Case Report

Rapid onset of myelodysplastic syndrome after treatment for anal cancer: A case report

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Anal cancer is a highly curable disease. Chemoradiotherapy has superseded surgery since it results in an equivalent survival with the benefit of a better functional outcome, as there is no need for colostomy. However, the long-term complications of definitive chemoradiotherapy for anal cancer have not been systematically described. In this report, we present the case of a woman who presented with therapy-induced myelodysplasia within a year after treatment for anal cancer.

A 58-year-old woman with no significant past medical history was diagnosed with squamous-cell carcinoma of the anal canal, during a work-up for hematochezia. She regularly drank moderate amounts of vodka in the evening, and was a heavy smoker. The anal cancer was treated in standard fashion with chemoradiation, the chemotherapy consisting of 5-fluorouracil and mitomycin C. Follow-up physical examination and imaging studies revealed a complete response, as well as a normal complete blood count (CBC) during the following months. One year after the end of treatment, a CBC performed 2 days prior to a scheduled visit revealed a platelet count of 15 x 10^9/L. The patient was immediately called to the clinic for an evaluation.

She denied any complaint. One to two weeks before the visit, she had been scratched by a pet cat. This was followed by fever, and swelling of the right hand. She was in good general condition, with normal vital signs. A tender right axillary adenopathy was felt. The remainder of the examination was normal.

The CBC showed the following values: white blood cell count 7.3 x 10^9/L, with a normal differential; hemoglobin 129 g/L, hematocrit 38.2 %, mean corpuscular volume 116 fL, platelet count 15 x 10^9/L. The blood smear was unremarkable, except for thrombocytopenia. Coagulation parameters were normal, as was serum creatinine level. Liver function tests results showed nonspecific abnormalities, consisting of elevation of aminotransferases and alkaline phosphatase levels. Total serum protein level was high at 87 g/L (normal 60 g-80 g/L), with normal albumin at 42 g/L.

The patient denied any excess of alcohol consumption. Vitamin B12 and folic acid levels were 434 pmol/L (normal greater than or equal to 133 pmol/L), and 17.2 nmol/L (normal greater than or equal to 11.8 nmol/L), respectively. A serum protein electrophoresis (SPEP) showed no monoclonal peak. The diagnosis of an immune mediated thrombocytopenia (ITP), either idiopathic or secondary to an infection, was entertained. Given the patient’s exposure to a cat, she was tested for Bartonella henselae antibodies. Antibody titers were high, 1:640 the week of the consultation, 1:1280 two weeks later. No response of the platelet count was observed after steroid and immune globulin therapy.

A bone marrow aspiration-biopsy showed hypercellularity with megaloblastoid changes, micromegakaryocytes, and a normal blast count of 2%. Cytogenetics revealed trisomy 8. No tumor cells were seen in the biopsy specimen. The diagnosis of myelodysplastic syndrome was made. The previous exposure to radiotherapy and chemotherapy suggested therapy-related MDS (t-MDS). Although not entirely ruled out, a concomitant diagnosis of myelodysplasia and anal cancer appears unlikely, given the entirely normal values of the CBC at the patient’s first consultation. In addition, we cannot entirely rule out that this patient presented sequentially two diseases that were not connected.
As no family match for stem-cell transplantation was identified, she was started on azacytidine, with normalization of the platelet count after six cycles. The duration of the remission after the end of treatment was only four months.

T-MDS is a rare but serious complication of chemotherapy and radiotherapy, resulting from DNA damage in the hematopoietic cells. It can be considered a consequence of the lack of selectivity of these therapeutic modalities, since they affect both normal and malignant cells. However, the exact pathogenic mechanism of this adverse reaction is not fully known.

Two classical presentations have been described in association with chemotherapy:

1. An earlier form, usually occurring within 3 years of exposure to inhibitors of topoisomerase II (1), and with typical abnormalities of chromosomes 11 and 21. Topoisomerase II inhibitors can cause DNA double-strand breaks within the loci of hematopoietic transcription factors (2).

2. A later form, associated with alkylating agents (3), with median time of onset of about 5 years after treatment. Many chromosomal abnormalities have been described, including trisomy 8. After formation of adducts by alkylators in the hematopoietic cells, faulty DNA repair mechanisms are postulated to lead to DNA double-strand breaks and chromosomal instability.

Radiotherapy-induced MDS typically appears several years after treatment, and is also associated with variable karyotypes (4). DNA damage in stem cells is probably the most important pathogenic mechanism, but aberrant signals to the stem cells from the irradiated microenvironment may also play a role (5). Although chemotherapy and radiotherapy exhibit synergistic effects in the treatment of some cancers, no published data suggest that combined-modality therapy necessarily results in a higher risk of myelodysplasia.

A particular feature of this case is the shortness of the latency period, not characteristic of radiotherapy nor of the specific chemotherapy she received (6). Although antimetabolites such as 5-fluorouracil have only rarely been associated with myelodysplasia, it is thought that they can contribute to it by depleting cells of folates, which are necessary to nucleotide biosynthesis, and, therefore, DNA repair (2).

Additional research is needed to estimate the prevalence of myelodysplasia in patients treated with chemoradiotherapy for anal cancer, as well as the individual contribution of different chemotherapeutic drugs and radiation techniques to this complication. Last but not least, an instructive feature of this case was the intercurrent cat-scratch disease, a confounding circumstance that had the potential of delaying diagnosis and initiation of effective therapy. In the setting of myelodysplasia, cat-scratch disease has been reported to present with widespread skin manifestations and late seroconversion, unlike what was observed in our case (7). At any rate, this case reminds us that coincidence is not always synonymous with causality.

References


