Original Article

Sister Mary Joseph Nodules Associated with Colorectal Cancer: A Case Series and Literature Review

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Key Words
Sister Mary Joseph's nodule;
Colorectal cancer

Introduction. Sister Mary Joseph's nodule is an umbilical metastatic tumor often originating from intra-abdominal and/or pelvic malignancies. It is an indicator of a poor prognosis. However, few studies in the past have correlated its clinical role among malignant diseases. Published case series are rare.

Methods. Cases in which umbilical nodules were documented were retrospectively included in this study. These cases were all treated and followed up at Mackay Memorial Hospital (including the Taipei main hospital and the Tamsui branch hospital) from December 2013 to July 2019.

Results. A total of 12 patients were enrolled in this study. The male-to-female ratio was 1:1.4. Patient ages ranged from 38 to 87 years, with a median age of 62.5 years. Nine (75%) of the 12 patients presented with stage IV disease initially. The histopathological type of most of the primary tumors and umbilical nodules was adenocarcinoma. The histological grade of 36.4% of the patients was poorly differentiated. Surgical treatment with a curative or palliative intent was performed for all patients. Eleven (91.7%) of the 12 patients received adjuvant chemotherapy. Nine patients (75%) died 2 years after diagnosis and initial treatment. All mortality cases were documented with disease progression. The patients were followed up at least 6 months. Patients who received aggressive treatment had an average survival of 21.5 months and a median survival of 16.5 months.

Conclusion. Umbilical nodule is rare, but is an indicator of intra-abdomino-pelvic advanced malignancy. It is usually associated with peritoneal carcinomatosis, and has a very poor prognosis. During follow-up, an umbilical nodule could be an initial symptom of recurrence, so physical examinations are important.

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Umbilical metastatic lesion resulting from intra-abdominal and/or pelvic malignancies is called a Sister Mary Joseph's nodule (SMJN). Sister Mary Joseph Dempsey (1856-1939) practiced as a surgical assistant to William J Mayo at St. Mary's Hospital in Minnesota from 1890-1915, and published the first article on this metastatic nodule and an intra-abdominal malignancy in 1928.[1,2] SMJN has an incidence of 1%-3% of all intra-abdominal or pelvic malignancies. Gastrointestinal malignancies, most commonly gastric, colon, and

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pancreatic, account for about 52% of cases, and gynecological cancers, most commonly ovarian and uterine, account for about 28% of the underlying sources. Also, 15-29% of all cases have an unknown origin.[3] SMJN is a poor prognostic indicator in patients with cancer, and survival is reported to be 2 to 11 months in patients not receiving treatment after diagnosis.[2]

Case reports and rare case series have been published in the past. Studies on SMJN are still limited, and no clear mechanism or clinical role for an umbilical metastatic lesion has been established. In this study, we present 12 cases with umbilical metastasis from a colorectal origin. We analyzed patient characteristics, clinical courses, and treatment. Literature was also reviewed. With this, we hope to be able to discover more of a relationship between SMJN and malignant diseases.

Materials and Methods

We retrospectively collected cases documented with an umbilical nodule in which the primary malignancy was of a colorectal origin from 2013 to 2019. All of the cases were treated and followed at Mackay Memorial Hospital (MMH) (including the Taipei main hospital and the Tamsui branch hospital). Mackay Memorial Hospital is a tertiary medical center and teaching hospital with a long history in Taiwan.

Data on patient characteristics and medical records were retrieved from the MMH electronic medical database. All patients were diagnosed with colorectal malignancies and documented with umbilical nodules. The data collected included age, gender, initial clinical presentation, timing of presenting the umbilical nodules, initial cancer staging, histology of the primary cancer and umbilical nodules, treatment received, timing of disease progression, tumor markers, and duration of survival. All patients were followed up at the colorectal or oncological outpatient department, and the clinical course of the disease and date of mortality was all documented.

Statistical data analysis

Statistical data analysis was performed using SPSS computer software version 17.0 (SPSS, Inc., Chicago, IL, USA). Data were summarized in the form of proportions and frequency tables for categorical variables. Continuous variables were summarized using medians and ranges.

Ethical consideration

Ethical approval to conduct the study was sought from the MMH ethics review committee before the commencement of the study.

Results

A total of 12 cases with SMJN associated with colorectal cancer were enrolled in the study. There were 5 (41.7%) males and 7 (58.3%) females; the male-to-female ratio was 1:1.4. Patient agesranged from 38 to 87 years, with a median of 62.5 years. Most patients (7, 58.3%) presented with abdominal pain initially. Two patients (16.7%) presented with an enlarging umbilical mass as the initial symptom of colorectal cancer. The initial presentations of the disease are listed in Table 1.

The origins of the colorectal cancers have been documented. There were 5 (41.7%) cases at the right-side colon, 1 (8.3%) at the descending colon, 4 (33.3%) at the sigmoid colon and 2 (16.7%) at the rectum (Table 2). Furthermore, the primary tumors were usually large. Seven (58.3%) patients presented with umbilical nodules at the time of diagnosis of colorectal cancer. Two (16.7%) patients had the chief complaint of

Table 1. Distribution of the patients according to initial presentation

Clinical presentation	Patients	Percentage
Abdominal pain	7	58.3
Abdominal fullness	4	33.3
Nausea/vomiting	3	25
Ascites	3	25
Umbilical mass	2	16.7
Fecal occult blood positive	2	16.7
Rectal bleeding	2	16.7
Bowel obstruction	2	16.7
Other symptoms	5	41.7

Table 2. Distribution of patients according to primary tumor location, initial cancer staging, histopathological type and tumor grade

Study variables	Patients	Percentage
Primary tumor site		
Right-side colon	5	41.7
Sigmoid colon	4	33.3
Rectum	2	16.7
Descending colon	1	8.3
Initial cancer staging		
Stage IV	9	75
Stage III	2	16.7
Stage II	1	8.3
Histopathological type		
Adenocarcinoma	10	83.3
Mucinous carcinoma	2	16.7
Tumor differentiation		
Poorly differentiated	4	33.3
Moderately differentiated	7	58.3
Not available	1	8.3

an enlarged umbilical mass (Fig. 1 and Fig. 2). Umbilical nodules were noted in the other 5 (41.7%) patients during follow-up. In these 5 patients, the median interval from initial diagnosis of colorectal cancer to observing the presence of the umbilical nodules was documented as 11 months. Ten (83.3%) of the 12 patients presented with stage IV disease initially, 1 (8.3%) was stage III disease, and 1 (8.3%) was stage II (Table 2). Intra-abdominal carcinomatosis was noted in 7 (77.8%) of the 10 patients with stage IV disease initially. Four (44.4%) patients were found to have distant metastasis (including the liver, lung and ovary) and concurrent peritoneal carcinomatosis. The locations of the metastases are listed in Table 3. Seven (58.3%) patients had umbilical nodules at the time of diagnosis, and all presented with stage IV disease. Carcinomatosis was noted in 5 (71.4%) patients who also presented with umbilical nodules initially. Five (41.7%) patients developed an umbilical mass during follow-up, accompanied with evidence of distant metastasis or intra-abdominal carcinomatosis.

Adenocarcinoma was the most common histopathological type of primary tumor, and accounted for 83.3% (10) of patients. The remaining 16.7% (2) were mucinous carcinoma. The umbilical nodules in the 8 patients with available pathological reports were all compatible with primary tumors. Histological differentiation was available for most (11) patients. Four (36.4%) had poor differentiation and 7 (63.6%) had moderate differentiation (Table 2). Ras mutation tests were ordered for all patients: half (50%) of the patients were ras wild-type and the other half (50%) were a K-ras mutation.

Surgical treatment with a curative or palliative intent was performed for all patients (Table 4). Eleven (91.7%) out of 12 patients received adjuvant chemotherapy. The 12th patient did not receive further treatment due to extreme old age (87 years old) and a cachexia status.

Survival after umbilical nodules were documented ranged from 1 to 63 months. Ten (83.3%) patients died within 24 months after the umbilical nodule was diagnosed. A total of 10 (83.3%) patients received aggressive treatment, and had an average survival of 21.5 months and a median survival of 16.5 months.

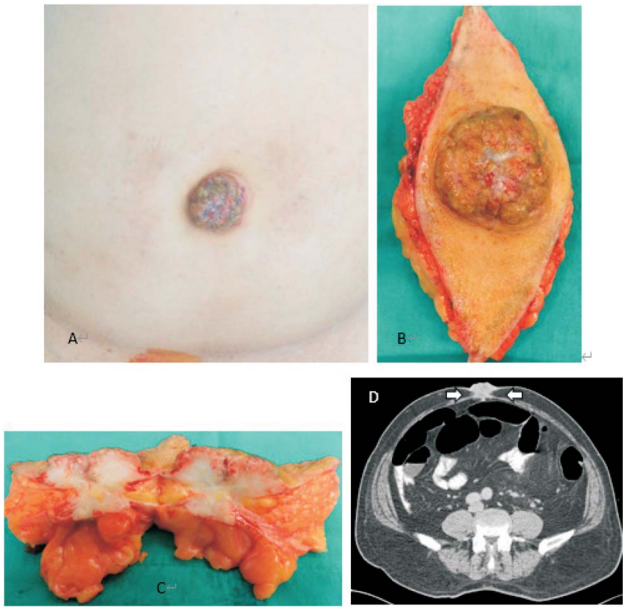

Fig. 1. A 66-year-old man presenting with an enlarging umbilical mass was diagnosed with sigmoid colon adenocarcinoma with umbilical, liver and lung metastases. Peritoneal and bladder invasion were also seen during surgery. (A) A 3.5-cm, hard, fungating mass in the umbilicus. (B) Resection of the umbilical tumor with a 1-cm safe margin. (C, D) Cross section of the umbilical tumor and computed tomography showed pictures of a full-thickness invasion of the abdominal wall from the peritoneum to the skin.

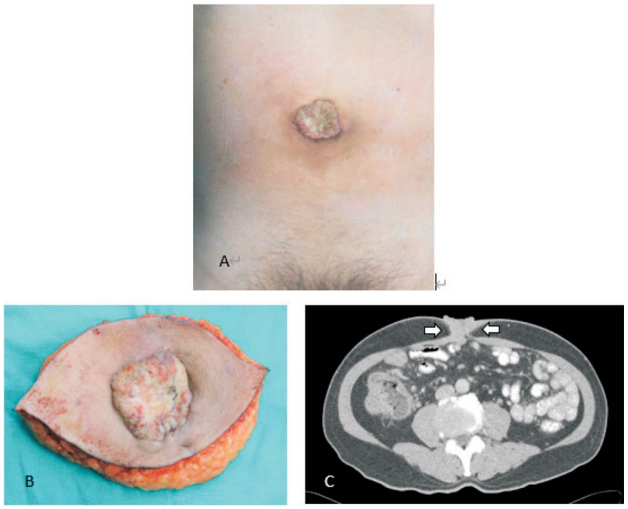

Fig. 2. A 61-year-old man presenting with an enlarging umbilical mass was diagnosed with ascending colon adenocarcinoma with umbilical metastasis in 2015. He underwent right hemicolectomy. The pathology report showed pT3N2aM1a adenocarcinoma. Adjuvant chemotherapy with FOLFOX was performed after colon resection. Lung metastasis was noted after 11 months, and he underwent lung resection. He is now a long-term survivor, with over 63 months. (A) A 4-cm, hard, fungating tumor in the umbilicus. (B) Excision of the umbilical tumor with a 1-cm safe margin. (C) Computed tomography showed a full-thickness invasion of the abdominal wall of the umbilical tumor.

Five patients who did not present at the time of diagnosis were followed at our outpatient department. Umbilical nodules were found in all patients, followed by disease progression (carcinomatosis, local recurrence or distant metastasis) within 1 year. Carcinoembryonic antigen doubling was also noted in these patients around the time the umbilical nodule was documented. Two older patients (84 and 87 years, respectively) received no aggressive treatment, and their survival was 1 and 3 months (Fig. 3).

The remaining 3 survivors were followed up at the colorectal surgery outpatient department for at least 6 months and are still under adjuvant chemotherapy. One of them is a long-term survivor (63 months) who initially presented with a single umbilical metastasis (Fig. 2). Radical surgery with an adequate margin was performed, and adjuvant chemotherapy was administered. Lung metastasis was found after 11 months, and lung resection was then performed. The patient is now under adjuvant chemotherapy. No sign of disease progression has been noted.

Table 3. Distribution of patients based on the location of the metastases

Location of metastases	Patients	Percentage
Omentum/peritoneum	9	75
Liver	9	75
Lung	7	58.3
Ovary	2	16.7
Bone	2	16.7
Spleen	1	8.3
Adrenal gland	1	8.3
Para-aortic lymph nodes	2	16.7
Iliac lymph nodes	2	16.7
Inguinal lymph nodes	1	8.3
Urinary bladder	2	16.7
Uterus	1	8.3

Table 4. Distribution of patients according to the type of surgical procedure performed

Surgical procedures	Patients	Percentage
Umbilical tumor excision	8	66.7
Right hemicolectomy	4	33.3
Laparoscopic surgery	4	33.3
Ileostomy	3	25
Salpingo-oophorectomy	3	25
Lung resection	3	25
Anterior resection	2	16.7
Left hemicolectomy	1	8.3
Lower anterior resection	1	8.3
Abdominoperineal resection	1	8.3
Colostomy	1	8.3
Hysterectomy	1	8.3
Liver resection	1	8.3

Discussion

Umbilical nodules are rare, and can be either benign or malignant. Benign umbilical nodules are known as ‘pseudo-Sister Mary Joseph’s nodules”. Endometriosis, fibroma, epithelial inclusion cysts, foreign body granuloma, keloid, and myxoma are possible causes of benign umbilical nodules. Primary umbilical malignancy accounts for 12-17% of cases. Pathological diagnoses include melanomas, basal cell carcinomas, squamous cell carcinomas, myosarcomas, and adeno-

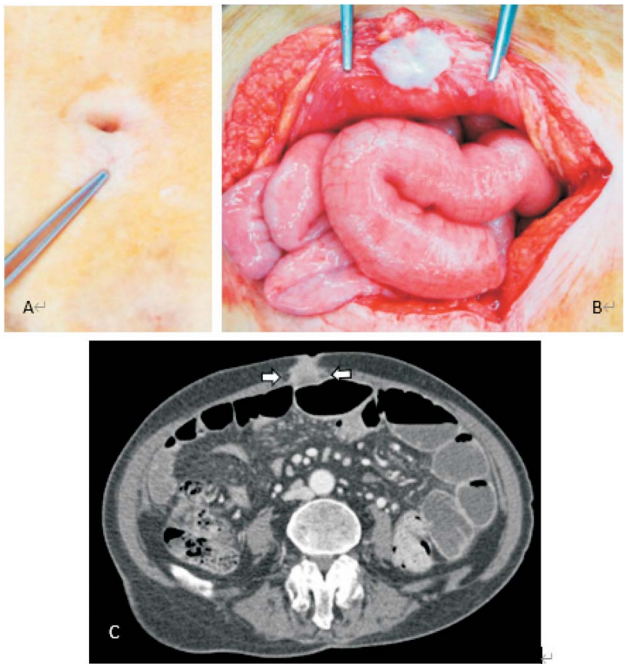

Fig. 3. An 87-year-old woman presented with abdominal pain and fullness, anorexia, and significant weight loss. She was finally diagnosed with sigmoid colon adenocarcinoma. Diffuse carcinomatosis causing bowel obstruction was noted during surgery. She then received palliative ileostomy. The patient expired 1 month after diagnosis. (A) A palpable hard mass beneath the umbilicus, no skin invasion. (B) Peritoneal side beneath the umbilicus. (C) Computed tomography compatible with the finding.

carcinomas. Most umbilical nodules are metastatic in nature and are called Sister Mary Joseph's nodules (SMJN). The most common histological type is metastatic adenocarcinoma. SMJN rarely metastasize from squamous cell carcinoma, sarcomas, mesotheliomas or melanomas.[4,5]

The most common primary site for umbilical metastasis is the gastrointestinal tract (35-65%). In men, gastric cancer accounts up to 25% of cases. A colorectal origin (10%) is the second most common, followed by the pancreas (7%). In women, ovarian malignancy is the most common primary source. However, about 15-29% of cases with umbilical metastasis have no definite primary site.[6,7] Jha AK et al. reported 2 cases of gallbladder origin that were inoperable and were treated with chemotherapy.[8] Haruki T et al. reported a case of advanced lung adenocarcinoma with peritoneal carcinomatosis; an umbilical nodule was found 26 months after the diagnosis.[9] Another case with an esophageal squamous cell carcinoma origin was reported by Mashimo Y et al.[10] Chalya PL et al. reported a series of 34 cases with umbilical metastasis originating, respectively, from the stomach, colorectum, pancreas, ovary, gallbladder and anus. However, there is very few case series has been reported.[11] This may be due to the rare incidence of umbilical metastasis.

According to the most recent data from the Taiwan Health Promotion Administration, colorectal cancer was the most common cancer among newly diagnosed cancers in 2015. Two patients in our study had an enlarged umbilical mass as the first presentation of colorectal cancer. So, umbilical metastasis in colorectal cancer should not be overlooked.

The mechanism of umbilical metastasis remains unclear. Possible routes of metastasis include direct invasion of the peritoneum beneath the umbilicus, such as through peritoneal seeding, or an indirect pathway, such as through lymphatic or hematogenous disseminations.[12] The umbilical skin is unique in its anatomical proximity to intra-abdominal and pelvic malignancies and its connection to venous and lymphatic systems. Contiguous extension is a strong mechanism supported by umbilical anatomical relations with the anterior peritoneum.[13] It is also connected to numerous venous drainages from the abdominal wall. Furthermore, it is a lymphatic intersection to deep lymphatic systems such as the para-aortic and internal mammary, and external iliac nodes and superficial nodes, including the axillary and inguinal nodes. Hori T et al. reported a case of colon cancer with umbilical metastasis. Using dynamic computed tomography (CT), they showed that the umbilical tumor enriches arterial and venous drainage from inferior epigastric vessels. The hematogenous pathway was possible in this case.[12] The above routes of metastasis may also explain the variety of malignancies that present with umbilical metastasis. In our study, 5 (41.7%) patients developed an umbilical mass during follow-up and most patients presented with carcinomatosis. This may explain the route of direct invasion by peritoneal seeding to the umbilicus.

SMJN is a poor prognostic factor and survival of untreated patients ranges from 2-11 months.[14] Even

with aggressive treatment, survival in the literature extended to just 17.6-21 months.[4] In our study, 2 patients received no aggressive treatment after the umbilical nodule was diagnosed, and survived just 1 and 3 months, respectively. Ten patients that received aggressive treatment had an average survival of 21.5 months and a median survival of 16.5 months, which was compatible with the literature. SMJN also indicates advanced intra-abdomino-pelvic malignancies with intra-abdominal carcinomatosis or distal metastasis.

Furthermore, in up to 40% of diagnosed malignancies, SMJN is also the first sign of disease relapse or progression.[14] Due to the above clinical characteristics, it is important to examine the umbilicus of every patient. Incisional biopsy or fine-needle aspiration cytology with the aid of histological analysis and immunohistochemical stain could differentiate the cellular type of 72% of unknown primary diseases.[15] Second-line diagnostic tools such as CT, magnetic resonance imaging, endoscopy and positron emission tomography could further help define the disease origin. Since colorectal cancer has become the most commonly diagnosed malignancy in our country, colonoscopy is a must-do examination.

Based on an observation of the 12 cases in our study, SMJN can indicate a number of clinical characteristics of patients. First, SMJN could be the first sign of malignancies and indicate advanced disease. Two of our patients came to the hospital due to umbilical nodules that had been enlarging for months. After examinations, colorectal cancer was diagnosed. One of cases even had liver and lung metastases at the time of diagnosis. Chen JS et al.[1] and Girijala RL et al.[13] reported similar cases. Second, umbilical nodules may indicate intra-abdominal carcinomatosis. Five of our patients with umbilical nodules at the time colorectal cancer was diagnosed were found to have intra-abdominal carcinomatosis intraoperatively. DeBardeleben J et al. reported the same in their study.[17] Last, SMJN could be a sign of disease recurrence or progression (local recurrence or distant metastasis). Five of our patients had clinical courses that involved the development of an umbilical mass, accompanied by evidence of local recurrence or distant metastasis.

Conclusion

Umbilical nodule is rare, but is an indicator of intra-abdomino-pelvic advanced malignancy. It is usually associated with peritoneal carcinomatosis, and with a very poor prognosis. During follow-up, an umbilical nodule could be the initial symptom of recurrence, so physical examination is important.

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原　著

原發於大腸直腸癌之肚臍轉移 – 案例分析與文獻回顧

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介紹　肚臍的轉移性腫瘤又稱做 Sister Mary Joseph's nodule (SMJN)，它與腹腔、骨盆腔內的癌症有著很大的相關性，並代表著原發癌症的遠處轉移與較差的預後。在文獻上只有零星的案例報告，系統性的案例分析更是少見。

方法　收集自 2013 年至 2019 年七月在馬偕醫院診斷或接受治療並在病歷上記載肚臍轉移之大腸直腸癌病患。我們統計及分析病人的年齡、性別、臨床表現、大腸直腸癌位置、疾病嚴重度、疾病進程、接受之手術、病理種類及分期以及死亡日期。所有病人資料皆從馬偕醫院資料庫取得並使用回溯式分析進行研究。

結果　在我們的研究中收集了 12 位病患，男女比例為 1:1.4。年齡範圍從 38 歲到 87 歲不等，年齡中位數為 62.5 歲。九位 (75%) 病人在診斷時已是第四期疾病。大多數病人的原發腫瘤及肚臍腫瘤的病理型態為腺瘤。全部的病人均有接受術治療。十一位 (91.7%) 病人有接受化學治療。九位 (75%) 病人在診斷後兩年內死亡。有接受積極治療的病人平均存活為 21.5 個月，中位數為 16.5 個月。

結論　肚臍的腫瘤跟腹腔、骨盆腔內的癌症有很大的關聯。它也是一個可以預測病人有晚期癌病的臨床表徵 (無論是腹膜轉移或是遠端轉移) 。在病人追蹤上，它的出現也可能是病人疾病有所變化時。同時它也是一個不好的預後因子。

關鍵詞　肚臍轉移、大腸直腸癌。