





# Unusual case of colorectal carcinoma with sarcoid-like mediastinal adenopathy and near-fatal DPD deficiency

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The liver is the commonest site for metastases in colorectal carcinoma; other isolated sites are considered extremely rare. 5-fluorouracil (5-FU) is the backbone of treatment for metastatic colorectal carcinoma (mCRC) and without it survival may be significantly reduced. It is primarily metabolised by dihydropyrimidine dehydrogenase (DPD). Testing for DPD deficiency is not a routine practice and toxicity will only manifest following drug challenge. There are limited standardised treatment guidelines in managing patients with severe drug reactions following 5-FU exposure. We describe a delayed presentation of life-threatening DPD deficiency in a patient with colorectal carcinoma and mediastinal lymphadenopathy. We describe our experience with chemotherapy in this difficult clinical scenario and highlight the importance of histological confirmation in unusual sites of metastatic disease.

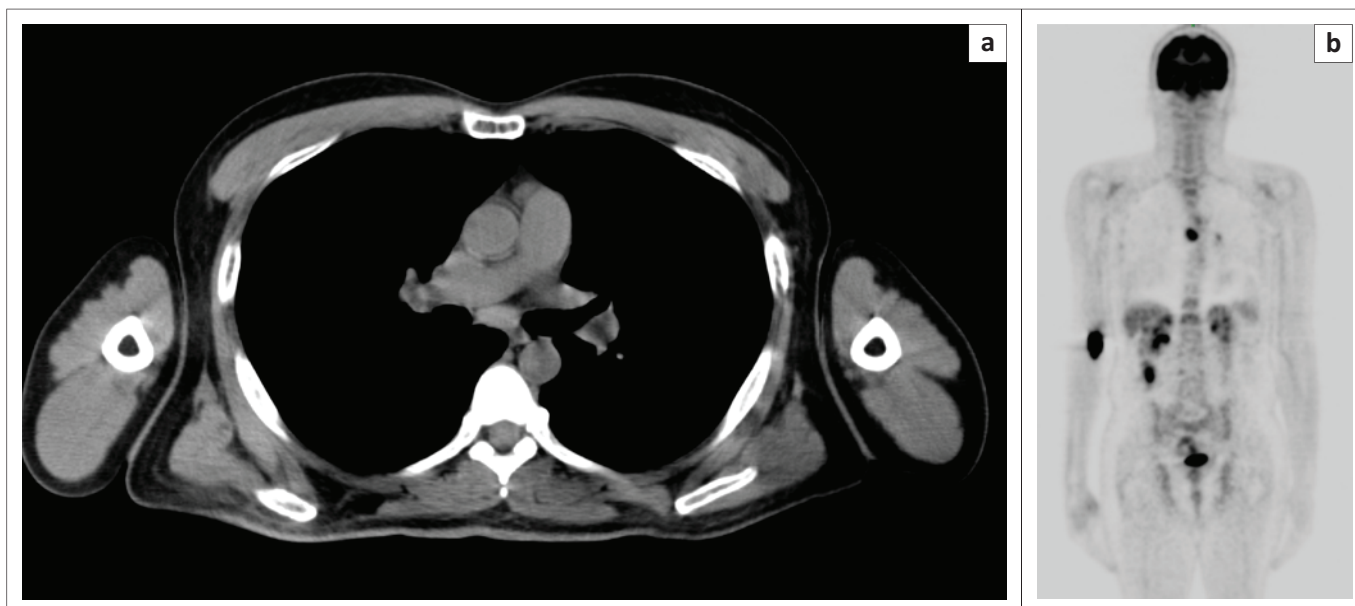
**Keywords:** colon cancer; FOLFOX; dihydropyrimidine dehydrogenase deficiency; chemotherapy; metastatic disease.

## Introduction

Colorectal carcinoma is the third most common malignancy and the second leading cause of cancer deaths worldwide.<sup>1</sup> Twenty-five percent of patients present with synchronous metastases at the time of diagnosis.<sup>2</sup> Imaging modalities for staging differ between institutions; the recommended approach is computed tomography (CT) or magnetic resonance imaging (MRI).<sup>3</sup> The role of positron emission tomography (PET) using 18F-fluorodeoxyglucose, integrated with CT (FDG-PET/CT) is not well established; it may be considered for surveillance in specific patient groups.<sup>4</sup> Based on drainage patterns of the portal venous system (primary means of haematogenous spread), metastatic colorectal carcinoma (mCRC) with isolated metastases not involving the liver is rare; the incidence of isolated lung metastases is 1.7% – 7.2% (predominantly with rectal carcinomas) and there are case reports describing thyroid metastases by-passing the liver.<sup>5,6</sup> However, there are only two case reports describing mediastinal metastases without other organ involvement.<sup>7,8</sup> A small proportion of patients with localised liver or lung metastases may be candidates for curative resection; however, the majority are palliated.<sup>9</sup> The prognosis for mCRC has improved since the 1990s when standard of care with 5-FU/leucovorin (FF) was associated with a median survival of 12 months.<sup>10,11</sup> 5-FU remains the backbone of treatment and is one of the commonest prescribed chemotherapeutic drugs; more than 80% is inactivated in the liver by the enzyme dihydropyrimidine dehydrogenase (DPD).<sup>4,12</sup> Dihydropyrimidine dehydrogenase activity is highly variable, with an estimated 3% – 5% of the general population being partially deficient with one population study suggesting that 31% – 34% of treated cancer patients exhibit dose-limiting toxicity.<sup>13,14</sup> Genetic variants in the DPD gene lead to enzyme deficiencies. Dihydropyrimidine dehydrogenase deficiency is not routinely tested for in all countries, including South Africa, and toxicity will only manifest on drug challenge. We describe a severe, delayed presentation of DPD deficiency in a patient with CRC and mediastinal adenopathy on FDG-PET scan at diagnosis.

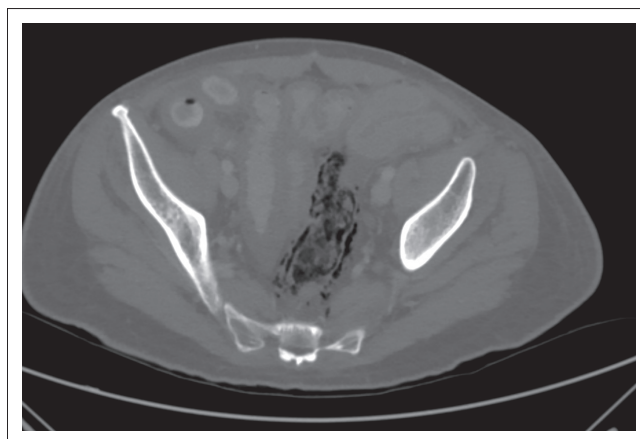
A 61-year-old male, non-smoker, with no history of alcohol use and a background of well-controlled familial hypercholesterolaemia and no other co-morbidities, presented with a chronic history of right-sided abdominal pain, weight loss and fatigue. Colonoscopy revealed an ‘apple-core’ lesion of the caecum with impending obstruction. Chest CT showed two left lower lobe pulmonary nodules (11 mm × 9 mm; 6 mm × 6 mm, respectively) with size-significant mediastinal lymphadenopathy but no liver metastases (Figure 1). A FDG-PET scan was performed.

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**FIGURE 1:** (a) Chest computed tomography (CT) and (b) positron emission tomography (PET) scan showing sub-carinal lymphadenopathy at the start of chemotherapy.

Standardised uptake value (SUV) of the two lung nodules was 2 and 0.5, respectively, with hypermetabolic, size-significant mediastinal lymphadenopathy (SUV sub-carinal node 8.5, pre-tracheal node 5.1 and aorto-pulmonary node 5.9). The patient was managed as mCRC, with secondaries to the left lung and mediastinum (Figure 1). Because of the risk of imminent obstruction, a right hemicolectomy with primary tumour resection and anastomosis was performed, prior to chemotherapy initiation. Histopathology demonstrated a moderately differentiated KRAS-mutant adenocarcinoma. Hepatic, renal and bone marrow functions were normal. FOLFOX6 and bevacizumab were commenced 4 weeks post-surgery and were well tolerated. The patient had a normal absolute neutrophil count (ANC) following his first cycle of chemotherapy ( $4.79 \times 10^9/L$ ). Forty-eight hours after his second cycle of chemotherapy, 2 weeks later, he developed a neutropaenic sepsis (temperature  $39^\circ C$ ; ANC  $0.01 \times 10^9/L$ ). He was hospitalised, commenced on broad-spectrum antibiotics and bi-daily granulocyte colony-stimulating factor (G-CSF) injections. The pyrexia resolved; however, his clinical condition worsened. He developed intractable diarrhoea, alopecia, mucositis and pancytopenia; he required multiple blood and platelet transfusions with no improvement in his neutrophil count despite treatment. He remained haemodynamically stable. Cultures were negative and repeat imaging showed no interval deterioration. Genetic testing for DPD deficiency confirmed a heterozygous IVS14 + 1G > A mutation. Ten-days after admission he developed worsening abdominal pain. Computed tomography showed pneumatosis intestinalis and extra-luminal air suggestive of a neutropaenic enterocolitis with rectal perforation (Figure 2). As a result of the resistant neutropaenia, he was not a suitable surgical candidate and conservative management with total parenteral nutrition, analgesia, repeat cultures and escalation of antibiotics was instituted. He deteriorated with signs of a multi-systemic inflammatory response: acute liver failure, encephalopathy,



**FIGURE 2:** Axial post-contrast computed tomography (CT) scan of the pelvis demonstrates pneumatosis coli of the rectum with extra-luminal air.

ataxia, resting tremor, severe malnutrition, bilateral pleural effusions and persistent bone marrow suppression. He did not require respiratory support or inotropes. The first improvement in the ANC was seen 12-days after admission and continued to improve as did his clinical and cognitive state. The perforation was locally contained, and no operative intervention was required. Viral, bacterial and TB cultures were negative and septic markers normalised. He was discharged after 28 days and not re-challenged with chemotherapy. Imaging showed no local recurrence or progression (no interval change in lung nodules and mediastinal adenopathy). Ultrasound-guided fine needle aspirate of both lung nodules and sub-carinal node was performed which showed normal bronchial tissue with no malignant cells and a granuloma with no malignant cells respectively. A repeat work-up for TB and sarcoidosis was negative. Having returned to baseline with normalisation of liver and bone marrow function, chemotherapy was restarted. Single dose oxaliplatin ( $130 \text{ mg/m}^2$ ) was commenced 3 months following the last cycle of standard chemotherapy which was well tolerated; three additional

cycles (full doses) were given at two-weekly intervals. Bevacizumab was not recommenced as a result of the recent gut pathology. The patient remained disease-free without chemotherapy for 13 months. On surveillance imaging, he was found to have a solitary segment 4A liver metastasis, amenable to local resection (left partial hepatectomy). Six-weeks after surgery, he was commenced on intravenous irinotecan 200 mg/m<sup>2</sup>, oxaliplatin 85 mg/m<sup>2</sup> (IROX) and bevacizumab 7.5 mg/kg. He completed nine of the planned 12 cycles which were to occur two-weekly; treatment delays of 21 days were permitted in the presence of side-effects. Oxaliplatin and irinotecan were omitted for the last three cycles because of liver derangement and early portal-hypertension (PHT) with sinusoidal fibrosis and thrombocytopaenia. Eleven-months after chemotherapy, and 3 years and 6 months after initial diagnosis, he remains disease-free with no local recurrence. Except for a mild residual peripheral neuropathy he has returned to baseline status with normalisation of liver function and resolution of his PHT.

## Discussion

Standardised uptake values (SUV) on FDG-PET scans  $\geq 2.5$  are accepted as malignancy; however, any metabolically active process may result in FDG accumulation.<sup>15</sup> In this case, the patient had a high SUV uptake of mediastinal adenopathy, with low uptake of both pulmonary nodules. Mediastinal involvement without any other organ involvement is an unusual presentation of metastases; hence, the need for tissue diagnosis after re-evaluating the clinical scenario. In this patient, the FNA findings of granulomas may explain the high SUV uptake, secondary to a sarcoid-like process which has been described in some malignancies either secondary to the cancer itself or cancer-associated treatments (chemotherapy/immunotherapy).<sup>16</sup> There has been a similar case description in a 63-year old woman with Stage 3 CRC.<sup>15</sup> The prevalence of sarcoid-like reactions on FDG PET/CT for cancer staging ranges between 0.6% and 1.1% and mediastinal nodes are a common site.<sup>17</sup> Tuberculosis is an important diagnosis of exclusion before the initiation of chemotherapy.

The patient had a life-threatening toxic reaction to 5-FU with grade 4 diarrhoea, neutropaenia, mucositis, alopecia, acute liver failure, psychomotor disturbances and encephalopathy which prevented re-challenging with this drug. There are limited standardised treatment options for patients with severe reactions: combinations of the currently available chemotherapeutic drugs may be used with varying results. Raltitrexed, similarly to 5-FU, is a thymidylate synthase inhibitor with a different toxicity profile and may be considered as an alternative single agent, or in combination with oxaliplatin (TOMOX) in patients with DPD deficiency; however, it is not easily accessible in South Africa.<sup>18</sup> A recent network meta-analysis showed that folinic acid, fluorouracil plus oxaliplatin (FOLFOX), folinic acid, fluorouracil plus irinotecan (FOLFIRI), irinotecan plus oxaliplatin (IROX) and raltitrexed plus oxaliplatin (TOMOX) all showed higher overall response rates and progression-free survival than FF,

or raltitrexed alone.<sup>19</sup> In this case, IROX with bevacizumab was associated with favourable results. Bowel perforation is a rare complication of bevacizumab.<sup>20</sup> The decision to re-challenge was made after careful analysis of risk versus benefit and only after disease recurrence, 19 months after the initial two cycles of bevacizumab and on full patient recovery. Re-challenging was associated with no further toxicity.

Because of cost implications and the absence of clear dosing guidelines, DPD deficiency is not routinely tested for in most countries, including South Africa.<sup>21</sup> The patient, in this case, had a delayed, severe, unpredictable presentation associated with a prolonged hospital admission and a protracted clinical course. There may be a role for proactive rather than reactive testing not only for clinical benefit but resource and cost implications too—one study showed that hospital admission for severe chemotherapy-related toxicity is significantly higher than the cost of prospective DPD testing of each patient commencing fluoropyrimidine chemotherapy.<sup>22</sup>

## Conclusion

We present a case of primary colon cancer with mediastinal lymphadenopathy suggestive of metastatic disease on PET scan. However, FNA was negative for metastases and showed granulomas. In cancer patients, sarcoid-like reactions may be a benign cause of FDG uptake on PET scans. A negative PET scan may be used to rule out metastases, but a positive uptake should be confirmed by histopathologic examination if clinical uncertainty exists, preferably before commencement of treatment. In patients who demonstrate severe toxicity to 5-FU maintaining a high clinical suspicion for DPD deficiency and testing early to prevent re-challenging with the drug should be considered. In challenging clinical cases such as this, various recognised drug combinations with dosing and frequency modification, may yield favourable survival outcomes.

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## Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this research article.

## Authors' contributions

S.P., O.T., J.D. and A.W. contributed to the writing of this case report.

## Ethical considerations

Ethical clearance for the study was obtained from the Human Research Ethics Committee of the University of the Witwatersrand (reference number: 190221).

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## Data availability

Data sharing is not applicable to this article as no new data were created or analysed in this study.

## Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors.

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