis: A case report

Ma DX, Ding XP, Zhang C, Shi P

- 3856** Successful multimodality treatment of metastatic gallbladder cancer: A case report and review of literature
Zhang B, Li S, Liu ZY, Peiris KGK, Song LF, Liu MC, Luo P, Shang D, Bi W
- 3866** Ischemic colitis after receiving the second dose of a COVID-19 inactivated vaccine: A case report
Cui MH, Hou XL, Liu JY
- 3872** Cryoballoon pulmonary vein isolation and left atrial appendage occlusion prior to atrial septal defect closure: A case report
Wu YC, Wang MX, Chen GC, Ruan ZB, Zhang QQ
- 3879** Surgical treatment for a combined anterior cruciate ligament and posterior cruciate ligament avulsion fracture: A case report
Yoshida K, Hakozaiki M, Kobayashi H, Kimura M, Konno S
- 3886** Successful robot-assisted partial nephrectomy for giant renal hilum angiomyolipoma through the retroperitoneal approach: A case report
Luo SH, Zeng QS, Chen JX, Huang B, Wang ZR, Li WJ, Yang Y, Chen LW
- 3893** Cryptococcal antigen testing of lung tissue homogenate improves pulmonary cryptococcosis diagnosis: Two case reports
Wang WY, Zheng YL, Jiang LB
- 3899** Combined use of extracorporeal membrane oxygenation with interventional surgery for acute pancreatitis with pulmonary embolism: A case report
Yan LL, Jin XX, Yan XD, Peng JB, Li ZY, He BL
- 3907** Dynamic navigation system-guided trans-inferior alveolar nerve implant placement in the atrophic posterior mandible: A case report
Chen LW, Zhao XE, Yan Q, Xia HB, Sun Q
- 3916** Anti-glomerular basement membrane disease with IgA nephropathy: A case report
Guo C, Ye M, Li S, Zhu TT, Rao XR
- 3923** Amniotic membrane transplantation in a patient with impending perforated corneal ulcer caused by *Streptococcus mitis*: A case report and review of literature
Hsiao FC, Meir YJJ, Yeh LK, Tan HY, Hsiao CH, Ma DHK, Wu WC, Chen HC
- 3930** Steriod for Autoimmune pancreatitis complicating by gastric varices: A case report
Hao NB, Li X, Hu WW, Zhang D, Xie J, Wang XL, Li CZ
- 3936** Antithrombotic treatment strategy for patients with coronary artery ectasia and acute myocardial infarction: A case report
Liu RF, Gao XY, Liang SW, Zhao HQ
- 3944** Mesh plug erosion into the small intestine after inguinal hernia repair: A case report
Xie TH, Wang Q, Ha SN, Cheng SJ, Niu Z, Ren XX, Sun Q, Jin XS
- 3951** Recurrence of infectious mononucleosis in adults after remission for 3 years: A case report
Zhang XY, Teng QB

- 3959** Vertical direction impaction of kissing molars: A case report

Wen C, Jiang R, Zhang ZQ, Lei B, Yan YZ, Zhong YQ, Tang L

LETTER TO THE EDITOR

- 3966** Comment on “Outcomes of different minimally invasive surgical treatments for vertebral compression fractures: An observational study”

Ma L, Luo ZW, Sun YY

ABOUT COVER

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Combined targeted therapy and immunotherapy in anaplastic thyroid carcinoma with distant metastasis: A case report

Dong-Xu Ma, Xiu-Ping Ding, Chi Zhang, Peng Shi

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Abstract

BACKGROUND

Anaplastic thyroid carcinoma (ATC), also called undifferentiated thyroid cancer, is the least common but most aggressive and deadly thyroid gland malignancy of all thyroid cancers[1]. It has poor prognosis, and is the leading cause of death from malignant thyroid tumors. The one-year survival rate is 20%, with a median overall survival (OS) of only 5 mo[2]. The aim of this report is to provide our experience in the diagnosis and treatment of ATC.

CASE SUMMARY

A patient with a thyroid mass underwent surgical treatment after developing symptoms of hoarseness. The resected tumor was pathologically diagnosed as ATC. Imaging examination revealed organ and lymph node metastasis. After multiple cycles of chemotherapy and local radiotherapy, the metastases were not relieved and gradually increased in size and new metastases appeared. The patient immediately received immunotherapy combined with targeted therapy. During treatment, immune-related adverse reactions occurred, which were improved after symptomatic treatment, and tolerated by the patient. The OS of the patient was more than 30 mo after immunotherapy combined with targeted therapy.

CONCLUSION

For metastatic ATC, surgical treatment, radiotherapy and chemotherapy have no significant effect on remission of the disease. However, immunotherapy has

made a breakthrough in the treatment of ATC.

Key Words: Anaplastic thyroid carcinoma; Distant metastasis; Nivolumab; Cabozantinib; Targeted therapy; Immunotherapy; Case report

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Core Tip: Anaplastic thyroid carcinoma (ATC) is a rare thyroid malignancy, it is extremely aggressive and has a very low survival rate. Immunotherapy combined with targeted therapy results in prolonged survival and good quality of life. We summarize the relevant clinical data and review the literature. This report aims to provide clinical experience in the treatment of an ATC patient by immunotherapy combined with targeted therapy.

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INTRODUCTION

Anaplastic thyroid carcinoma (ATC) is an undifferentiated tumor which is derived from follicular epithelial cells of the thyroid. The annual incidence of ATC is 1-2/1 000000 and accounts for 1%-2% of all thyroid carcinomas[3]. The prognosis of patients is associated with age, socioeconomic status, distant metastases, surgery, chemotherapy, etc[4,5]. At present, there is no definite or standardized treatment for ATC in order to prolong the survival of patients. Treatments include surgery, radiation, chemotherapy, immunotherapy, and targeted therapy. Patients are often diagnosed at advanced stages of the disease and it is difficult to completely remove ATC by surgery[6]. As a result, the overall response rate is usually very low, so is the overall survival rate. Due to the poor prognosis and lack of treatment, molecular characterization of the tumor may provide more targets and provide patients with more therapeutic options[7]. We here summarize the clinical diagnosis and treatment of an ATC patient. The patient showed significant improvement in survival following targeted therapy and immunotherapy.

CASE PRESENTATION

Chief complaints

A 65-year-old man was admitted to hospital due to hoarseness, cough and expectoration for 3 mo.

History of present illness

He was found to have a thyroid mass on physical examination.

History of past illness

The patient had no relevant medical history.

Personal and family history

There was no personal history of tobacco or alcohol consumption or any other family medical history.

Physical examination

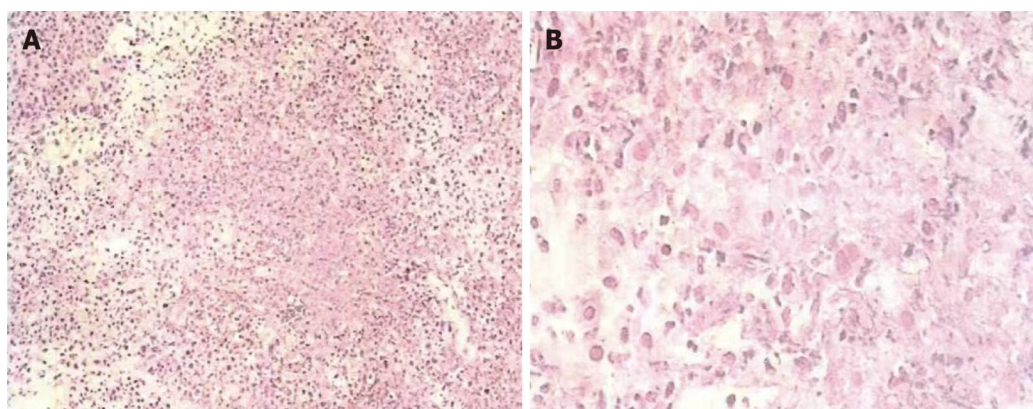
Neck examination showed no abnormal sign.

Laboratory examinations

Laboratory examination were unremarkable.

Imaging examinations

He was found to have thyroid nodules on thyroid ultrasound. And underwent thyroidectomy. Pathological diagnosis of the resected tissue suggested the possibility of ATC (Figure 1). Ten days later, positron emission tomography-computed tomography (PET-CT) showed multiple metastases in the



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Figure 1 Pathological features. A: First, the border was unclear, invasive growth was wide, and there was no capsule, and second, the tumor was extensively necrotic; B: Nuclear pleomorphism was evident, cells were small, and diffusely distributed, and finally, mitotic activity was high and invasion was strong.

right hilar and mediastinal lymph nodes, and left adrenal metastases (Figure 2). One month later, CT re-examination showed that mediastinal lymph node and left adrenal metastases were larger than before (Figure 3A). During chemotherapy, repeated CT showed that the mediastinal lymph nodes were not significantly changed, and left adrenal metastases were larger (Figure 3B). Brain magnetic resonance imaging (MRI) showed a cerebellar mass, which was considered to be metastasis (Figure 3C). In these two years of combination therapy, the results of regular review of brain MRI are as follows (Figure 4).

FINAL DIAGNOSIS

The patient was diagnosed with ATC with brain and adrenal metastases.

TREATMENT

The patient received multiple cycles of chemotherapy after thyroidectomy. During this period, the patient received radiotherapy to the thyroid tumor bed and metastases, with a planned prescribed dose of 2.0 Gy/fraction × 28 fractions. After the appearance of brain metastases, He then received radiotherapy for cerebellar metastases at a prescribed dose of 3.0 Gy/fraction × 14 fractions. After recurrence of metastasis, nivolumab (240 mg every two weeks) was administered in combination with cabozantinib (40 mg) for two years. During the treatment, the patient experienced some immune-related adverse events (irAEs) and vascular endothelial growth factor receptor-tyrosine kinase inhibitor toxicity, mainly gastrointestinal toxicity and pneumonia, manifested as abdominal pain, diarrhea, cough and dyspnea. However, the patient developed arteriovenous thrombotic events, which were considered to be caused by cabozantinib, so the drug was discontinued. But the patient insisted on anti-programmed death-1 (PD-1) therapy for two years, during which time, after symptomatic treatment with glucocorticoids, the grade of irAEs could be controlled below grade 1[8]. After re-follow-up, the dose of nivolumab was changed to 200 mg once every three weeks. The whole treatment process of patients is shown in Table 1.

OUTCOME AND FOLLOW-UP

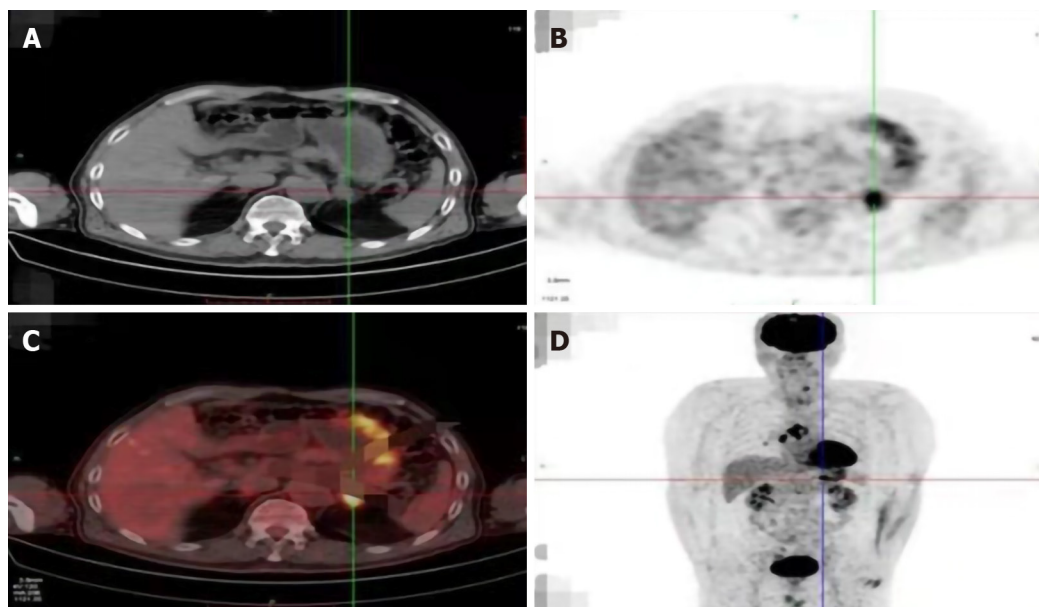
The patient's cerebellar and adrenal lesions were significantly reduced, and the corresponding symptoms also disappeared gradually. Clinical benefit was observed over 30 mo.

DISCUSSION

ATC has a high degree of malignancy and rapid progression, and its imaging diagnosis is difficult[9]. The positive rate of fine needle aspiration cytology is not high, and confirmation of the diagnosis mostly relies on postoperative pathology[10]. The patient in this report developed hilar and mediastinal lymph node and adrenal metastases, and was treated with chemotherapy, palliative radiotherapy and targeted

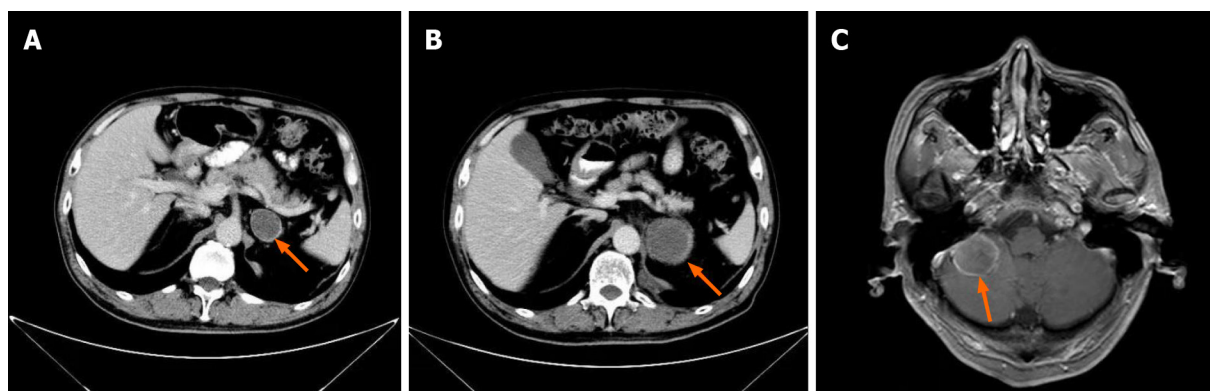
Table 1 Summarize the treatment of this case

Treatment mode	Starting and ending time	Efficacy
Surgery	August 30, 2017	Tumor resection; Disease progression
Chemoradiotherapy	October, 2017-April, 2018	Brain metastasis
Targeted therapy (Cabozantinib)	May, 2018-April, 2020	Organ metastases gradually shrink
Immunotherapy (Nivolumab)	July, 2018-	Prolonged progression-free survival



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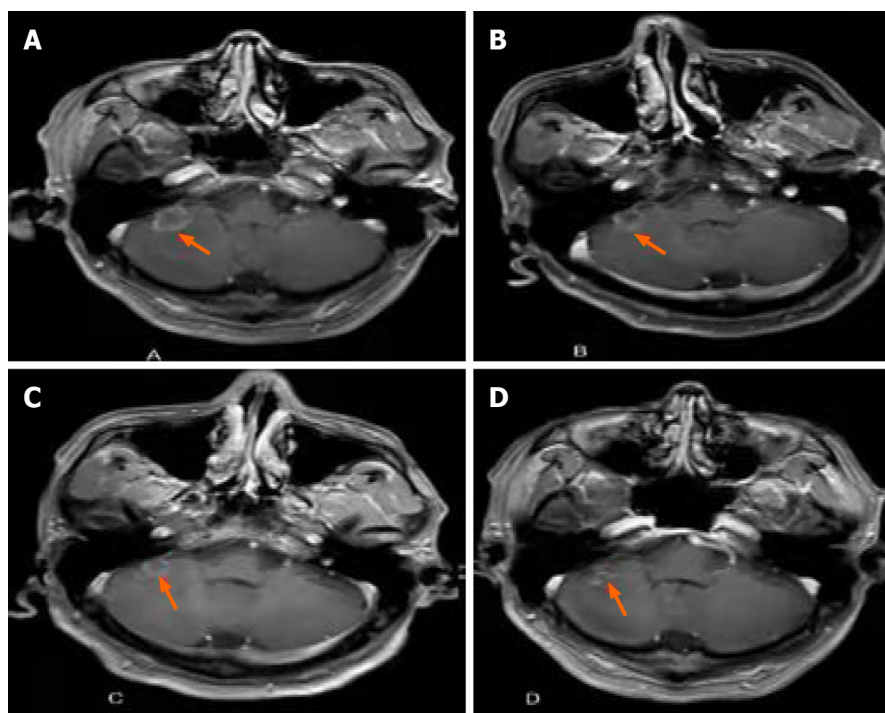
Figure 2 Positron emission tomography-computed tomography showed left adrenal metastases (On September 14, 2017). A: Computed tomography (CT) showed left adrenal metastasis; B: Cross-sectional positron emission tomography (PET) showed left adrenal metastasis; C: PET and CT fused layer showed left adrenal metastasis; D: Coronal PET-CT showed left adrenal metastasis.



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Figure 3 Metastasis during chemotherapy. A: Left adrenal lesion after two cycles of TP chemotherapy; B: Significant enlargement of the left adrenal lesion after chemotherapy; C: Brain metastases.

therapy, but the disease was not controlled. He was subsequently treated with targeted therapy combined with immunotherapy. Nivolumab is a monoclonal antibody that can bind to the PD-1 receptor, which can block the interaction between PD-1 and PD-L1/PD-L2, alleviates inhibition of the PD-1 pathway-mediated immune response, and restores tumor-specific T cell immunity. This combination allows the tumor cells that are otherwise induced by T cells to be released, in order to re-identify the tumor cells and attack and kill them[11]. By targeted therapy, it means that appropriate anti-cancer drugs are used to precisely hit cancer cells, thereby killing tumor cells and preventing



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Figure 4 Changes in brain metastases during combined immune and targeted therapy. A: Brain magnetic resonance imaging in October 2018; B: Brain magnetic resonance imaging in January 2019; C: Brain magnetic resonance imaging in June 2019; D: Brain magnetic resonance imaging in December 2019.

continued tumor growth[12]. The targeted anti-cancer drug can specifically select the carcinogenic site and combine with it to produce an effect *in vivo*, inducing apoptosis of tumor cells, but does not affect the normal tissue cells around the tumor; thus, it will not damage the normal cells of the body[13]. However, a single targeted therapy does have some limitations. Cancer cells can become resistant; the targets themselves change due to mutation, so that targeted therapy does not interact well with them [14]. Similarly, after long-term immunotherapy, tumor cells may undergo further variation, thereby evading the inhibition effect of immunotherapy. In addition, targeted therapies can also modulate immune responses. By analyzing the advantages and disadvantages of targeted drugs and immunotherapy, we have realized that these two therapies may have complementary effects in cancer treatment, and the combination of the two may increase the therapeutic effect[15]. In the present case, The resected tumor tissue was sent for immunohistochemical analysis and targeted next generation sequencing. However, only the RET gene was mutated. Treatment with Immunologicals may not have a significant therapeutic effect. So we used Cabozantinib. At that time, Nivolumab was relatively mature, more experiments were performed in other cancers, the safety was high, and furthermore, the subjective willingness of patients was strong, and the drugs were purchased and used on their own. the patient was treated with cabozantinib and nivolumab, and clinical benefit was seen over 30 mo. At present, the patient is alive and regularly followed up. In this patient, it was confirmed that immunotherapy and/or targeted therapy against PD-1 may be an effective treatment strategy for ATC, which can prolong survival of patients with ATC and may provide more treatment possibilities. Of course, there are still some issues to be resolved. While immunotherapy can relieve the disease and improve the patient survival, it will also cause immune-related adverse reactions. Therefore, to select a more appropriate treatment strategy according to individualized risk and benefit is important. However, it is expected that the survival rate of ATC can be improved by immune combined targeted therapy.

CONCLUSION

In this case report, it was confirmed that immunotherapy and/or targeted therapy against PD-1 may be an effective treatment strategy for ATC, which can prolong the survival of patients with this disease and provide more treatment possibilities. Finally, it is hoped that some treatment options can be better improved through immune combined targeted therapy to improve the survival rate of ATC.

FOOTNOTES

Author contributions: Ma DX wrote this paper; Shi P joined the surgery and revised the paper; Zhang C collect the information and follow up of the patient; Ding XP joined the targeted therapy and immunotherapy.

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