FOLFIRI Chemotherapy-Induced Diabetic Ketoacidosis
Carlos Tavares Bello*, Ricardo Castro Fonseca, João Sequeira Duarte and Carlos Vasconcelos
Endocrinology Department of the Hospital de Egas Moniz, Lisboa, Portugal

Abstract
Diabetic ketoacidosis (DKA) is a frequently encountered medical emergency that usually develops in the setting of severe insulin deficiency. It may be the initial clinical presentation of newly diagnosed diabetes mellitus; however, it is usually triggered by a severe medical illness or insulin therapy omission in patients with previously diagnosed diabetes mellitus. FOLFIRI (FOLinic acid, 5-fluorouracil and IRInotecan) is a systemic chemotherapy regimen frequently employed in the management of advanced colorectal carcinoma. Besides the common and well known hematological toxicity, 5-fluorouracil based chemotherapy has been associated with new onset diabetes and worsening glycemic control in known diabetics. The authors report on a case of DKA in a previously well-controlled type 2 diabetic patient upon exposure to FOLFIRI chemotherapy.

Keywords: Diabetes; Ketoacidosis; FOLFIRI; 5-Fluorouracil

Introduction
Diabetic ketoacidosis (DKA) is a frequent life-threatening condition developing in the setting of severe insulin deficiency accompanied by high contrarregulatory hormone levels (glucagon, catecholamines, cortisol and growth hormone). It is characterized by a high anion gap metabolic acidosis, hyperglycemia and elevated circulating ketone bodies. In the majority of cases, DKA is triggered by infection or inadequate insulin therapy [1]. DKA may also be drug induced, corticosteroids, thiazides, neuroleptics and sympathomimetics being the "usual suspects" [1,2].

5-fluorouracil-based chemotherapy for colorectal cancer has also been associated with worsening glycemic control in diabetics and with new onset diabetes in 11.6% of patients [3,4]. The authors report on a case of DKA in a previously well-controlled type 2 diabetic patient upon exposure to FOLFIRI chemotherapy.

Case Report
A 74-year-old Caucasian male patient with a known medical history of arterial hypertension, hypercholesterolemia, obesity (BMI 27 mg/kg/m² with associated comorbidity), type 2 diabetes mellitus and colorectal adenocarcinoma presented to the emergency department with one-week duration complaints of lethargy, lassitude, polyuria, polydipsia. Nausea and vomiting were reported only on the previous night and no fever, chills, dyspnea, urinary complaints or any other symptoms were present. The patient was tachycardic (135 bpm), normotensive (BP 135/76 mmHg), afebrile (36°C), tachypneic (30 cycles per minute) and growth hormone). It is characterized by a high anion gap metabolic acidosis, hyperglycemia and elevated circulating ketone bodies. In the majority of cases, DKA is triggered by infection or inadequate insulin therapy [1]. DKA may also be drug induced, corticosteroids, thiazides, neuroleptics and sympathomimetics being the "usual suspects" [1,2].

5-fluorouracil-based chemotherapy for colorectal cancer has also been associated with worsening glycemic control in diabetics and with new onset diabetes in 11.6% of patients [3,4]. The authors report on a case of DKA in a previously well-controlled type 2 diabetic patient upon exposure to FOLFIRI chemotherapy.

Diabetes is a known complication of 5-FU based chemotherapy regimens. Feng et al. retrospectively studied 422 colorectal cancer patients treated with 5-FU and found an elevated incidence of new onset diabetes (11.6%) and impaired glucose tolerance (11.3%). Altered glucose metabolism developed more frequently during therapy but in 24% arose 14.5 months after completion of therapy. Severe hyperglycemia (>250 mg/dL) was described in 16.7% of the cases and one patient died of DKA. The majority of (the) cases were treated with medical nutritional therapy alone and insulin was required in only 27.5% of the patients. [3] Older studies (Tayek et al. and Köhne et al.) also reported on the adverse metabolic effects of 5-FU based regimens [5,6]. Although the precise underlying pathophysiological mechanisms of hyperglycemia in this setting still remain elusive, animal studies have nevertheless suggested a defective glucose mediated insulin secretion with adjuvant chemotherapy with FOLFIRI (FOLinic acid+5-fluorouracil+IRInotecan) with disease remission. One year later, due to hepatic metastases, he underwent surgical metastasis resection and was treated with a 2nd FOLFIRI cycle. diabetes mellitus was diagnosed after the 2nd cycle and it was reasonably controlled with medical nutritional therapy alone (HbA1c of 7% and a fasting blood glucose of 140 mg/dL 8 months after the end of the 2nd cycle). It was only 4 months after the beginning of the 3rd cycle that the DKA episode took place. A total of 3 cycles were completed with a 5-FU cumulative dose of 34 sg/m².

Currently, the patient is well, with regular follow up in the Endocrinology clinic with progressively smaller insulin requirements- Insulin Glargine 24 Units at bedtime and no prandial insulin requirements. His HbA1c is 6% with no self-reported hypoglycemias. C-peptide level in follow up is 8.6 ng/mL (with blood glucose of 121 mg/dL). Regarding the colorectal adenocarcinoma outcome, 2 years after the patient is alive with persistent disease (pulmonary and hepatic metastasis).

Discussion
Diabetes is a known complication of 5-FU based chemotherapy regimens. Feng et al. retrospectively studied 422 colorectal cancer patients treated with 5-FU and found an elevated incidence of new onset diabetes (11.6%) and impaired glucose tolerance (11.3%). Altered glucose metabolism developed more frequently during therapy but in 24% arose 14.5 months after completion of therapy. Severe hyperglycemia (>250 mg/dL) was described in 16.7% of the cases and one patient died of DKA. The majority of (the) cases were treated with medical nutritional therapy alone and insulin was required in only 27.5% of the patients. [3] Older studies (Tayek et al. and Köhne et al.) also reported on the adverse metabolic effects of 5-FU based regimens [5,6]. Although the precise underlying pathophysiological mechanisms of hyperglycemia in this setting still remain elusive, animal studies have nevertheless suggested a defective glucose mediated insulin secretion with adjuvant chemotherapy with FOLFIRI (FOLinic acid+5-fluorouracil+IRInotecan) with disease remission. One year later, due to hepatic metastases, he underwent surgical metastasis resection and was treated with a 2nd FOLFIRI cycle. diabetes mellitus was diagnosed after the 2nd cycle and it was reasonably controlled with medical nutritional therapy alone (HbA1c of 7% and a fasting blood glucose of 140 mg/dL 8 months after the end of the 2nd cycle). It was only 4 months after the beginning of the 3rd cycle that the DKA episode took place. A total of 3 cycles were completed with a 5-FU cumulative dose of 34 sg/m².

Currently, the patient is well, with regular follow up in the Endocrinology clinic with progressively smaller insulin requirements- Insulin Glargine 24 Units at bedtime and no prandial insulin requirements. His HbA1c is 6% with no self-reported hypoglycemias. C-peptide level in follow up is 8.6 ng/mL (with blood glucose of 121 mg/dL). Regarding the colorectal adenocarcinoma outcome, 2 years after the patient is alive with persistent disease (pulmonary and hepatic metastasis).

Discussion
Diabetes is a known complication of 5-FU based chemotherapy regimens. Feng et al. retrospectively studied 422 colorectal cancer patients treated with 5-FU and found an elevated incidence of new onset diabetes (11.6%) and impaired glucose tolerance (11.3%). Altered glucose metabolism developed more frequently during therapy but in 24% arose 14.5 months after completion of therapy. Severe hyperglycemia (>250 mg/dL) was described in 16.7% of the cases and one patient died of DKA. The majority of (the) cases were treated with medical nutritional therapy alone and insulin was required in only 27.5% of the patients. [3] Older studies (Tayek et al. and Köhne et al.) also reported on the adverse metabolic effects of 5-FU based regimens [5,6]. Although the precise underlying pathophysiological mechanisms of hyperglycemia in this setting still remain elusive, animal studies have nevertheless suggested a defective glucose mediated insulin secretion with adjuvant chemotherapy with FOLFIRI (FOLinic acid+5-fluorouracil+IRInotecan) with disease remission. One year later, due to hepatic metastases, he underwent surgical metastasis resection and was treated with a 2nd FOLFIRI cycle. diabetes mellitus was diagnosed after the 2nd cycle and it was reasonably controlled with medical nutritional therapy alone (HbA1c of 7% and a fasting blood glucose of 140 mg/dL 8 months after the end of the 2nd cycle). It was only 4 months after the beginning of the 3rd cycle that the DKA episode took place. A total of 3 cycles were completed with a 5-FU cumulative dose of 34 sg/m².
caused by 5-FU induced ultrastructural pancreatic beta-cell damage [7]. This changes are thought to be permanent in the majority, being self-limited in only 25.2% of cases in studies with 40 months of follow up [3].

The authors report a case of a patient with a previously reasonably well controlled diabetes mellitus (possibly 5-FU induced) that had a sudden diabetic glycemic decompensation after the third cycle of systemic chemotherapy (FOLFIRI). No other precipitant was found namely no other medical illnesses like serious infection, cardiovascular event or pancreatitis. Additionally, no dexamethasone nausea protocol was employed in this patient, excluding any possible contribution of glucocorticoids; no evidence suggesting type 1 diabetes (negative anti islet cell, insulin and GAD antibodies) were present and, cross sectional imaging that was done allowed to exclude any pancreatic secondary involvement. So far, there are no known diabetogenic effects associated with Irinotecan or Folinic Acid.

In the described case, the low initial C-peptide levels in the setting of hyperglycemia are evidence of the insulin secretory defects that contributed to the DKA. With cessation of chemotherapy there was a progressive decline in insulin requirements and recovery of c-peptide levels. Nevertheless, the patient did not return to baseline glucose control.

The outlined case aims to draw attention to a rare adverse event of FOLFIRI chemotherapy and to remind the importance of blood glucose monitoring before and during 5-FU based chemotherapy. Treatment related diabetes is frequent and severe life-threatening hyperglycemia, despite rare, may arise even in previously well controlled diabetic patients.

References
1. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN (2009) “Hyperglycemic crises in adult Patients with diabetes.” Diabetes Care 7: 1335-1343.
2. Joseph A, Charles WV, Wilson JC, Michael K, Timothy HBS (2004) Fatal olanzapine-induced hyperglycemic ketoacidosis.; Am J Forensic Med Pathol 25: 172-175.
3. Feng JP (2012) “Secondary diabetes associated with 5-fluorouracil-based chemotherapy regimens in non-diabetic patients with colorectal cancer: Results from a single-centre cohort study.” Colorectal Dise 1: 27-33.
4. Nakano T, Miyata G, Ondoda K, Ichikawa H, Kamel T, et al. Hyperosmolar hyperglycemic nonketotic coma after chemoradiotherapy for esophageal cancer. Esophagus 11(4): 273-276.
5. Tayek JA (1992) “Metabolic Response to Chemotherapy in Colon Cancer Patients.” JPEN J Parenter Enteral Nutr 16: 6.
6. Köhne CH (1997) Modulation of 5-fluorouracil with methotrexate and low-dose N-(phosphonacetyl)-L-aspartate in patients with advanced colorectal cancer. Results of a phase II study. Eur J Cancer; 33: 1896-1899.
7. Feng JP (2010) Impact of 5-fluorouracil on glucose metabolism and pancreatic pathology in rats. Chinese journal of gastrointestinal surgery 13: 935-938.