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ORIGINAL ARTICLE

Sister Mary Joseph Nodule: An Update on Characteristics and Outcomes

Don Chamil Codipilly, MD[1], Claire L. Jansson-Knodell, MD[1], Sajan Jiv Singh Nagpal, MBBS[2], Seth Sweetser, MD[2]

[1] Department of Internal Medicine, Mayo Clinic, Rochester, MN.
[2] Department of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN.

ABSTRACT

Objectives: We aimed to assess and update the characteristics of patients with Sister Mary Joseph Nodules (SMJN) to define patient outcomes in regards to type of cancer and mortality.

Background: The SMJN is a well-known manifestation of intraabdominal malignancy. The majority of published case reports demonstrate that SMJNs typically arise from a gastrointestinal or gynecologic source. Furthermore, these patients have a dismal prognosis, with many patients dying within a few months of diagnosis.

Methods: We reviewed patients seen at Mayo Clinic between January 1, 1992 and March 31, 2017 with the Sister Mary Joseph Nodule. Pathology reports were reviewed to confirm biopsy-proven umbilical metastasis. Abstracted data included basic demographics at diagnosis, site of primary malignancy, treatment, and survival.

Results: 113 patients were identified. Median survival from the time of diagnosis of SMJN was 14.6 months (follow-up ranging from 0.4 to 231.5 months). 2-year mortality was 88.4%, and 5-year mortality was 95.4%. 47.8% had a primary gastrointestinal (GI) malignancy (31.5% of which were colorectal), 35.4% had a primary gynecologic malignancy (52.5% of which were ovarian), and 4.4% had a primary hematologic malignancy.

Greater survival was associated with gynecologic compared to GI neoplasia (35.7 months vs. 15.7 months; $p = 0.02$). Treatment with both chemotherapy and surgery (average survival, 42.7 ± 8.6 months) was associated with improved survival compared to treatment with chemotherapy alone (mean 19.1 months; ± 1.8 months) or no treatment (mean 4.0 ± 0.24 months; $p < 0.01$).

Conclusions: Most SMJNs are of a gastrointestinal (colonic) or gynecologic (ovarian) origin. SMJNs of gynecologic origin have better survival compared to tumors with a GI origin. Treatment with chemotherapy and surgery, regardless of primary tumor type is associated with better survival as compared to chemotherapy alone or to no treatment.

INTRODUCTION

Metastatic disease protruding through the umbilicus is known as a Sister Mary Joseph nodule (SMJN). The association of metastatic intra-abdominal malignancy and umbilical nodules bears the namesake of Sister Mary Joseph Dempsey (1856-1939), who was one of Dr. William Mayo's surgical assistants (Powell, 2011). She observed the relationship between umbilical nodules noted during pre-operative skin preparation and widespread intra-abdominal malignancy noted during surgery (Mayo, 1928). The SMJN is typically no greater than 5 cm in diameter, and is often described as hard, indurated, or firm. There may be fissuring, necrosis, or ulceration with associated bloody, serous, or mucinous discharge (Abu-Hilal & Newman, 2009).

SMJN is an ominous sign reflecting an advanced stage of the underlying malignancy, and is often associated with a poor prognosis. There is a paucity of longitudinal data on the outcomes of patients with SMJN and whether the presence of this physical examination finding still portends a worse prognosis despite advancement in cancer chemotherapeutics.

In order to better understand the modern prognostic implications of SMJN, the aims of this study were to better define the baseline characteristics of patients with SMJN, to assess prognosis stratified by cancer primary and to determine the effects of aggressive treatment in patients with SMJN.

METHODOLOGY

This study was approved by the Mayo Clinic Institutional Review Board (study number: 17-001928). It was a retrospective review of the electronic medical record and included patient charts from January 1992 through March 2017. Using our institution's Advanced Cohort Explorer, we conducted an initial keyword search for the words "Sister Mary Joseph Nodule," "Sister Mary Joseph," "umbilical metastasis," and "umbilical nodule." We were able to identify all patients who presented with a SMJN within that time period.

Clinician notes containing these keywords were then independently reviewed by two authors, DCC and CLJK, and only patients with a physical examination consistent with a likely umbilical metastasis were shortlisted. Of these, only patients with biopsy-proven malignant lesions based on review of the pathology interpretation by staff pathologists at our institution were included in the final analysis. Types of biopsy samples included in the analysis were fine needle aspiration (FNA), punch biopsies, or excisional biopsies. Patients without a physical examination indicating an umbilical metastasis, those without a biopsy of such a lesion, or those with indeterminate or non-malignant biopsy results were excluded.

Data was abstracted on patient demographics at the time of diagnosis (including age, gender and race), primary cancer site, treatment modalities, and date of death or last follow up. Appropriate statistical tests were used for comparison of means, where applicable. The Wilcoxon rank sum test was used for survival analyses (Mann & Whitney, 1947). Statistical analyses were performed with institutionally licensed copies of Microsoft Excel and JMP Pro (Cary, NC, USA).

RESULTS

A total of 113 biopsy-proven malignant umbilical nodules were included in the final analysis. Basic demographics are shown in Table 1. The average age at presentation was 64 years (range 21-95 years), and the majority of patients were white females. In total, 61.1% of the patients did not have an established history of cancer at the time of SMJN identification.

The majority of patients had a primary gastrointestinal malignancy (47.8%) followed by gynecologic malignancy (35.4%). The ovaries were the most common source of malignancy originating from a single

organ, and 18.6% of all SMJN patients had ovarian cancer. Details of the underlying malignancies in our study population are shown in Table 2. Of the 40 males in the cohort, 77.5% (31/40) presented with a primary GI malignancy. Of these, 10 were pancreatic cancers and 9 were colorectal cancers. Only 8.8% of SMJNs were attributed to gastric cancer; historically, this was believed to be the most common malignancy associated with SMJNs. Of the 73 females in the cohort, 40 (54.8%) presented with a gynecologic malignancy, of which 21 (28.8%) were due to ovarian cancer. Lung, renal, and soft-tissue malignancies were infrequently associated with umbilical nodules.

Clinical follow-up of these patients ranged from 0.4 months to 231.5 months. Overall, median survival was 14.6 months (IQR 5.2-30.0 months). For patients initially presenting with a SMJN, median survival was 10.2 months (IQR 5.6-32.2 months). For patients not initially presenting with a SMJN, median survival from cancer presentation was 92.3 months (IQR 50.0-180.8 months). In this population, median survival at the appearance of a SMJN was 15.4 months (IQR 4.0-25.2 months), with a median of 27.8 months (IQR 11.4-41.7 months) from initial cancer diagnosis to presentation of a SMJN (mean 37.0 months). Of patients with at least 2 and 5 years of clinical follow-up, 2-year mortality was 88.4% (61/69), and 5-year mortality was 95.4% (83/87), respectively.

In patients presenting initially with a SMJN, gynecologic cancers were associated with longer average survival times as compared to primary GI malignancies (35.7 months vs 15.7 months; $p = 0.02$) (Figure 1). Regardless of primary cancer site, treatment with both chemotherapy and surgery (average survival, 42.7 months) was associated with improved survival compared to treatment with chemotherapy alone (average survival, 19.1 months) or no treatment (average survival, 4.0 months; $p < 0.01$) (Figure 2).

DISCUSSION

In this retrospective study, we present findings from a large cohort of patients who presented with a Sister Mary Joseph Nodule. While the majority of these patients had a primary malignancy arising from the GI tract, the ovary is the single most common organ leading to umbilical metastatic disease. Our study shows that survival in patients with SMJNs continues to remain dismal, with a median survival of just over 11 months for those presenting initially with a SMJN. However, gynecologic malignancies were associated with a better survival as compared to their gastrointestinal counterparts. Furthermore, the receipt of combination chemotherapy and surgery is associated with better survival as compared to patients who received no treatment or chemotherapy alone.

Our results mirror the general prognoses of metastatic cancers, as stage IV ovarian, uterine, cervical, colorectal, esophageal, and gastric cancers all portend a rather dismal 5-year survival of less than 30% (Siegel, Miller, & Jemal, 2016). Our findings in this cohort did reveal better outcomes in patients with a SMJN compared to a Tanzanian population with SMJN, despite an older age in our study (Chalya, Mabula, Rambau, & McHembe, 2013). The difference in survival can be explained in part by the source of the primary malignancy. Chalya et al. reported over 40% of their patients had gastric cancer (Chalya et al., 2013), which differs significantly from the distribution of malignancies in our cohort. Metastatic gastric cancer, with its 4% rate of 5-year survival, carries a significantly worse prognosis compared to patients with metastatic colorectal (12%, 5-year survival) or epithelial ovarian cancers (17%, 5-year survival) ("Cancer Facts & Figures 2017 ", 2017), which were the leading malignancies in our cohort. This likely reflects the shifts in cancer incidence that has been noted over the last quarter century in the Western world (Torre, Siegel, Ward, & Jemal, 2016). Other possible causes for this observation include improved access to care in the West overall and specifically, our institution's status as a quaternary referral center with availability of state-of-the-art cancer treatment modalities. These findings also parallel trends with improved survival from cancers overall. Finally, a part of the difference may be also be explained by genetic and dietary influences resulting from the heterogeneity of the populations involved in these studies.

Similar to other reports in the literature, the majority of men in our study were found to have gastrointestinal malignancy, while women were more likely to be diagnosed with a gynecologic malignancy (Gabriele, Conte, Egidi, & Borghese, 2005; Schickler, Abdallah, McClung, & Shahzad, 2016). However, the finding of an unknown primary in our cohort was significantly lower than has been reported. In their review of 77 umbilical metastases, Papalas and Selim found that in up to 15% of cases, a primary cancer could not be found (Papalas & Selim, 2011). This difference is likely due to the improved availability of special stains that allow for a more accurate identification of the primary malignancy. In contrast to our study, they also demonstrated that men were more likely to have a primary genitourinary source of malignancy.

Our findings also indicate a significant improvement in survival associated with active treatment of the underlying malignancy. The combination of chemotherapy and surgery was associated with the greatest improvement in survival, with a mean survival of 42.7 months, which is greater than that reported previously in the literature (Barrow, 1966; Khan & Cook, 1997; Panaro et al., 2005). Case series and reports have suggested that the initiation of aggressive treatment, including surgery, radiation, and chemotherapy can increase survival to a mean of 21 months after lesion detection (Calongos, Ogino, Kinuta, Hori, & Mori, 2016; Iavazzo et al., 2012).

To our knowledge, this is the largest study of patients with SMJN. The strengths of our study include the use of a cohort constructed from an accurately maintained electronic and histopathological database with detailed, longitudinal follow-up. Only histologically confirmed cases of SMJN were included. This methodological rigor may have excluded patients with metastatic umbilical nodules which were never biopsied, but it allows a more strictly defined sample of patients with SMJN. One limitation of our study is the lack of a search methodology using International Classification of Diseases (ICD) which is commonly employed in large database studies. However, the lack of an ICD code for SMJN makes it challenging to use this approach. Moreover, starting with the ICD codes of most likely malignancies associated with SMJN would have introduced selection bias at the study outset. For this reason, a text-based search of the electronic medical record using appropriate keywords was performed. Also, a major limitation of code-based studies – even if an ICD code existed for SMJN – is the prevalence of coding errors, which are common. Alternatively, documentation of our broad search words in patient notes is unlikely to occur mistakenly at the same frequency as coding errors. Despite the detailed insight into malignancies leading to SMJN provided by our study, our results are only representative of a predominantly Caucasian population treated at a large tertiary referral center in the Midwestern United States. Therefore, these results may not be generalizable, especially to developing countries where malignancy frequency and distribution may be different. In addition, while our results may suggest an aggressive treatment approach for SMJN patients, it should be kept in mind that the prognosis for these patients is still expected to be dismal. Further, our study is unable to specifically shed light on the quality of life for patients who chose to undergo aggressive treatment. These considerations should be accounted for when having goals-of-care discussions with these patients to allow for more patient-centered care.

In conclusion, in this large, retrospective study from a quaternary referral center in the Midwestern United States, the majority of patients with histologically proven SMJNs have malignancies arising from the gastrointestinal or gynecologic tract. While SMJNs have historically been thought to arise from a gastric primary, our study shows that the ovaries in women and the colon in men are the most common sources of SMJN. Although survival outcomes mirror those of metastatic cancers, aggressive treatment with chemotherapy may offer a more favorable prognosis.

Corresponding Author: Seth Sweester, MD (Sweetser.Seth@mayo.edu)

Author Contributions: Dr. Codipilly is a resident in the department of Internal Medicine at the Mayo Clinic Rochester. He was instrumental in the collection and analysis of the data and writing of the manuscript. Dr. Jansson-Knodell is a resident in the department of Internal Medicine at the Mayo Clinic Rochester. She was instrumental in the collection and analysis of the data. Dr. Nagpal is a fellow in the department of Gastroenterology and Hepatology at the Mayo Clinic Rochester. He assisted in the conduct of the study and drafting of the manuscript. Dr. Sweetser is a gastroenterologist in the department of Gastroenterology and Hepatology at the Mayo Clinic Rochester. He was instrumental in the design and conduct of the study, the collection and analysis of the data, and writing of the manuscript. None of the authors have any financial disclosures and all approve the final manuscript for submission.

Conflict of Interests: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. The authors report no conflicts of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. All authors approved the final manuscript for submission.

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Table 1. Basic Demographics

Average age at diagnosis, years (range)	64 (21-95)
Male	35.4%
Caucasian	88.5%
Known prior cancer	38.9%
Average time in months from initial diagnosis to presentation of SMJN (range)[a]	41.2 (3.1-323.8)

[a]In patients already known to have prior history of cancer

Table 2. Distribution of primary malignancy

Primary tumor sites	Females N (%)	Males N (%)	N (%)	Mean (±S.D.) age of SMJN presentation (years)
Gastrointestinal	**23**	**31**	**54 (47.8)**	**63.4 (±14.5)**
Colorectal	8 (34.8)	9 (29.0)	17 (15.0)	
Pancreas	3 (13.0)	10 (32.3)	13 (11.5)	
Gastric	6 (26.1)	4 (12.9)	10 (8.8)	
Gallbladder/Cholangiocarcinoma	4 (17.4)	3 (9.7)	7 (6.2)	
Appendix	2 (8.7)	3 (9.7)	5 (4.4)	
Pancreaticobiliary	1 (4.3)	-	1 (0.9)	
Duodenal	-	1 (3.2)	1 (0.9)	
Gynecologic			**40 (35.4)**	**63.9 (±15.0)**
Ovary			21 (18.6)	
Endometrial			7 (6.2)	
Fallopian Tube			4 (3.5)	
Primary peritoneal			3 (2.7)	
Mullerian			2 (1.8)	
Uterine leiomyosarcoma			1 (0.9)	
Breast			1 (0.9)	
Cervical			1 (0.9)	
Hematologic	**2**	**3**	**5 (4.4)**	**60.8 (±10.9)**
Non-Hodgkin's lymphoma	2 (100)	2 (66.7)	4 (3.5)	
Plasma cell neoplasm with anaplastic features	-	1 (33.3)	1 (0.9)	
Other	**8**	**6**	**14 (12.3)**	**65.5 (±14.6)**
Neuroendocrine	2 (25)	1 (16.7)	3 (2.7)	
Mesothelioma	1 (12.5)	1 (16.7)	2 (1.8)	
Lung	1 (12.5)	1 (16.7)	2 (1.8)	
Renal	-	1 (16.7)	1 (0.9)	
Carcinoid	1 (12.5)	-	1 (0.9)	
Prostate	-	1 (16.7)	1 (0.9)	
Angiosarcoma	1 (12.5)	-	1 (0.9)	
Melanoma	-	1 (16.7	1 (0.9)	
Nasal Sinus	1 (12.5)	-	1 (0.9)	
Unknown	1 (12.5)	-	1 (0.9)	
			Total = 113	$p = 0.93$

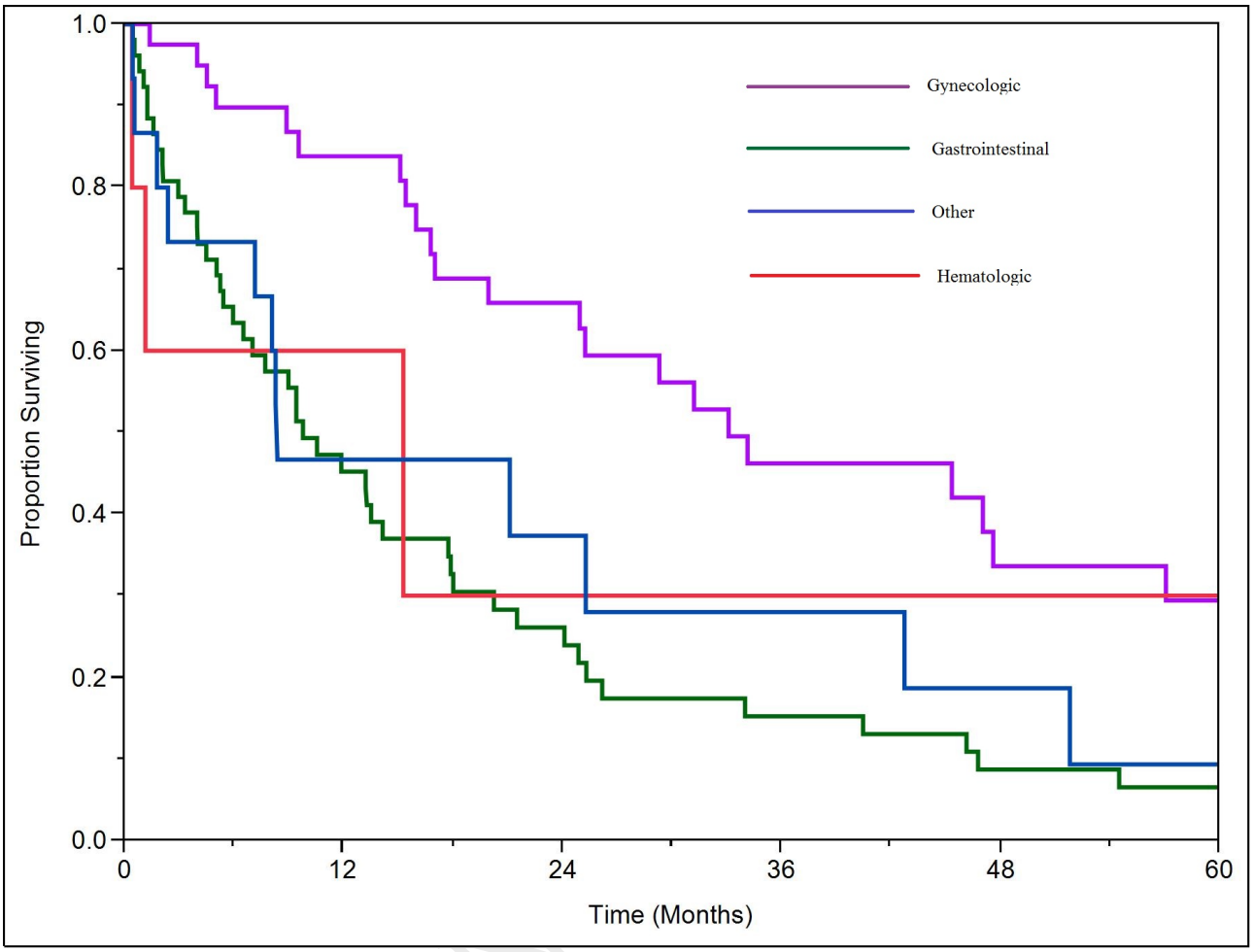

Figure 1. Survival Curve by Primary Site of SMJN (Wilcoxon rank sum $p < 0.001$)

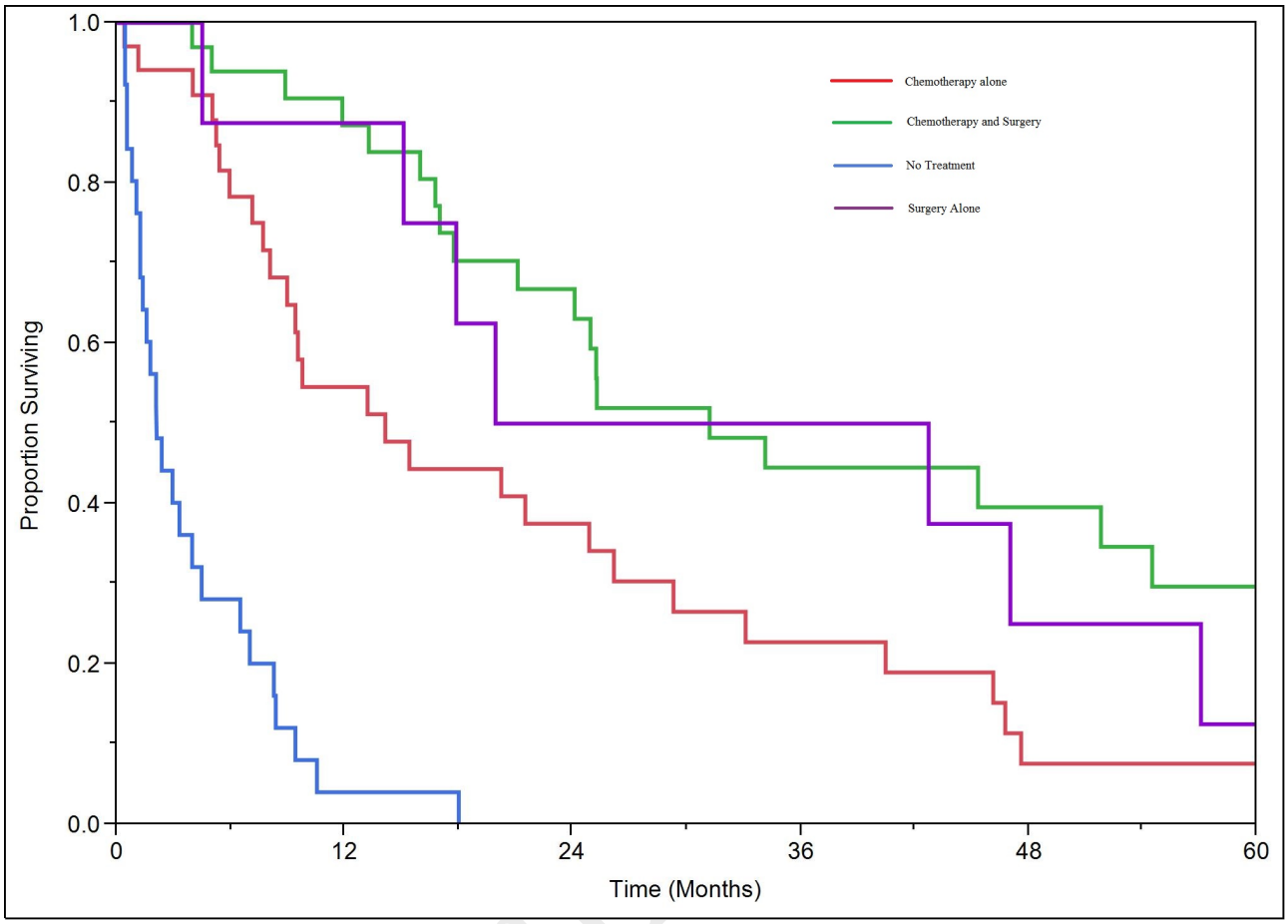

Figure 2. Survival Curve by Treatment Modality (Wilcoxon rank sum $p < 0.001$)