Incidental Gastric Signet Ring Cell Carcinoma: A Call for an Aggressive Approach

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ABSTRACT **Background:** Signet ring cell carcinoma (SRCC) is classified as an undifferentiated gastric carcinoma with poor prognosis. Early SRCCs are associated with improved prognosis.
Objectives: To describe the outcomes of incidental SRCC.
Methods: In this case series, 900 medical charts of patients with SRCC were screened to identify patients with incidental SRCC, defined as diagnosed in random, non-focal-lesion-targeted biopsies.
Results: Six patients were diagnosed with incidental SRCC and underwent gastrectomy. The final pathology of five patients revealed one or more small foci of early SRCC without lymphovascular invasion. Only one patient had no evidence of malignancy. The median follow-up after surgery was 4.2 years (50 months, range 37–90 months). No deaths or recurrences were recorded during the follow-up period. These results resemble the reported survival rate for early SRCC.
Conclusions: An aggressive surgical approach in incidental gastric SRCC patients is recommended, as they have a chance for long-term survival.

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Gastric signet ring cell carcinoma (SRCC) is classified as poorly differentiated adenocarcinoma, diffuse type, and poorly cohesive by the Japanese Gastric Cancer Association [1], Laurén classification [2], and the World Health Organization (WHO) classification [3]. Several studies have reported that advanced SRCC has a poor prognosis compared with other types of gastric cancer with increased lymph node involvement and peritoneal seeding [4,5]. Therefore, total or subtotal gastrectomy is generally the treatment of choice.

Nevertheless, early SRCCs have a significantly improved prognosis compared with more invasive T stages of SRCC. Several studies demonstrated a better overall survival compared with early non-SRCC gastric tumors [6-11].

To the best of our knowledge, no studies to date have described the recommended management or outcomes of incidental SRCC identified in random non-targeted biopsies only. The aim of this study was to describe our experience with a small series of patients with incidental SRCC.

PATIENTS AND METHODS

In a descriptive study approved by the institutional review committee, 900 medical charts of patients with SRCC at Hadassah Medical Center and Rambam Health Care Campus in Israel, during the years 1995–2018, were screened to identify patients with incidental SRCC. Incidental SRCC was defined as diagnosed only in random, non-targeted, biopsies, and no focal lesion identified by high-definition endoscopy and imaging studies. The pathology reports of these six patients included the words *random biopsies*. The biopsies were taken by endoscopic biopsy mapping that included a minimum of eight non-targeted biopsies from non-focal lesions, two from each of the following sites of the stomach: antrum, lesser curvature, greater curvature, and the incisura. The WHO classification for histologic typing of gastric tumors was followed. SRCC was defined as an adenocarcinoma in which a predominant component (more than 50% of the tumor) is made up of isolated or small groups of malignant signet ring cells containing intracytoplasmic mucin [12]. Cytokeratin AE1/3 immunostaining was used when there were only a few signet ring cells in the specimen to confirm the diagnosis of SRCC. All endoscopic pathology slides were revised for the purpose of this study by one or more pathologists in each center and SRCC was confirmed according to recent WHO guidelines.

Preoperative evaluation of all six patients included blood count to assess for anemia or thrombocytopenia that needed to be treated before surgery. Moreover, all six patients underwent chest, abdominal, and pelvic computed tomography (CT) scans to evaluate for metastasis. An endoscopic ultrasound was performed in one patient following CT scan to exclude submucosal invasion. A 18F-fluorodeoxyglucose positron-emission tomog-

raphy/computed tomography (PET/CT) scan was performed in two patients following CT scan to exclude distant metastasis.

Patient follow-up lasted until the end date of 30 January 2022.

RESULTS

DEMOGRAPHICS AND PRE-SURGERY FINDINGS

During the years 1995–2018, 2300 patients were diagnosed with an endoscopic biopsy of gastric carcinoma at Hadassah and Rambam tertiary medical centers in Israel. Of those, 900 patients were confirmed with SRCC.

Of the entire cohort, we describe six patients who were diagnosed with incidental SRCC. Five patients (83%) were male, and the mean age at diagnosis was 60 years (range 43–77). Epigastric pain was present in five patients (83%), and dyspepsia was present in three patients (50%). Other presenting symptoms included nausea, vomiting, anorexia, melena, and anemia. No suspicious focal gastric lesions or lymphovascular involvement were demonstrated on imaging tests. Demographics and preoperative findings of the patients are described in Table 1.

ENDOSCOPY FINDINGS

High-definition endoscopy revealed one of the following diffuse macroscopic findings: mild gastritis, atrophic gastritis, mucosal erosion, or thickening of mucosal folds. SRCC was identified in one single random biopsy. Three patients underwent repeated endoscopies to confirm the diagnosis before the final decision of surgical intervention. Two of these patients with repeated endoscopic biopsies showed no evidence of malignancy. Endoscopy findings are described in detail in Table 2.

PATHOLOGY FINDINGS AND FOLLOW-UP AFTER SURGERY

All six patients underwent gastric resection (three total gastrectomy and three subtotal gastrectomy). Pathology slides of these patients were reviewed. The pathology results are described in Table 2. Classification was conducted according to the WHO [12]. The final pathology after gastrectomy of five patients (83%) revealed one or more small foci of early SRCC stage T1 (limited to the mucosa [T1a] or the submucosa [T1b] without lymphovascular invasion or surgical margins involvement). The sixth patient had no evidence of malignancy in the final surgical specimen; hence, the endoscopic biopsy of this patient was revised and the endoscopic diagnosis of SRCC was confirmed. Postoperative biopsies were free of SRCC, probably due to section sampling error. To rule out patient-sample mismatch, we compared genetic testing from the biopsies and each patient's blood test to determine compatibility.

Post-surgery clinical charts of all six patients were revised. All six patients visited the surgery clinic for follow-up 3 to 6 months after surgery and then approximately every year after the first visit. Follow-up methods included history and physical examination and CT scans of the chest, abdomen, and pelvis, with no evidence of local recurrence or lymphovascular involvement. Of note, the follow-up did not include esophagogastroduodenoscopy.

Pathology findings and follow-up after surgery are described in detail in Table 3. All six patients had no evidence of disease during the last follow-up CT scan (i.e., the cutoff date of 30 January 2022).

Patient 3 was followed during 1995–2000 for 5 years after

Table 1. Demographics and pre-surgery findings

Patient number	Age, in years	Sex	Medical history	Presenting symptoms	Blood tests prior to surgery	Types of imaging*
1	53	Male	Depression and obstructive sleep apnea	Low levels of vitamin B12 in a routine blood test	Normal blood count	CT scan of the chest, abdomen, and pelvis EUS
2	77	Male	–	Epigastric pain and melena	Normal blood count	CT scan of the chest, abdomen, and pelvis
3	68	Male	–	Epigastric pain and anorexia	Normal blood count	CT scan of the chest, abdomen, and pelvis
4	64	Female	BRCA1 positive breast cancer after bilateral mastectomy and preventive hysterectomy with salpingo-oophorectomy	Epigastric pain, dyspepsia, and anemia	Anemia of 10.4 gr/dl hemoglobin	CT scan of the chest, abdomen, and pelvis PET/CT scan of the chest, abdomen, and pelvis
5	43	Male	–	Epigastric pain and dyspepsia	Normal blood count	CT scan of the chest, abdomen, and pelvis
6	54	Male	Crohn's disease treated by ileocecal resection	Epigastric pain, dyspepsia, nausea, and vomiting	Normal blood count	CT scan of the chest, abdomen, and pelvis PET/CT scan of the chest, abdomen, and pelvis

*No suspicious focal gastric lesions or lymphatic involvement were demonstrated by imaging

CT = computed tomography, EUS = endoscopic ultrasound, GI = gastrointestinal, PET/CT = ^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography

Table 2. Endoscopy findings

Patient number	Endoscopy macroscopic findings	Biopsy results
1	2 endoscopies from 2 different clinics showed diffuse severe atrophic gastritis	Endoscopy 1: One mucosal fragment from the antrum was infiltrated by intramucosal SRCC Endoscopy 2: few antral foci infiltrated by poorly differentiated SRCC (cytokeratin positive) in the background of severe chronic active gastritis and intestinal metaplasia
2	Mild gastritis of the body	Foci of high-grade dysplasia with intestinal metaplasia and infiltrates of SRCC
3	Diffuse thickening of mucosal folds	One mucosal fragment from the greater curvature was infiltrated by SRCC
4	3 endoscopies revealed few mild mucosal erosions of the antrum	Endoscopy 1: tiny focus of intramucosal SRCC Endoscopy 2: diffuse gastritis Endoscopy 3: reactive antral gastropathy
5	Diffuse severe mucosal erosion of the antrum	Moderately differentiated SRCC in the background of severe chronic active gastritis
6	2 endoscopies revealed diffuse mild chronic gastritis of the body and antrum	Endoscopy 1: One mucosal fragment from the body was infiltrated by SRCC (positive immunostaining AE1/AE3). Diffuse oxynthic cell pseudo hypertrophy (suspected PPI-related) was noted in the background Endoscopy 2: negative for malignancy of any kind

PPI = proton-pump inhibitor, SRCC= signet ring cell carcinoma

Table 3. Pathology findings and follow-up after surgery

Patient number	Type of surgery	Timing of surgery (months from endoscopy)	Final pathology	Lymph node involvement	Follow-up* (months)
1	Subtotal gastrectomy	4	Prepyloric region showed intestinal metaplasia with area of early gastric cancer, well to poorly differentiated adenocarcinoma with areas of diffusely infiltrating SRCC poorly differentiated mucosal SRCC	0 of 18	90
2	Subtotal gastrectomy	1	Diffuse gastritis and intestinal metaplasia. antral region showed areas of early gastric cancer, poorly differentiated SRCC restricted to the mucosa	0 of 6	50
3	Total gastrectomy	1	Diffuse acute and chronic gastritis. Small focus of early gastric cancer, SRCC limited to the submucosa, was found in the greater curvature region	0 of 14	60
4	Total gastrectomy	1	Small foci of SRCC, limited to the submucosa, were found in the antral region	0 of 22	48
5	Total gastrectomy	1	Foci of poorly differentiated SRCC, limited to the mucosa, were found in the antral region	0 of 20	50
6	Subtotal gastrectomy	4	Significant pseudo hypertrophy of oxyntic cells. Foveolar hyperplasia, mild inflammation, and reactive glandular atypia. No evidence of malignancy. No metaplasia or dysplasia. 40 tissue sections were examined	0 of 4	37

*Follow-up in months after surgery. During the follow-up period, no deaths or recurrences were documented. Computed tomography scan of the chest, abdomen, and pelvis was performed at 3 months after surgery and every year after

SRCC = signet ring cell carcinoma

surgery. He died 10 years after surgery, at the age of 78 years. There are no available records in our system to the cause of death. Follow-up CT scans performed during the years 1995–2000 demonstrated no evidence of disease.

DISCUSSION

Incidental gastric SRCC is a rare finding and to date has rarely been reported in the English literature. Our limited cohort of patients shows the importance of random biopsies during routine endoscopies as incidental SRCC may be diagnosed in patients with no macroscopic evidence of disease. These pathological findings should not be overlooked as early gastrectomy in these patients may be the only chance for a cure. To the best of our knowledge, no studies to date have discussed the recommended management or outcomes of incidental SRCC identified only on random biopsies.

Bamboat et al. [6] analyzed the oncological outcomes of patients with gastric adenocarcinoma stratified by stage and histology. In that study the reported 5- and 10-year cancer specific death

rates for early SRCC were 0 and 4%, respectively. We presented a case series of six patients with incidental finding of SRCC without any evidence of macroscopic disease. Our survival analysis showed 0% cancer specific death among this small cohort of patients during a median follow-up of 50 months, results like those reported by Bamboat and colleagues [6].

Our study has several limitations including a small sample size, its retrospective nature, and the lack of standardized preoperative or surveillance evaluation strategy. For example, only three of six patients in this study went through more than one endoscopy to confirm the diagnosis of SRCC prior to operative decision.

According to guidelines from the National Comprehensive Cancer Network (NCCN) [13] and the European Society for Medical Oncology (ESMO) [14], all patients with suspected or histologically confirmed gastric cancer should undergo a CT scan of the chest, abdomen, and pelvis. EUS or PET/CT are not mandatory according to the current guidelines. Based on our limited experience, patients with an incidental finding of SRCC should undergo a second endoscopy with high-definition endoscope using chromoendoscopy, magnification and narrow band imaging. A thorough mapping of the stomach should be performed with numerous biopsies.

Surveillance in these patients is somewhat controversial. In patients presenting with carcinoma in situ undergoing subtotal gastrectomy surveillance, endoscopy is recommended every 3 to 6 months for the first 2 years and a yearly endoscopy in the next 3–5 years. Surveillance endoscopy is not necessary for patients following total gastrectomy, regardless of stage [14].

CONCLUSIONS

We presented a cohort of six patients (from an entire cohort of 900 patients) who were diagnosed with incidental SRCC by random endoscopic biopsies from the stomach, without focal endoscopic and radiologic findings. Early gastrectomy is a treatment option for incidental SRCC as it is associated with excellent survival.

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I believe the greatest gift I can conceive of having from anyone is to be seen, heard, understood, and touched by them. The greatest gift I can give is to see, hear, understand, and touch another person.

Virginia Satir (1916–1988), American author and psychotherapist, recognized for her approach to family therapy

Since when do we have to agree with people to defend them from injustice?

Lillian Hellman (1905–1984), American playwright, prose writer, memoirist, and screenwriter