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LETTER TO THE EDITOR

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UFT-induced haemolytic anaemia

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Abstract A case of haemolytic anaemia in a patient under treatment with UFT for metastatic colon cancer is reported. Haemolytic anaemia has previously been associated with many other chemotherapeutic agents, but not with UFT, an oral anticancer agent combining tegafur (Ftorafur, a prodrug of 5-fluorouracil) and uracil.

Key words UFT · Haemolytic anaemia · Immunohaemolysis

The second-generation oral anticancer agent UFT is an antineoplastic drug combining tegafur (Ftorafur, a prodrug of 5-fluorouracil) and uracil in a 1:4 molar ratio. Clinical trials in Japan have demonstrated the activity of UFT in colorectal, gastric, breast, and head and neck carcinomas [8]. UFT has schedule-dependent differences in toxicity, the dose-limiting toxicity in a 28-day schedule being diarrhoea. Other toxicities include nausea, vomiting, fatigue, and stomatitis. Myelosuppression is infrequent and hand-foot syndrome and neurological toxicity are not found [4].

We report an episode of haemolytic anaemia occurring during treatment with UFT in an 80-year-old male patient with metastatic colon cancer and a prior history of hypertension under treatment with amlodipine and hydrochlorothiazide. He was admitted with a 1-week history of severe asthenia and jaundice. He had been diagnosed 3 months before with an adenocarcinoma of the transverse colon which had invaded the subserosa and had affected seven out of nine lymph nodes, and had been treated surgically. A metastatic nodule was observed during segmentary colectomy in the right lobe of the liver. Following surgery, the CEA level was 9.1 μg/l (normal level < 4.81 μg/l), haemoglobin was 126 g/l, and the MCV was 87 fl/cell, and coagulation times were normal. An abdominal ultrasound revealed two metastatic liver nodules (both more than 2 cm) on segments V and VI. UFT 400 mg/m^2 per day orally without interruption was started.

The patient completed 8 weeks of therapy and during the last week, he complained of progressive asthenia and anorexia. He had no fever, and blood pressure was normal. Scleral icterus without choluria, bilateral palmar redness and a 4-cm enlarged painless liver were observed, without signs of active bleeding. Laboratory tests revealed a haemoglobin level of 66 g/l, a MCV of 103 fl/cell and a HDW of 22.5% (normal range 10–15.5%), a white blood cell count of 2.66×10^9/l, an absolute neutrophil count of 0.99×10^9/l, and a platelet count of 214×10^9/l. Cobalamin and folate levels were normal. The reticulocyte count was 3.9%. A polyvalent direct Coombs test (DAT) was negative. The haptoglobin level was < 0.2 g/l (normal range 0.7–2.8 g/l). Serum LDH was 11.7 μkat/l (normal range 3.9–7.5 μkat/l), bilirubin 47 μmol/l (normal range 4–24 μmol/l) and CEA 8.5 μg/l. The coagulation study revealed a lack of vitamin K-dependent factors, with a prothrombin ratio of 1.53 and plasma levels of factors II, VII and X of 25.3 U/dl (normal range 80–120 U/dl). Fibrinogen was normal. Serology for hepatitis B virus was positive for IgG anti-HBs, anti-HBe and anti-HBc. Anti-HCV was negative. A repeated abdominal ultrasound did not disclose liver disease.

Transfusion of 3 U of packed red blood cells and parenteral vitamin K were indicated. Therapy with UFT was stopped on clinical suspicion of haemolytic anaemia. Basal treatment with amlodipine and hydrochlorothiazide was not discontinued. Haemoglobin levels stayed above 120 g/l with no further drops. Jaundice disappeared, and bilirubin and haptoglobin levels returned to normal. DAT remained negative. The patient was discharged 7 days after admission. He maintained an excellent status for more than 9 months without any further clinically similar occurrence.

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Three types of haemolytic anaemia in association with antineoplastic agents have been described: microangiopathic haemolytic anaemia (MAHA), immune haemolytic anaemia, and oxidative haemolysis [2]. Isolated cases of immune haemolytic anaemia secondary to treatment with antitumor agents, including cisplatin, methotrexate, teniposide and melphalan [2] (and more recently oxaliplatin [1, 3] and carboplatin [6]), have been reported.

To our knowledge, this is the first report associating haemolytic anaemia with UFT. Although it is difficult to be prove causality, the temporal relationship between UFT intake and the appearance of haemolytic anaemia, and the rapid recovery and no relapse after the drug was stopped, support a causal connection and rule out the underlying malignancy as the cause of the anaemia. Even though hydrochlorothiazide is clearly related to immune haemolytic anaemia [7], it was not discontinued during or after admission, making unlikely a causative effect. There is no known association between amlodipine and haemolytic anaemia.

Lack of renal failure and thrombocytopenia makes MAHA related to UFT very unlikely. The incidence of a negative DAT in patients with immunohaemolytic anaemia is reported to be between 2% and 4%. Possible explanations are low concentrations of IgG molecules bound per red cell, low affinity antibodies, or the involvement of IgA or IgM immunoglobulins. Lack of experience in our laboratory of indirect antiglobulin testing with an oral agent and the quick recovery of our patient led us reluctantly to give up the attempt using this determination to establish beyond doubt that UFT was the offending drug [1, 3]. With a negative DAT, a possible explanation could have been the disturbance of red blood cell metabolism due to exposure to UFT. However, this effect of UFT is usually more acute in onset than in this case, and the patient had no history of a previous haemolytic episode, altered red blood cell morphology or an enzymatic defect such as G6PD deficiency.

Based on previous reports of Coombs-positive haemolytic anaemia in patients under treatment with 5-fluorouracil [5] (for which Ftorafur is a prodrug), we believe that our patient suffered a UFT-induced immunohaemolytic anaemia.

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