CASE REPORT

Synovial metastasis of the knee in a *KRAS* mutant rectal adenocarcinoma patient

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SUMMARY

Synovial metastasis is an unusual entity in solid tumours and only a few cases have been reported in the literature. We report a case of synovial metastasis of the knee in a young patient with progressive rectal adenocarcinoma and review previously published case reports of synovial involvement in advanced colorectal carcinomas. Synovial metastasis is just one of the multiple possibilities of differential diagnosis in patients with cancer suffering from monoarthritis. Radiological tests (plain radiographs, bone scans, MRI of the joint and so forth) can be unspecific and cytological examination of the synovial fluid and/or histology of synovial biopsies is essential for a definitive diagnosis so as to tailor the best treatment for patients. Given the poor prognosis associated with these intra-articular secondaries, treatment is often limited to palliation.

BACKGROUND

Colorectal cancer is the third most common cancer in both men and women.¹ In Australia, it is currently estimated to be the second most common cause of cancer-related deaths. Survival rates for metastatic colorectal cancer (mCRC) increased significantly between 1950 and 2000 from 41% to 66%. In Australia, the age-standardised mortality rate decreased from 31 deaths per 100 000 persons in 1968 to 16 deaths per 100 000 in 2013.² This improvement in the average prognosis for patients with mCRC (from a poor prognosis with best supportive care to over 2-year survival) is due to advances in surgery, chemotherapeutic agents and monoclonal antibodies.^{3–5} With advances in treatment options, the incidence of metastases at previously uncommon locations is rising. It is well accepted that colorectal cancers mainly metastasise to the liver, lung and peritoneum; other metastatic sites such as the pancreas, heart, brain and distant lymph nodes are not well studied and generally only described in case reports.^{6–8}

Synovial metastases are rare events. Approximately 40 cases of synovial metastases of adenocarcinoma have been previously reported to the best of our knowledge.^{9–10} Of these, 15 case reports involving colorectal cancer have been documented to date. Here, we describe a case of metastatic rectal adenocarcinoma to the knee from our institution, highlighting this rare event and illustrating the potential diagnostic dilemma.

CASE PRESENTATION

A 31-year-old woman was diagnosed with T3N2 rectal adenocarcinoma in July 2013 after a 7-month history of diarrhoea and rectal bleeding. Her mucinous rectal adenocarcinoma was Kirsten rat sarcoma virus (*KRAS*) oncogene homologue mutant and showed normal expression of MLH1, MSH2, MSH6 and PMS2 proteins. With this immunohistochemistry, associated Lynch syndrome was thought to be unlikely.

The patient underwent neoadjuvant chemoradiotherapy followed by laparoscopic ultra-low anterior resection in December of 2013. This demonstrated a pathological T3N2a tumour with minimal tumour regression. She was treated with adjuvant capecitabine–oxaliplatin which was ceased secondary to side effects (oxaliplatin allergic reaction).

In February 2015, the patient presented with a persistent cough and was found to have extensive lung and liver involvement. The patient was commenced on first-line palliative chemotherapy with irinotecan and bevacizumab. Following disease progression, with suspected brachial plexus involvement secondary to a left upper lobe lesion, the patient received 30 Gy of palliative radiation. Subsequently, the patient continued on active surveillance due to limited systemic options.

INVESTIGATIONS

In March of 2016, following CT demonstration of progressive disease within the lung and liver, the patient was admitted with a 1-month history of right knee pain and swelling. Physical examination revealed a large right knee effusion. A knee aspirate was performed by rheumatology following review. No crystals or organisms were seen in the knee aspirate specimen and rheumatic serologies were all negative.

An MRI was also performed during admission—an X-ray of the right knee carried out in February had been unremarkable. The MRI demonstrated a large joint effusion with diffuse thickening and nodularity of the synovium without any local bone abnormalities confirmed by a bone scan. On imaging, this was reported to be consistent with villonodular synovitis (figure 1). Analgesia was optimised and orthopaedic involvement was sought with a plan for elective open synovectomy.

The patient was again admitted a month later with a pain crisis secondary to worsening pain in the right knee. On examination, the right knee was diffusely tender and there was a large effusion. A

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Figure 1 MRI right knee proton density-weighted sagittal image demonstrates a large joint effusion, and diffuse thickening and nodularity of the synovium with homogenous enhancement. No evidence of bony erosion or bone marrow oedema. Enlarged lymph nodes are noted in the superior popliteal fossa.

repeat MRI right knee was performed which demonstrated a substantial increase in the synovial thickening with an ongoing diagnosis of progressive villonodular synovitis. Open right synovectomy was undertaken on the 2 May 2016. Macroscopically the synovium was exuberant and friable (figure 2). Histopathology confirmed metastatic adenocarcinoma (figure 3). CDX2 and CK20 immunohistochemical staining were consistent with a colorectal primary. RAS/BRAF statuses were not repeated in the knee surgical specimen given that information was available from resected rectal primary.

Figure 2 Macroscopic picture of synovium right knee. An enlarged, unorientated and irregularly shaped portion of glistening gelatinous tissue measuring 180x80 up to 50 mm. Sectioning through the tumour demonstrates a uniform, gelatinous consistency.

Figure 3 Biopsy of the synovium. Picture showing infiltration of the synovial membrane by adenocarcinomatous glands, displaying cribriform growth pattern, typical of colorectal origin (H&E-safran, original magnification $\times 40$). Immunohistochemistry was performed and the malignant cells demonstrated strong nuclear labelling with antibodies for CDX2 and CK20 in keeping with a colorectal primary.

TREATMENT

The patient subsequently completed palliative radiotherapy to the right knee and, in July 2016, she was started on oral trifluridine/tipiracil in the context of an Expanded Access Programme.

OUTCOME AND FOLLOW-UP

Sadly, our patient passed away a month later from rapid progressive disease, 5 months after her right knee symptoms had started.

DISCUSSION

Synovial metastases from solid tumours are a rare entity with few reported cases found in the literature. Lung adenocarcinoma is the most common primary solid tumour associated with this unusual entity, followed, respectively, by colorectal carcinomas and malignant melanomas.^{9 10} Generally speaking (and more specifically in the case of colorectal adenocarcinomas), the metastatic synovial involvement is usually monoarticular and the most commonly affected joint is the knee, although the involvement of other joints such as hips,^{11–13} temporomandibular joints (TMJs)¹⁴ or shoulders¹⁰ has also been reported. Clinically, the usual presentation is a week or month-long history of joint pain, swelling and stiffness of the articulation and it is common to find on physical examination signs of an intra-articular effusion^{9 11} as was noted in our case.

Among the 15 previously reported cases of synovial metastases secondary to colorectal tumours in the literature (summarised in table 1), in only five cases, the clinical presentation of monoarthritis precluded the diagnosis of mCRC; the other 10 patients had all had a diagnosis of colorectal cancer prior to being diagnosed with synovium metastases. The differential diagnoses for a monoarthritis de novo in an oncology patient remain wide, including: septic arthritis, gout, avascular necrosis, other inflammatory conditions and various rheumatic disorders.^{9 11}

Since 1962, when the first confirmed case of synovial metastasis to the finger in a patient with lung cancer was reported by Karten and Bartfeld,¹⁵ several authors have proposed two major differing hypotheses on the mechanism of metastatic deposits in the synovium. The first is direct haematogenous spread to

Table 1 Summary table of reported metastatic synovial cases secondary to colorectal cancers (CRC)

Author (Reference)	Year of publication	Country	Age	Sex	Primary CRC location	Synovial metastasis location	Presenting symptom	Cytology	Synovial biopsy	Radiology changes	Bone scan changes	Surgical resection	RDT	CTX	Survival (months)
Goldenberg <i>et al</i> ²³	1975	USA	62	F	Colon	Knee	No	+ve	+ve	Degenerative	Nil	No	Yes	Yes	2
Graham <i>et al</i> ¹³	1976	UK	51	F	Colon	Hip	No	NR	+ve	Nil	Nil	No	Yes	NR	NR
Newton <i>et al</i> ²⁶	1984	UK	83	F	Colon	Knee	Yes	-ve	+ve	Lytic	↑ Uptake	No	Yes	No	'Short'
MacAfee <i>et al</i> ¹⁴	1993	USA	59	M	Colon	TMJ	Yes	-ve	+ve	Lytic	NR	Yes	Yes	Yes	12
Hatem <i>et al</i> ²⁵	1997	USA	61	M	Colon	Knee	Yes	NR	NR	Synovial thickening (CT)	Nil	NR	NR	NR	NR
Zissiadis ²⁷	2000	Australia	59	M	Colon	Knee	No	+ve	+ve	Lytic	↑ Uptake	No	Yes	NR	4
Beckers <i>et al</i> ^{*17}	2002	Belgium	83	M	Colon	Knee	No	-ve	+ve	Lytic	↑ Uptake	NR	NR	NR	3
Devis <i>et al</i> ²⁸	2005	USA	70	F	Rectum	Knee	No	-ve	+ve	NR	NR	No	NR	NR	NR
Ruparella <i>et al</i> ¹¹	2006	UK	28	M	Colon	Hip	Yes	+ve	NR	Nil	↑ Uptake	No	No	Yes	4
Capovilla <i>et al</i> ¹⁰	2006	France	74	F	Rectum	Shoulder	No	NR	+ve	Degenerative	NR	No	NR	Yes	5
Curral <i>et al</i> ⁸	2008	UK	72	M	RSJ	Knee	Yes	-ve	+ve	Nil	↑ Uptake	Previous TKR	Yes (twice)	NR	6
Rothenberg <i>et al</i> ¹²	2014	USA	51	M	Rectum	Knee	No	+ve	NR	NR†	NR‡	TKR	NR	NR	NR
Rothenberg <i>et al</i> ¹²	2014	USA	62	M	Rectum	Hip/knee	No	-ve	NR	Lytic	↑ Uptake	Yes	NR	NR	NR
Dhanda <i>et al</i> ¹⁸	2014	Singapore	54	M	Colon	Knee	No	NR	+ve	Soft tissue mass (MRI)	NR	NR	NR	NR	NR
Ozler <i>et al</i> ²⁹	2014	Turkey	85	F	Colon	Knee	No	-ve	NR	NR	NR	TKR§	NR	NR	NR
Present case report	2016	Australia	31	F	Rectum	Knee	No	-ve	+ve	Nil	Nil	No	Yes	Yes	5

* Article written in French.

† Soft tissue mass contiguous with the patella on MRI.

‡ PET-CT scan showed increased fluorodeoxyglucose uptake corresponding to the right knee mass with patellar involvement.

§ Patient underwent TKR with the diagnosis of osteoarthritis and villonodular lesions on the synovium were seen. Surgical specimen showed metastatic adenocarcinoma.

+ve, positive; -ve, negative; ↑, increased; CRC, colorectal cancer; CTX, chemotherapy; F, female; M, male; NR, not reported; RDT, radiotherapy; RSJ, rectosigmoid junction; TKR, total knee replacement; TMJ, temporomandibular joint.

the synovium (in our case, this theory is more plausible as our patient's bone scan was negative for osseous metastases). The second hypothesis is direct spread from a juxta-articular bone, in which the tumorous cells first metastasise to the bone and then spread further to the synovial cavity.^{16 17} For now, however, the exact mechanism of dissemination continues to remain unclear.

In spite of the rarity of such secondaries, this case highlights the importance of considering metastatic adenocarcinoma in a patient with cancer with a painful joint effusion. As described above, the diagnosis of this entity can be challenging. Plain radiographs of the affected joint can be normal or with unspecific degenerative changes if there is no bone disease. On the other hand, whole-body bone scans may also be negative in the absence of osseous disease, as illustrated by our case report, supporting the theory of haematogenous spread to the joint. Both MRI and ultrasound are more sensitive at detecting bone erosion than simple X-rays and can help to delineate the soft tissue pathology and to tailor an appropriate surgical approach.^{12 18} In this case, on MRI, the nodular synovium demonstrated homogenous enhancement and, in the absence of confirmatory cytology, was felt to be radiologically consistent with non-specific villonodular synovitis, a joint disease characterised by inflammation and overgrowth of the joint lining.¹⁹

With regard to the histopathological diagnosis of synovial metastases, joint aspiration of the synovial fluid for cytological evaluation is usually one of the first tests in the diagnostic work-up given its utility and because it is an easy technique to perform. Synovial fluid is usually haemorrhagic, although it can be also purulent mimicking septic arthritis. After arthrocentesis, these joint effusions tend to reaccumulate rapidly following aspiration, usually after a few days or, like in our case, a few weeks. However, the low sensitivity of the synovial cytology should be noted, with approximately only 30%–40% of cases positive for malignant cells.^{16 20} In our case, cytological assessment of the synovial fluid was negative for adenocarcinoma cells and synovial biopsy was needed for a definitive diagnosis. Arthroscopic synovial biopsy is a simple and 'easy to carry out' technique which allows direct inspection of the synovial cavity as well as synovium resection for histological examination.²¹

Synovial metastases are usually associated with cancers that are both extensive and rapidly progressive. Sadly, patients with articular metastases have an ominous prognosis, with an average survival of less than 5 months from the time that a synovial metastasis is diagnosed.^{20 22 23} However, there are always exceptions to every rule. MacAfee¹⁴ reported the case of a newly diagnosed patient with mCRC with a synovial metastasis to the TMJ who survived 12 months after initial diagnosis following radiotherapy and debulking surgery of the right TMJ. This seems to be the longest survival reported for a patient with mCRC with synovial metastasis in the literature. As can be seen in our summary table of reported cases of patients with mCRC with synovial metastases, only half actually provide information about outcomes. This is due to the fact that some of these case reports are intended for a predominantly radiological audience, with an emphasis on key imaging features, on radiological disease patterns and differential diagnosis.^{12 18 24 25} Consequently, these reports lack specific clinical information on treatments and patient survival.

It is also important to underscore the lack of prognostic markers for the development of synovial metastatic disease in mCRC. The 15 cases of mCRC with intrasynovial metastases reported in the literature have been described over a 40-year period, whereas the determination of the *KRAS*/*RAS*/*RAF* mutational status and microsatellite instability (MSI) has become an essential tool for managing patients with mCRC in just the last

decade. No information regarding the mutational status in the *KRAS*, *B-Raf proto-oncogene serine/threonine kinase (BRAF)* or *MSI statuses* is documented in any of these case reports.

For the patient who develops synovial metastases, early diagnosis is important so that appropriate palliative treatments are commenced, including palliative synovectomy, radiotherapy, systemic chemotherapy and, of course, adequate pain management in a multidisciplinary manner.^{9 10 14} In our case, as in some of the reported cases, the patients have completed several lines of palliative oncology treatment and the options for further active chemotherapy +/- monoclonal antibodies are limited (or nil), while in some cases, the patients' level of fitness and rapid clinical deterioration contraindicate further cancer treatment. Curative treatment like joint resection with prosthesis might be considered in cancers with good biology and/or in oligometastatic disease, although we have not found any case reported in this regard.

Learning points

- Synovial metastases are a rare event; however, the presence of neoplastic disease should not be underestimated in a patient who presents with unusual joint findings in the setting of colorectal cancer.
- Careful diagnosis is important which can be made with either cytological examination of the synovial fluid or synovial biopsy if cytology is negative.
- This clinical entity confers generally poor prognosis, with an average survival of less than 5 months.
- The present case serves as an important reminder of a rare example of metastases to the synovium of any solid tumour, included colorectal cancer.

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