

Gastric carcinoma subsequent to myelodysplastic syndrome with t (1; 19) chromosome translocation

A rare case report and its potential mechanisms

Wenqing Yu, MD^{a,b}, Gaoyang Chen, MD^c, Yunpeng Sun, MD^d, Sujun Gao, MD^a, Wei Li, MD^a, Jiuwei Cui, MD^a, Jingnan Sun, MD^{a,*}

Abstract

Rationale: Myelodysplastic syndrome (MDS) is a heterogeneous malignant hematologic disease with median overall survival ranging from six months to more than ten years. Solid tumor rarely occurs in combination with MDS and the underlying pathogenesis and prognostic significance still remain controversial.

Patient concerns: Here we report a relative low risk myelodysplastic syndrome-refractory cytopenia with multilineage dysplasia (MDS-RCMD) patient, with a rare t(1; 19) chromosome translocation. This patient also suffered from gastric carcinoma.

Diagnoses: Gastric carcinoma, Myelodysplastic syndrome with t (1; 19) chromosome translocation.

Interventions: This patient received radical operation for gastric carcinoma and erythropoietin infusion.

Outcomes: The patient took follow up visits every 2 to 3 months in past years and now he is in stable disease without further treatment.

Lessons: We reviewed the mechanism of MDS complicated by solid tumor and concluded the potential mechanisms of this patient. The interactions between potential factors may play a role in oncogenesis which, however, need an in-depth study of its operating mechanism.

Abbreviations: ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, CBC = complete blood count, COX-2 = cyclooxygenase-2, CT = computed tomography, EFS = event free survival, MDS = myelodysplastic syndrome, RUNX = runt related transcription factor, TGF-β = transforming growth factor-β, VEGF = vascular endothelial growth factor.

Keywords: chromosome translocation, gastric carcinoma, mechanism, myelodysplastic syndrome

1. Introduction

Myelodysplastic syndrome (MDS) is a group of clonal BM neoplasms, which characterized by abnormal myeloid cell differentiation, ineffective hematopoiesis, refractory cytopenia and a tendency to evolve into acute myeloid leukemia (AML).^[1]

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WY and GC contributed equally to this study.

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^a Cancer Center, the First Hospital of Jilin University, Jilin, ^b Department of Hematology, Yantai Affiliated Hospital of Binzhou Medical University, Yantai, ^c Research Center, the Second Hospital of Jilin University, Jilin, ^d Cardiovascular Surgery Department, the First Hospital of Jilin University, Jilin, People's Republic of China.

* Correspondence: Jingnan Sun, Cancer Center, the First Hospital of Jilin University, Jilin, 130021, People's Republic of China (e-mail: jingnansun@126.com).

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However, cases of solid tumors simultaneously with or subsequent to primary MDS have rarely been reported. Previous studies have reported a series of rare MDS cases associated with solid tumors. Du et al^[2] reported a 47-year-old female suffering from MDS and cervical carcinoma. Takahashi et al^[3] reported a 66-year-old male suffering from synchronous double cancers of the stomach and the papilla of Vater subsequent to primary MDS. Eun Joo Lim et al^[4] reported a case of early gastric cancer suffering from MDS. We herein present a case of gastric cancer subsequent to MDS with t (1; 19) chromosome translocation and explore the possible mechanisms. The patient has provided informed consent for publication of the case. Ethical clearance and approval including the patient's informed consent for publication was obtained from the Ethics Review Committee at the first hospital of Jilin University (Changchun, Jilin, China, Project Reg. No: 2018-036).

1.1. Case presentation

A 55-year-old male was admitted to the First Hospital of Jilin University presenting with "fatigue for more than 7 years, aggravated for 1 week" on April 30, 2014. Seven years ago, he went to Sino-Japanese Fellowship Hospital of Jilin University because of fatigue symptoms. Complete blood count (CBC) showed anemia with hemoglobin of 59 g/L. After bone marrow aspiration, he was diagnosed as MDS-refractory cytopenia with multilineage dysplasia (MDS-RARS) and took cyclosporin, thalidomide, retinoic acid orally. Red blood cell suspension was transfused occasionally for supportive care. However, the

Table 1**The results of laboratory examination.**

Examination Items	Results	Reference ranges	Unit of results
WBC	2.8	3.5–9.5	$\times 10^9/L$
Hb	37	110–150	g/L
PLT	85	100–300	$\times 10^9/L$
MCV	97.8	80–100	fL
MCH	30.1	27–32	pg
MCHC	308	320–360	g/L
EPO	>792.00	2.59–18.5	mIU/ml
SI	26.6	7–30	umol/L
TIBC	32.4	31–51	umol/L
SF	3270	22–322	ug/L
Reticulocyte percentage	0.3	0.5–2.5	%
Reticulocyte absolute value	10	31–82	$\times 10^{12}/L$

EPO=erythropoietin, Hb=hemoglobin, MCH=mean corpuscular hemoglobin, MCHC=mean corpuscular hemoglobin concentration, MCV=mean corpuscular volume, PLT=platelet, SF=serum ferritin, SI=serum iron, TIBC=total iron binding capacity, WBC=white blood count.

symptoms were not improved obviously and the regular examination was not taken. The fatigue symptom aggravated 1 week ago and CBC showed severe pancytopenia.

Physical examination (June 1, 2014) showed severe anemia and a 3×4 cm mass was palpated in upper abdomen (hard, no mobility, and painless). Laboratory examination results were shown in Table 1. Bone marrow was hypercellular, nuclear hypersegmentation and deceased granules accounted for 16% of myeloid lineage. Mature red blood cells were in different size, macrocyte, with internuclear bridging and nuclear budding. Exocellular iron++++, intracellular iron 58%. Ringed sideroblasts accounted for 8%.

He accepted supportive therapy and further examination. Further physical examination (June 2, 2014) still showed an abdominal hard mass in upper abdomen. The patient didn't have any digestive symptoms history. Tumor markers carbohydrate antigen 724 (CA-724, reference range: 0.1–7 U/mL) increased to 99.99 U/mL, the cytokeratin 19 fragment (CYFRA21-1, reference range: 0.1–4 ng/mL) increased to 25.61 ng/mL and the carcinoembryonic antigen (CEA, reference range: 0–5 ng/mL) increased to 468.58 ng/mL. The enhanced computed tomography (CT) image of full abdomen showed space-occupying lesions in gastric body and gastric antrum with multiple lymph node enlargement (Fig. 1A), which indicated to be gastric cancer with a stage of T4aN3aMx. Further bone marrow cytogenetics (Fig. 2) showed 46,XY, der (19), t (1;19) (q23;p13),^[5] 46,XY,^[2] with no fusion transcripts and gene mutation. EPO and red blood cell suspension transfusion therapy was started until his hemoglobin was more than 80 g/L. Gastroscopy presented with a large

irregular ulcer type of neoplasm between the lesser curvature and antrum of the stomach with uncleaned moss and ooze blood (Fig. 1B). Pathological examination showed low differentiated adenocarcinoma. Above all, the patient's diagnosis was "MDS-RCMD (IPSS score: medium risk-1, IPSS-R score: medium risk, WPSS score: high risk), gastric adenocarcinoma (T3N3a)." The patient then received radical operation for gastric carcinoma and infused erythropoietin subcutaneously.

2. Discussion

As with all the other myeloid neoplasms, a large amount of data has recently become available on recurrent mutations in MDS. The most commonly mutated genes with in MDS are SF3B1, TET2, SRSF2, ASXL1, DNMT3A, RUNX1, U2AF1, TP53, and EZH2.^[6] E2A/PBX1 fusion gene is rare to occur in MDS. The t (1;19) (q23;p13) chromosome translocation is observed in about 3% to 5% of B-cell acute lymphoblastic leukemia (ALL) and is usually associated with an adverse prognosis.^[7] The t (1; 19) chromosome translocation juxtaposes the E2A gene from chromosome 19 with the PBX1 gene on chromosome 1, leading to the production of fusion transcripts and chimeric protein that contains transcriptional activating motif of E2A and the DNA-binding homeodomain of PBX1. This genetic change has 2 different forms: balanced translocation t (1;19) and the unbalanced translocation der (19) t (1; 19) (q23, p13). The ratio of 2 forms is 4:3. However, it has never been reported in MDS patient. This patient was diagnosed as MDS-RCMD, with der (19) t (1;19) unbalanced translocation, but E2A/PBX1 fusion gene is negative. The inconsistency also appeared in Thousand's analysis due to translocation locus and PCR sensitivity.^[8] Although being an independent adverse prognostic factor, the prognostic value of E2A/PBX1 fusion gene in ALL patients is still controversial.^[9] Recent study^[5] suggests that E2A/PBX1 positive ALL patients may have a good response to treatment after increasing the intensity of chemotherapy and regular follow-up, with 5-year event free survival (EFS) from St. Jude children's hospital in America up to 80% to 85%.^[10] So it's considered to be an intermediate factor in childhood ALL. There is no report about MDS with t (1; 19) (q23;p13) chromosome translocation, and according to IPSS-R risk stratification the prognostic significance of this chromosome abnormality is classified into intermediate-risk group. This patient took cyclosporine and thalidomide discontinuously for nine years, with no regular examination. When he was diagnosed as gastric cancer four years ago; he received surgery and refused chemotherapy. After regular follow up every 2 to 3 months, he is in stable disease without further treatment.

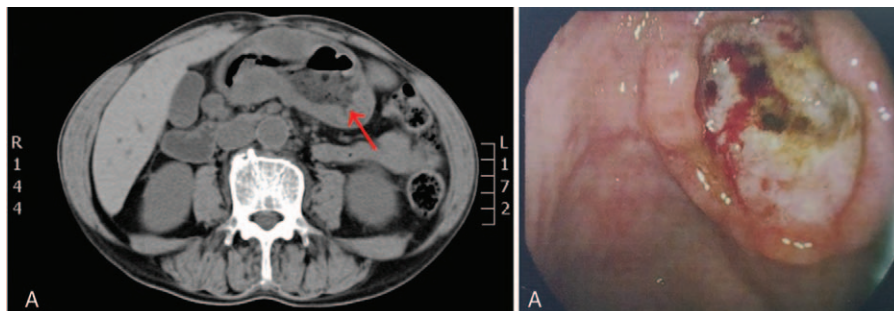


Figure 1. A, The image of enhanced CT and the red arrow showed space-occupying lesions in gastric body. B, Gastroscopy showed a large irregular ulcer.

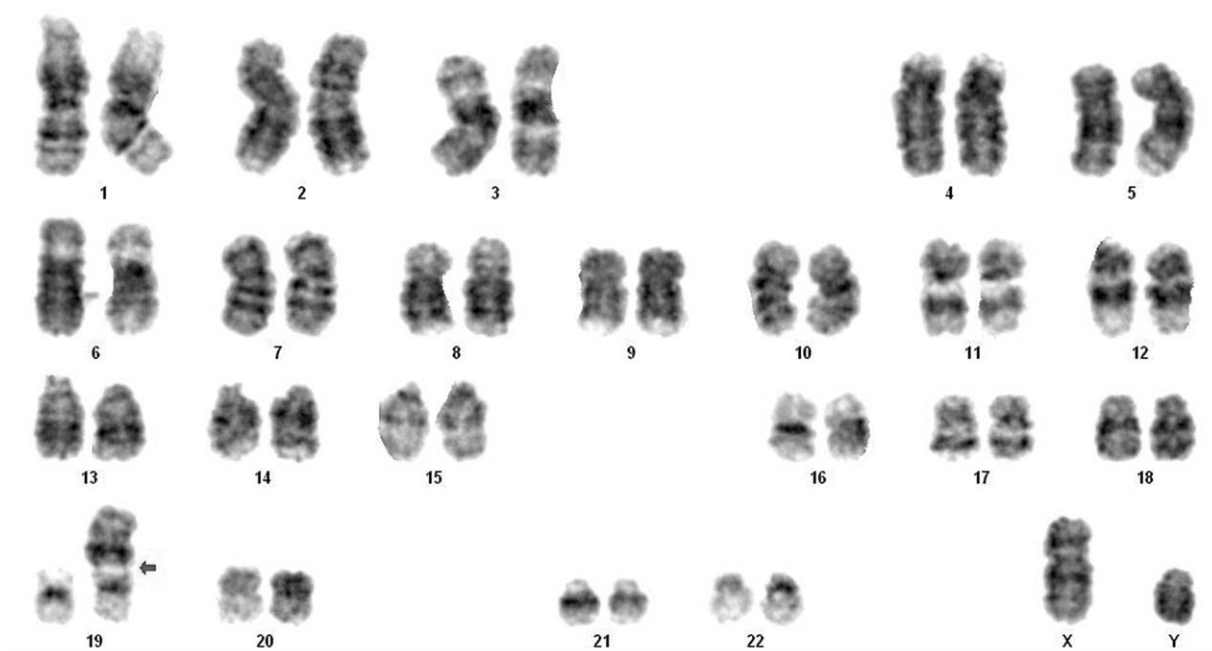


Figure 2. Chromosome G banding pattern of the patient. The arrow shows abnormal chromosome of t (1; 19) (q23; p13).

Here we discuss the possible pathogenesis of MDS with gastric cancer. It has been acknowledged that after chemotherapy and/or radiotherapy some patients with solid tumor will get secondary malignant disease,^[11] but it is rare in MDS patients with gastric cancer. We discuss the potential mechanism of MDS complicating with gastric carcinoma.

2.1. MDS leads to defects of immune surveillance and using immunosuppressive drugs further aggravates immunodeficiency

Fichmond Prehn first proposed the theory of “immune disturbance” in 1972. In his opinion, a “weak” immune reaction can promote the growth and metastasis of tumor cells, which means there’s a bi-directional response for immune response to tumor, in comparison with the theory that strong immune response can protect the body.^[12] More specifically, the spontaneous tumor won’t trigger an appropriate immune response to kill itself initiatively. On the contrary, it often triggers the immune response and doesn’t have enough ability to protect the body. Then the growth and proliferation of tumor cells was enhanced. It’s also been reported that patients taking immunosuppressive drug have a high incidence of solid tumor. This may be due to the immune dysfunction of body, which leads to the decline of immune surveillance function in cancer.

2.2. The co-factors in the process of MDS and gastric cancer

2.2.1. Transforming growth factor- β (TGF- β). TGF- β belongs to a group of TGF super-family that regulates cell growth and differentiation. TGF- β controls a series of cell response and the homeostasis of most organizations in human body. It is of vital importance in the process of cell proliferation, differentiation and apoptosis, especially fibroblast growth and collagen production.^[13] In tumors, TGF- β can be either a proto-oncogene or a tumor suppressor, depending on cell context and tumor stage. However, TGF- β can play the role of biology only when in

combination with its receptor. At present, there are 3 kinds of receptors with high affinity on human cell surface: T β R1, T β R2, and T β R3. The first 2 are requisite molecules in TGF- β signal transduction process. TGF- β 1 is regarded as a tumor suppressor in the early stage of carcinogenesis. In the early stage, cells present as growth advantage as a result of TGF- β inhibiting proliferation. And in the later stage, TGF- β can help providing a suitable microenvironment for tumor growth, invasion and metastasis via stimulating angiogenesis, immunosuppression and compounding of extracellular matrix.^[14] It has been shown that conditional loss of TGF- β signaling due to dominant negative mutation in T β R2 leads to increased susceptibility to gastrointestinal carcinogenesis in mice.^[15] The plasma levels of TGF- β have been reported to be elevated in previous studies^[16] and are confirmed by TGF- β immunohistochemical staining in selected studies.^[17]

2.2.2. Vascular endothelial growth factor (VEGF). VEGF is a highly specific vascular endothelial cell mitosis peptide cloned from leukemia cell line HL-60. VEGF can enhance vascular endothelial cell mitosis selectively, stimulate endothelial cell proliferation, promote angiogenesis, participate in vascular matrix remodeling and promote the release of inflammatory molecules. Angiogenesis and signaling via angiogenic cytokines have increasingly been recognized as an important process in the growth of both solid tumors and hematologic malignancies including MDS. Bellamy et al^[18] found that VEGF expression was relatively lower in normal bone marrow granulocyte but higher in original and immature neutrophils, monocytes and its receptors in patients with MDS. VEGF can stimulate leukemogenesis and the release of inflammatory cytokines, while its neutralizing antibody can inhibit the leukemia clone formation that reveals the VEGF can promote leukemia progenitor cell growth in MDS by autocrine and then induce ALIP phenomenon. Clinical studies found that hematological malignancy patients who had higher serum VEGF levels had significantly shorter progression free survival and their pre-treatment plasma VEGF levels were associated with response to chemoimmunotherapy.^[19] This postulate also builds on the

clinical trial data in solid tumors where anti-VEGF therapy has already been found to improve clinical outcome in patients with solid carcinoma.^[20,21]

2.2.3. COX-2. Cyclooxygenase-2 (COX-2) is the rate-limiting enzyme catalyzing transformation of membrane phospholipids arachidonic acid into prostaglandins chemicals. It's a membrane bound protein which exists in nuclear membrane and microsome membrane, mainly locating in the cytoplasm and nucleus. Cox-2 is rarely expressed in most normal tissue in normal physiological conditions, while it is highly expressed in diverse kinds of malignant tumor tissues. Cox-2 also participates in a various pathological process of many diseases.^[22] Studies have shown that cox-2 expression level was higher in MDS patients than that in normal control group.^[23] It is regarded as one of the important prognosis indicators in MDS. There are results suggesting that cox-2 could induce VEGF expression in tumor cells which then lead to the oncogenesis.^[24]

2.2.4. RUNX family. Runt related transcription factor 1 (RUNX1) is a member of RUNX transcriptional factor family. It plays an important role in the development process of normal cells and is the key factor in regulating hematopoiesis. Inactivating RUNX1 mutations have been frequently found in a variety of myeloid neoplasms, including MDS and cytogenetically normal AML.^[25,26] Therefore, RUNX1 has been regarded as a beneficial tumor suppressor for myeloid leukemogenesis. In addition, studies have shown that RUNX1 is also associated with the development of gastric cancer and other tumors.^[27] RUNX3 can promote the secretion of digestive enzymes.^[28] Animal experiments showed that if the gene was silencing, the regulation of cell number will be in disorder and cells in stomach will proliferate, resulting in stomach cancer. The RUNX3 expression level decreases with the progress of cancer. Sakakura et al^[29] found the expression of RUNX3 downregulated by 78% in 9 gastric cancer cell lines and the downregulation rate of RUNX3 was 75% in gastric cancer and 100% in patients with peritoneal metastasis, which is significantly different with that in normal gastric mucosa. The recovery of RUNX3 can inhibit tumor growth and metastasis in animal models. All these findings indicate that Runx3 is a tumor suppressor gene and its inactivation may lead to the occurrence of gastric cancer. Besides, Otto et al^[30] found that somatic mutations in RD gene region of RUNX3 could lead to gene deletion, which was involved in the pathogenesis of acute leukemia.

3. Conclusion

In summary, we presented a rare MDS case of gastric cancer which may subsequent to MDS with t(1; 19) chromosome translocation. After a systematic discussion of the possible mechanism of its occurrence, we drew following conclusions that E2A/PBX1 fusion gene and t(1; 19) could be positive in MDS, but sometimes not simultaneously. Although this genetic abnormality in ALL is well known to be an intermediate risk factor, its significance in MDS remains to be further investigated. The immune system can influence the occurrence, development, and outcome of the tumor. Long-term and extensive use of immunosuppressive drugs can destroy the immune surveillance of the lymphatic network. Hematologic malignancies and solid tumors share a set of common factors, which may play a role in oncogenesis. However, it needs an in-depth study of the underlying mechanism.

Author contributions

Conceptualization: Jingnan Sun.

Data curation: Wenqing Yu, Yunpeng Sun.

Formal analysis: Gaoyang Chen.

Investigation: Wenqing Yu, Yunpeng Sun, Sujun Gao, Jiuwei Cui.

Methodology: Wenqing Yu, Gaoyang Chen, Yunpeng Sun, Jiuwei Cui.

Software: Gaoyang Chen, Sujun Gao.

Supervision: Wei Li.

Validation: Gaoyang Chen, Jiuwei Cui.

Visualization: Jingnan Sun.

Writing – original draft: Wenqing Yu, Gaoyang Chen.

Writing – review & editing: Wei Li, Jingnan Sun.

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