Therapy-associated myelodysplastic syndrome with monosomy 7 arising in a Muir-Torre Syndrome patient carrying *SETBP1* mutation

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Abstract. Muir-Torre Syndrome (MTS) is a rare hereditary autosomal dominant cancer syndrome and is linked to hereditary non-polyposis colorectal carcinoma (Lynch Syndrome). Individuals develop various skin neoplasms in addition to colorectal, endometrial and upper gastrointestinal malignancies. Therapy-associated myelodysplastic syndrome (T-MDS) is an aggressive hematologic malignancy and is considered a pre-leukemic phase. T-MDS is associated with prior exposure to chemo- and radiotherapy that potentially results in DNA damage. The current case report presents a 74-year-old male MTS patient with prior history of solid tumors and radiation therapy with new onset cytopenia. A subsequent bone marrow biopsy revealed multilineage dysplasia with a high blast count and a diagnosis of high grade T-MDS was rendered. FISH and G-banded karyotype analyses revealed 5q deletion and monosomy 7. This is a unique case of T-MDS arising in the setting of MTS. Secondary malignancies including MDS and acute leukemia may occur in cancer survivors and are often associated with an unfavorable prognosis. This case demonstrates the need to be aware of the risk of secondary hematologic malignancies in cancer patients and a thorough clinical and lab work-up are warranted in patients with persistent or transfusion requiring cytopenia(s).

Introduction

Hereditary non-polyposis colorectal carcinoma (HNPCC) is an autosomal dominant genetic disorder characterized by

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a deficiency of DNA mismatch repair proteins (1-3). This deficiency leads to the formation of various neoplasms including colorectal carcinoma and malignancies of the endometrium, ovary, stomach, small bowel, and pancreas. Muir-Torre Syndrome (MTS) is subtype of HNPCC characterized by the additional presence of various dermatologic neoplasms including sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas (1-3). HNPCC is not traditionally associated with hematologic malignances (4).

MDS is defined by the World Health Organization (WHO) as a group of clonal bone marrow neoplasms characterized by ineffective hematopoiesis, manifested by morphologic dysplasia in hematopoietic cells and peripheral cytopenia (5). Therapy-related MDS (t-MDS) is a subtype of MDS defined by the WHO as a distinct category in the classification of patients who develop myeloid neoplasms following cytotoxic therapy (5). Associations between t-MDS and several germline mutations have been established but, to our knowledge, no association between t-MDS and MTS has been reported.

Case report

Patient and methods. A 74-year-old male with MTS presented with a new onset anemia. Approximately 10 years previously, the patient was treated at an outside hospital for a variety of malignancies including gastric adenocarcinoma, colorectal adenocarcinoma, prostatic adenocarcinoma, and multiple cutaneous neoplasms. The patient reported undergoing several surgical operations including a resection of approximately 70% of his stomach for gastric adenocarcinoma. While specific details of his treatment are unavailable, the patient reported being treated with fluorouracil (5-FU) and radiation for his gastric adenocarcinoma.

Initial complete blood count revealed a hemoglobin of 7.6 g/dl, a reticulocyte count of 2.59, and a platelet count of 95,000 platelets/dl. Given the patient's history and new onset anemia, an evaluation including a peripheral blood smear and bone marrow biopsy was performed. FISH analysis and a hematologic panel of next generation sequencing were performed on the bone marrow specimen. Written informed consent was obtained from the patient.
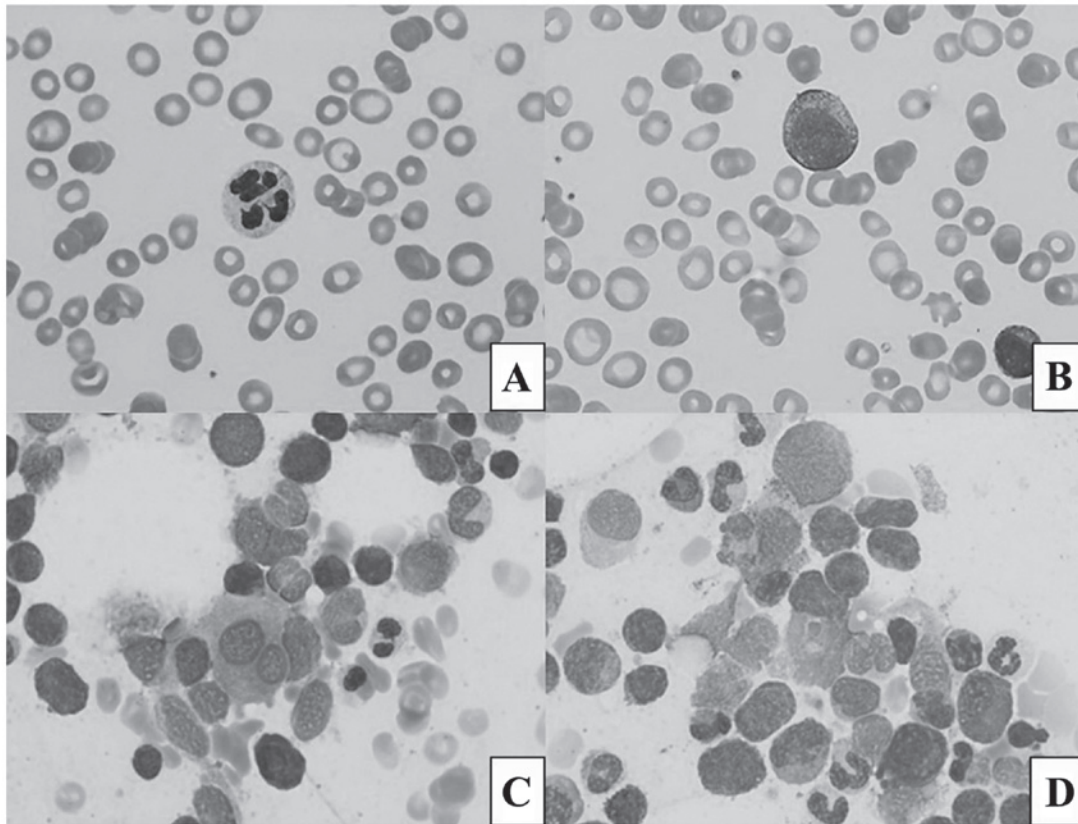
Figure 1. (A) Hypersegmented neutrophil, peripheral blood (Wright-Giemsa, original magnification x1,000). (B) Blast, peripheral blood (Wright-Giemsa, original magnification x1,000). (C and D) Dysplastic changes in all three lineages, bone marrow aspirate (Wright-Giemsa, original magnification x1,000).
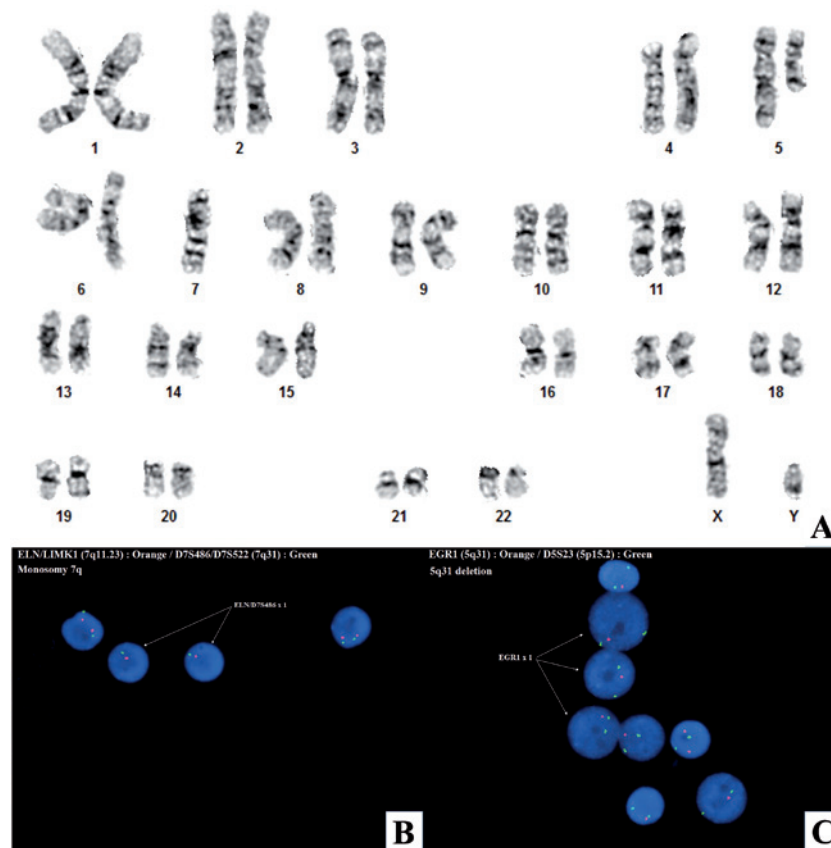

Figure 2. Cytogenetic analysis (A) G-banded karyotype demonstrating 5q13q33 deletion and monosomy 7 [45,XY,del(5)(q13q33),-7], (B) Interphase FISH analysis demonstrating monosomy 7q. Note the deletion of the ELN/LIMK1 orange probe at 7q11.23 and the D7S486/D7S522 green probe at 7q31, (C) Interphase FISH analysis demonstrating 5q31 deletion. Note the deletion of the EGR1 orange probe at 5q31.

Results

The peripheral blood smear revealed dysplastic, hypo- and hypersegmented neutrophils and rare blasts (Fig. 1A and B). The bone marrow biopsy revealed megakaryocytic, erythroid and myeloid dysplasia (Fig. 1C and D) and concurrent flow cytometry revealed an increased portion of blasts (12%). FISH analysis (Fig. 2), revealed 5q31 deletion and monosomy 7q in ~88% of interphase cells (Fig. 2B and C). G-banded chromosome analysis demonstrated an interstitial 5q13q33 deletion and monosomy 7 in all 20-metaphase cells examined [45,XY,del(5)(q13q33),-7] (Fig. 2A). A hematologic panel of next generation sequencing was performed on the bone marrow revealing mutations in *SETBP1* p.G870S and *NF1* p.S340Cfs*12. The patient was diagnosed with refractory anemia with excess blasts grade II (RAEB-2). A final diagnosis of t-MDS was rendered based on prior radiation history, multilineage dysplasia and unfavorable karyotype. The patient's age and existing co-morbidities pose a significant challenge for the available treatment modalities. The current patient is an unlikely candidate for stem cell transplant which is the only potentially curative modality in MDS.

Discussion

Establishing a diagnosis of t-MDS vs. de novo MDS is a difficult task. In 50 to 70% of t-MDS cases, rearrangements in the chromosome 5 and/or 7 are present (6). The average time until onset of t-MDS depends on the type and amount of chemotherapy used. For alkylating agents and topoisomerase inhibitors the average time until onset of t-MDS is 5 to 7 years and 2 to 3 years, respectively. Different chemotherapy agents are associated with different genetic mutations; alkylating agents being associated with rearrangements in chromosome 5 and/or 7 (6-10). Our patient presumably developed t-MDS over 10 years after his treatment with 5-FU and radiation. T-MDS is traditionally associated with alkylating agents and topoisomerase inhibitors. However, cases of 5-FU derived t-MDS have also been reported (11). While HNPCC is not traditionally associated with hematologic malignancies, mutations in mismatch repair genes have been detected in hematologic malignancies and MDS (4,12,13). Also, there are reports of HNPCC families with neurofibromatosis like syndromes and increased incidences of hematologic malignancies (4). A second unrelated primary MDS in a patient with HNPCC is another possibility. While 10 years is longer than the average time until onset of MDS and establishing a definitive etiology may be impossible, the multilineage dysplasia, complex karyotype and history of chemotherapy and radiation are indicative of t-MDS.

Next generation sequencing of the marrow indicated that Muir-Torre syndrome may have played a more important role than chemotherapy/radiation in the pathogenesis of our patient's t-MDS. Our patient's bone marrow had a mutation in *SETBP1* p.G870S. As in our patient, *SETBP1* p.G870S mutations are associated with monosomy 7 (14). Counterintuitively, while monosomy 7 is associated with t-MDS, *SETBP1* p.G870S is not commonly associated with t-MDS (6-10,15). Fabiani *et al* specifically examined *SETBP1* mutations in t-MDS and found only 2.83% (3 of 106) of their therapy related myeloid neoplasm patient cohort had *SETBP1* point

mutations (15). The other mutation detected in our patient was *NF1* p.S340Cfs*12. *NF1* mutations are thought to be causative mutations of neurofibromatosis. Evans *et al* found *NF1* mutations in 97.08% (166/171) of familial cases of neurofibromatosis type 1 (16). Interestingly, there are reports of HNPCC families with increased incidences of hematologic malignancies and neurofibromatosis like syndromes (4).

Recently a new diagnostic category, 'myeloid neoplasms with germline predisposition', was established by the WHO (5). The genes currently implicated in this category are not involved in HNPCC. However, unlike other hematologic conditions such as chronic myelogenous leukemia, MDS is a cytogenetically heterogeneous disease (17). As more research is conducted, other germline mutations such as those involved in HNPCC, maybe correlated with MDS.

There is an increased frequency of t-MDS in breast cancer survivors who have germline mutations in breast cancer susceptibility genes. One recent study found 21% (10/41) of breast cancer survivors with t-MDS had inherited mutations in at least one of the following genes: *BRCA1*, *BRCA2*, *TP53*, *CHEK2*, or *PALB2* (6). T-MDS has also been reported to occur at an increased frequency in patients with an inactivating polymorphism in *NQ01* gene and the glutathione S-transferase P1 gene (18,19). These genes both produce enzymes responsible for metabolizing toxic byproducts of chemotherapy agents. It has been hypothesized that certain populations may be susceptible to developing t-MDS due to an impaired ability to repair DNA damage or an impaired ability to metabolize chemotherapeutic agents (10).

MTS is caused by an impaired ability to repair DNA damage, but establishing a correlation with t-MDS may be difficult due to MTS's low prevalence. Further studies examining the relationship between t-MDS and MTS are needed. As therapies continue to improve and life expectancies increase, long term complications of chemotherapy and radiation such as t-MDS may become more prevalent. Genetically screening patients undergoing chemotherapy, and maintaining a central database may allow us to further elucidate which patients have an increased risk of developing t-MDS.

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