CASE REPORT

A rare cause of susceptibility to neutropenic sepsis in a patient with metastatic pancreas cancer

Beatriz Suarez Martinez-Falero,¹ Roopinder Gillmore²

¹Royal Free London NHS Foundation Trust, London, UK
²Department of Oncology, Royal Free London NHS Foundation Trust, London, UK

Correspondence to
 Dr Roopinder Gillmore,
 roopinder.gillmore@nhs.net

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SUMMARY

A 71-year-old patient receiving combination chemotherapy (irinotecan, oxaliplatin and 5-fluorouracil (5-FU)) for metastatic pancreas cancer was admitted after her first cycle of chemotherapy with a severe and unexpectedly prolonged episode of neutropenic sepsis associated with pancytopenia and marked mucositis. Owing to the unusual picture, the patient was tested for mutations in the gene encoding the enzyme dihydropyrimidine dehydrogenase (DPD)—an enzyme involved in the metabolism of the chemotherapy drug 5-FU. The patient was found to be heterozygous for a mutation, DPD IVS14+1G>A, leading to the severe toxicity exhibited following this regimen caused by delayed metabolism of 5-FU. She was treated aggressively with supportive care and recovered from this episode. Importantly she was subsequently switched to an alternative chemotherapy regimen to treat her disease. She continues to maintain an excellent quality of life some 9 months after her initial diagnosis on third-line chemotherapy.

BACKGROUND

Neutropenic sepsis is a recognised complication of systemic anticancer therapy and can be associated with a high incidence of mortality and morbidity.¹ Following an episode of severe neutropenic sepsis, it is routine practice to either dose reduce subsequent cycles of chemotherapy or in some cases continue with the same dose of chemotherapy but administer 'prophylactic' G-CSF. In this case either of those management plans could have led to irreversible organ failure or death due to a rare but recognised genetic predisposition to toxicity of 5-FU. Recognising an unusual presentation of a common scenario facilitated appropriate investigation resulting in a radical change in the patient's long-term management plan.

CASE PRESENTATION

A 71-year-old woman presented to the primary care with non-specific symptoms of abdominal discomfort and increasing fatigue. After referral to the gastroenterology department she had an upper gastrointestinal (GI) endoscopy which was normal and a CT colonoscopy which demonstrated a locally advanced pancreatic mass with multiple peritoneal deposits. She proceeded to a biopsy of the peritoneal disease which confirmed a moderately differentiated adenocarcinoma in keeping with a pancreas primary. She was thus diagnosed with metastatic pancreas cancer. In view of her good performance status she was offered treatment

with combination chemotherapy consisting of oxaliplatin, irinotecan and 5-FU (FOLFIRINOX) based on recent data demonstrating a significant survival benefit.²

Seven days after her first cycle of chemotherapy she developed marked mucositis leaving her unable to eat and drink due to severe oral and retrosternal pain. She was subsequently admitted to hospital 9 days following her first cycle of chemotherapy having lost 4 kg in weight. By this stage she had developed nausea, vomiting and repeated episodes of diarrhoea.

On examination she was clinically dehydrated with a tachycardia of 120 bpm, had postural hypotension and had fever at 38.2°C. Her oral mucosa was severely ulcerated, exhibiting grade 3 mucositis. She had type 7 stools and had developed alopecia.

INVESTIGATIONS

Blood results on admission (day 9 post cycle 1 chemotherapy):

Hb 6.5 g/dL, white cell count (WCC) $0.92 \times 10^9/L$, platelet count $44 \times 10^9/L$, neutrophil count $0.03 \times 10^9/L$, sodium 137 mmol/L, potassium 3.3 mmol/L, creatinine 47 mol/L, albumin 33 g/dL and C reactive protein 183 mg/L.

During the next few days the patient remained persistently neutropenic and thrombocytopenic, as demonstrated in [figures 1 and 2](#).

Microbiology results:

- ▶ Negative fungal culture of ulcer swabs.
- ▶ Normal skin flora isolated from oral swabs.
- ▶ No bacterial growth from blood cultures after 10 days of incubation.
- ▶ Negative urine culture.

TREATMENT

The patient was treated initially empirically for neutropenic sepsis with aggressive fluid rehydration, broad spectrum antibiotics, according to local hospital policy and anti-fungal therapy for severe mucositis. Despite the concomitant administration of granulocyte colony-stimulating factor (G-CSF) to stimulate bone marrow proliferation, she remained profoundly neutropenic for over a week. Furthermore, her severe thrombocytopenia, coupled with extensive GI tract ulceration, led to the development of malaena on day 5 of admission, requiring transfusion of two pools of platelets and high dose intravenous proton-pump inhibitors.

During this time symptom palliation was challenging. Her oral and retrosternal pain did not resolve

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Figure 1 Neutrophil count throughout admission.

with standard analgesia and mouthwashes (such as difflam) and she required a patient-controlled morphine syringe driver for 12 days, and the use of a cocaine-based mouthwash. She received supportive intravenous fluid replacement and electrolyte replacement throughout. The use of a nasogastric feeding tube was commenced at day 11 of admission and removed 8 days later once she tolerated small amounts of oral intake. The initial delay in insertion was due to the potential risk of bleeding coupled with the inability of her GI mucosa to absorb nutrients in its ulcerated state.

Thirty days after her initial emergency presentation the patient was discharged home having had intensive input from physiotherapy and the dietician.

OUTCOME AND FOLLOW-UP

Owing to her unusually prolonged period of neutropenia and thrombocytopenia, and the associated marked mucositis and hair loss after only one cycle of chemotherapy, the patient's blood was sent for genetic analysis of dihydropyrimidine dehydrogenase (DPD) gene mutations. The results revealed she was heterozygous for the DPD gene mutation IVS14+1G>A. This mutation leads to decreased activity of the enzyme responsible for the metabolism of 5-FU, resulting in the build-up of toxic levels of 5-FU, responsible for her unusually severe reaction to the FOLFIRINOX chemotherapy regimen.

Following discharge from hospital the patient was subsequently seen in the oncology outpatients. In view of the known DPD mutation, a change in her chemotherapy treatment was required and she was switched to single agent gemcitabine.³ However, after 3 months of treatment she symptomatically deteriorated and a CT scan confirmed disease progression. She was thus switched to a combination treatment with gemcitabine and oxaliplatin and continues to be on this treatment 9 months after the initial diagnosis of metastatic pancreas cancer.⁴

Figure 2 Platelet count throughout admission.

DISCUSSION

The liver enzyme DPD is the initial rate-limiting enzyme responsible for the catabolism of ~85% of all administered 5-FU. The remainder 15% is accountable for the cytotoxic effect which inhibits DNA and RNA synthesis, conferring the desired therapeutic effect.

In individuals with partially inactive DPD enzyme, the levels of cytotoxic 5-FU metabolite can build up to toxic levels. These patients have an increased risk of developing life-threatening neutropenia and the onset of toxicity often occurs twice as fast compared with patients with normal DPD activity. To date, 39 different genetic mutations and polymorphisms have been identified with the most common being the IVS14+1G>A mutation, as was the case in our patient.⁵

Currently, it is not routine to test for DPD enzyme activity prior to commencement of fluoropyrimidine therapy. In terms of measuring the levels of enzyme activity this would be highest in the liver but a liver biopsy is not without its own risks. Peripheral blood lymphocyte DPD levels may be used as a surrogate marker but methods are still laborious and importantly the absolute levels of DPD do not always correlate with the severity of 5-FU toxicity. Furthermore, routine genetic mutational analysis is flawed since many mutations are not associated with change in enzyme activity.⁶

Learning points

- ▶ 5-fluorouracil (5-FU) is used in the treatment of pancreatic cancer as part of the FOLFIRINOX regime.
- ▶ A mutation present in up to 5% of the population, DPD IVS14+1G>A can lead to abnormal function of the enzyme responsible for the metabolism of 5-FU, leading to life-threatening toxicity.
- ▶ Toxicity commonly presents with severe mucositis, alopecia and prolonged pancytopenia.
- ▶ No reliable methods of screening are available yet.
- ▶ This case highlights the importance of early recognition of these symptoms, adequate treatment and the need to change chemotherapeutic regime once the mutation is identified.

Contributors RG and BSM-F both looked after the patient on the ward and diagnosed the genetic predisposition to 5-FU toxicity. It was BSM-F's idea to write up the case and she wrote the initial drafts. RG aided with the writing and editing of the case report.

Competing interests None.

Patient consent Obtained.

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