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Treatment response to eribulin and anlotinib in lung metastases from rare perianal adenoid cystic carcinoma: a case report

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Adenoid cystic carcinoma (ACC) is a rare salivary glands tumor and often displays aggressive behavior with frequent relapse and metastasis. The terminal ACC lacks standard treatment guidelines and is always accompanied by poor prognosis. Here, we report a case of rare perianal ACC who received resection and palliative adjuvant radiation. Five years later, PET-computed tomography (CT) showed perianal recurrence and multiple pulmonary metastases. Combined chemotherapy with doxorubicin, carboplatin and cyclophosphamide was applied for two cycles but ineffective. Further next-generation sequencing analysis of perianal tissue demonstrated the v-myb avian myelobastosis viral oncogene homolog and nuclear factor I/B fusion gene and two novel BCL-6 corepressor (BCOR) mutations (p.F1106Tfs*5 and p.L1524Hfs*8). The therapy was switched to eribulin and anlotinib and has been performed for eight cycles. At recent follow-ups, MRI and CT examinations revealed the diminishing perianal and pulmonary lesions. This study presented the first case of perianal ACC with multiple pulmonary metastases and particular BCOR mutations, who presented a durable response to eribulin and anlotinib, providing a potential therapeutic option for advanced refractory ACC. ***Anti-Cancer Drugs*** **33: e548–e554 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.**

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Introduction

Adenoid cystic carcinoma (ACC) is a rare malignant tumor of the salivary glands, counting for less than 1% of the head and neck cancers [1]. ACC has also been reported arising from other relatively few sites, including trachea [2], breast [3], lacrimal gland [4] or skin [5]. It occurs most often between the ages of 40 and 60 years with no specific hereditary or environmental risk factors [6]. Although ACC exhibits a relatively slow clinical course, its long-term prognosis is poor due to the high rates of local recurrence and distant metastasis [7,8]. The most frequently metastatic sites mainly include lungs (70%), bones (6%) and liver (3%) [8,9]. Surgical resection followed by postoperative radiation is the recognized treatment of ACC cases [6]. Whereas, metastatic ACC is generally more aggressive and incurable due to the lack of effective systemic therapies. Chemotherapy and targeted therapies have proven poor response rate and survival benefit [6,10]. Recent studies suggest that the microtubule inhibitor eribulin [11] and antiangiogenic therapy [12,13] could control ACC to some extent. Here, we report the first case of advanced perianal ACC with multiple pulmonary metastases that presented a durable response to eribulin and anlotinib after the failure of conventional radiotherapy and chemotherapy.

Case presentation

A 45-year-old Asian male presented with perianal and lumbosacral pain in January 2015. MRI discovered perianal soft tissue masses, and a tylectomy of the lump was carried out. The patient was diagnosed as a rare perianal adenoid cystic by surgical pathology and received adjuvant radiation. The disease was controlled for 5 years until June 2020, when the patient showed perianal and sacrococcygeal pain again. PET-CT showed perianal, sacrococcygeal, posterior part of the corpus cavernosum penis soft tissue masses, and multiple pulmonary metastatic nodules (Fig. 1a). Fine-needle aspiration biopsy of perianal lump confirmed the tumor recurrence (Fig. 2). Immunohistochemistry (IHC) suggested that P63(+), S100(-), Ki67(15% +), Calponin(+), SATB2(+), CDX-2(-), Syn(-), CgA(-). Bronchoscopy biopsy revealed a small amount of atypical gland infiltration (Fig. 3), and immunohistochemistry showed TTF-1 (-), P63 (margin +), Ki67 (about 20% +), SMA (+), CK7

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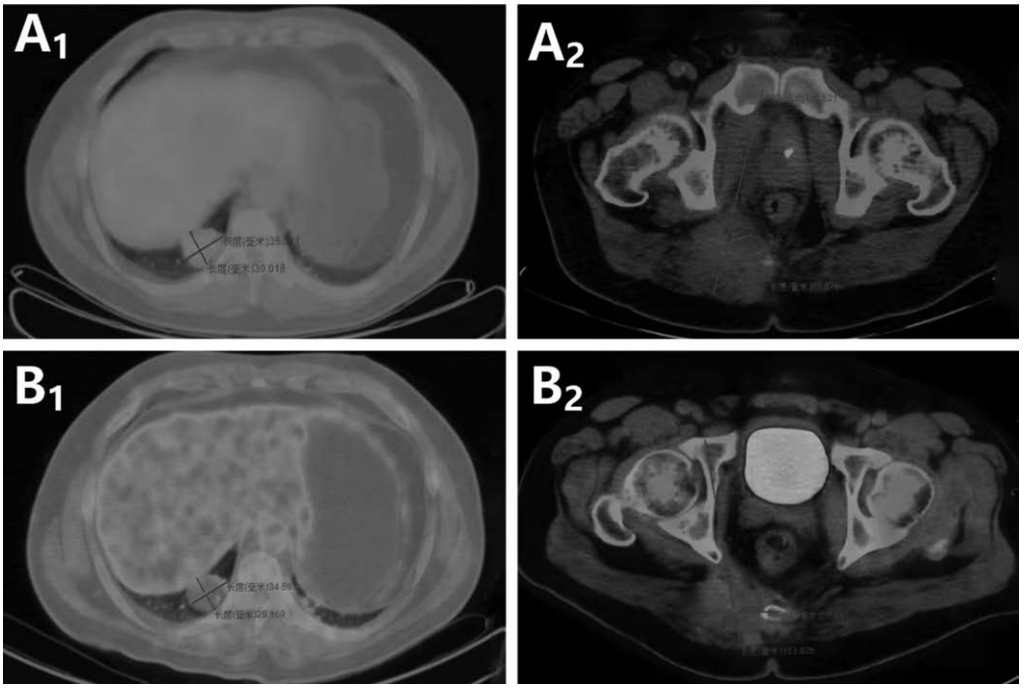
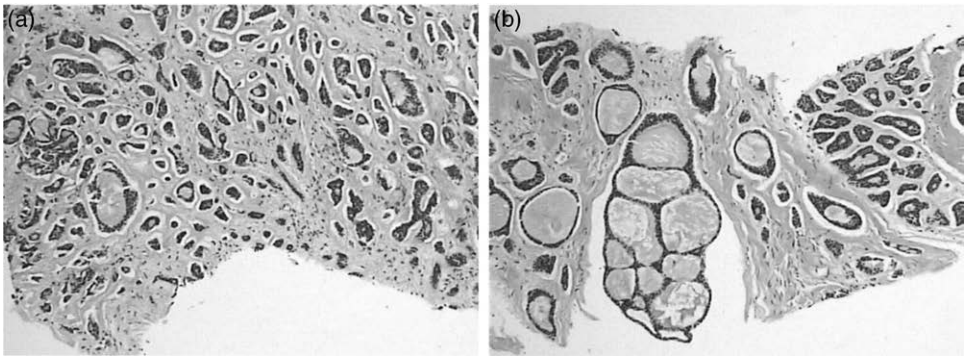
Fig. 1



PET-CT contrast of patient. (a1–a2) Baseline PET-CT in June 2020 showed multiple lesions in lung and crissum. (b1–b2) Repeat PET-CT in November 2020 showed shrunken lesions.

Fig. 2



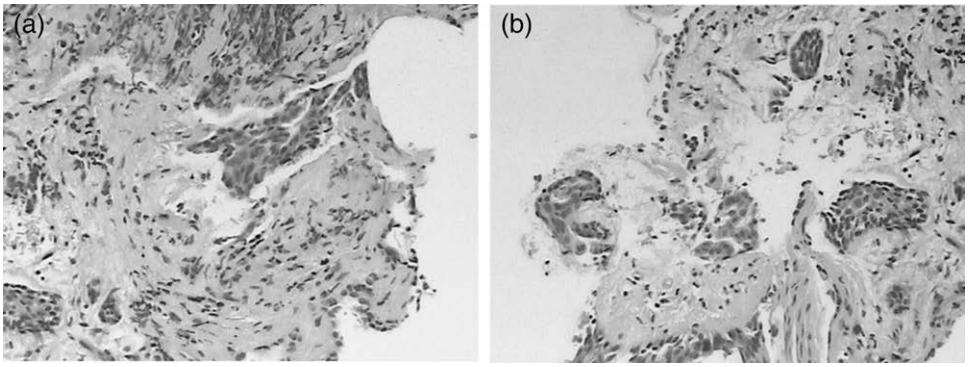
Hematoxylin and eosin staining of perianal lump, ×100 (a), ×200 (b).

(++), which was considered lung metastatic adenoid cystic carcinoma. Combined chemotherapy with doxorubicin, carboplatin and cyclophosphamide was applied for two cycles. However, perianal pain and asthma of the patient got worse, and chest computed tomography (CT) and perianal MRI showed enlarged lesions (Figs. 4a, 5a). Further next-generation sequencing analysis of formalin-fixed paraffin-embedded perianal tissue demonstrated the v-myb avian myelobastosis viral oncogene homolog and nuclear factor I/B (MYB-NFIB) fusion gene (Fig. 6) and two unusual BCL-6 corepressor (BCOR) gene mutations (Fig. 7). The therapy was switched to eribulin (1.4 mg/m^2, on days 1 and 8 of a 21-day cycle) and anlotinib (12 mg per day, on days 1–14, 21 days per cycle), which decreased the levels of multitumor markers, alleviated pain and gasp and reduced the lesions (Fig. 1b). Up to now, this new treatment mode of combined eribulin with anlotinib has been carried out for eight cycles with no apparent side effects. At the last follow-up in May 2021, repeat imaging examinations revealed shrunken lesions of the lung and crissum (Figs. 4b–d, 5b).

Discussion

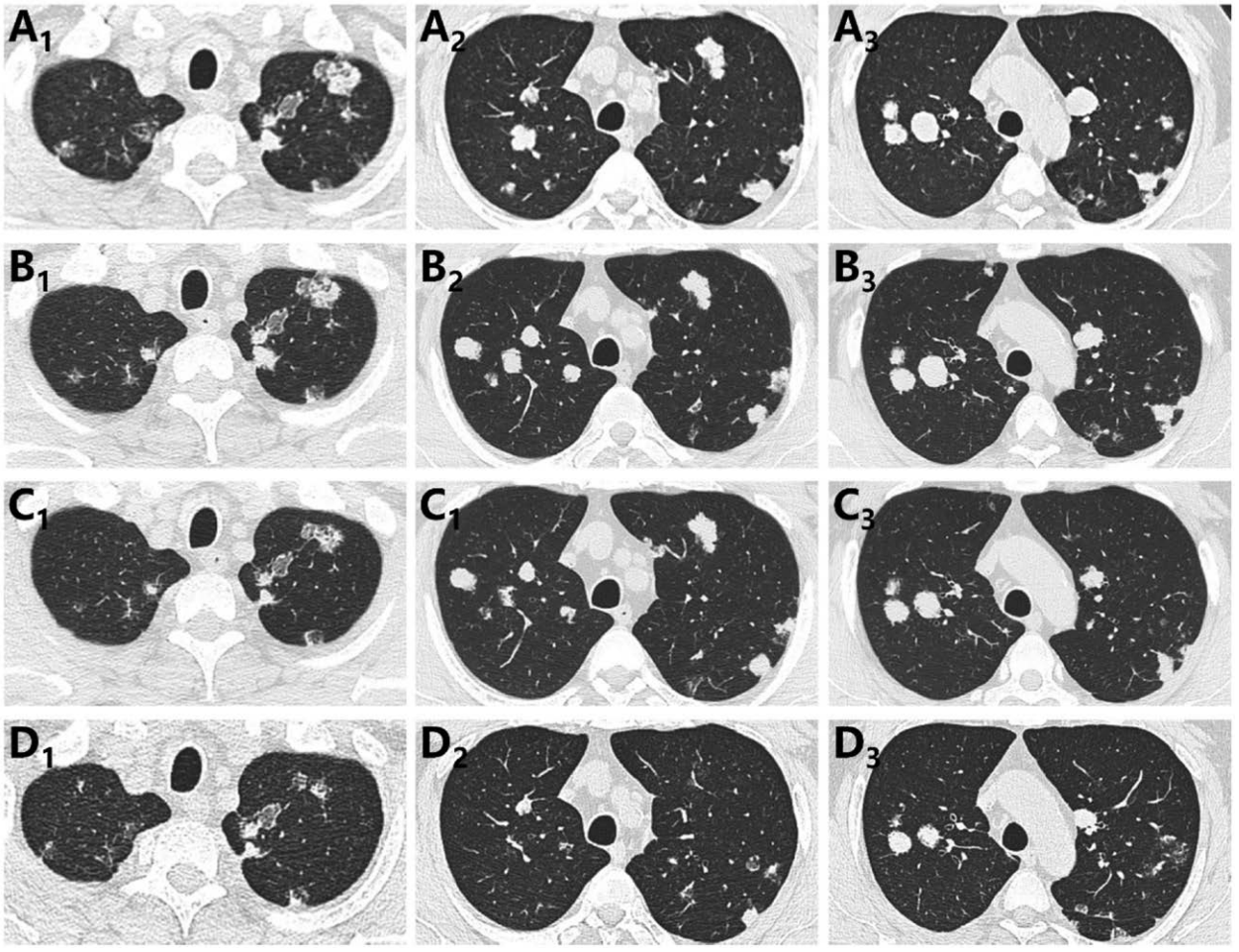
ACC is traditionally regarded as an indolent disease, but often displays aggressive behavior with frequent relapse

Fig. 3



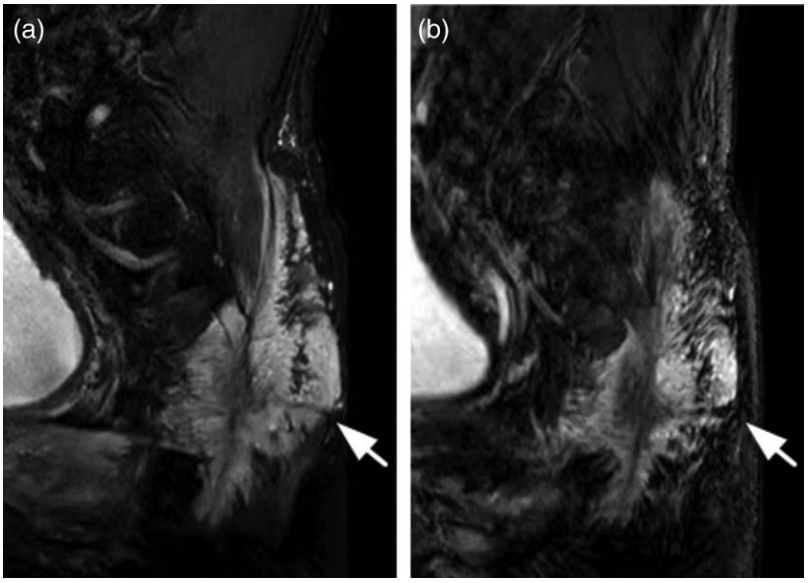
Hematoxylin and eosin staining of pulmonary metastatic nodule, ×200.

Fig. 4



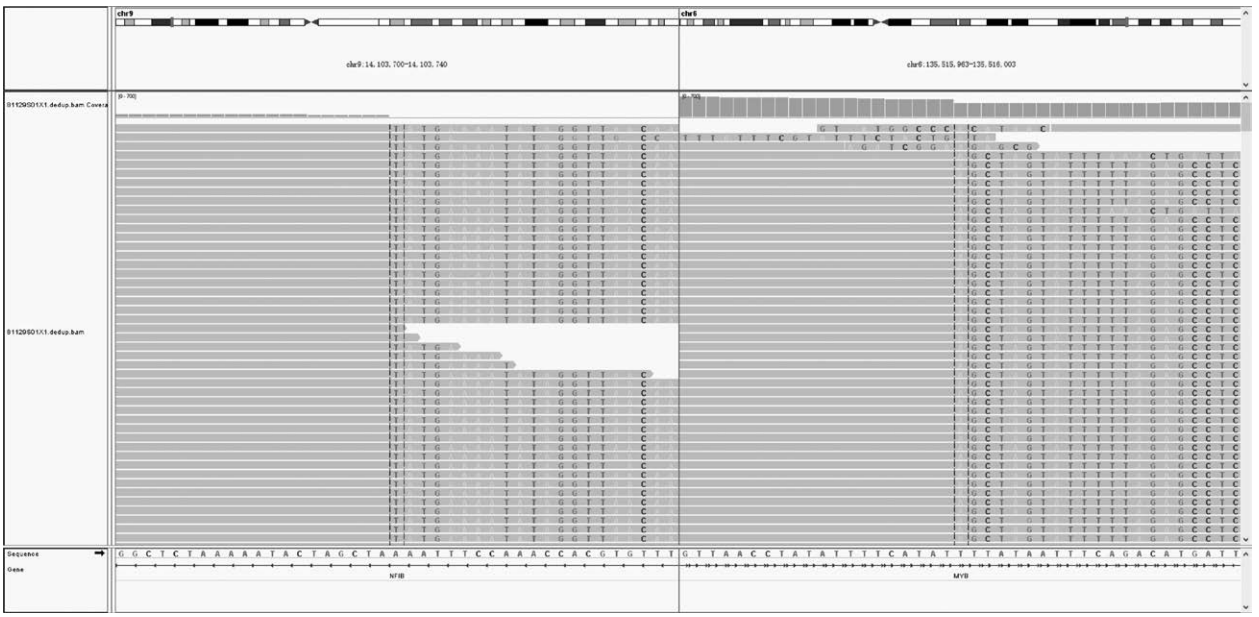
Chest CT showed decrescent lesions in both lungs. Notes: (a1–a3) In September 2020. (b1–b3) In January 2021. (c1–c3) In March 2021. (d1–d3) In May 2021.

Fig. 5



Perianal T1-weighted MRI. Notes: (a) In September 2020. (b) In May 2021.

Fig. 6

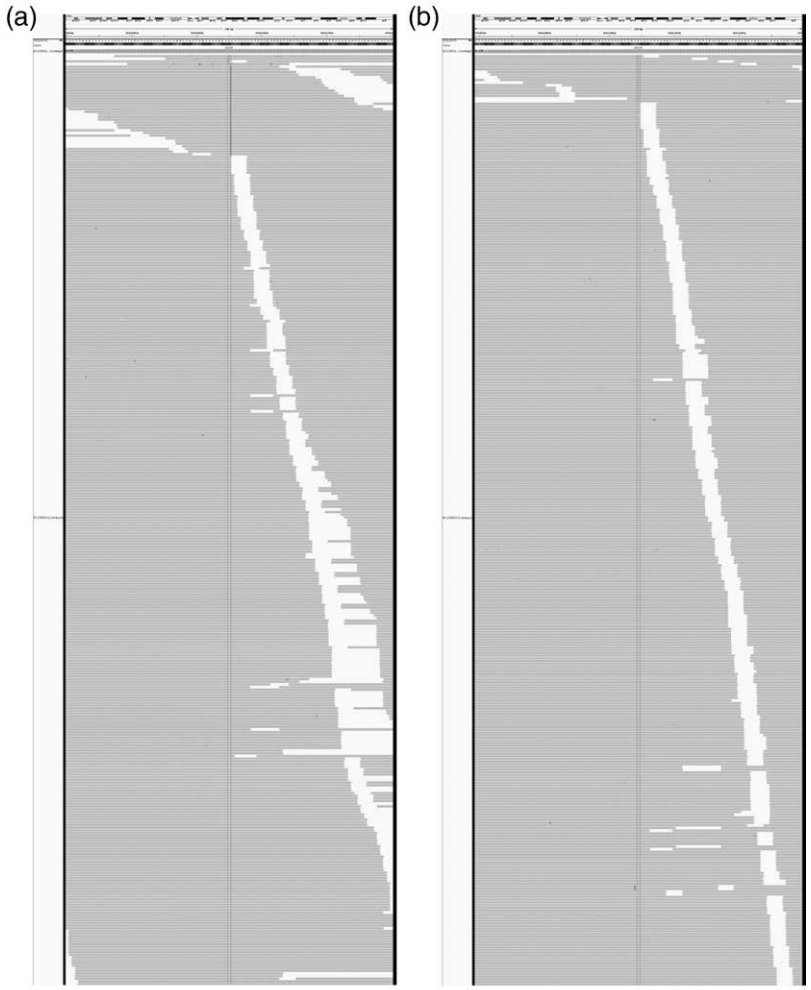


Next-generation sequencing analysis of formalin fixed paraffin embedded perianal tissue demonstrated MYB-NFIB fusion gene in September 2020. MYB-NFIB, v-myb avian myelobastosis viral oncogene homolog and nuclear factor I/B.

and metastasis [6]. The pathogenesis underlying ACC is still unclear, and one possible carcinogenic factor is the MYB-NFIB fusion gene which is caused by t(6;9)(q22–23;p23–24) translocation [14]. It is the most prevalent gene alteration in ACC and leads to the over-expressed MYB-NFIB transcripts and overactive MYB target genes, which are involved in cell cycle control, apoptosis, cell adhesion and angiogenesis [6,14]. The mean incidence of MYB-NFIB fusion in ACC was 54%, and it is highly specific diagnostic indicator [15].

Besides MYB-NFIB, another rare cancer-associated gene mutation was found in our case, BCOR gene mutation. Previous research has shown that it may play a role in

Fig. 7



Next-generation sequencing analysis found two unusual BCOR gene mutations in September 2020. (a) p.F1106Tfs*5 (c.3316_3324delinsAC) in Exon 7. (b) p.L1524Hfs*8 (c.4566_4569dup) in Exon 12. BCOR, BCL-6 corepressor.

the pathogenesis of metastatic ACC [16]. It's worth noting that two novel BCOR mutations of this patient, p.F1106Tfs*5 (c.3316_3324delinsAC) and p.L1524Hfs*8 (c.4566_4569dup), were identified in ACC for the first time. Both the scarce tumor site and genetic mutation determined the special value of this case.

There is no consensus or standard guidelines for the treatment of advanced ACC at present. For locoregional recurrence, more aggressive treatments are recommended, such as surgery or radiotherapy. Therapy for widely metastatic ACC is more challenging and depends primarily on systemic treatment [6]. Standard chemotherapy is a widely accepted treatment for patients with symptomatic metastases or fast-growing disease. However, overall response rate and the level of evidence for chemotherapy are low, and the survival benefit is limited. Moreover, after the failure of the first-line chemotherapy, there are no feasible alternatives as second-line chemotherapy [17]. Thus, chemotherapy may not be a viable option for this case after the resistance to combined first-line chemotherapy. As for immunotherapy, it is not effective because of the low tumor immunogenicity and absent PD-L1 expression in ACC [6]. In terms of targeted therapy, many new drugs directed against novel therapeutic targets have been developed. But owing to the low mutational burden of ACC, targeting epidermal growth factor receptor, c-KIT, fibroblast growth factor receptor (FGFR) and so on with single agents could not control ACC effectively and prolong the survival time [18]. Given the translocation MYB-NFIB of this patient, several trials have evaluated the antitumor effect of targeted agents against pathways activated by MYB, but the promising results with statistical significance have not been obtained [19,20].

Recently, nontaxane microtubule inhibitor eribulin attracted extensive attention owing to its reliable antitumor

activity. Eribulin can bind to the high-affinity site of the extension end of the microtubule to block its extension, and then induce the G2/M cycle arrest and apoptosis [21]. In addition, eribulin can induce tumor vascular remodeling and improve blood perfusion in the core area of the tumor, thereby increasing the delivery and accumulation of antitumor drugs [22,23]. A phase II clinical trial explored the activity of eribulin in recurrent metastatic salivary gland malignancies, among them the most common histologies were ACC. Disease control was observed in 90% of patients without obvious toxic and side effects. However, the objective responses to eribulin were uncommon [11]. Therefore, we combined eribulin and anlotinib in the present case to further improve the antitumor effect.

Anlotinib, a multitarget receptor tyrosine kinase inhibitor, can significantly inhibit angiogenesis by inhibiting vascular epidermal growth factor receptor (VEGFR)-1, -2, and -3, platelet-derived growth factor receptor-α and -β, and FGFR-1, -2, -3 and -4 and so on. Moreover, anlotinib can inhibit c-Kit, Ret, Aurora-B, macrophage-colony-stimulating factor and DDR1 to reduce tumor cell proliferation [24,25]. Angiogenesis inhibitor is a critical component in ACC treatment [6,18]. The microvessel density and VEGFR expression were closely related to the worse survival of ACC [12]. Some studies indicated that when combined with eribulin, antiangiogenic therapy could play a stronger antitumor effect [26,27]. The underlying mechanism might be that they could synergistically stabilize the blood vessels inside of the tumor and increase the delivery of chemotherapeutic drugs into tumor, which are advantageous to suppress the tumor growth and metastasis. Based on the above, off-label eribulin and anlotinib were administered after full consultation with the patient, which achieved a complete remission of regional pain and reduced lesions without notable side effects.

In summary, this study presented the first case of terminal perianal ACC patient with two novel BCOR mutations (p.F1106Tfs*5, p.L1524Hfs*8), who responded well to eribulin and anlotinib and achieved a prolonged survival time, providing a feasible treatment option for such a patient. More clinical cases and further prospective studies are warranted to assess its safety and validity for treating advanced refractory ACC.

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All authors have read and approved the final manuscript. All authors confirm that they have met the criteria for authorship as established by the International Committee of Medical Journal Editors, believe that the article represents honest work, and are able to verify the validity of the results reported.

Conflicts of interest

There are no conflicts of interest.

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