Pembrolizumab combined with Axitinib in ASPSCR1-TFE3 gene fusion translocation renal cell carcinoma: a case report and literature review

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Case Report

Keywords: Renal cell carcinoma, ASPSCR1-TFE3 gene fusion, Immuncheckpoint blockadeinhibitor, Anti-VEGF receptor tyrosine-kinase inhibitors

Posted Date: October 6th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2101971/v1

Abstract

Background: Translocation renal cell carcinoma (tRCC) is a subtype of nccRCC driven by MiT/TFE gene fusion. The demographic characteristics of tRCC include younger age at diagnosis, later staging at diagnosis, high degree of malignancy, poor prognosis, and female majority. There are currently no standard guidelines for the diagnosis and treatment of this type of kidney cancer. Objective: To investigate the efficacy of immuncheckpoint blockadeinhibitor combined with anti-VEGF receptor tyrosine-kinase inhibitors in ASPSCR1-TFE3 gene fusion translocation renal cell carcinoma(tRCC).

Case presentation: The paper describes a case of a 42-year-old Chinese female presented enlargement of multiple lymph nodes. Percutaneous aspiration cytology of the tumor on the left side of neck lymph node was confirmed to be malignant. Combined with pathology, PET-CT and genetic testing, the patient was diagnosed with ASPSCR1-TFE3 gene fusion tRCC with multiple metastases (left kidney, cT1aN1M1, stage IV), involving lymph nodes,liver, and bone. The patient was treated with Pembrolizumab combined with Axitinib. Up to June 2022, the patient's progression-free survival time was was more than 2 years, lesions in left kidney, lymph nodes, liver and bone reached stable status, partial response, complete response and stable status, respectively. The patient can receive treatment for side effects.

Conclusions: The report of this case could provide a helpful strategy for combination therapy of PD-1 antibody and VEGFRs inhibitor in rare ASPSCR1-TFE3 gene fusion tRCC.

Introduction

Renal cell carcinoma (RCC) is the second commonest cancer in urinary system. The most common pathological type of RCC was clear cell RCC (ccRCC), the other non-clear cell RCCs (nccRCC) include chromophobe RCC, papillary RCC, unclassified RCC, and rare classification such as MiT family translocation RCC, collecting duct carcinoma (CDC) and renal medullary carcinoma. Translocation renal cell carcinoma (tRCC) is a subtype of nccRCC driven by MiT/TFE gene fusion. The demographic characteristics of tRCC include younger age at diagnosis, later staging at diagnosis, high degree of malignancy, poor prognosis, and female majority [1]. Translocation renal cell carcinoma (tRCC) accounts for 20%-40% of RCC incidence in children and only 1% -1.6% of RCC incidence in adult. There are currently no standard guidelines for the diagnosis and treatment of this type of kidney cancer. Here we presented a case of a 42-year-old Chinese female with ASPSCR1-TFE3 gene fusion tRCC metastasized to liver, lymph nodes, and bone, who was treated with Pembrolizumab and Axitinib. Up to June 2022, the patient has been progression-free survival time was more than 2 years.

Case Report

A 42-year-old Chinese female presented with enlarged cervical lymph nodes as the first symptom in May 2020. Ultrasonography showed multiple enlarged lymph nodes in left neck and subclavian region (the maximum size was about 3.8×2.1 cm). CT showed multiple enlarged lymph nodes in left neck, supraclavicular fossa, armpit, retroperitoneum, inguinal region, pelvic cavity and regions around left adrenal region, abdominal aorta and vena cava, extensive irregular soft tissue nodules around retroperitoneal and iliac vessels, multiple lymph nodes which were considered as metastatic lymph nodes (Fig. 1).Left kidney cyst with calcification was also identified (Fig. 1). The immunohistochemical results of neck lymph nodes were CD10(+), PAX-2(+), PAX-8(+), RCC(+), P504S(+), TFE-3(+), CgA(-), Inhibin-a(-), Ki67(+,30%), Napsin A(-), S-100(+), TG(-), TTF-1(-), CA9(+), CD117(YR145) (-), CK7(-), HMB-45(-), AE1/AE3(-), PD-L1(22C3) TPS 20% (Fig. 2). Pathological findings supported metastatic RCC, which was prone to Xp11.2 translocation RCC. Genetic testing showed a breakage of 28% of TFE3 gene, ASPSCR1-TFE3 gene fusion, with a mutation abundance of 20.3%, low tumor mutation burden (TMB-L) and microsatellite stable (MSS). EGFR, ERBB2, ALK, ROS1, MET, RET, BRAF, KIT, PDGFRA, BRCA1/2, KRAS, NRAS, NTRK1/2/3, PALB2 and PIK3CA were not fused, rearranged or mutated. 18F-FDG PET/CT showed low-density nodular with calcification in the upper part of the left kidney (1.5×2.1 cm, SUVmax 3.4), multiple enlarged lymph nodes (diameter of 0.5–7.1 cm, SUVmax 1.9–5.6) in the left of neck, supraclavicular and subclavian fossa, armpit, pectoralis major and submuscular space, mediastinum, T11-L4 vertebral bodies and arteries and muscles around iliac fossa. Osteolytic lesions in the L1, 3 and 4 vertebral bodies was considered as metastases (SUVmax 3.8–4.2) (Fig. 3).

Treatment

The patient was diagnosed as ASPSCR1-TFE3 gene fusion tRCC (left kidney, cT1aN1M1, stage IV) and multiple metastases of lymph nodes, bone and liver. The patient were treated with 200 mg Pembrolizumab infusions per 3 weeks and 5 mg Axitinib orally twice daily. One week later, the patient developed extensive macular rash on face, neck, upper and lower limbs, chest and back, which accounted for nearly 50% of total body surface area. The patient was discontinued of Axitinib treatment. According to the 2020 CSCO guidelines for the management of toxicities associated with immune checkpoint inhibitors, the patient received prednisone acetate orally (0.5 mg/Kg) and rashes completely disappeared after 17 days of hormonotherapy. The treatment was restarted at second cycle, to reduce skin irritant reaction and other related adverse events, the dose of Pembrolizumab was reduced to 100 mg infusions per 3 weeks and 5 mg Axitinib orally twice daily. After two cycles of treatment, the imaging assessment showed lymph nodes at neck reached partial response, abdominal lymph nodes and the left kidney lesions were stable and hepatic lesions achieved complete response (Fig. 4). 18F-FDG PET/CT showed significant no decrease of low-density nodular lesion in left kidney and no abnormal radioactive concentration. Multiple enlarged lymph nodes partially disappeared, and some lymph nodes significantly smaller than before. Radiometabolic activity of multiple osteolytic lesions at the first, third and fourth lumbar vertebras reduced than before image assessment suggested that the scheme was beneficial to patients' disease control, therefore, the treatment was continued to be used.

Up to June 2022, a total of 25 cycles of Pembrolizumab and Axitinib were received, and tumors at left kidney, lymph nodes, liver and bone were assessed as stable disease, partial response, complete response and stable disease, respectively. The adverse events were rash (CTCAE grade 3), secondary hypertension (CTCAE grade 3), secondary hypothyroidism (CTCAE grade 2) and diarrhea (CTCAE grade 1).

Discussion

In 1991, Tomlinson [2] published the first pediatric case report about tRCC, which was found in a 17-month-old child. It was a group of neoplasms distinguished by chromosomal translocations with breakpoints involving the TFE3 transcription factor gene, which mapped to the Xp11.2 locus. The only recurrent focal alteration in tRCC was homozygous deletion at the CDKN2A/2B locus (9p21.3) [3]. An analysis of arm-level copy number alterations among 17 tRCC cases in the TCGA cohort revealed the most frequent alterations to be a hemizygous loss of chromosome 3p (28.6%), chromosome 9p (23.5%), chromosome 18 (29.4%), and chromosome 22q (18.8%), as well as a gain of 17q (20.0%). MiT / TFE gene fusion is a recognized genetic lesion in tRCC. There are two chromosomal rearrangements in Xp11.2 tRCC, translocation and inversion, among which the balanced translocation of the chromosome is the main one. The balanced translocation was characterized by the fracture of TFE3 gene at Xp11.2 and the interchangeover with the broken genes on other chromosomes. DNA double-strand breaks (DSBs) occur before chromosome rearrangement and are a prerequisite for gene fusion [4]. The main known pathogenesis of TFE3 include: TFE3 affects lysosomal signaling and autophagy through its interaction with Wnt /β-chain proteins and regulation of mTOR .

Eighteen fusion partners of TFE3 gene had been reported so far[5–7]. The most common TFE3 gene fusion partners were ASPSCR1, SFPQ1, PRCC and NONO. The tumors formed by TFE3 gene translocation and fusion are called TFE3-related tumors, mainly seen in the following diseases: Xp11.2 translocation/TFE3 gene fusion-related RCC; Alveolar soft-part sarcoma (ASPS); Epithelioid hemangioendothelioma (EH) with TFE3 gene fusion; Perivascular epithelioid cell tumor (PEComa) with TFE3 gene fusion.

Cases published in the last 10 years regarding renal cancer in TFE3 were reviewed. 30 cases of TFE3 nccRCC were reported [6,8–28] (Table 1). Among them, there were 16 males and 14 females, ranging in age from 3 to 72 years old, and 3 patients younger than 18 years old.At initial diagnosis, there were 11 patients with stage I, 5 patients with stage II, 2 patients with stage III, 8 patients with stage IV and 4 patients with unknown stage. There were 27 patients who received surgery, 2 patients did not received surgery, and 1 patient's operation condition was unknown. Twenty-two patients underwent FISH testing, and 8 patients did not show FISH testing in cases. Patients with TFE3 fusions included ASPSCR1 (n = 6), EWSR1 (n = 2), NONO (n = 1), SFPQ1 (n = 2), PRCC (n = 1), and 11 patients had unknown fusion status.Other treatments received included: chemotherapy (n = 2), radiotherapy (n = 3), TKI (n = 5), ICI (n = 10), VEGFR (n = 4), mTOR (n = 1), and some patients received multiple treatments.Before 2017, the medical treatment was mainly TKI or follow-up observation, and after 2018, the patient started received multiple treatments including ICI. Patient survival varied from 5 to 100 months.

Table 1
Previously reported patients with in TFE3 RCC.

No	Publication year	Author	Gender	Age (y)	stage	surgery	TFE3	Other treatment	OS (m)	Follow up
1	2022	Aldera AP, et al.[8]	F	47	II	Y	FISH	N	6	A
2	2021	Paksoy N, et al.[9]	F	31	IV	Y	IHC	VEGFRi,TKI,ICI, R	21	D
3	2021	Martini DJ, et al.[10]	F	23	IV	Y	FISH, SFPQ1	ICI	22	A
4	2021	Manogna D, et al.[11]	M	64	IV	N	IHC	VEGFRi, ICI	12	A
5	2021	Li L,et al.[12]	F	24	IV	Y	IHC	VEGFRi, R	52	A
6	2021	Zhang HZ, et al.[13]	M	41	II	Y	FISH	N	6	A
7	2020	Wang Y, et al.[14]	M	38	I	Y	FISH	N	12	A
8	2020	Lang XP, et al.[15]	M	33	I	Y	FISH, EWSR1	N	6	A
9	2019	Jin M, et al.[16]	F	60	NA	Y	IHC	Chemo	36	D
10			F	22	IV	Y	IHC	Chemo	84	D
11			M	25	III	Y	IHC	N	36	D
12			M	36	NA	NA	FISH	NA	24	D
13	2019	Yu W, et al.[17]	M	57	IV	Y	FISH, NONO	N	7	D
14	2019	Xu ZY, et al.[18]	F	19	II	Y	FISH, ASPSCR1	ICI	38	A
15			M	23	I	Y	FISH, ASPSCR1	ICI	40	A
16			F	59	I	Y	FISH, ASPSCR1	ICI	5	A
17			M	48	I	Y	FISH, ASPSCR1	ICI	7	A
18			M	30	I	Y	FISH, PRCC	ICI	4	A
29	2018	Karashima T, et al. [19]	F	56	I	Y	FISH, ASPSCR1	N	92	A
20	2018	Rua Fernández OR, et al. [20]	M	44	III	Y	IHC	VEGFRi,TKI,ICI, mTOR	56	A
21	2018	FukudaH, et al.[6]	F	57	IV	Y	FISH, EWSR1	TKI, ICI, R	43	A
22	2017	El Naili, et al.[21]	M	23	NA	Y	IHC	TKI	11	D
23	2017	Ma J, et al.[22]	M	3	I	Y	FISH	N	15	A
24	2017	Schaefer BA, et al. [23]	M	14	I	Y	FISH	N	100	A
25			F	18	IV	N	FISH	TKI	12	D
26	2017	Cardili L, et al.[24]	F	36	I	Y	FISH	N	6	A

Abbreviations: Y,Yes; N, No; NA, Not known; M, male; F, female; y: years; m, months; D, dead; A, alive;OS, overall survival; VEGFi, vascular endothelial growth factor inhibitor; TKI,tyrosine kinase inhibitors; mTOR, mammalian target of rapamycin; Chemo, Chemotherapy; R, Radiotherapy; ICI,Immuncheckpoint blockadeinhibitor

No	Publication year	Author	Gender	Age (y)	stage	surgery	TFE3	Other treatment	OS (m)	Follow up
27	2016	Yu L, et al.[25]	M	40	II	Y	FISH, ASPSCR1	N	6	D
28	2016	Iinuma K, et al.[26]	F	72	NA	Y	FISH	N	8	A
29	2015	Zhan HQ,et al.[27]	M	21	I	Y	FISH, SFPQ1	N	50	A
30	2014	Parihar A, et al.[28]	F	34	II	Y	FISH	N	5	A

Abbreviations: Y,Yes; N, No; NA, Not known; M, male; F, female; y: years; m, months; D, dead; A, alive;OS, overall survival; VEGFi, vascular endothelial growth factor inhibitor; TKI,tyrosine kinase inhibitors; mTOR, mammalian target of rapamycin; Chemo, Chemotherapy; R, Radiotherapy; ICI,Immuncheckpoint blockadeinhibitor

TFE3 nccRCC has no standard treatment recommendation in the guidelines. McDermott, DF [29]et al. study shows: for patients with unclassified histology received Pembrolizumab, the DCR was 30.8%, the median PFS was 2.8 months, and the median OS was 17.6 months. Rini BI [30] et al. study shows: median PFS was 15.1m for patients received Pembrolizumab combine with Axitinib. The objective response rate was 59.3% in the Pembrolizumab and Axitinib group. These 2 studies showed a benefit of PD-1 antibody treatment for RCC.

In this case, the patient did not receive radical surgery. The patient were treated with Pembrolizumab and Axitinib. The patient developed a severe rash after receiving the standard therapeutic dose of 200 mg Pembrolizumab. Dose reduction of Pembrolizumab still showed good therapeutic efficacy. During the treatment, multiple examinations showed that the enlarged superficial lymph nodes were partially reduced and partially disappeared, the abdominal lymph nodes were significantly reduced, the left kidney lesion, bone were stable and hepatic lesions is complete disappear. PFS was more than 25 m. The patient has not developed serious side effects and is generally in good condition.

Conclusion

In summary, the patient's PFS was 25m. For patients with TFE3 nccRCC, Pembrolizumab combine with Axitinib are recommended treatment options. The latest NCCN guidelines recommend participation in a clinical trial as a preferred strategy for patients with nccRCC. Ongoing and recruited clinical trials such as: A Study to Compare Treatments for a Type of Kidney Cancer Called TFE/Translocation Renal Cell Carcinoma (tRCC) (Drug: Axitinib, Biological: Nivolumab). We look forward to the results of clinical trials.

Abbreviations

CT, computed tomography; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography

Declarations

Ethics approval and consent to participate

This case report was approved by the Institutional Review Board of Xijing Hospital, The Fourth Military Medical University (approval no. XJLL-KY20222004), and written informed consent was obtained from the patient.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. Proof of consent to publish from study participant can be requested at any time.

Data Availability Statement

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare no conflict of interest.

Funding

This work was supported by Natural Science Basic Research Program of Shaanxi (Program No.2021JZ-35).

Author contributions

Conceptualization, HM.Z.,YM.B. and XW.W.; visualization, YM. B. and Y.L.; analyze, Y. L. and HC. J.; follow-up, ZH.L. and JH. S.; writing-original draft preparatio, YM.B. and XW.W.; writing-review and editing, HM.Z. and YM.B.; supervision, HM.Z. All authors read and approved the final manuscript.

Acknowledgements

None

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Figures

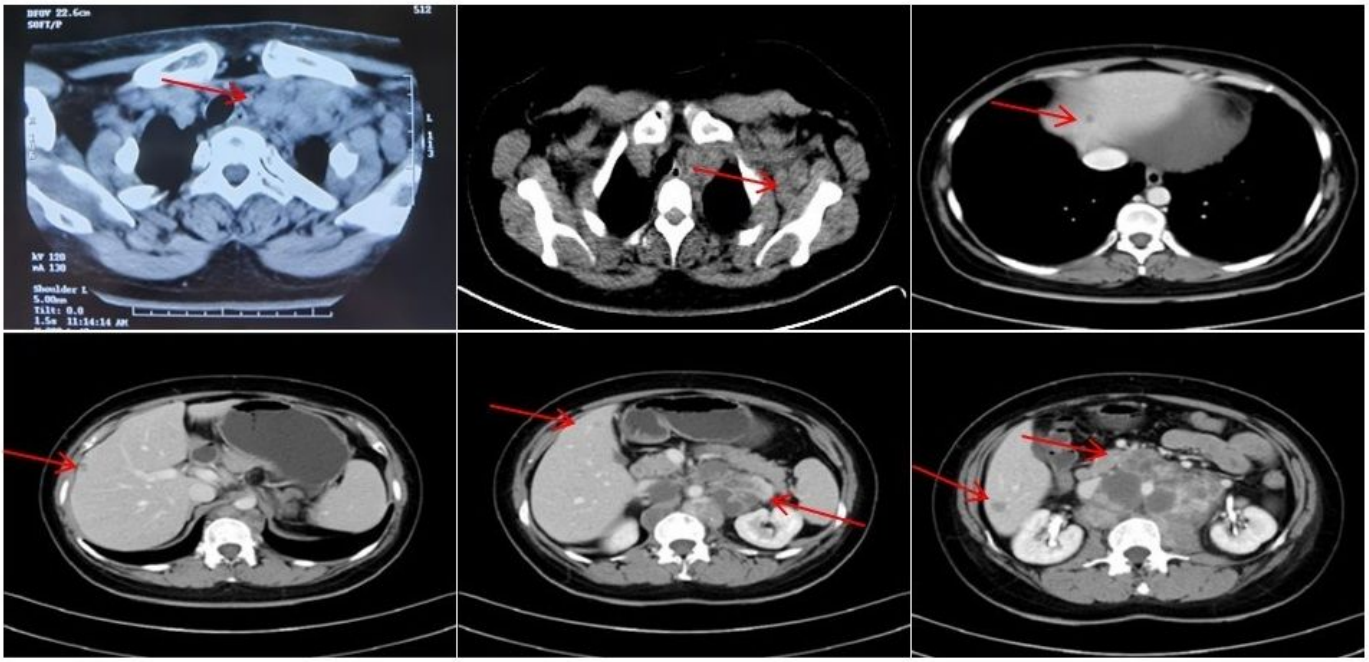

Figure 1

Contrast-enhanced CT: Before treatment

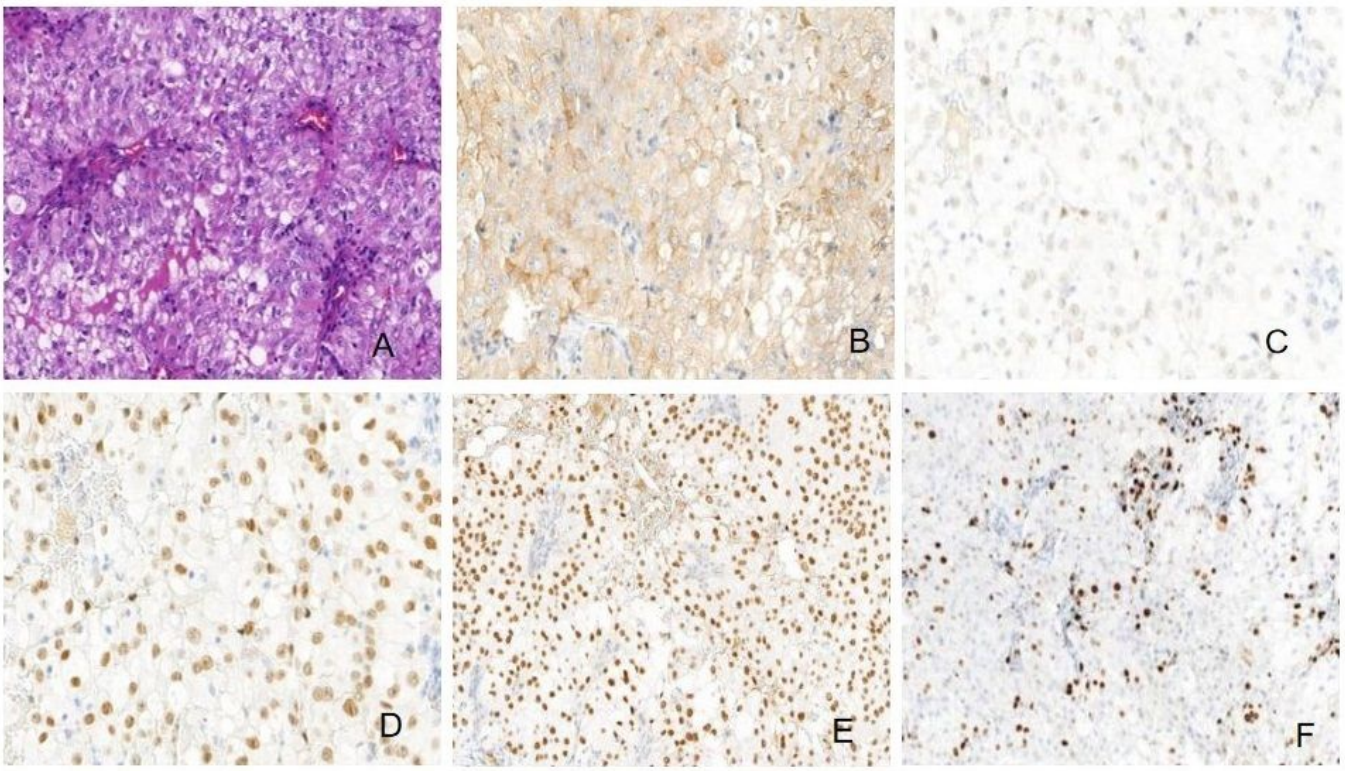

Figure 2

Histopathological findings of the tumor. A HE: The tumor cells were arranged papillary around the fibrovascular axis, with abundant cytoplasm, eosinophilic or radiolucent, and prominent nucleoli. Magnification x100. B: RCC positive. Magnification x200. C: PAX-2 positive. Magnification, x200. D: PAX-8 positive. Magnification, x200. E: TFE3 positive. Magnification, x100. F: Ki67 30% positive. Magnification, x100.

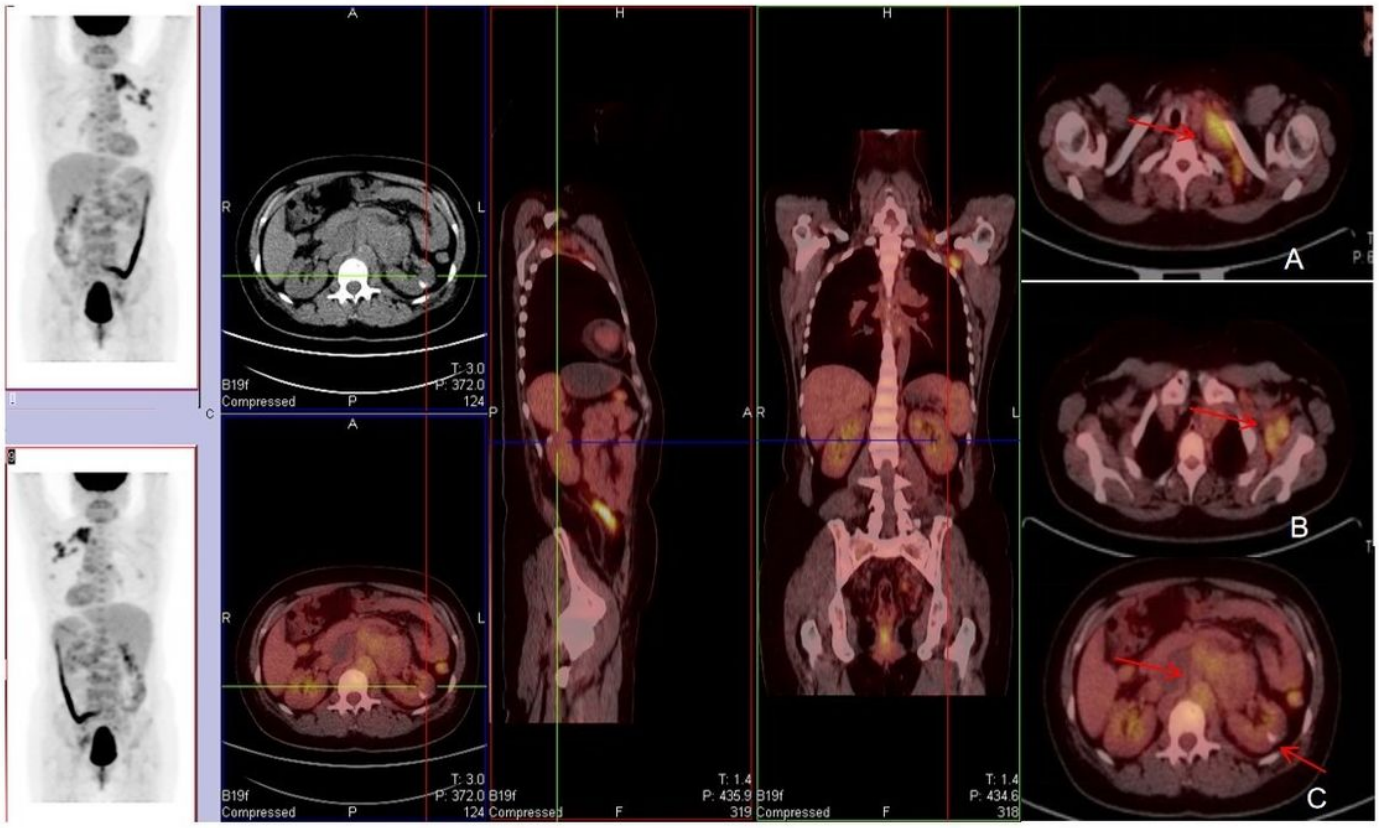

Figure 3

PET/CT (18F-FDG):Before treatment

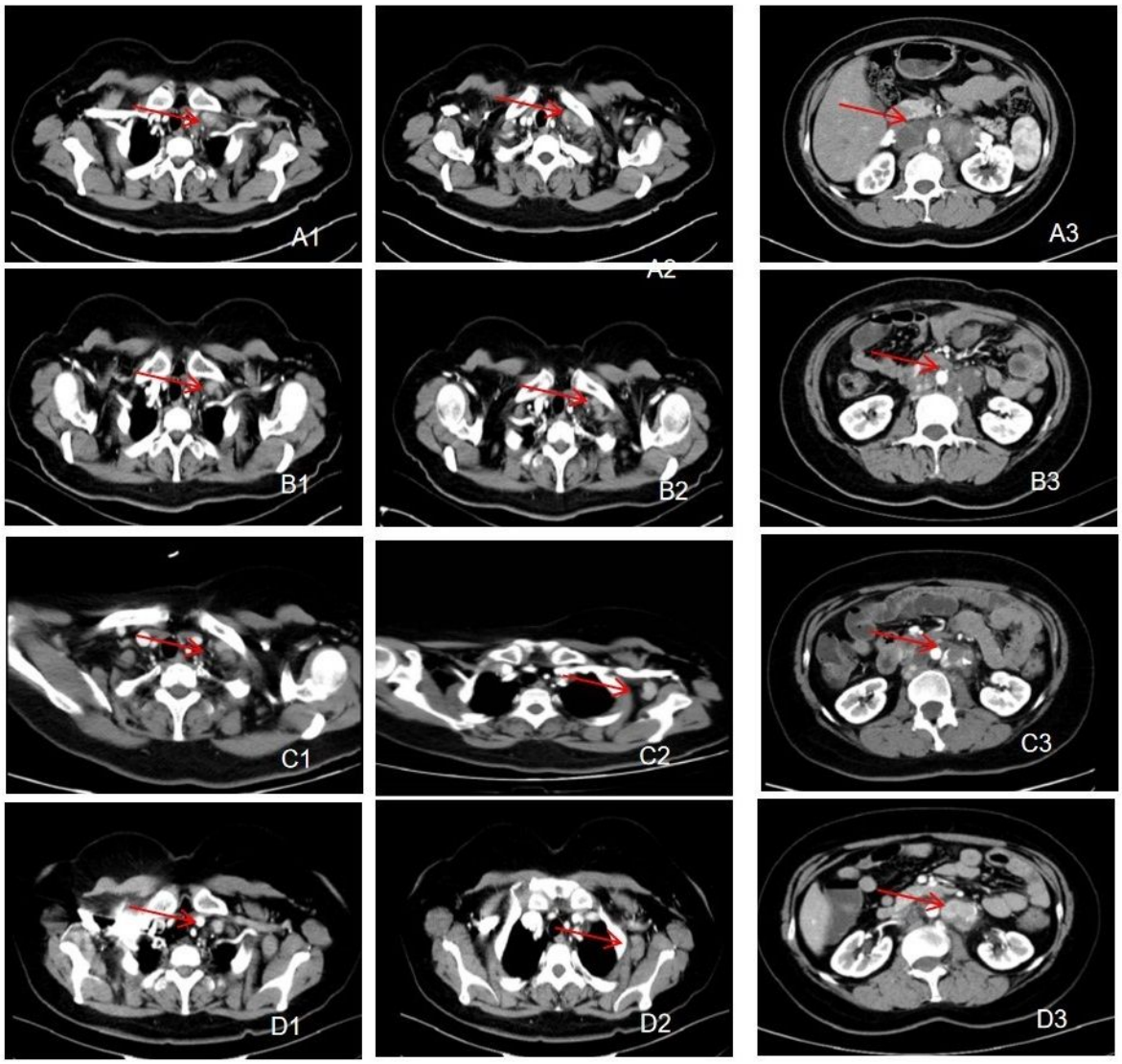

Figure 4

Contrast-enhanced CT: A1-3:after 2 months of treatment, B1-3:after 9 months of treatment, C1-3:after 16months of treatment, D1-3:after 25months of treatment