


Treatment of Abdominal Desmoplastic Small Round Cell Tumor Induces Acute Myeloid Leukemia-M5: A Case Report and Literature Review

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Abstract: Desmoplastic small round cell tumor (DSRCT) is a rare and highly aggressive malignancy. Most patients are diagnosed at a late stage with poor prognosis. The treatment usually includes combined intensive chemotherapy, cytoreductive surgery, radiotherapy, and targeted therapy. Due to the low incidence rate and dismal survival, there is currently a lack of case reports on DSRCT with concurrent leukemia. We report a case of a young patient who achieved disease stabilization for 14 months after receiving 6 cycles of chemotherapy and whole abdominal radiation therapy (WART), followed by consolidation treatment with anlotinib. However, the treatment was terminated due to the development of Acute Myeloid Leukemia-M5 (AML-M5). Multimodal therapy may provide a survival benefit for rare tumors that lack standard treatment. However, intensive chemotherapy and extensive radiotherapy carry a risk of inducing secondary malignancies. This is the first reported case of concurrent DSRCT and AML-M5 with short intervals between onset.

Keywords: desmoplastic small round cell tumor, whole abdominal radiation therapy, anlotinib, therapy-related acute myeloid leukemia

Introduction

Desmoplastic small round cell tumor (DSRCT) is a rare and highly aggressive sarcoma with an annual incidence of approximately 0.2–0.5 per 100,000¹. It often occurs in male children and adolescents, with a peak incidence between 20 and 25 years of age, and frequently involves the abdomen and pelvic cavity with distant metastasis. Without hallmark clinical manifestations, most patients are diagnosed at an advanced stage and are difficult to treat with curative resection. Treatment strategies include maximum cytoreductive surgery, high-intensity systemic chemotherapy, targeted therapy, intraperitoneal hyperthermic chemotherapy, and radiation therapy; however, the treatment effect is unsatisfactory and the overall prognosis is poor.

Therapy-related acute myeloid leukemia (t-AML) is a late complication of cytotoxic chemotherapy and/or radiotherapy for malignant and non-malignant diseases.² t-AML accounts for about 7% of AML patients^{3–5} and is mostly associated with non-Hodgkin's lymphoma. It is estimated that the incidence of t-AML will increase with more patients receiving radiotherapy and chemotherapy, and with the extension of the overall survival time for malignant tumors.

In this report, we present the first case of abdominal DSRCT with widespread metastasis that was treated with comprehensive antitumor therapy and developed treatment-related acute myeloid leukemia 7 months later.

Case Presentation

The patient was a 32-year-old male who visited the hospital on March 18th 2020, with a lower abdominal mass that had been present for more than three months. He had no medical or family history of tumors. Enhanced CT showed multiple nodules and masses in the abdominal cavity and hepatic capsule, multiple enlarged lymph nodes in the bilateral diaphragmatic angle, retroperitoneum, bilateral iliac vessels, and multiple bone metastases (Figure 1). Dense radioactive shadows were detected on the bone scan, indicating a high possibility of bone metastasis. No obvious abnormalities were found during the colonoscopy. CT-guided puncture biopsy of the lower abdominal mass was performed, and the pathology results indicated DSRCT (Figure 2). Immunohistochemistry revealed positive expression of EMA, Vimentin, Desmin, NSE, CD99 and CK (pan), and next-generation sequencing (NGS) of the tissue samples showed a TERT gene promoter region mutation (C.-263g > A) and EWSR1 rearrangement (WT1-EWSR1) (Figure 2). No genetic abnormalities were seen on the NGS of the blood samples (Burning Rock Dx, OncoScreen Plus Panel).

The diagnosis was confirmed as abdominal DSRCT with multiple abdominal cavities, lymph nodes, and bone metastases. P6 chemotherapy (alternating IE and HD-VAC) was initiated on March 21, 2020. The patient showed a partial response after three cycles of VAC chemotherapy. However, after the fourth and fifth cycles of IE, CT re-evaluation suggested enlarged lesions next to the left iliac vessels, whereas the remaining lesions in the abdominal cavity and multiple swollen lymph nodes decreased in size (Figure 3). The bone metastases remained unchanged. The patient continued to receive the sixth cycle of VAC chemotherapy and underwent whole abdominal radiation therapy (30 Gy/1.5 Gy×20F for PTV and 45 Gy/2.25 Gy×20F for the left iliac vessel lesion) starting from September 1, 2020, which resulted in adverse reactions such as nausea, vomiting (grade 2), diarrhea (grade 2), leukopenia (grade 4), and thrombocytopenia (grade 4). Radiotherapy was discontinued after 16 treatments, with doses of 24 Gy in the abdominal cavity and 36 Gy in the left iliac vascular lesion. CT reexamination one month later revealed a decrease in the size of multiple nodules and masses in the abdomen and pelvis (Figure 3), slightly shrunken multiple nodules in the liver capsule, and no changes in the retroperitoneal and iliac vascular lymph nodes. The patient started taking anlotinib orally (12 mg qd d1-14 q3w) on October 27, 2020, and developed diarrhea (grade 1). A CT scan on December 5, 2020, showed disease stability, and the patient continued to receive anlotinib as targeted therapy.

However, the absolute monocyte count increased progressively in April 2021 (Figure 4). The patient presented to the hematology department on May 10, 2021, with an absolute monocyte count of $9.60 \times 10^9/L$. Bone marrow cytology, biopsy, and flow cytometry immunophenotyping suggested acute myeloid leukemia-M5 (AML-M5) (Figure 4). Karyotype analysis of the bone marrow cells showed translocation between chromosomes 11 and 19 (Figure 4).

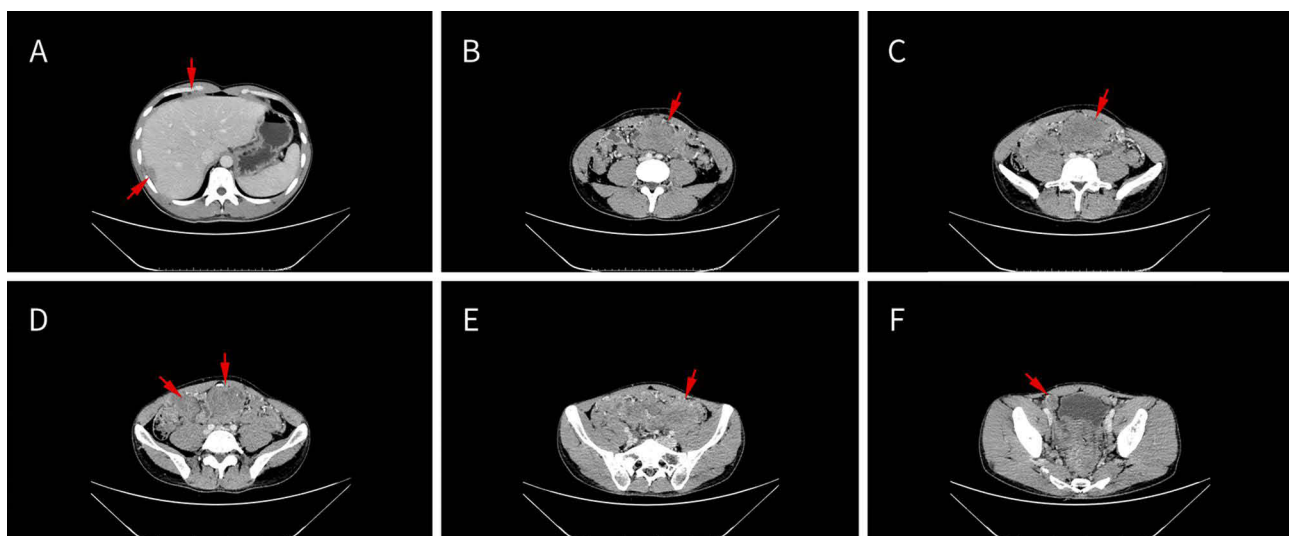


Figure 1 (A) Abdominal and pelvic CT scan reveals multiple nodules and masses present on the liver capsule (red arrow), (B) the largest lesion measuring approximately 87mm x 53mm and located in the mid-abdomen (red arrow), (C–F) there are also multiple nodules and mass lesions within the abdominal cavity (red arrow).

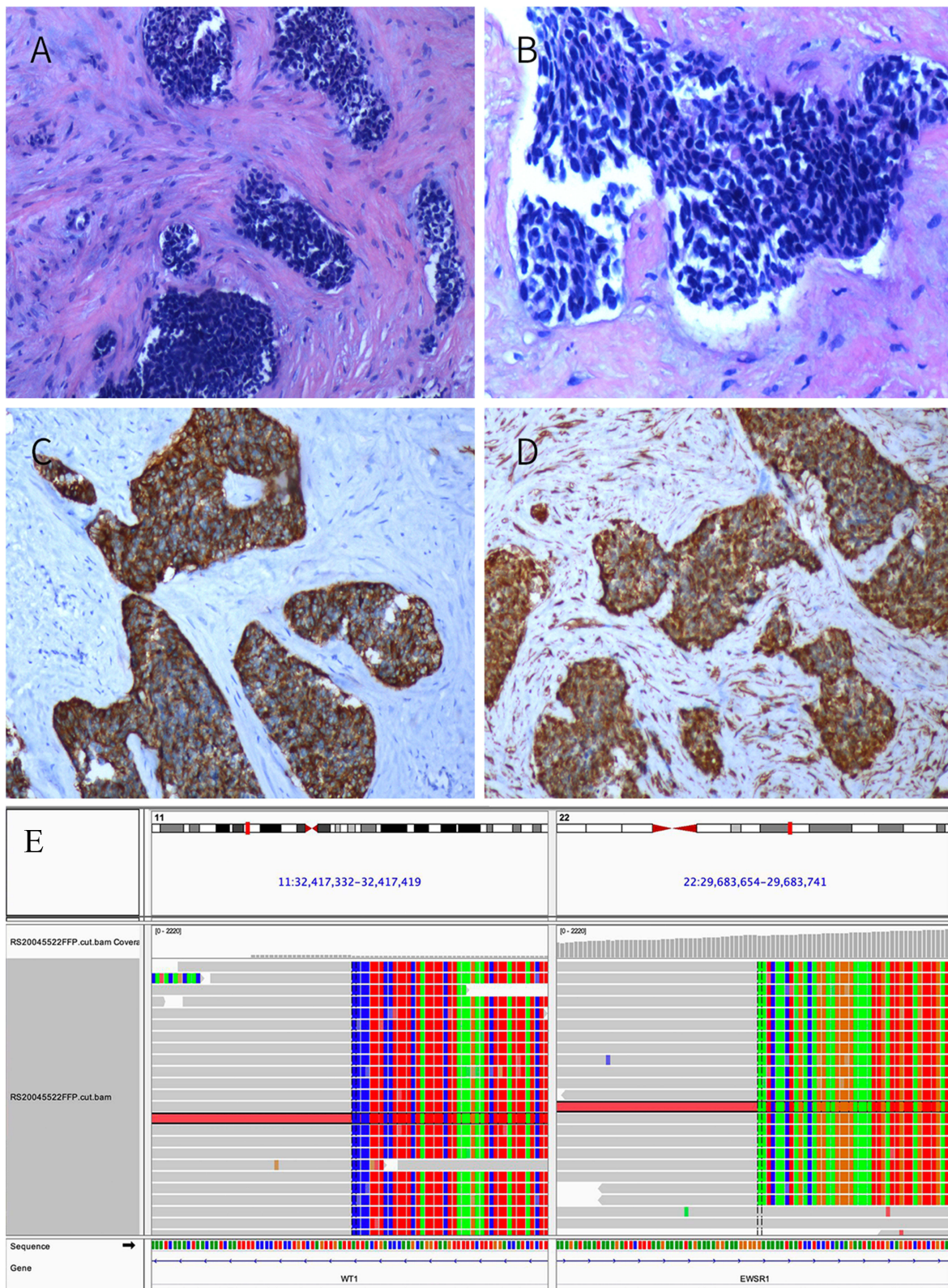


Figure 2 The pictures of tumor pathology sections: (A) HE×10, (B) HE×20, (C) EMA +, (D) vim +. (E) NGS of primary abdominal tumors showing WT-EWSR1 rearrangement. Burning Rock Dx, OncoScreen Plus Panel (Contains 520 genes).

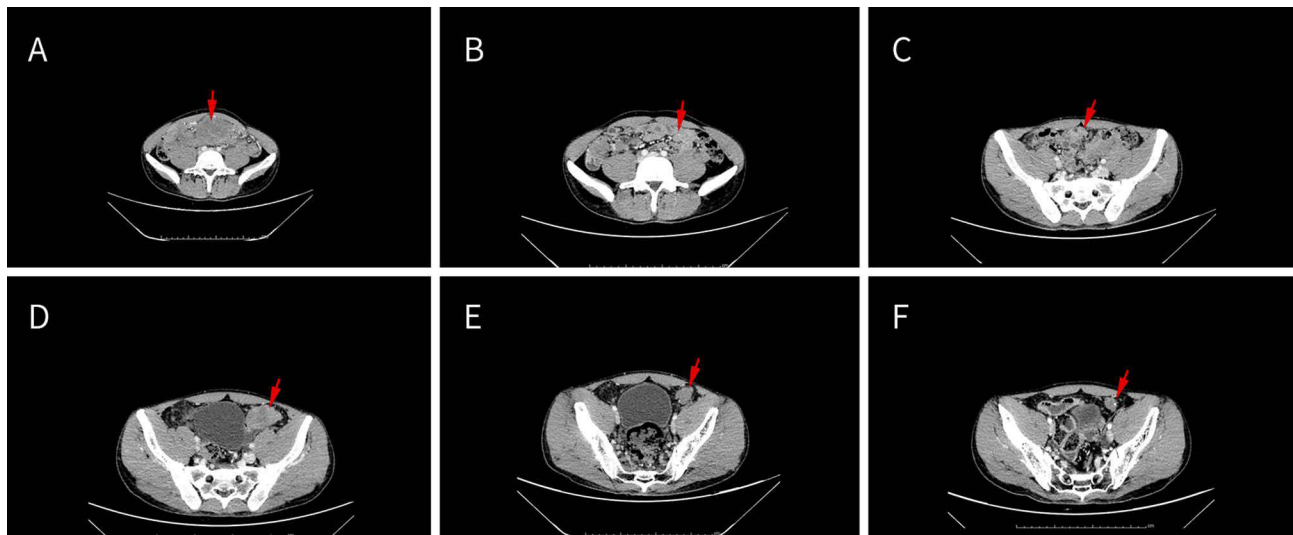


Figure 3 (A) Before chemotherapy, CT scan reveals abdominal masses (red arrow), (B,C) after 2 cycles of chemotherapy, abdominal masses was shrinking (red arrow), (D) after 5 cycles of chemotherapy, enlarged lesions next to the left iliac vessels (red arrow), (E) 1 month after radiotherapy, the lesions decreased (red arrow), (F) 3 months after radiotherapy, the lesions decreased further (red arrow).

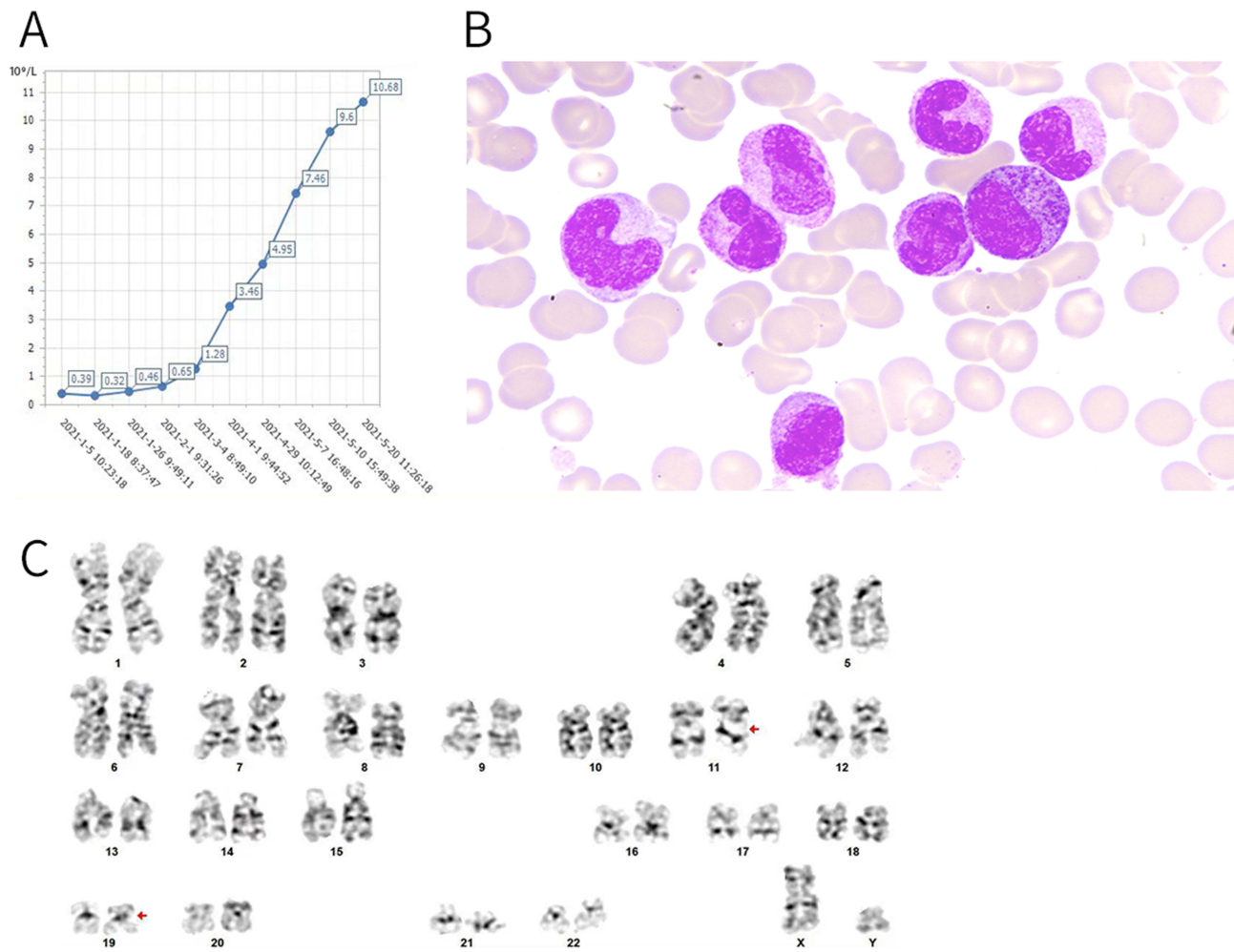


Figure 4 (A) Progressive increase in absolute monocyte count, (B) bone marrow cytology: significant increase in immature monocytes, (C) Karyotype:46, XY, t (11:19) (q23;p13)[19]/46, XY[1].

Screening of 24 fusion genes in myeloid leukemia revealed an MLL-ELL fusion gene. The detection of seven gene mutations related to CMML revealed no mutations at these gene sites. The patient was diagnosed with acute myeloid leukemia-M5. The patient refused further treatment and died of white blood cell stasis, abnormal coagulation, and cardiac arrest on August 12, 2021.

Discussion

Desmoplastic small round cell tumor (DSRCT) is a rare malignant tumor that primarily occurs in the abdomen and pelvic cavity⁶ with unclear histogenesis. It mainly involves the retroperitoneum, pelvic cavity, omentum, and mesentery, and typically presents with extensive abdominal serosa involvement. Common clinical manifestations include lumps, distension, abdominal pain, constipation, and nausea, without specificity. DSRCT belongs to the small round cell tumor family, and typical DSRCT exhibits multiple immunohistochemical phenotypes,⁷ with most cases expressing desmin, vimentin, EMA, and cytokeratin, as well as neural markers, such as NSE and CD57. More than 90% of patients have a specific T (11; 22) (p13; Q12) Chromosome heterotopia.⁸ The EWSR1 gene located at 22q12 and WT1 gene located at 11p13 undergo translocation, recombination, and fusion (EWS-WT1 gene fusion).

Radical resection is the only curative treatment for DSRCT. Studies have shown that the 3-year survival rate of patients who underwent surgery was 58%, whereas those who did not undergo surgery had no survivors after 3 years.⁹ Advanced patients with extraperitoneal metastases are primarily treated with systemic therapies. Chemotherapy can reduce tumor size and mortality. Studies have indicated¹⁰ that P6, IE, and HD-VAC alternating therapy can achieve a disease control rate of 100%. This therapy included the VAC regimen (cyclophosphamide 4200mg/m²+ vincristine 2mg/m²+ doxorubicin 75mg/m²) in the first, second, third, and sixth cycles and the IE regimen (ifosfamide 9g/m²+ etoposide 500mg/m²) in the fourth, fifth, and seventh cycles. It is a typical chemotherapeutic treatment for DSRCT, and hematological toxicity with 45% grade 3–4 bone marrow suppression is the most important dose-limiting toxicity. Radiotherapy is commonly used to relieve local symptoms and is a supplementary treatment to surgery and chemotherapy. Whole-abdominal radiation therapy (WART) can be used as a consolidated chemotherapy method for small abdominal lesions. In a retrospective study¹¹ of 103 patients with DSRCT, the 3-year survival rates of the radiotherapy and non-RT groups were 61.2% and 37.6%, with mean survival time of 40.3 and 28.3 months ($P < 0.05$). The average dose of patients receiving WART was 26.95 Gy (range, 20–33 Gy), and the main adverse reactions were acute gastrointestinal reactions such as nausea, diarrhea, and acute hematological toxicity.

Although the combination of chemotherapy, surgery, and radiotherapy significantly improves the survival rate of patients with DSRCT, the overall prognosis remains poor because the majority of patients experience disease recurrence and die within three years. Therefore, there is an urgent need to develop new and effective treatments with lower toxicity. EWSR1-WT1 gene fusion¹² is distinctive feature of DSRCT. This translocation upregulates the expression of PDGFR α , VEGF, and other proteins related to tumor and vascular cell proliferation. Tyrosine kinase inhibitors (TKI) targeting VEGF, VEGFR α , and other proteins involved in tumor vascular proliferation have also been used in clinical practice. In a relatively large retrospective study,¹³ among the 29 patients with DSRCT treated with pazopanib, 16 showed stable disease, 1 showed partial remission, and 1 showed complete remission. The disease control rate was 62% and the median progression-free survival was 5.4 months.

Two other cases have reported patients treated with anlotinib. One patient had metastasis to the right inguinal lymph nodes and greater omentum lymph nodes after radical surgery and 6 cycles of chemotherapy (ifosfamide + liposomal doxorubicin). After 4 cycles of anlotinib treatment, the lymph nodes was significantly reduced.¹⁴ Another patient received chemotherapy (vincristine, epirubicin, and ifosfamide) combined with anlotinib after the debulking surgery. The disease was partially relieved after two cycles of treatment, and anlotinib was used for maintenance therapy after six cycles of treatment. The response lasted for nearly two years, with the major side effects being hypertension, proteinuria, and hematochezia.¹⁵ The patient we reported took oral anlotinib for maintenance treatment after radiotherapy, and the disease remained stable with mild diarrhea for more than half a year. The treatment was stopped owing to acute myeloid leukemia-M5; however, the DSRCT lesion remained stable at the time of cessation.

The pathogenesis of t-AML includes direct induction of fusion oncogenes by chromosomal translocation, induction of genomic instability, creation of a leukemia-promoting environment by bone marrow damage induced by radiotherapy and

chemotherapy, and selection of pre-existing drug-resistant hematopoietic cell clones.¹⁶ The latency period of t-AML is typically associated with the type of cytotoxic treatment. t-AML caused by topoisomerase II inhibitors such as etoposide or anthracycline drugs usually occurs within 2–3 years of treatment, whereas t-AML caused by alkylating agents or radiotherapy has a longer latency period of 5–10 years.¹⁷ There exists a significant temporal interval from the initiation of treatment to confirmed diagnosis. In a Swedish retrospective study of 220 treatment-related cases treated with allo-HSCT, the median time from cytotoxic exposure to t-AML diagnosis was 54.7 months (2.3–441.8 months), with a minimum of only 2.3 months.¹⁸ The equilibrium translocation that occurs in topoisomerase II inhibitor-associated t-AML often involves the 11q23 rearrangement, 21q22.1 rearrangement.¹⁹ In this case, the patient was detected to carry an 11q23 (MLL) abnormality. However, initial Next-Generation Sequencing (NGS) analysis of peripheral blood and tumor tissue specimens did not reveal any germline or somatic mutations associated with AML. The diagnosis of t-AML was made only 7 months after antitumor therapy, which may have been related to the high intensity of chemotherapy and extensive radiotherapy, as well as the accelerated pathogenesis by the subsequent consolidation therapy with anlotinib.

The prognosis after t-AML diagnosis is very poor, with a median overall survival of only 8 months.²⁰ Hematopoietic cell transplantation is the only treatment option for AML. It is applicable to patients with moderate or poor-risk t-AML and high-risk AML with a small residual disease burden.²¹ Trilaciclib, an inhibitor of CDK4/6, has been proven effective in protecting the bone marrow from chemotherapy in small-cell lung cancer.²² Whether it can protect the bone marrow and reduce the incidence of treatment-related hematological malignancies in other tumors requires further investigation. The patient's monocyte count significantly increased seven months after intensive chemotherapy and WART. Bone marrow morphology and biopsy confirmed the diagnosis of acute myeloid leukemia-M5 with a short interval between disease onset and rapid progression. The patient lost confidence, refused further treatment, and died of leukostasis, abnormal coagulation function, and cardiac arrest two months later.

Conclusion

In conclusion, we reported the first case of acute myeloid leukemia-M5 complicated by abdominal DSRCT after multimodal therapy. This case highlights the importance of individualized multimodal treatment strategies for rare cancers. Additionally, it underscores the need to closely monitor the risk of a secondary tumor induced by high-intensity radiotherapy and chemotherapy. Rational drug selection or combination regimens, as well as the use of CDK4/6 inhibitors to protect the bone marrow and reduce the incidence of hematologic malignancies, deserve further investigation.

Data Sharing Statement

The original contributions of this study are as follows. Further inquiries can be directed to the corresponding author.

Ethics Statement

Institutional approval was waived to publish the case details due to local regulation. Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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