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Successful treatment of c-kit-positive metastatic Adenoid Cystic Carcinoma (ACC) with a combination of curcumin plus imatinib: A case report

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ABSTRACT

Adenoid cystic carcinoma (ACC) is an aggressive malignant neoplasm of the secretory glands. Conventional chemotherapy has poor effectiveness against metastatic ACC. Thus, a novel effective therapy is needed against metastatic ACC.

A majority of ACCs (up to 94%) express c-kit. Imatinib is monoclonal antibody with specific activity against c-kit but has not been found to be effective in treating patients with ACC in which c-kit is overexpressed and activated. The NF-κB and mTOR pathways have been shown that ubiquitously and concurrently activated, indicating that the inhibition of these pathways may represent a novel treatment approach for patients with ACC. Curcumin has been shown to inhibit NF-κB and NF-κB-related pathways. 43-year-old patient was diagnosed ACC from submandibular salivary gland. After complete resection of tumor adjuvant radiotherapy was initiated. Seven years later multiple lung metastases were detected and ACC was confirmed by re-biopsy. First-line chemotherapy failed. NF-κB and c-kit were overexpressed in the metastatic specimens. Therefore, we treated the patient with metastatic chemoresistant ACC with imatinib 400 mg/day and intravenous curcumin 225 mg/m^2 twice a week plus oral bioavailable curcumin Arantal® 2 × 84 mg/day. At 24 months, we observed near complete anatomic and complete metabolic response. To our knowledge, this is the first report of a patient with a c-kit-positive ACC that is successfully treated with the combination of imatinib and curcumin in an integrative approach.

1. Introduction

Adenoid cystic carcinoma (ACC), also known as cylindroma, is a rare but highly aggressive adenocarcinoma arising within secretory glands. It mainly occurs in the salivary glands and breast tissue.[1–3] ACC accounts for approximately 22% of all salivary gland malignancies and represents approximately 1% of all head and neck malignancies.[4] ACCs typically grow at a slower pace than other carcinomas. However, ACC is regarded as a high-grade neoplasm, with radical resection predominantly followed by postoperative radiotherapy consequently as the current treatment of choice.[5–7] Nonetheless, regional and distant recurrences are relatively common following the local treatment of primary ACC tumors. Hematogenous metastasis is common, particularly to lung, bone, and liver.[5,8]

There is currently no consensus regarding the most appropriate treatment of metastatic ACC, with ACC typically resistant to systemic chemotherapy. Laurie et al. evaluated the effectiveness of chemotherapy for ACC and reported a mean survival of 11 months in a patient with metastatic ACC and that the major objective responses were rare, with stable disease being

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more common.[9] Molecular targeted therapies have therefore been evaluated because of the poor response of ACC to conventional chemotherapy. Up to 94% of patients with ACCs reportedly express c-kit (also known as CD117) proto-oncogene,[10] which may represent a future therapeutic target. Imatinib is an inhibitor of several protein-thyrosine kinases, including those associated with breakpoint cluster region-abelson (Bcr-Abl), platelet-derived growth factor receptors (PDGF-R), and c-kit.[11] Imatinib has demonstrated antitumor activity for the inhibition of tyrosine-kinase proteins. The tumor control rate of imatinib is reportedly over 80% in patients with Gastrointestinal Stromal Tumors (GIST). Six studies have previously assessed the impact of imatinib in the treatment of ACC, with only two objective responses reported in 71 evaluable patients.[9] It is suggested that c-kit may play a key role by accelerating mobilization of tumor cells.[12] However, since the data regarding the effect of c-Kit inhibition on ACC are conflicting, reducing c-Kit activity may not be sufficient to inhibit ACC's progression.[12]

Curcumin, a polyphenol, is the major biologically active component of turmeric that is derived from the dried rhizome of the *Curcuma longa* plant.[13] Recent evidence has indicated curcumin suppresses all three stages of carcinogenesis: initiation, promotion, and progression.[14] Curcumin is a highly pleiotropic molecule that modulates numerous targets including the activation of transcription factors, receptors, kinases, cytokines, enzymes, and growth factors.[15] Due to the pleiotropic nature of curcumin, curcumin has been shown to potentiate the effectiveness of imatinib and have utility in overcoming imatinib resistance.[16,17] Sun et al. demonstrated curcumin as a potent inhibitor of ACC progression *in vitro* and *in vivo*.[18]

Herein, we report a patient with a c-kit-positive ACC treated with curcumin plus imatinib.

2. Case presentation

In September 2013, a 50-year-old male patient with a seven year-history of ACC was admitted to our Oncology Clinic because of multiple lung metastases and failure of first-line chemotherapy.

Seven years ago, in October 2006, the patient presented to the Ear, Nose, and Throat (ENT) Clinic with a complaint of painless, slow-growing mass under the jaw for about two and a half years. He was medically fit. Clinical examination revealed a freely mobile firm submandibular mass, measuring approximately 3 × 3 cm. The rest of the head and neck examination was within normal limits, with no evidence of lymphadenopathy. Patient was life time non-smoker and he did not have any comorbid disease. Ultrasonographic evaluation detected a submandibular mass originating from the salivary gland and measuring 3.5 × 3 cm in size. Because of the suspicious sonographic appearance, fine needle aspiration biopsy was performed stat. The result confirmed the diagnose of Adenoid Cystic Carcinoma (ACC), and after surgery it was staged as T2 (3.5 cm) N0 M0 stage III. Perineurial, but not lymphatic invasion was observed. Radiotherapy at a total dose of 60 Gy was initiated following resection with a 1-mm safe margin.

Seven years later, the patient was re-admitted with fatigue and shortness of breath. Multiple metastatic masses with a maximum diameter of 75 mm were detected by computed tomography (CT) imaging. Re-biopsy of a metastatic mass was performed and confirmed metastatic ACC to lung (Figs. 1 and 2). A standard 3-week regimen of cisplatin (80 mg/m^2 day 1) plus etoposide (100 mg/m^2 days 1–3) was initiated in the hospital. However, the patient's condition worsened after two cycles of chemotherapy, with CT scan imaging demonstrated progression of the metastatic lesions. Patient's Eastern Cooperative Oncology Group (ECOG) performance status has changed from ECOG 0 to 1 during last 3 months before his admission to our clinic.

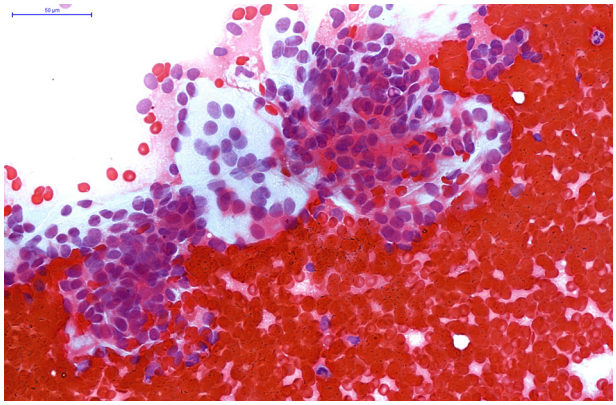

Fig. 1. Staining of the biopsy specimen of a metastatic mass with Papanicolaou (Pap) stain. (PAP staining; ×100).

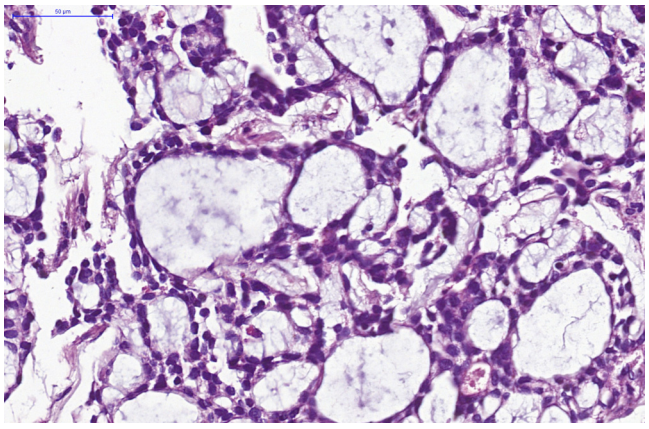

Fig. 2. Tubules and cribriform nests of basaloid cells lining cystic spaces filled with homogenous material [hematoxylin and eosin (H&E); × 200].

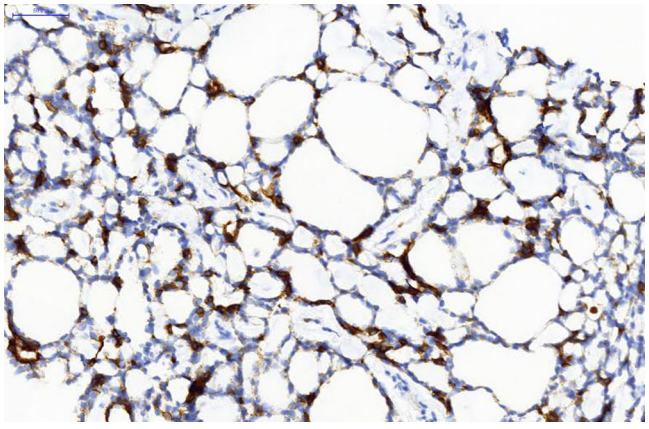

Fig. 3. Adenoid cystic carcinoma demonstrating c-kit expression (c-kit × 400).

In our clinic, firstly tumor tissue c-kit and Nuclear Factor kappa B (NF-κB) expression were evaluated from re-biopsy material. c-kit immunohistochemistry demonstrated strongly positive, with 60% of tumoral cells found to express c-kit (Fig. 3). NF-κB p65 over expression was shown with immunohistochemical method. Pathological evaluation showed +3 positive staining (Fig. 4a, b). F-18 fluorodeoxyglucose (FDG) Positron Emission Tomography – Computed Tomography (PET/CT) was used in restaging and confirming metabolically active multiple lung metastases (lung masses SUV_{max} 4.81 g/ml and mediastinal lymph nodes SUV_{max} 4.52 g/ml; Fig. 5a, b).

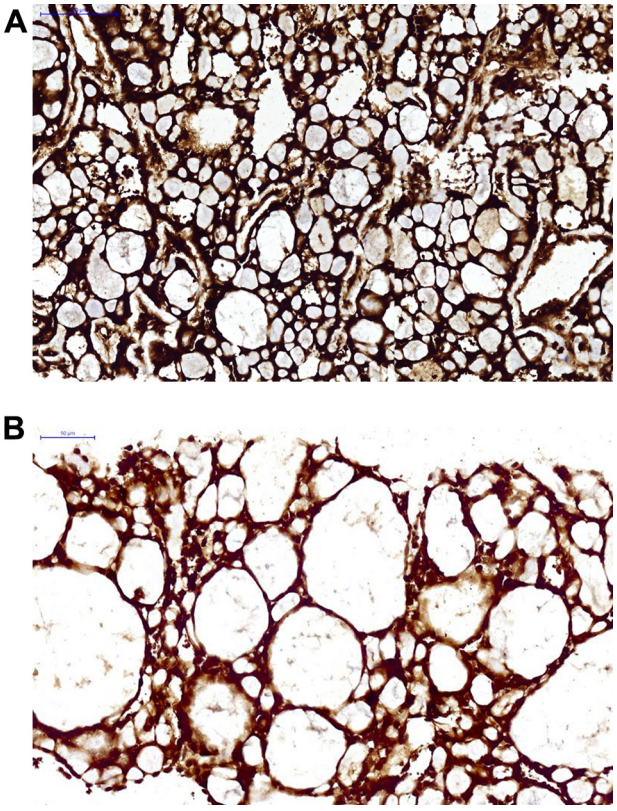

Fig. 4. (a and b). Immunohistochemistry adenoid cystic carcinoma tissue labelling NF-kB p65 (phospho S536) with ab86299 at 1/200 (1 μg/ml). Detection: 3,3′-Diaminobenzidine (DAB). [(a) ×100, (b)×400].

After the first evaluation, we planned a combination treatment with imatinib and off-label use of curcumin integratively. Informed consent was provided by the patient, and treatment with imatinib 400 mg/day and curcumin administration was initiated both orally and intravenously. We used water soluble and intravenous administrable curcumin (Burg-Apotheke, Germany, Patent application number: DE 102012219219 A1). One of the authors of the current case report (*i.e.* HS) has extensive experience of intravenous curcumin treatment. According to his experience, dosages below 450 mg/m^2 is well tolerated by human and only minor and reversible hematological changes such as echinocyte formation and some signs of hemolysis are observed dose dependently, above the dosages of 300 mg/m^2 (unpublished data). Our preclinical data shows that 225 and 300 mg/m2 dose has similar effect (unpublished data). In total, 225 mg/m^2 curcumin in 1000ml normal saline was administered intravenously over 2–3 h, using a non-di-(2-ethylhexyl)phthalate (non-DEHP) in-line filter twice a week. At 30 min prior to the administration of curcumin, diphenhydramine 50 mg and ranitidine 50 mg in 50-ml normal saline was administered intravenously over a period of 20 min.

Oral curcumin Arantal® 2 × 2 capsules were also administered. Arantal® which contains 42 mg curcumin, is a highly bioavailable turmeric extract with a solubility in water 4000 times greater than free curcumin. Two capsules of Arantal® (84 mg) are 15 times more bioavailable than free curcumin in terms of final plasma concentration.[19]

Tumor responses to treatment were evaluated after 2 months of treatment by CT and PET. According to RECIST (Response Evaluation Criteria In Solid Tumours) criteria, stable disease was observed. Metabolic response was defined according to the PET response criteria of the European Organization for Research and Treatment of Cancer,[20] with a partial metabolic response achieved (lung masses SUV_{max} 2.30 g/ml and mediastinal lymph nodes metabolic inactive). Accordingly, the patient's condition was seen to improve. The same regimen was continued for 6 months, with a PET/CT scan at this time indicating anatomically significant reduction of the tumor masses. The lung lesions were seen to have decreased by 80% in volume, with metabolically significant regression observed (SUV_{max} 1.03 g/ml) and no uptake in mediastinal lymph nodes (complete metabolic response; Fig. 6a, b). Oral bio-optimized curcumin Arantal® 2 × 84 mg/day and imatinib 400 mg/day have been administered since cessation of the 6 months i.v. curcumin treatment. At the most recent evaluation performed in August 2015, PET/CT imaging demonstrated near complete anatomic and complete metabolic response (Fig. 7a, b). The last check up done in April 2016 showed that physical examination and laboratory evaluation were normal.

No side effects were observed during the treatment period. Hematologic and liver function parameters were evaluated weekly during the first 2 months, every 2 weeks during the next 2 months, and then every 4 months. Intravenous curcumin was well tolerated with no toxicity or adverse reactions observed. Bio-optimized curcumin (Arantal®) was well tolerated with no toxicity observed.

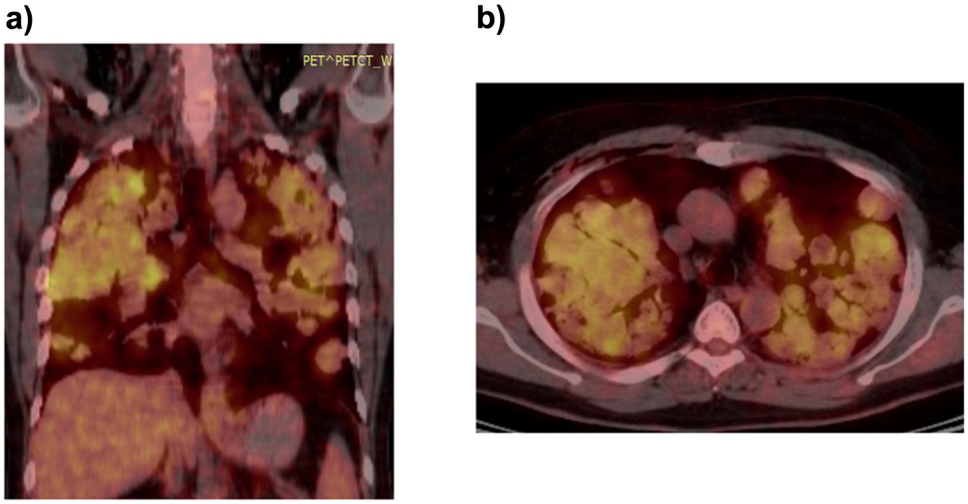

Fig. 5. Axial (a) and coronal-fused PET/CT (b) images. Bilateral lung metastasis demonstrated high-FDG uptake.

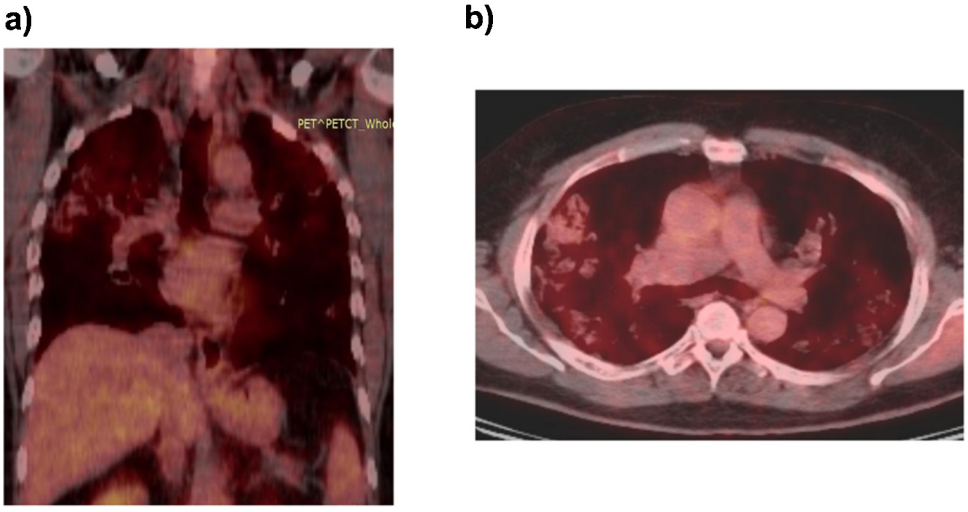

Fig. 6. PET/CT imaging of the Thorax at 6 months.

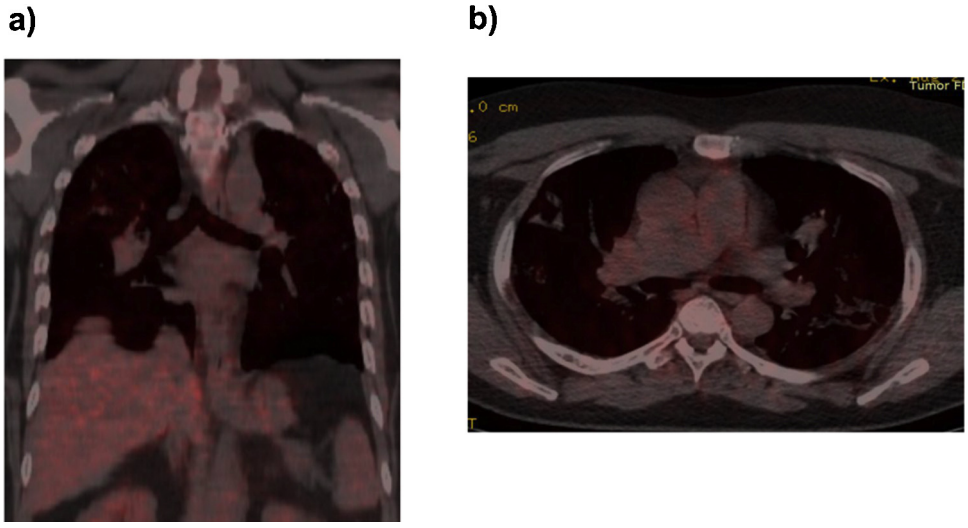

Fig. 7. PET/CT imaging of the lung at 24 months. (a, b) PET/CT imaging at 24 months demonstrating significant FDG uptake in residual fibronodular densities in the lung (complete metabolic response).

3. Discussion

Overexpression of c-kit has been reported in the majority of patients with ACC.[10] Imatinib is a specific inhibitor of Bcr-abl, PDGFR, and c-kit and has demonstrated significant effectiveness in the treatment of mutation-positive diseases such as chronic myelocytic leukemia (CML) and GIST.[21,22] Six studies involving 71 patients have previously assessed imatinib activity in ACC with objective responses observed in only two patients.[9] However, stable disease was observed in 34 (47%) patients.

Several possibilities may explain the lack of activity of imatinib in patients with metastatic ACC with wild-type c-kit expression. Heinrich et al. reported response rates to imatinib were dependent on the exact type of mutation present in 127 patients with GIST.[23] In patients harboring exon 11 c-kit mutation, the partial response rate was 83.5%, whereas patients with exon 9 c-kit mutation had a partial response rate of 47.8%. In contrast, no objecting responses were observed in patients without detectable c-kit or PDGFR mutations.[23] However, Vila et al. reported c-kit mutations are most frequently observed on exons 11 and 9.[24] Spontaneous genomic alterations during disease progression may also explain the failure of imatinib. This effect has been well documented in patients with of CML. In the progression phase (accelerated and blastic phase) of CML, additional genomic alterations develop, sensitivity toward imatinib decreases and, ultimately, the disease becomes entirely resistant. An analogous pattern may also be involved in the progression of metastatic ACC.

Sun et al. demonstrated the Phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3 K)/Akt/Inhibitor of nuclear factor kappa-B kinase subunit alpha (IKK-α)/NF-κB pathway is ubiquitously activated in ACC and plays an essential role in the evasion of apoptosis.[25] These experiments indicated agents associated with downregulation of the PI3 K/Akt/IKK-alpha/NF-κB signaling pathway may represent promising therapies for ACC. Meanwhile, Guo et al. reported curcumin and imatinib exert synergetic antileukemia effects through the inhibition of imatinib-mediated overactivation of Akt/mammalian target of rapamycin (mTOR) signaling and downregulation of Bcr-Abl gene expression.[26]

Curcumin inhibits cellular proliferation and downregulates constitutive activation of growth-signaling pathways in both newly diagnosed patients and imatinib-resistant patients.[26] Sun et al. assessed the activation status of both mTOR and NF-κB pathways in relation to PI3K/Akt/IKK signaling both *in vivo* and *in vitro*.[18] This study demonstrated that NF-κB and mTOR pathways were ubiqui-

tously and concurrently activated in patients with ACC. However, curcumin has been shown to significantly inhibit *in vitro* growth, migration, invasion, and angiogenesis in ACC cells and prevent the *in vivo* growth and angiogenesis of ACC tumors in mice through dual inhibition of both NF-κB and mTOR pathways *via* the PI3K/Akt/IKK signaling axis.[17] They also reported that concurrent activation of the mTOR and NF-κB pathways was correlated with malignant progression in ACC. Further, Zhang et al. reported NF-κB is involved in the malignant progression of ACC.[27]

Curcumin has been shown to inhibit NF-κB and NF-κB-related proteins and pathways.[28,29] Although almost all ACCs are c-kit mutation positive, the effectiveness of imatinib in such cases is limited. Six different trials evaluated the effectiveness of imatinib in metastatic ACC and demonstrated an overall partial response rate of 2.8%. We believe ours is the first case of ACC successfully treated with curcumin plus imatinib, indicating the NF-κB pathway is involved in the development and progression of ACC. However, the effectiveness of curcumin treatment alone for ACC treatment was not evaluated. We believe combination therapy (imatinib plus curcumin) represents the most appropriate therapy for ACC in patients where c-kit and NF-κB positivity are detected.

To date, no studies have reported any toxicity associated with the use of curcumin in either animals or humans.[30]; however, there is a low potential for CYP450-mediated drug interactions at physiologic serum concentrations of curcumin. Our clinical experience with more than 3000 curcumin infusions in cancer patients suggests that curcumin is safe as no serious negative drug interactions have been observed. Preliminary data also indicate curcumin does not interact with other chemotherapy agents metabolized and/or eliminated *via* the primary drug metabolizing CYP450 pathways.[31]

3.1. Strengths and limitations

Therefore, the strength of this study lies in that preclinical *in vivo* and *in vitro* data support the hypothesis of the study that curcumin is a safe supplement and has potential clinical utility in the treatment of metastatic ACC therapy. On the other hand, this study has several limitations. The findings are based on a single patient without any comparison group; therefore, statistical significance cannot be evaluated in that report. In addition to this, although follow-up care is especially important in the first five years after the treatment, the data presented in this study has been limited by the observations of 30 month duration of the treatment. Dosage arrangement of curcumin is based on the unpublished documents and previous experience of the authors. Recurrent case reporting or case series may help to strengthen the evidence of this case report.

4. Conclusions

Up to date, the effectiveness of curcumin and imatinib, either alone or in combination, has not been validated in terms of improving progression-free survival with complete metabolic and radiologic responses in patients with ACC. However, curcumin apparently potentiates and overcomes resistance to chemotherapeutics and small molecule cancer drugs.

We suggest that besides c-kit, activation of NF-κB and mTOR pathways should be evaluated in all ACC patients, and if NF-κB and related pathways activation is identified, adding curcumin supplementation to treatment plan should be considered.

Integrative medicine brings conventional and complementary approaches together in a coordinated way. We believe that this is the first report of ACC treatment with intravenous and oral bio-optimized curcumin with imatinib. Well designed clinical trials are requested to determine the criteria of patients who are most suitable for curcumin combination.

Consent

WriBTen informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare no potential conflict of interest.

Author contributions

MD, as the primary medical oncologist of the patient, carried out the treatment protocol,
HS, consulted as a radiation oncologist,
IY, carried out the imaging studies,
DS, carried out the imaging studies,
HD, carried out the PET scanning,
IY, consulted as the previous radiation oncologist of the patient,
SA, carried out the immunoassays,
ATA, consulted as integrative medicine specialist.

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