A 45-year-old male patient with TNM stage III rectal cancer presented with fatigue, dyspnea, icterus and darkening of urine for the last 1-2 days. He had been operated for rectal adenocarcinoma (low anterior resection) 7 months ago and had received pelvic radiotherapy and 11 cycles of FOLFOX-4 regimen thereafter. No serious adverse event had been observed, except for mild neuropathy. One day after the last dose of oxaliplatin administration (cycle 12), while the patient was on 5-FU infusion, he developed fatigue, scleral icterus and darkly coloured urine. He did not have any other systemic diseases and denied using any other drugs except ondansetron. Laboratory results were as follows: hemoglobin 5.7 g/dL (10.7 g/dL before the cycle), indirect/direct bilirubin 3.74/0.5 mg/dL, LDH 750 U/mL, reticulocyte 3.6% and haptoglobin levels undetectable. Direct coombs test was positive, indirect coombs test was negative. Three packs of red blood cells were transfused and treatment with prednisone 40 mg/day for 7 days was started with the diagnosis of acute autoimmune hemolytic anemia (AIHA). At the end of 7 days, hemoglobin level was 10.4 g/dL and bilirubin and LDH levels returned to normal. As this was already the last planned cycle, chemotherapy was discontinued.

FOLFOX-4 is the standard adjuvant treatment in lymph node positive colorectal cancer. It consists of bolus infusions of oxaliplatin 85 mg/m² on day 1, leucovorin 200 mg/m² and 5-fluorouracil (5-FU) 400 mg/m² followed by 22-hours continuous infusion of 600 mg/m² 5-FU via a portable pump on day 1 and day 2, every 15 days. Common side effects are cumulative sensory neuropathy, diarrhoea, mild myelosuppression and mucositis, most of which are shared by both 5-FU and oxaliplatin. Our patient developed severe AIHA after the 12th cycle of FOLFOX-4, which is an uncommon complication after this regimen. Detailed immunologic tests were not performed to distinguish the offending drug in our case; however both oxaliplatin and fluorouracil were reported to cause acute AIHA in the literature. Oxaliplatin induced AIHA was reported to occur mostly after several cycles of treatment and was suggested to have two mechanisms; i.e. both immune complex type and penicillin type (drug adsorption). Platinum salts can act as haptens by binding to serum proteins and repeated exposure to these complexes can promote hypersensitivity reactions. Bolus and protracted infusion of 5-FU had also resulted in AIHA, as well as UFT (uracil-tegafur) in one case. Oxaliplatin and 5-FU are generally used in combination in colorectal cancer treatment and acute hemolysis should be kept in mind as a rare but potentially fatal complication in patients receiving FOLFOX regimens (FOLFOX-4, -6, -7). Prompt discontinuation of the drugs and treatment with corticosteroids and plasmapheresis in severe cases are essential. It is not rational to discontinue both of these two highly effective drugs in a patient who will continue to receive chemotherapy for colorectal cancer in the adjuvant or metastatic setting, therefore determination of the offending drug is crucial.
REFERENCES


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