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CASE REPORT

Indolent Nodal Relapse of Colon Carcinoma with Associated Tumor Thrombus Invading the Superior Mesenteric Vein

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Introduction

Approximately 50–60% of patients with colorectal cancer develop metastatic disease, with the liver, lungs, and peritoneum being the commonest sites of occurrence. While there is data supporting the role of metastatectomy for liver disease, especially when occurring metachronously, evidence is limited for resection of extrahepatic disease. However, there is some evidence that judicious use of salvage surgery has a role in well-selected patients. This case highlights the extremely rare diagnosis of superior mesenteric vein (SMV) tumor thrombus related to metastatic nodal recurrence of colon cancer in a 54-year-old male with a history of T3N2b colon cancer. We present the diagnostic and management issues associated with this complex case which demonstrated an unusual pattern of recurrence.

Case Report

A 54-year-old gentleman who, during active surveillance for a low-grade Gleason 3+3 prostate cancer diagnosed in 2012, complained of progressive colicky left iliac fossa and suprapubic pain in November 2013. A CT urogram showed circumferential narrowing of the proximal transverse colon with adjacent mesenteric fat stranding and lymph nodes measuring up to 1.5 cm in transverse diameter. A subsequent colonoscopy confirmed a fungating transverse colon tumor, and biopsies established a diagnosis of signet ring adenocarcinoma of the colon.

A staging CT of thorax/abdomen/pelvis (TAP) demonstrated a mesenteric deposit anterior to the liver. The patient underwent laparoscopy to evaluate for presence of peritoneal disease, and a right hemicolectomy was undertaken after only a small mesenteric deposit was identified. Final histology showed this to be a T3N2b poorly differentiated mucinous adenocarcinoma with 8 of 18 lymph nodes involved. Tumor margins were negative for malignancy. The tumor displayed strong positive staining for all four microsatellite markers MLH1, MSH2, MSH6, and PMS2 confirming microsatellite stability. An activating mutation of the *K-RAS* gene was detected. The perioperative CEA was 6.7.

The patient was referred for consideration of adjuvant chemotherapy. His past medical history was notable for hypercholesterolaemia, hypertension controlled with medication, and an episode of atrial fibrillation in the post-operative period. His Eastern Cooperative Oncology Group (ECOG) performance status was 0. Adjuvant modified FOLFOX-6 (5-fluorouracil, leucovorin, oxaliplatin) chemotherapy was recommended, and the patient completed 12 cycles in September 2014. Oxaliplatin was omitted at cycle 12 due to the development of peripheral neuropathy. He was commenced on a surveillance program with clinical review, CEA, and CT imaging every 6 months.

A CT TAP in March 2015 showed, a 2.7 × 1.7-cm soft tissue deposits in the peritoneum adjacent to the anastomotic site. To clarify the significance of this lesion, a PET-CT was undertaken and no fludeoxyglucose (FDG) uptake within the lesion was observed. A surveillance colonoscopy demonstrated no suspicious findings. Following multidisciplinary review, it was recommended to continue surveillance and a subsequent CT TAP in September 2015 showed stable appearances.

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In March 2016, updated CT imaging demonstrated an interval increase in the peritoneal soft tissue lesion to 4.1 cm which was extending into the SMV. Further evaluation with PET-CT demonstrated FDG avidity [standardized uptake value (SUV) 10.0] within the SMV, giving a radiologic impression of SMV thrombus and an adjacent elliptical soft tissue density in the root of the mesentery invading the SMV (Fig. 1). The patient was commenced on anticoagulation for tumor thrombus, and following multidisciplinary discussion, he was referred for consideration for curative intent surgery. Of note, CEA was 28.7, increased from 5 in September 2015.

Findings at laparotomy included a nodal mass at the stump of the middle colic artery growing around and invading the SMV and its five principle tributaries in the root of the mesentery and malignant palpable thrombus in the SMV extending into the retropancreatic portal vein. The mass was resected. SMV and portal vein tumor thrombectomy and reconstruction were performed. Histologic analysis confirmed a lymph node replaced by high-grade mucinous adenocarcinoma with signet ring differentiation, 45 mm in maximum dimension. Focal extracapsular extension was seen and margins were free of tumor (closest 1 mm). Tissue removed during thrombectomy was consistent with tumor thrombus from metastatic colonic adenocarcinoma at histologic evaluation (Fig. 2). Given that he has resected stage IV disease and is at high risk of recurrence, chemotherapy with FOLFIRI (fluorouracil, leucovorin, irinotecan) was recommended.

The patient's most recent imaging showed stable occlusion of the SMV at its origin adjacent to the surgical site in the retroperitoneum consistent with chronic thrombus and no evidence of local or distant recurrence at an 18-month interval from surgery.

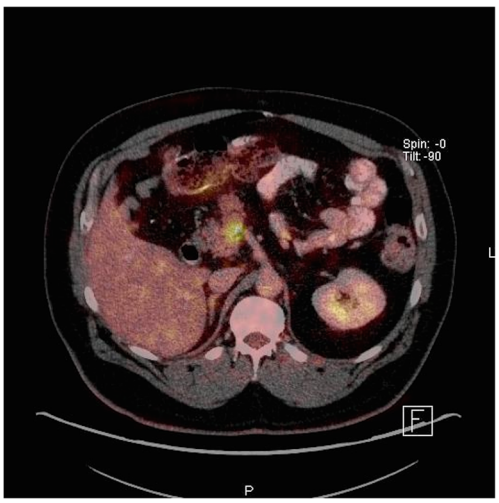

Fig. 1 PET-CT image depicting FDG avid nodal recurrence with associated tumor thrombus in the SMV

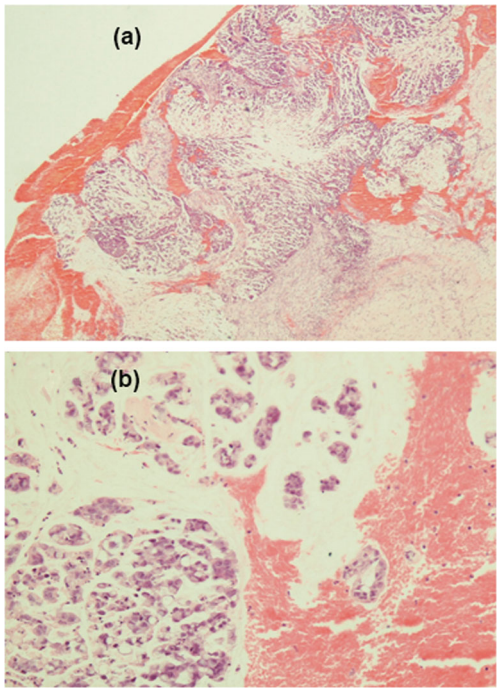

Fig. 2 **a**, **b** SMV tumor thrombus; images depict poorly differentiated signet ring adenocarcinoma with pools of mucin and surrounding red blood cells

Discussion

Worldwide, colorectal cancer (CRC) is the third most commonly occurring cancer in men and the second most common in women [1]. Despite optimal oncologic surgical resection and use of (neo) adjuvant therapies including chemotherapy and radiotherapy, there is a significant risk of relapse. At the time of this patient's original diagnosis with stage IIIC disease, his estimated 5-year survival is approximately 44% [2].

There is a clear role for adjuvant chemotherapy in patients with stage III disease where an improvement in disease-free and overall survival has been demonstrated in several studies [3–5]. In the setting of recurrent metastatic disease, even after complete resection, many patients experience future relapse, and when alive at 5 years, it is often with active disease—only 20–30% remain in long-term remission [6–8]. After initial treatment, active surveillance with periodic imaging is thought to be justified given that early detection of asymptomatic recurrences, as in our patient's case, will increase the proportion of patients who are candidates for curative intent resection of metastatic disease [9]. A survival benefit from such an approach has been shown in several meta-analyses, and studies have shown that patients with asymptomatic recurrences are more likely to be eligible for potentially curative resection than patients with symptomatic recurrences. Patients are also more likely to undergo R0 resection and have better progression-free and overall survival rates after surgical resection of metastatic disease [10–12].

An unusual feature of our case was the presence of tumor thrombus, a highly uncommon occurrence in CRC. Tumor thrombus refers to the presence of intravascular metastases with thrombotic elements. They are usually associated with retroperitoneal tumors such as renal cell, adrenal, and bladder carcinomas and have also been reported in hepatocellular carcinoma, uterine, and testicular cancers, but there are few reported cases of tumor thrombus occurring in association with CRC [13–16]. Tumor thrombus has been associated with inferior outcomes in other malignancies such as hepatocellular carcinoma and renal cell carcinoma [17–19]. However, given the paucity of data regarding tumor thrombus in colorectal cancer, its impact on prognosis is unclear.

PET-CT imaging to delineate between tumor thrombus and non-malignant thrombus has been reported to have utility in a number of cancers, but data with regard to colon cancer is extremely limited. The fusion of functional and anatomical imaging allows enhanced ability to differentiate between tumor and bland thrombus, as in our patient, where PET-CT demonstrated FDG uptake within the SMV suggestive of tumor thrombus rather than bland thrombus [20–22].

Sharma et al. described 24 patients with tumor thrombus of different etiologies and concluded that the mean SUVmax was 3.2 in the benign thrombosis group compared to 6.0 in the tumor thrombosis group [23]. Our patient had a SUVmax of 10, suggesting a diagnosis of tumor thrombus, findings subsequently corroborated at surgery.

However, it is important to note that septic thrombus can also demonstrate FDG uptake and that FDG uptake depends on and correlates with the avidity of the primary tumor and size of the tumor thrombus, i.e., if the primary tumor is non-FDG avid or small in size, then the tumor thrombus may be non-avid or undetectable respectively. Differentiating between bland thrombus versus tumor thrombus in patients with malignancy may be of value in guiding appropriate management which may in turn improve patient outcomes [24].

This presence of SMV tumor thrombus in this case represents an unusual pattern of recurrence and invasion that can potentially be explained by the tumor propagating along the pathway of venous drainage. The transverse colon, the site of our patient's primary disease, is drained by the middle colic vein which drains into the SMV and subsequently the portal vein. Thus, it is important to understand the venous anatomy in order to recognize the pattern of dissemination of disease in these instances. Of note, our patient was diagnosed with signet ring carcinoma, known to be an aggressive subtype of CRC that account for only 1–2% of all CRCs. The signet ring subtype is associated with a high risk of relapse and has a propensity for peritoneal recurrence [25, 26].

A second unusual finding in our case was the indolent nature of the recurrence whereby initial concern regarding a possible lesion in the mesentery was alleviated when PET-CT demonstrated no evidence of increased FDG avidity and a CEA was normal. While the optimal intensity of follow-up remains uncertain, our patient underwent six monthly surveillance in keeping with most guidelines which recommend more intensive follow-up during the first 3 years and less surveillance after year 5. When the question of recurrence arose, a PET-CT was completed. An intensive surveillance approach in this case allowed detection of an asymptomatic recurrence at an early stage which subsequently permitted an aggressive curative intent approach to be considered. Resection of liver and lung metastases has been demonstrated to result in improved 5-year survival rates of 30–40% and 48% respectively [27–29]. While isolated retroperitoneal nodal disease recurrence has been associated with a poor prognosis [30, 31], there is some data which suggests a potential role for resection of isolated nodal recurrence, particularly paraaortic nodal recurrence, in selected patients [32–34]. This data suggests that patients with longer disease-free intervals, lower CEA levels, and favorable histology may be appropriate candidates in which to consider aggressive resection [32]. There remain no data to guide the optimal post-treatment surveillance strategy for this group.

The NCCN guidelines recommend that perioperative (pre- or post-surgery) therapy be administered for approximately 6 months in order to increase the likelihood that residual micrometastatic disease be eradicated. In a pooled analysis of two small trials with a combined 278 patients that utilized adjuvant therapy after liver resection, a 5-FU/leucovorin regimen demonstrated a strong trend toward improved outcomes with systemic therapy in this setting (disease-free survival [DFS] 27.9 vs. 18.8 months; HR 1.32, $p = 0.058$) [35]. Thus, adjuvant therapy was recommended in this case. Given that our patient had previously received FOLFOX in the adjuvant setting and had residual neuropathy, he was treated with FOLFIRI. This regimen has not been demonstrated to be superior to LV5FUs (leucovorin, 5-FU 400 mg/m^2 bolus, continuous 5-FU infusion, 2400 mg/m^2 over 46 h) as adjuvant therapy following resection of colorectal liver metastases [36]. However, this study closed prematurely, and with 306 patients accrued, it may have been insufficiently powered to demonstrate a significant DFS benefit. On the other hand, the lack of clear benefit may also relate to the absence of efficacy observed with irinotecan in stage III disease. However, FOLFIRI is a standard regimen in the metastatic setting [37].

In conclusion, SMV tumor thrombus related to colon carcinoma is extremely rare, and its presence has unclear implications for prognosis. Close surveillance, aggressive use of salvage surgery at recurrence, and administration of perioperative chemotherapy is likely to have had a positive impact on this patient's outcome.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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