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CASE REPORT

Secondary acute promyelocytic leukemia following chemotherapy for gastric cancer: A case report

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Abstract

Therapy-related acute myeloid leukemia (t-AML) refers to a heterogeneous group of myeloid neoplasms that develop in patients following extensive exposure to either cytotoxic agents or radiation. The development of t-AML has been reported following treatment of cancers ranging from hematological malignancies to solid tumors; however, to our knowledge, t-AML has never been reported following treatment of gastric cancer. In this study, we report the development of t-acute promyelocytic leukemia in a cT4N1M0 gastric cancer patient after an approximate 44 mo latency period following treatment with 4 cycles of oxaliplatin (OXP) (85 mg/m^2 on day 1) plus capecitabine (1250 mg/m^2 orally twice daily on days 1-14) in combination with recombinant human granulocyte-colony stimulating factor treatment. Karyotype analysis of the patient revealed 46,XY,t(15;17)(q22;q21)[15]/46,idem,-9,+add(9)(p22)[2]/46,XY[3], which, according to previous studies, includes some "favorable" genetic abnormalities. The patient was then treated with all-trans retinoic acid (ATRA, 25 mg/m^2/d) plus arsenic trioxide (ATO, 10 mg/d) and attained complete remission. Our case illuminated the role of certain cytotoxic agents in the induction of t-AML following gastric cancer treatment. We recommend instituting a mandatory additional evaluation for patients undergoing these therapies in the future.

Key words: Gastric cancer; Acute promyelocytic leukemia; Oxaliplatin; Capecitabine; Chemotherapy

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Core tip: In the current study, t-acute promyelocytic leukemia (t-APL) was likely induced by treatment with

oxaliplatin, capecitabine and recombinant human granulocyte-colony stimulating factor. The gastric cancer patient, classified as clinical stage cT4N1M0, had a rare karyotype: 46,XY,t(15;17)(q22;q21)[15]/46,idem,-9,+add(9)(p22)[2]/46,XY[3]. This case demonstrates that certain cytotoxic agents can induce t-APL in gastric cancer. We recommend mandatory additional evaluation for patients undergoing this treatment regimen.

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INTRODUCTION

Therapy-related acute myeloid leukemia (t-AML) refers to a heterogeneous group of myeloid neoplasms that develop in patients following extensive exposure to either cytotoxic agents or radiation[1]. In the past few decades, survival rates for cancer patients have improved, resulting in an increased risk of t-AML[2]. However, it is worth noting that while t-AML shares common phenotypic features with *de novo* AML, t-AML is relatively resistant to conventional therapies for leukemia. Additionally, t-AML has an overall poor prognosis with a median life expectancy of 8-10 mo following diagnosis[3].

While the underlying cause of t-AML remains to be elucidated, the development of t-AML has been confirmed to correlate with certain cytotoxic drugs. According to previous reports, alkylating agents (busulfan, carboplatin), topoisomerase-2 inhibitors (doxorubicin, mitoxantrone), antimetabolites (5-fluorouracil, fludarabine), antimicrotubule agents (docetaxel, paclitaxel) and growth factors (granulocyte-macrophage colony-stimulating factor; G-CSF) associate with the development of t-AML, although often with a varying latency period[4-6]. Interestingly, the chemical structure and dosage of these agents greatly affect the t-AML profile. For example, treatment with an alkylating agent usually results in a common subtype of t-AML, which is observed in approximately 75% of patients after 5-7 years of exposure. This subtype is often characterized by the loss of all or part of chromosomes 5 or 7[7]. Contrastingly, treatment with topoisomerase Ⅱ inhibitors often result in gene rearrangements involving 21q22 with a latency ranging from 1-3 years[7].

Recently, a relatively distinct subgroup of t-AML was reported as "good" leukemia. This "good" leukemia refers to acute promyelocytic leukemia (APL) characterized with inv(16)/t(15;17) or more rarely t(8;21)[8]. To our knowledge, t-acute promyelocytic leukemia (t-APL) has yet to be reported following treatment of gastric cancer.

CASE REPORT

A 68-year-old man, diagnosed with gastric cardia cancer, was referred to Shanghai Changzheng Hospital (Shanghai, China) in March 2007 (Figure 1A, B). Post-operative analysis confirmed a poorly differentiated adenocarcinoma with penetrating invasion of the gastric wall. One out of the 29 regional lymph nodes was positive for cancer cell infiltration (Figure 1C, D). According to the TNM/UICC staging system, the patient classified as cT4N1M0 (ⅢC). The patient then underwent 4 cycles of chemotherapy with oxaliplatin (OXP) (85 mg/m^2 on day 1) and capecitabine (1250 mg/m^2 orally twice daily on days 1-14) until August 2007. Treatment ended when the patient developed violent emesis. In the subsequent visit, the patient had recovered well, with no additional complications. On April 15, 2011, the patient suddenly presented fatigue and high fever (39.2 ℃). A blood examination indicated pancytopenia. The patient was treated with recombinant human granulocyte-colony stimulating factor (rHu-G-CSF), followed by a bone marrow biopsy. Peripheral smear analysis revealed an abnormal increase in the amount of myeloblasts and promyelocytes (91.5%), with leukemic hiatus (Figure 2A, B). Chromosome-based analysis revealed structural rearrangements involving chromosomes 9, 15 and 17. The patient's karyotype was 46,XY,t(15;17)(q22;q21)[15]/46, idem,-9,+add(9)(p22)[2]/46,XY[3]. Additionally, the Bcr1 subtype of the promyelocytic leukemia/retinoic acid receptor-alpha (PML/RARα) fusion gene was positive, whereas the Bcr2 and Bcr3 subtypes of the PML/RARα fusion were negative (Figure 3). According to WHO-based classification, these results verified the diagnosis as t-AML (M3a, which is also referred as t-APL). Routine blood examination indicated the following: red blood cells at 2.35 × 10^{12}/L, white blood cells at 1.8 × 10^9/L, absolute neutrophil count at 0.67 × 10^9/L, hemoglobin at 75 g/L, and platelets at 81 g/L. The patient then underwent induction therapy with all-trans retinoic acid (ATRA, 25 mg/m^2 per day) plus arsenic trioxide (ATO, 10 mg/d). Other supportive therapies were provided when necessary; these therapies included platelet and fresh frozen plasma transfusions as well as antibiotic administration. The patient presented complete remission (CR) in June 2011, and thus far, no other complications have been recorded.

DISCUSSION

As a relatively distinct subgroup of t-AML, t-APL is usually characterized with excellent prognosis. Regarding t-APL development, epirubicin and mitoxantron represent the most commonly implicated cytotoxic drugs[9]. In the current study, we investigate

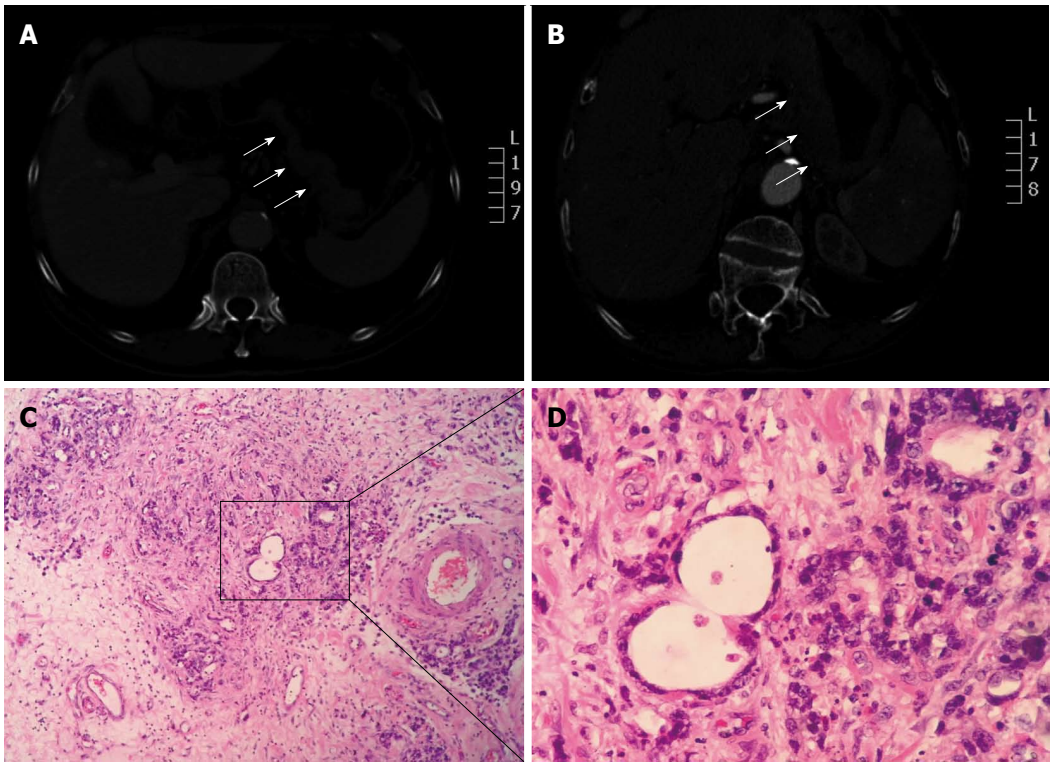

Figure 1 Upper abdomen computed tomography scan. A: Plain computed tomography (CT) indicated a localized, irregularly-shaped mass in the stomach; however, no obvious lymph node metastasis was observed; B: Contrast-enhanced CT scan revealed inhomogeneous enhancement of the gastric wall lesion; C, D. Biopsy results pathologically confirmed the diagnosis of a poorly differentiated adenocarcinoma. Microscopic examination revealed obvious atypical nuclei and large, bizarre, multinucleated cell mitosis. Generally, the normal structure of gastric gland was lost. (Hematoxylin and eosin staining, C: Magnification × 100; D: Magnification × 400).

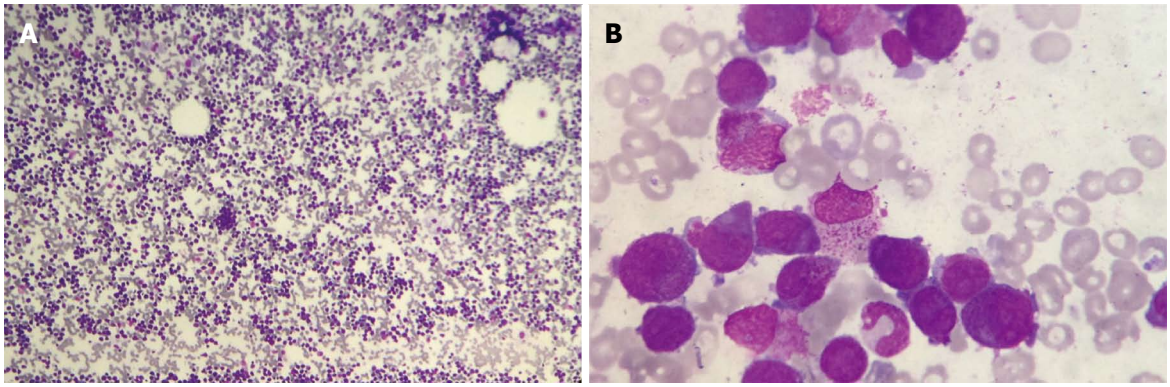

Figure 2 Peripheral blood smear, bone marrow biopsy and immunohistochemistry results revealed that the total number of primitive cells plus immature leukemia cells account up to 91.5% (2% + 89.5%) of the total cell population. Leukemic hiatus was detected, which supports the diagnosis of acute myeloid leukemia (M3a, APL). (Hematoxylin and eosin staining, A: Magnification × 10; B: Magnification × 400).

the occurrence of t-APL in gastric cancer, which was likely induced by OXP and capecitabine treatment. The patient was finally cured with a treatment regimen of ATRA plus ATO. To our knowledge, this study represents the first report of t-APL diagnosed following treatment of gastric cancer (Table 1).

While the underlying cause of t-AML remains to be fully elucidated, we have established the importance of DNA damage, which includes methylation and intra- and inter-strand DNA cross links[10]. Platinum-based agents kill cancer cells through the formation of DNA adducts; these adducts lead to the formation of intra- and inter-strand DNA cross links that ultimately disrupt the processes of DNA replication and transcription[11]. Previous studies have reported an association of cisplatin and carboplatin treatment with the onset of therapy-related leukemia (TRL); however, the role of OXP in TRL was overlooked. As shown in Table 1, t-AML was diagnosed in 3 of the 6 reports regarding OXP-related TRL. Furthermore, only 1 report of OXP-related TRL was confirmed as t-APL[12-17]. In Merrouche *et al*[12], a female patient was treated with LVFU2,

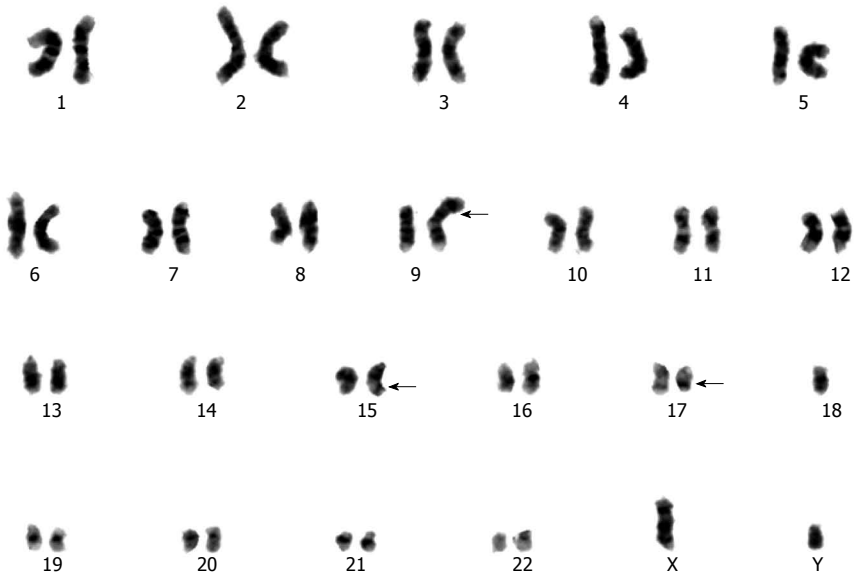

Figure 3 Chromosomal analysis *via* karyotype revealed 46 chromosomes with abnormities present in chromosomes 9, 15, and 17. Unbalanced translocation occurred in chromosomes 15 and 17. 46,XY,t (15;17)(q22;q21)[15]/46,idem,-9,+add(9)(p?22)[2]/46,XY[3].

Table 1 Reports of therapy-related leukemia development following oxaliplatin and/or capecitabine-containing chemotherapy

Ref.	Patient, age (yr)/gender	Primary cancer	Chemotherapy regimen	TRLs	Karyotype
Merrouche *et al*[12]	65/female	Colon	LVFU2, Irinotecan, OXP	APL	46,XX,add(6)(p23),-13,add(14)(p11),-16,add(17)(q?),-21,+3 mar
Carneiro *et al*[13]	56/female	Cecum	FOLFOX-4, FOLFOX-6	AML	Partial deletions of chromosomes 5, 7, 20, and 21, as well as trisomy 8 and loss of chromosomes 3 and 1
Merlin *et al*[14]	65/female	Colorectal	FOLFOX-4	ALL	Not available
Damodaran *et al*[15]	63/male	Esophagus	Capecitabine, OXP	AML	47,X,der(Y)t(Y;3)(q12;q21),+8(21)
Buxhofer-Ausch *et al*[16]	56/male	Colon	Capecitabine, 5-FU, Irinotecan, OXP	CML	Positive for Philadelphia chromosome
Kadikoylu *et al*[17]	66/male	Rectum	Cetuximab, OXP, Irinotecan, Capecitabine	CML	Positive for Philadelphia chromosome
Shapiro *et al*[18]	63/female	Cecum	Capecitabine	MLL	t(6;11) with breakpoint 11q23
Tansley *et al*[19]	66/male	Colon	Capecitabine	AML	Not available
Rashidi *et al*[20]	58/male	Rectum	Capecitabine, Radiation	APL	46,XY, t(15;17)(q24;q21)

APL: Acute promyelocytic leukemia; AML: Acute myeloid leukemia; ALL: Acute lymphoblastic leukemia; CML: Chronic myeloid leukemia; MLL: Chronic lymphoblastic leukemia; FOLFOX: Oxaliplatin plus 5-fluorouracil (5-FU); LVFU2: Leucovorin plus 5-FU; TRLs: Therapy-related leukemias.

irinotecan and OXP 12 mo prior to t-APL diagnosis. The karyotype examination indicated (46,XX,add(6)(p23),-13,add(14)(p11),-16,add(17)(q?),-21,+3mar), which differed from the commonly reported t(15;17)(q22;q21) translocation[12]. Furthermore, Carneiro *et al*[13] reported a study of a female patient, first treated by FOLFOX-4 (OXP plus 5-fluorouracil [5-FU]) followed by FOLFOX-6 plus bevacizumab. Importantly, 28 mo prior to t-AML development, her karyotype revealed trisomy 8, loss of chromosomes 3 and 11, as well as partial deletions in chromosomes 5, 7, 20 and 21[13]. In Damodaran *et al*[15], a male patient with esophageal cancer received OXP plus capecitabine, with additional radiation treatment 29 mo prior to the emergence of t-AML. His karyotype was 47,X,der(Y)t(Y;3)(q12;q21),+8(21). Merlin *et al*[14] reported t-ALL diagnosis in a female patient 12 mo after administration of FOLFOX-4. Unfortunately, the corresponding karyotype analysis was not performed in this study[14]. In colorectal cancer, 2 cases of therapy-related chronic myeloid leukemia (t-CML) following OXP treatment tested positive for Philadelphia chromosome[16,17]. In Buxhofer-Ausch *et al*[16], a male patient was treated by cetuximab, OXP, irinotecan and capecitabine 18 mo prior to t-CML diagnosis. Contrastingly, in Kadikoylu *et al*[17], a male patient was administered with capecitabine, 5-FU, irinotecan and OXP 12 mo prior to detection of t-CML.

However, the aforementioned case studies involved complex chemotherapy schedules, which complicate the process of defining the tumorigenic potential of a single drug. As shown in Table 1, capecitabine-induced t-AML was previously reported in 2 studies[18,19]. Furthermore, Rashidi *et al*[20] reported a case involving

capecitabine-induced t-APL with a karyotype of 46,XY,t(15;17)(q24;q21). Surprisingly, treatment with G-CSF was correlated with the development of TRL[21]. The results from these studies make it difficult to determine which agent is imperative in the development of TRL. Additionally, these studies highlight the considerable variation in the average time between treatment and onset of TRL. In our study, the patient was treated by OXP plus capecitabine and G-CSF, with a 44 mo latency period prior to onset of t-APL. The karyotype analysis of our patient presented 46,XY,t(15;17)(q22;q21)[15]/46,idem,-9,+add(9)(p22)[2]/46,XY[3], which was unlike previous studies. Balanced chromosome translocations were observed, although at low frequency, in t(15;17)(q22;q11). This genetic abnormality is often associated with treatments involving topoisomerase-2 inhibitors[22,23]; however, in an uncommon occurrence, balanced chromosome translocations were observed in our patient who was treated with OXP, capecitabine and G-CSF.

The prognosis of t-AML is thought to be worse than *de novo* AML, with a reported 5-year survival rate of less than 10%[24]. In Kayser *et al*[25], patients with t-AML were characterized with significantly inferior 4-year relapse-free survival (24.5% *vs* 39.5%) and 4-year overall survival (25.5% *vs* 37.9%) than *de novo* AML. Interestingly, karyotype variation provides key insight on the final outcome of t-AML patients[26]. As reported by Kern *et al*[27], patients with a favorable karyotype were characterized with a significantly higher median survival time (26.7 mo) compared to patients with an unfavorable karyotype (5.6 mo). However, in t-APL, these parameters are distinct from that of t-AML. t-APL patients with t(15;17)/PML-RARα have a complete remission rate of 63.6% compared to *de novo* APL (92.5%). Accordingly, the overall survival in t-APL is inferior to *de novo* APL (51% *vs* 84%)[28]. In our case, the patient partially displayed a favorable karyotype (t(15;17)/PML-RARα) and attained complete remission. However, further study is required to elucidate the function of other chromosomal abnormalities (for example, chromosome 9) in this outcome.

Our study presents the novel case of t-AML/t-APL following treatment of gastric cancer. We suggest establishing an additional evaluation process for patients undergoing treatment with certain cytotoxic therapies. For patients with t-APL, our case emphasized the importance of certain "favorable" genetic abnormalities. While standard treatment protocol is likely to yield a favorable outcome for patients, additional studies are required to elucidate the underlying process of t-APL development.

COMMENTS

Case characteristics

A 68-year-old man was diagnosed with gastric cardia cancer and was classified as cT4N1M0 (or ⅢC), according to the TNM/UICC staging system.

Clinical diagnosis

After surgery, post-operative examination of the patient confirmed a poorly differentiated adenocarcinoma with penetrating invasion of the gastric wall. Out of 29 regional lymph nodes, 1 tested positive for cancer cell infiltrate.

Differential diagnosis

Based on clinical symptoms, imageological examination and post-operative pathological analysis, the patient diagnosis was definitive.

Laboratory diagnosis

Routine hematological examination indicated the following: red blood cells (2.35 × 10^{12}/L), white blood cells (1.8 × 10^{9}/L), absolute neutrophil count (0.67 × 10^{9}/L), hemoglobin (75 g/L), and platelets (81 g/L).

Imaging analysis

Computed tomography scan indicated a localized, irregularly-shaped mass in the stomach. No obvious lymph node metastasis was observed.

Pathological diagnosis

Post-operative pathological examination confirmed gastric cancer. Bone marrow biopsy indicated acute myeloid leukemia. Leukemic hiatus was diagnosed as the total number of primitive cells plus immature leukemia cells accounted for 91.5% (2% + 89.5%) of the total cell population.

Treatment

Oxaliplatin, capecitabine and recombinant human granulocyte-colony stimulating factor was administered for the treatment of gastric cancer. All-trans retinoic acid and arsenic trioxide was delivered to treat t-acute promyelocytic leukemia (t-APL).

Related reports

In the literature, development of t-AML is rarely associated with treatment regimens involving oxaliplatin, capecitabine and recombinant human granulocyte-colony stimulating factor. The role of these cytotoxic agents in t-AML development remains unclear.

Term explanation

Therapy-related acute myeloid leukemia (t-AML) refers to a heterogeneous group of myeloid neoplasms that develops in patients who were extensively exposed to cytotoxic agents or radiation during prior treatment.

Experience and lessons

This case study elucidated that specific cytotoxic agents induce t-APL in gastric cancer patients. We recommend additional evaluation and follow-up for patients undergoing these therapies in the future.

Peer-review

This case report adds some information to the current literature. The case report and the discussion are well-written. They successfully managed a case of therapy-related acute myeloid leukemia. This case report provides an important update on therapy-related acute myeloid leukemias and presents an interesting patients who after diagnosis including karyotype analysis and treatment entered complete remission. The report is well illustrated and the authors well summarized current literature.

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