Metastatic sigmoid colon adenocarcinoma and tumour-related sarcoid reaction: A case report and literature review

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Main Text

Introduction

The association between malignancy and tumour-related sarcoid reaction is well-documented, characterised by the formation of non-caseating granulomas within tumour stroma, regional lymph nodes and non-regional tissues. It is recognised in both haematological and solid malignancies, with increasing case reports in non-metastatic and metastatic colon cancer. The clinical significance of tumour-related sarcoid reaction remains unclear, with contradicting and inconsistent data likely reflecting a complex immuno-pathophysiological response in a heterogeneous group. We herein present a case report of a thirty-two-year old female diagnosed with concurrent metastatic sigmoid colon adenocarcinoma and pulmonary granulomatous disease suggestive of a tumour-related sarcoid reaction.

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Case Report

A thirty-two-year old Australian born female presented for assessment of a change in bowel habit, characterised by six months of diarrhoea with post prandial abdominal cramping and occasional bleeding per rectum. Her symptoms progressed with an unintentional weight loss of 15 kilograms and the development of bilateral lower limb lesions, typical of erythema nodosum. There were no rheumatological or respiratory symptoms.

She had no concurrent medical illnesses and no previous episodes indicative of chronic inflammatory bowel disease. She had no known significant demographic or genetic risk factors for autoimmune disease, granulomatous disease or malignancy, with no identifiable exposure risk and a benign family history. The patient was a non-smoker.

Initial assessment revealed a moderate iron deficiency anaemia, with a haemoglobin of 93g/L, and an active inflammatory state marked by an elevated C-reactive protein, 36.7mg/L, and erythrocyte sedimentation rate, 43mm/hr. Faecal microscopy revealed erythrocytes and leukocytes with no pathogenic organisms. Coeliac serology was negative.

Colonoscopy was performed showing a large stenosing sigmoid colon tumour, 35mm from the rectum. Biopsy histopathology and immunostaining was consistent with a moderately differentiated adenocarcinoma with intact expression of mismatch repair proteins. The colonoscopy was otherwise unremarkable, with no features suggestive of underlying inflammatory bowel disease. Staging contrast computer tomography in conjunction with whole body 18F-fluorodeoxyglucose (FDG)

positron emission tomography revealed a large metabolically active primary sigmoid colon carcinoma, 70mm in diameter, with associated regional mesenteric nodal disease. Multiple FDG avid hepatic lesions across several segments were found, the largest 15mm, highly suggestive of metastases.

Additionally, several small bilateral FDG avid pulmonary nodules and symmetrical bilateral hilar and mediastinal lymphadenopathy were identified; the symmetrical nature suggestive of granulomatous disease. This was investigated via an endobronchial ultrasound guided transbronchial needle aspiration, with cytology revealing non-necrotising granulomas consistent with a sarcoid reaction (Figure 1).

The patient underwent an uncomplicated high anterior resection with radical mesenteric nodal clearance. Histopathology confirmed the diagnosis of a moderately differentiated adenocarcinoma, invading through the muscularis propria into pericolic fat with small vessel lymphovascular invasion. Clear margins of the primary carcinoma were achieved. Two of fifty-eight lymph nodes showed metastatic carcinoma and three foci of isolated extra-mural tumour deposits were identified.

Further management involved induction and consolidation chemotherapy, with folinic acid, 5-fluorouracil and irinotecan in combination with cetuximab. Staged resections of hepatic metastases were completed, with histopathology showing evidence of well-formed granulomas within the metastatic tumour stroma and adjacent parenchyma.

Subsequent imaging showed successful clearance of the primary carcinoma, nodal and hepatic metastatic disease. The pulmonary nodules and bilateral hilar and mediastinal lymphadenopathy completely resolved on serial computer tomography, accompanied by resolution of bilateral lower limb erythema nodosum. The patient is currently in a state of clinical remission.

Discussion

The association between malignancy and tumour-related sarcoid reaction is well-documented, albeit an uncommon phenomenon. It is characterised by the formation of non-caseating granulomas without evidence of sarcoidosis.¹ It has a variable presentation, occurring either concurrently at the time of malignancy diagnosis or developing at a later point in time; with case reports describing sarcoid reactions developing during active treatment and others arising years after curative therapy. These non-caseating granulomas have been identified within the tumour stroma, in regional lymph nodes draining carcinomas and in non-regional tissues.¹ In the case report presented there was histological evidence of granulomas within the tumour stroma of hepatic metastases, in the adjacent parenchyma and in non-regional tissues.

Tumour-related sarcoid reactions are seen in both haematological malignancies, including Hodgkin and non-Hodgkin lymphoma, and solid malignancies, including breast, gastric, lung, nasopharyngeal, renal and testicular.^{2, 3, 4, 5, 6, 7} Such reactions are a rare occurrence in colonic carcinoma, however have increasingly been described in both metastatic and non-metastatic disease.^{8, 9, 10, 11, 12, 13, 14}

The exact immuno-pathophysiology driving this process is not well understood and likely represents a complex process in a heterogeneous group. Proposed mechanisms include an immunological response to neoplastic cells directed towards components of tumour cells or necrotic debris, either occurring locally within the tumour stroma or in response to vascular or lymphatic embolization. An alternative mechanism is the generation of an immunological response towards a substance released from the tumour that is transported systemically.^{1, 8, 9, 15, 16}

The patient described in this case report, presented with a constellation of evolving gastrointestinal symptoms along with systemic symptoms and signs consistent of an active inflammatory disease. She was diagnosed with sigmoid colon adenocarcinoma with regional mesenteric nodal disease and several bi-lobar hepatic metastases. Staging computer tomography and FDG positron emission tomography revealed asymptomatic bilateral pulmonary nodules and symmetric bilateral hilar and mediastinal lymphadenopathy, suggestive of granulomatous disease; a diagnosis confirmed by endobronchial ultrasound guided transbronchial needle aspiration and cytology. These findings highlight the lack of specificity associated with computer tomography and FDG positron emission tomography and the difficulty when determining correct staging in the presence of tumour-related sarcoid reaction.^{13, 17}

Given the patient's relatively young age the diagnosis of metastatic sigmoid colonic adenocarcinoma was surprising. This entertains the possibility of sarcoidosis preceding and representing a risk factor for the identified malignancy, as oppose to a tumour-related sarcoid reaction. This is an area of contention in the literature. Studies have shown increased cancer incidence in the setting of sarcoidosis, concluding systemic sarcoidosis as a risk factor for malignancy.^{18, 19} However, temporal

inconsistencies are repeatedly described along with distinct differences in group characteristics when comparing sarcoid reactions in the setting of malignancy against sarcoidosis occurring in the general population.²⁰ These variable findings may reflect a heterogeneous group with different immuno-pathophysiological mechanisms. In the case report presented, the paucity of chronic symptoms preceding the presentation, in combination with the improvement of radiological and clinical features of granulomatous disease following treatment, supports that the metastatic sigmoid colon adenocarcinoma led to a tumour-related sarcoid reaction.

The clinical significance of tumour-related sarcoid reactions in the setting of colon adenocarcinoma remains unclear, with data in other malignancies showing conflicting and inconsistent findings relating to prognosis. Studies have reported improved prognosis in Hodgkin lymphoma with sarcoid reactions in regional lymph nodes.^{2, 21} However, in a small case series looking at primary lung cancer there was no significant prognostic difference.²² Variable outcomes have been observed in gastric cancer; with published data showing improved prognosis in the setting of regional lymph node sarcoid reactions whilst other studies suggest sarcoid reactions in both regional lymph nodes and spleen to be associated with advanced stages of disease.²³

This case report emphasises the importance of clinical vigilance when assessing patients with systemic granulomatous disease for possible underlying malignancy. It also highlights the difficulty when staging colon adenocarcinoma, as tumour-related sarcoid reactions show similar findings on computer tomography and FDG positron emission tomography as metastatic disease; with histopathology representing the only definitive means to distinguish between the two entities.

Further studies focusing on the clinical significance and prognostic value of tumour-related sarcoid reactions in colon adenocarcinoma are required.

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Figure Legends

- Figure 1** Endobronchial ultrasound guided transbronchial needle aspiration cytology: non-necrotising granulomas

Figure 1 - M De Gregorio.jpg

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Title Page

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Abstract

The association between malignancy and tumour-related sarcoid reaction is well-documented, characterised by non-caseating granulomatous disease in haematological and solid malignancies. Its occurrence in colon cancer is rare and of unclear clinical significance. We herein present a case report of a thirty-two-year old female diagnosed with concurrent metastatic sigmoid colon adenocarcinoma and pulmonary granulomatous disease suggestive of a tumour-related sarcoid reaction.

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