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Clinical Complete Response of Aggressive Fibromatosis to Apatinib and Celecoxib: A Case Report

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Abstract

Aggressive Fibromatosis (AF) is a rare disease that originates from fibroblasts in deep soft tissues. Surgery and radiotherapy are the main treatment options, while there is still controversial with systematic treatment for patients who cannot undergo surgery or radiotherapy. Here, we reported a case of a 53-year-old Chinese woman with gastric cancer combined with aggressive fibromatosis. She was firstly diagnosed early gastric cancer, which was curative by surgery. While, a solid mass located in the epigastric region was detected at a follow-up examination after 2 years. Then, puncture biopsy of abdominal mass was conducted, and subsequent histopathology confirmed aggressive fibromatosis. The patient received apatinib combined with celecoxib. Amazingly, the tumor was regressed remarkably, and achieved clinical Complete Response (cCR). In conclusion, apatinib combined with celecoxib was an effective and safe treatment strategy for aggressive fibromatosis.

Keywords: Aggressive fibromatosis; Apatinib; Celecoxib; cCR: Gastric Cancer

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Introduction

Aggressive Fibromatosis (AF) is a rare, clonally proliferative neoplasm that originates from fibroblasts in deep soft tissues. It is characterized by invasive growth and a tendency towards local recurrence without distant metastasis [1]. AF can be clinically classified by tumor location into three types: Extra-abdominal AF (50%-60%), abdominal AF (25%) or intra-abdominal AF (12%-15%) [2].

The etiology of AF is not fully understood, but it has been shown to be associated with genetic, estrogen status and physical factors [3]. The treatment options comprise surgical removal, radiotherapy, chemotherapy, hormonal therapy, and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) [4]. Although surgery is recommended for primary aggressive fibromatosis, it is not amenable once recurrence occur (with a recurrent rate of about 20%-80%) [5]. Radiotherapy can be utilized in patients with recurrent or unresectable tumors [6], but its use is debated due to the associated severe side effects. When these two modalities are not applicable or fail to control the disease, systemic treatments can be considered. Here, we reported about the use of apatinib and celecoxib in a patient with AF who had undergone total gastrectomy and esophagojejunostomy for gastric cancer.

Case Presentation

In September, 2018, a 53-year-old Chinese woman presented to our hospital with epigastric pain. Gastroscopic examination revealed a type IIC lesion in the middle segment of the small curvature of the gastric body. The pathological findings on gastroscopic biopsy suggested a poorly differentiated adenocarcinoma and signet-ring cell carcinoma. Subsequently, total gastrectomy and esophagojejunostomy was performed on October 10th, 2018. Postoperative pathology revealed signet-ring cell carcinoma, 2.5 cm × 1.5 cm, with multifocal distribution, limited to the mucosal layer, no involvement of vascular nerves, negative lymph nodes (0/24), and negative margin. Concurrently, the patient was diagnosed with stage I gastric cancer (pT1N0M0). Immunohistochemistry staining: CK7 (+), CD19 (+), MUC2 (-), Ki-67 (<1%). No recurrence or metastasis occurred during follow-up.

In August 2020, a follow-up abdominal Computed Tomography (CT) scan detected a 6.0 cm × 4.0 cm solid mass located in the epigastric region (Figure 1). Positron Emission Tomography-Computed Tomography (PET-CT) showed a 6.2 cm × 4.2 cm solid mass with a high metabolic

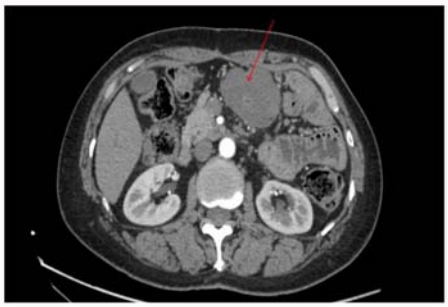

Figure 1: Abdominal CT scan before treatment with apatinib and celecoxib.

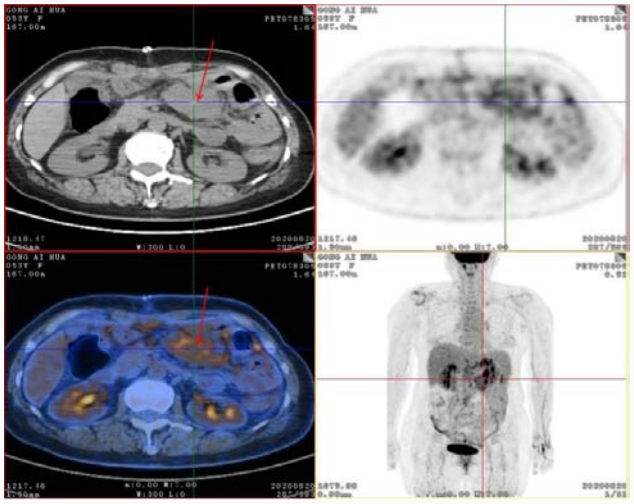

Figure 2: PET-CT showed a 6.2í-4. 2 cm solid mass with high metabolic expression in the left upper quadrant (SUVmax=6.2).

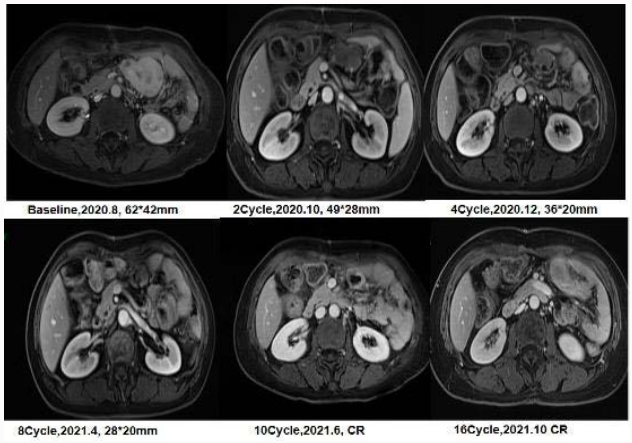

Figure 3: MRI scan before and after apatinib and celecoxib treatment showing PR and cCR.

expression in the left upper quadrant (SUVmax = 6.2) (Figure 2). Therefore, exploratory laparotomy was performed, and the mass was found to be unresectable due to involvement with superior arterial mesenterica. We conducted a Magnetic Resonance Imaging (MRI)-guided puncture biopsy of abdominal mass, and subsequent histopathology confirmed aggressive fibromatosis. The immunohistochemical analysis revealed the following: β-catenin(+), Bcl-2(+), Ki-67(5%), CK(-), SMA(-), S-100(-). Mutation in CTNNB1 gene was identified by tissue Next-Generation Sequencing (NGS, 3D Med). From September 2020 to December 2020, the patient received celecoxib (100 mg, bid, po) combined with apatinib (500 mg, qd, po) for four cycles. The treatment resulted in a significant reduction in the size of the abdominal mass to 3.6 cm × 2.0 cm (Figure 3), achieving Partial Response (PR), evaluating by MRI examination. Then, 14 months after initiating treatment, MRI showed a remarkable regression of the tumor mass (Figure 3), and clinical Complete Response (cCR) was achieved. The patient's overall health status remained stable during consistent treatment. After the second evaluation of cCR, the patient was advised to discontinue the treatment. Her most recent MRI (February 2023) continued to show cCR (Figure 3). At the time of writing, the patient is on follow-up with no clinical signs of recurrence.

Discussion

AF is defined as an abnormal fibroblastic growth in deep soft tissue. Currently, the etiology of the disease has not been established. About 25% of AF cases have a history of trauma. In our case, the patient underwent surgery for gastric cancer. Despite low risk of recurrence or metastasis of stage I gastric cancer, a differential diagnosis should be made to exclude the possibility of gastric cancer metastasis. Herein, we performed a thorough evaluation of the tumor and re-punctured it to ascertain the pathology, and a final diagnosis of AF was confirmed in the patient.

The tumor mass in our case was not amenable to surgery, due to its location, or to radiotherapy, because of its size. The patient received molecular-targeted treatment and subsequently achieved a cCR after 14 months of treatment. However, the decision to use conventional chemotherapy or hormonal therapy is controversial due to severe side effects such as marrow toxicity and the risk of endometrial cancer [7]. Therefore, there is an urgent need to develop new treatment regimens that are both effective and safe. Previous studies suggest that Tyrosine Kinase Inhibitors (TKIs) may offer promising therapeutic outcomes. Imatinib is the first TKI employed for the treatment of AF, but has shown limited clinical efficacy (response rate: 6%-19%) [8,9]. Pazopanib has been evaluated in a retrospective study. The response rates were 37.5% and median Progression-Free Survival (PFS) was 13.5 months [10]. A randomized, double-blind, phase III trial from Gounder et al. demonstrated the activity of sorafenib with a response rate of 33%, PFS rate of 89% at 1 year and 81% at 2 years [11]. Recently, Zheng et al. reported that partial response to anlotinib was reached in 38.1% of patients, and the 3-month, 6-month, and 12-month PFS rates were 95.2%, 90.5%, and 84.0%, respectively [12].

Previous studies show that Wnt/β-catenin signaling pathway is aberrantly activated in AF, which triggers the activation of Cyclooxygenase (COX), over-expression of the Vascular Endothelial Growth Factor (VEGF), and activation of PI3K-AKT-mTOR signaling pathway [13]. Apatinib, a new-generation oral tyrosine kinase inhibitor approved for gastric cancer, targets not only VEGFR-2, but also PI3K-AKT-mTOR signaling pathway. Apatinib has demonstrated favorable therapeutic effects across various malignant tumors [14]. When apatinib is combined with celecoxib, a COX inhibitor, the therapeutic outcomes may be further improved. In our case, the combination of celecoxib and apatinib resulted in a cCR.

Conclusion

There is an urgent need for more effective and less toxic drugs for AF. To our knowledge, this is the first report to document the

achievement of cCR in patients with AF using apatinib and celecoxib. It seems that this treatment strategy is effective and safe, and could be a promising therapeutic option. Further studies are needed to confirm the efficacy and safety of apatinib and celecoxib in AF.

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