

Long-Term Survival of PD-1 Inhibitor Combined with Antiangiogenic Agents in a Patient with Pulmonary Sarcomatoid Carcinoma Complicated with Esophageal Cancer: A Case Report and Literature Review

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Abstract

Pulmonary sarcomatoid carcinoma (PSC) is a highly aggressive rare subtype of non-small cell lung cancer (NSCLC). PSC is known for its poor prognosis and low sensitivity to conventional treatments such as chemotherapy, radiation, and adjuvant therapies. In recent years, the application of targeted therapy and immunotherapy in this field has made progress. Although programmed cell death 1 (PD-1) inhibitors have been reported to show favorable antitumor effects in PSC patients with high programmed death-ligand 1 (PD-L1) expression, the efficacy of PD-1 inhibitors in combination with antiangiogenic drugs has not been investigated. Here, we report for the first time a case of dual-source cancer with low expression of PD-L1 and microsatellite stability (MSS) which showed continuous response to sintilimab combined with anlotinib as first-line treatment and achieved a long progression free survival (PFS) of 24 months with no serious adverse reactions. This case presents a new therapeutic prospect for PSC and a potential to enhance its prognosis and treatment strategies.

Introduction

Pulmonary sarcomatoid carcinoma (PSC) is a rare subtype of non-small cell lung cancer (NSCLC), defined as poorly differentiated and accounts for 0.1-0.4% of all lung malignancies^[1]. PSC patients may benefit from surgery at early stages of the disease; however, most cases are only diagnosed at advanced stages and, therefore, denied the opportunity to undergo surgical treatment. A retrospective analysis of PSC patients (the National Cancer Database (1998-2011)) showed that 48% were stage IV cases with a median OS of 5.4 months, while the median OS was 16.9 months for stage I-II and 5.8 months for stage III patients^[2]. A number of retrospective studies have shown that PSCs are highly resistant to first-line chemotherapy agents, and therefore associated with poor prognosis^[3, 4]. In recent years, PD-1 inhibitors have gradually become the main treatment for NSCLC, a retrospective study showed that PD-1 inhibitors alone can be beneficial for PSC as second-line or third-line treatment^[5]. However, the efficacy of PD-1 inhibitors combined with antiangiogenic agents as first-line treatment for PSC has not been proven.

We herein report for the first time (in accordance with the CARE reporting checklist) a case of dual-source cancer with low expression of PD-L1 and microsatellite stability (MSS) which showed a remarkable continuous response to sintilimab combined with anlotinib as first-line treatment. Our findings bring hope to PSC patients who cannot benefit from traditional treatments.

Case Presentation

A 69-year-old male with a long history of smoking was admitted to our hospital. Chest computed tomography (CT) scan revealed a 39*29mm mass in the left lower lobe and another 31*24mm mass near the hilum in the left lower lobe. The patients showed no obvious symptoms at the initial stage of diagnosis and did not receive any treatments prior to the protocol presented in this report. Chest positron emission tomography - computed tomography (PET-CT) revealed a 43*33mm mass in the left lower lobe and a 21*13mm mass near the hilum in the left lower lobe. CT-guided lung biopsy was conducted. Immunohistochemistry (IHC) analysis of the biopsy samples from the lung lesions revealed spindle cell malignancy of the left lung with necrosis, and sarcomatoid carcinoma was considered (Figure 1a). The final diagnosis was sarcomatoid carcinoma of the lung (cT2N2M0, cstage IIIA, UICC version 8). IHC analysis of lung tumor biopsy samples revealed less than 1% programmed death-ligand 1 (PD-L1) expression on tumor cells (clone 22C3, Dako), mismatch repair (MMR) protein detection suggested microsatellite stability (MSS) (Figure 1b, 1c), with no driver-gene mutations observed. In addition, this patient also had in-situ esophageal squamous cell carcinoma (Figure 4a, 4b). However, due to the poor prognosis of PSC and based on patient's wishes, esophageal squamous cell carcinoma was not treated. Patient's consent and cooperation, and the availability of all necessary tools and technologies created no further challenges during the completion of diagnosis or throughout the treatment.

Due to the high resistance of PSC to conventional first-line chemotherapy and the absence of target gene mutations, the patient received sintilimab (200mg/ body weight, once in every 21 days) in combination with anlotinib (12mg, once daily for 14 days followed by 7 days off). No changes in therapeutic protocol were introduced throughout the course of treatment.

After two cycles of treatment, CT results started to show significant reduction in the size of lung lesions. CT, MRI, and other examinations were performed regularly throughout the treatment to evaluate the changes. The best curative effect observed was partial response (PR), and after 24 months of treatment, a significant reduction in size was observed in both lung lesions (lower left

lung mass was reduced from 43*33mm to 13*8mm and the hilar mass was reduced from 21*13mm to 13*6mm). Improvements in the esophageal lesions were also observed (Figure 2, 3, 4c).

There were no serious adverse reactions observed during the treatment or severe discomfort/symptoms reported by the patient. As of the writing of this report, patient's progression free survival (PFS) was 24 months. In view of the good treatment effect and tolerable adverse reactions in the treatment process, the patient was very satisfied with the treatment, had a good compliance and continuously expressed his satisfaction and gratitude to the doctor.

All performed procedures which involved human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Discussion

PSC is a rare type of NSCLC that contains sarcomatoid cells or sarcomatoid differentiation. According to the 2015 World Health Organization (WHO) classification, PSC can be divided into five subgroups: pleomorphic carcinoma (PC), spindle cell carcinoma (SCC), giant cell carcinoma (GCC) carcinosarcoma, and pulmonary blastoma^[6]. PSC patients are mostly middle-aged or elderly men who smoke, with no specific clinical symptoms. Most patients develop metastases at early stages and cannot be operated on, which leads to poor prognosis. In an analysis of clinical characteristics of 38 patients with PSC, median survival was 21 months, and 1-year, 3-year, and 5-year survival rates were 68.4%, 31.6%, and 18.4%, respectively^[7]. The 5-year survival rate was extremely low compared to other types of NSCLC.

Advanced PSC patients are highly resistant to first-line chemotherapy. A retrospective study showed that median PFS and median overall survival (OS) were 2.7 and 4.3 months respectively for PSC patients treated with first-line chemotherapeutic drugs^[8]. How to improve the prognosis of PSC patients is a difficult problem. At present, a variety of gene mutations have been found in PSC patients, of which EGFR, TP53, KRAS, ALK and MET are the most common. Lococo et al. analyzed mutations in 49 PSC patients and found that 39 (80%) patients had at least one mutation, and that patients with PSC mutations had a shorter survival compared to those without mutations^[9]. Another analysis showed that of 33 PSC patients, 72% had at least one genetic mutation, 58% had TP53 mutations, and 30% had KRAS mutations^[10]. Such findings can be used as a reference for targeted therapy. It has been reported that afatinib combined with crizotinib could lead to partial remission in PSC patients^[11]. Unfortunately, retrospective studies have shown that the majority of Chinese population cannot benefit from EGFR-TKI drugs due to low EGFR mutation rates. There are only few reports of the use of targeted drugs for other targets in PSC patients; therefore, the efficacy of targeted therapy in PSC patients is still largely unknown.

The rapid development of immunotherapy in recent years has changed the direction of tumor therapy. A retrospective study suggested that PD-L1 expression in PSC patients was higher than that in NSCLC patients, with a significant immune infiltration^[12]. The expression of PD-L1 in tumor tissues has become a common and preferable biomarker for predicting the efficacy of immunotherapy. The high expression of PD-L1 provides a biological basis for immunotherapy. In a report of 5 patients with advanced PSC, the response rate after immunotherapy was 80%, the median OS was between 14 and 33 months, and one patient was fully responsive^[13]. In multiple case reports, first-line immunotherapy has resulted in a variety of benefits for patients with PSC (Table 1). Registration trials of immunotherapy for PSC patients are also listed in this article (Table 2). However, in our case, PD-L1 expression was negative (TPS < 1%). In a retrospective study of 37 PSC patients treated with nivolumab as second or third line, the ORR and OS were 0% and 1.84 months in patients with negative PD-L1 expression, respectively^[5]. Considering the high resistance of PSC patients to first-line chemotherapy, the absence of EGFR, ALK and other genes' mutations, the low expression of PD-L1, and the characteristics of MSS, we believe that the application and benefits of PD-1 inhibitor monotherapy would be limited in this case. Therefore, we adopted the treatment strategy of combination therapy to fit the specific needs of this patient.

Table 1
Case reports of first-line treatment for pulmonary sarcomatoid carcinoma.

First author(year)	Number of patients	Pathological diagnosis(staging)	PD-L1 expression	Treatment regimen	PFS, months	OS, months
Yoko Matsumoto (2017) ^[24]	1	PPC, IIB	PD-L1 (+), >50%	pembrolizumab	2.5+	NA
Tozuka (2018) ^[25]	1	PPC, IV	PD-L1 (+), >50%	pembrolizumab	5	NA
Xiaofeng Li (2018) ^[26]	1	PSC, IV	NA	apatinib	14+	NA
Hirokazu Tokuyasu (2019) ^[27]	1	PPC, IV	PD-L1 (+), 100%	pembrolizumab	17+	NA
Vineeth Sukrithan (2019) ^[13]	5	PSC	PD-L1 (+), >75%	pembrolizumab	11+-29+	14+-33+
Federica D'Antonio (2019) ^[28]	1	PSC, IV	PD-L1 (+), >50%	pembrolizumab	3	NA
Emanuela Cimpeanu (2020) ^[29]	1	PSC, IIIA	PD-L1 (+), >50%	pembrolizumab	14+	NA
Feng-Wei Kong (2020) ^[30]	3	PSC, III-IV	PD-L1 (+)	nab-paclitaxel+ carboplatin+ apatinib	6+,6+,7	NA
Fengwei Kong (2020) ^[31]	1	PSC, IIIB	PD-L1 (+)	camrelizumab +doxorubicin	20+	NA
Hirokazu Taniguchi (2021) ^[32]	1	PSC, IIB	PD-L1 (+), 1%	Pembrolizumab+ carboplatin+ pemetrexed	3	NA
OS=overall survival, PFS=progression-free survival, PSC=pulmonary sarcomatoid carcinoma, PPC=pulmonary pleomorphic carcinoma						

Table 2
The registered trials of immunotherapy therapy for PSC patients

Identifier	Year	Study design	Regimen	Estimated enrollment	Treatment lines	Primary endpoint	Status	Country
NCT02834013	2016	Single-arm	Nivolumab and Ipilimumab or nivolumab monotherapy	818	2nd line and beyond	ORR	Recruiting	America
NCT03022500	2017	Single-arm, phase II study	durvalumab+ tremelimumab	18	1st line and beyond	Response rate	Active, not recruiting	South Korea
NCT04224337	2020	Single-arm, phase II study	Durvalumab+ doxorubicin+ ifosfamide	34	1st line and beyond	Response rate	Recruiting	South Korea
ChiCTR2000031478	2020	Single-arm, phase II study	Camrelizumab +albumin-paclitaxel and carboplatin	15	2nd line	ORR, DCR, PFS	Recruiting	China
NCT04725448	2021	Single-arm, phase II study	Toripalimab +Bevacizumab,Nab-paclitaxel +Carboplatin	27	1st line	PFS	Recruiting	China

ORR=objective response rate, DCR=disease control rate, PFS=progression-free survival.

In general, tumor growth and metastasis are dependent on neovascularization, and hypoxic-driven vascular endothelial growth factor (VEGF) is a major regulator of angiogenesis. The response to immunotherapy is associated with the immune invasion of tumor microenvironment (TME). However, VEGF blocks T cells infiltration by down-regulating lymphocytes, interferes with T cells functions^[14,15], promotes myeloid-derived suppressor cell (MDSCs), induces proliferation and differentiation of regulatory T cells (Tregs), and inhibits maturation of dendritic cells (DCs) precursors, which lead to immunosuppression of the TME^[15,16]. Anti-angiogenic drugs can reverse the immunosuppressive effect caused by VEGF, and also normalize the tumor vascular system and promote the delivery of T cells and other immune effector molecules. On the other hand, ICIs can normalize the tumor vascular system and increase the infiltration and killing function of effector T cells by activating them^[17,18]. In addition, vascular normalization can improve the efficiency of drug delivery. This combination therapy form is being explored in multiple solid tumors.

Impower150 is the first phase III study of the combination of immunotherapy and anti-angiogenic agents in NSCLC. In all patients, the combination group (atezolizumab + bevacizumab + carboplatin + paclitaxel, ABCP) showed significant improvement in PFS and OS, with median PFS of 8.4 months and median OS of 19.5 months compared to 6.8 months, and 14.7 months in (bevacizumab + carboplatin + paclitaxel, BCP) group, respectively^[19]. Based on the research results of IMpower150, ABCP four-drug combination has become the first-line treatment recommendation for non-squamous NSCLC in the National Comprehensive Cancer Network guidelines of the United States. In the JVDF clinical trial, ramucirumab combined with pembrolizumab treated NSCLC with a median PFS of 9.7 months^[20]. Meanwhile, at the 2019 World Lung Cancer Congress, Professor Baohui Han reported the efficacy of

sintilimab combined with anlotinib as first-line treatment of advanced NSCLC with negative driver genes, with an objective response rate (ORR) of 72.7%, a disease control rate (DCR) of 100%, and a median PFS of 15 months^[21]. This treatment regimen has shown good results in NSCLC patients, but its application in PSC has not been reported, and, therefore, improving the prognosis of PSC is still a challenge. At this year's ASCO meeting, the IMbrave150 study published the results of first-line treatment of patients with hepatocellular carcinoma (HCC) with atezolizumab combined with bevacizumab, the median OS was 19.2 months for all patients and 24.0 months for the Chinese subpopulation^[22]. In the REGONIVO study, the combination of regorafenib and nivolumab overcame the disadvantage of immunotherapy in MSS type tumors^[23]. Previously, MSS-type tumors have been at a disadvantage to benefit from immunotherapy. The successful finding of REGONIVO study is believed to be that regorafenib, by blocking multiple targets, can influence immune-related mechanisms and reverse anti-tumor immune activities. Similarly, anlotinib, as a novel multi-target antiangiogenic agent, has long been approved as a third-line treatment for NSCLC. Despite the low expression of PD-L1 and the characteristics of MSS, our patient still benefited from this combination therapy. The patient's PFS reached 24 months and the esophageal lesion was improved, which far exceeded the benefits previously reported in PSC patients. Our findings present this combination therapy as a potential treatment for advanced PSC patients with negative driver-gene mutations. However, since this is the first investigation of this combination therapy in PSC, and due the inclusion of only one case in this report, future studies with larger sample sizes are needed to investigate the feasibility and efficacy of this scheme.

Combining immunotherapy with antiangiogenic agents as anti-tumor therapeutic strategy has enhanced patients' survival in a variety of solid tumors. However, a further investigation of best drug combinations, doses, and treatment plans are still encouraged. A further consideration of improvements to increase efficacy, yet reduce toxicity and tolerance in patients is also needed in future studies. In addition, no biomarker has been found that can accurately predict the efficacy of such therapeutic combination. Such problems should be addressed and investigated to improve the application of the combination of immunotherapy and anti-angiogenic drugs.

Conclusion

To our knowledge, this is the first report of sintilimab and anlotinib combined therapy in a patient with PSC. Our findings revealed a long PFS of 24 months with no serious adverse reactions during treatment and showed that such therapeutic combination has synergistic anti-tumor effects. Such findings indicate greater clinical benefits for PSC patients in specific and NSCLC patients in general. Future studies with larger sample-size are still needed to further clarify the benefit and application of this combination in PSC on a larger scale; however, our findings magnify the potential to improve current treatment plans provided to PSC patients.

Declarations

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Availability of data and material

Not applicable.

Author Contributions

Shuyue Jiao and Xiao Zhang drafted the manuscript and the collation of the case. Hong Tang and Hui Zhu critically revised the paper. Ruilin Wang and Shaomei Li participated in the collection and sorting of images and the format editing of the article. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

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Ethics approval

The case report complies with the current laws of the country in which he was performed.

Informed consent

Informed consent was obtained from the patient.

Consent for publication

The patient declared to consent to the publication of the current paper.

Conflict of Interest

The authors declare no conflict of interest.

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Figures

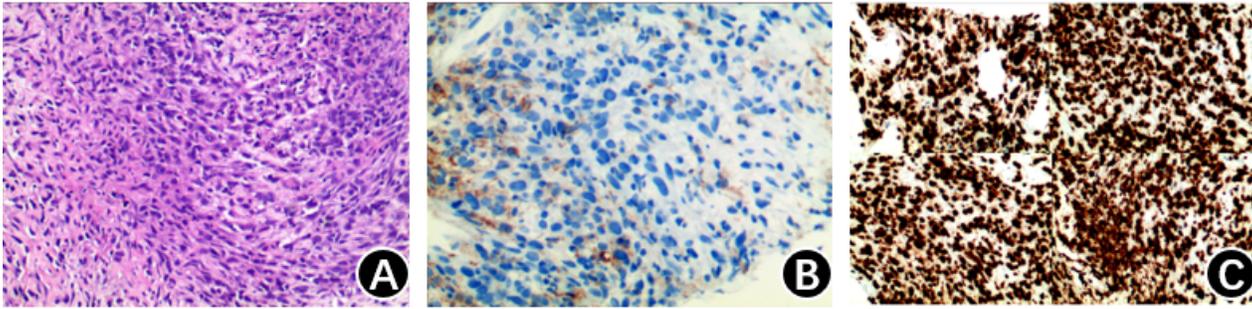


Figure 1

Pathological analysis of the specimen from primary lung cancer site taken from a patient with pulmonary sarcomatoid carcinoma. (a) Hematoxylin and eosin stain, 100x. (b) Immunohistochemical examination showed that less than 1% of the tumor cells expressed PD-L1, 200 x. (c) Immunohistochemical examination showed MSS, 400 x.

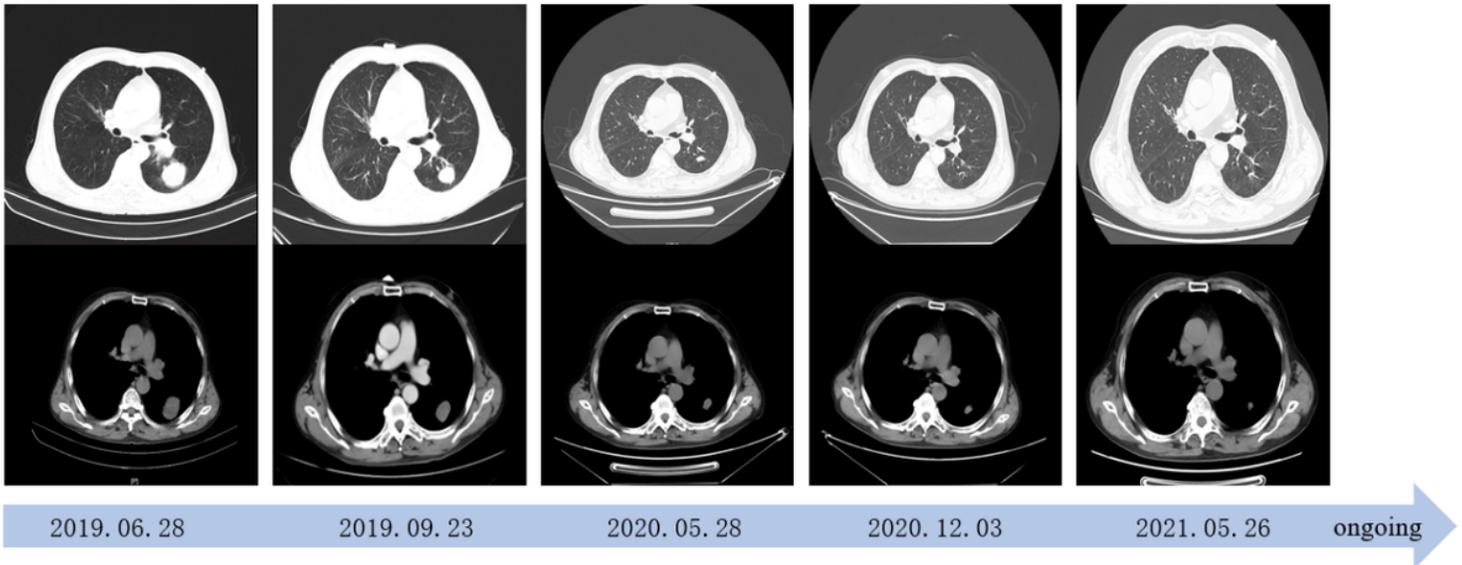


Figure 2

Patient's treatment time-line and changes in chest computed tomography scan of the lung during the course of treatment.

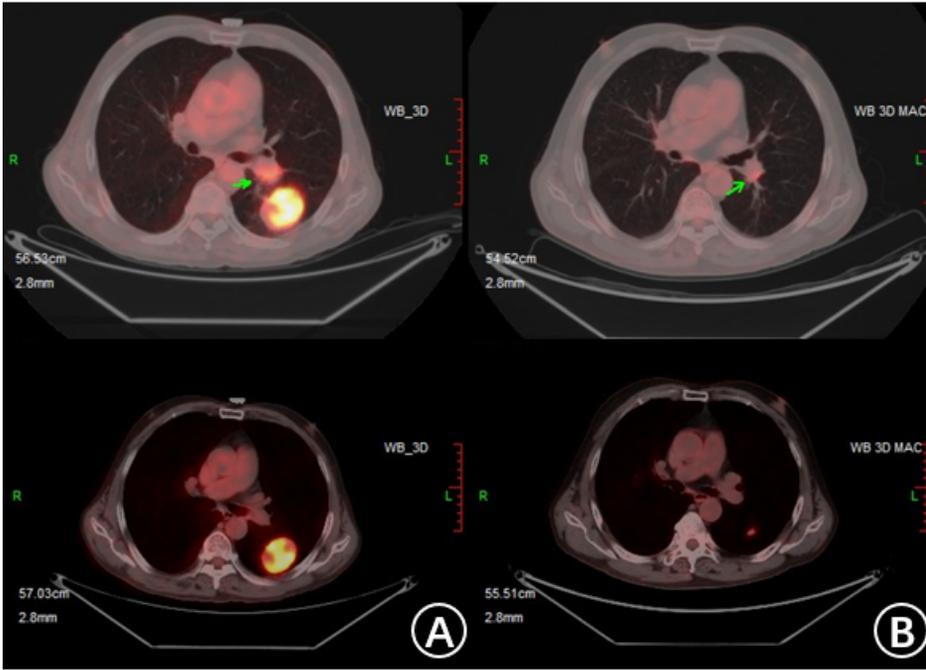


Figure 3

Chest positron emission tomography - computed tomography. (a) Before treatment, an fluorodeoxyglucose-avid 43*33mm mass in the lower left lung with the maximum standardized uptake value of 10.6, and an fluorodeoxyglucose-avid 21*13mm mass near the hilum of the lower left lung with the maximum standardized uptake value of 7.4. (b) After 24 months of treatment with sintilimab combined with anlotinib, the tumor in the lower left lung was 13*8mm with the maximum standardized uptake value of 3.3, and the hilar mass in the lower left lung was 13*6mm with the maximum standardized uptake value of 4.0.

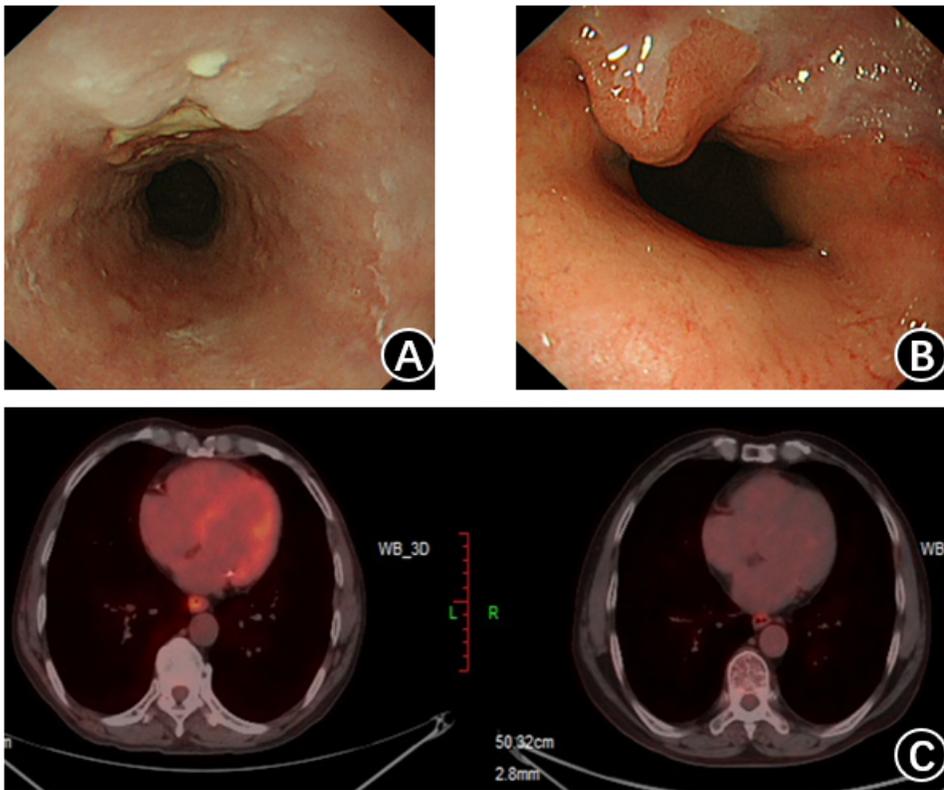


Figure 4

Esophageal squamous cell carcinoma in situ. (a) In the upper esophagus. (b) At cardia. (c) Improvements observed in esophageal lesions.