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Krukenberg Tumors: Can Management Be Improved?[1]

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Abstract
Objective: The Montefiore Medical Center experience with women with gastrointestinal (GI) cancer was reviewed to: (1) evaluate clinical parameters in patients with Krukenberg tumor (GI cancer metastatic to the ovaries) and (2) evaluate oophorectomy in GI cancer patients. ***Methods:*** (1) Charts of all female patients admitted between 1985 and 1996 with gastric or colon cancer were reviewed. ***Results:*** The frequency of Krukenberg tumor was 7/1,021 (0.7%). The median age at presentation was 39.5 years (range 35–80); 5 were premenopausal, 2 of whom were postpartum. Krukenberg tumor was significantly more common in the premenopausal patients with gastric cancer ($p = 0.002$), colon cancer ($p = 0.001$), and in both sites combined ($p < 0.001$). Our rate of pregnancy-associated Krukenberg tumors (28.6%) was significantly higher ($p < 0.05$) than that found in 4 of 5 large studies. The average survival of our 7 patients was 12.3 months (range 4 days to 26 months), with secondary debulking and chemotherapy offering 1 patient the longest longevity. Only 19/788 (2.4%) women had oophorectomy during their colon cancer surgery revealing 2 (10.5%) Krukenberg tumors, 6 (31.6%) benign solid or cystic ovarian tumors, and 11 (57.9%) normal or atrophic ovaries. ***Conclusions:*** Krukenberg tumors are rare. There is no uniformity of data reported in the literature. Krukenberg tumors were more common in premenopausal women with gastric or colon cancer compared to postmenopausal women. Our rate of pregnancy-associated Krukenberg tumors appeared to be higher compared to other studies. Prophylactic oophorectomy in pre- and postmenopausal women should be considered at the time of GI cancer surgery, and requires further study. A national registry combined with prospective, multisite studies are needed to gather data and evaluate treatment.

Introduction

Krukenberg tumors have been traditionally defined as gastrointestinal (GI) malignancies metastatic to the ovary [1–8]; however, some authors have included other types of tumors metastatic to the ovary (e.g., breast, endometri-

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al, thyroid, bronchi, kidney, and melanoma) [9–12]. Review of the literature on Krukenberg tumors revealed inconsistent data. Many of the earlier papers described pathology and commented briefly, if at all, on prognosis [9, 13–16]. Later papers addressed more clinical features of Krukenberg tumors [1–7, 10–12]. Some were case reports of a few patients [4–8, 17], others were larger series covering many years because of the low incidence of Krukenberg tumors [1–3, 9–12, 15, 16]. The lack of uniformity of information made it difficult to compare data to evaluate factors that could improve the usual poor prognosis.

The lack of consensus about treatment as well as the relatively long survival of one of our patients with a good quality of life led us to review this medical center's last 11 year experience with Krukenberg tumors. Our focus was to (1) examine demographic and clinical features, (2) identify any relationship of the functional status of the ovaries on metastases, and (3) report observed trends of effects of therapeutic approaches.

Materials and Methods

A computerized medical record review of all women admitted to Montefiore Medical Center (MMC) with a diagnosis of gastric or colon cancer between January 1985 and April 1996 was performed to establish the frequency of Krukenberg tumor and to assess use of oophorectomy at the time of GI cancer surgery. In addition, a literature search (Index Medicus plus MEDLINE) was undertaken to evaluate the historical experience.

Fisher's exact test was used to compare differences by menopausal status and recent pregnancy. Menopausal status was assigned if the last menstrual period was over 1 year prior, or if the patient was over age 50 when menstrual data were not available.

Results

Review of 1,021 charts of women with GI carcinoma followed by the Gynecology, Surgery and Medical Oncology services of MMC revealed 233 gastric and 788 colon primaries. Among these, 7 (0.7%) had Krukenberg tumors: 2 (0.9%) were gastric and 5 (0.6%) were colon primary. One patient has been reported previously [17].

Among the 233 gastric primary patients, only 11 were premenopausal, with 2 (18.2%) having Krukenberg tumors. None of the 222 postmenopausal women with gastric cancer had ovarian metastases ($p = 0.002$). Among the 788 colon primary patients, 41 were premenopausal, with 3 (7.3%) having Krukenberg tumors. Only 2 (0.3%) of 747 postmenopausal women with colon cancer had ovarian metastases ($p = 0.001$). The association of ovarian metastases with premenopausal status holds also for gastric and colon cancer patients combined ($p < 0.001$) (table 1).

Table 1. GI cancer type and menopausal status of MMC/NCB patients with Krukenberg tumors, 1985–1996

Type of cancer	Premenopausal (<50 years)		Postmenopausal (≥50 years)		p[1]
	n	%	n	%	
Gastric	2/11	18.2	0/222	–	0.002
Colon	3/41	7.3	2/747	0.3	0.001
All cancers	5/52	9.6	2/969	0.2	<0.001

[1] Fisher's exact test.

Selected clinical data on the patients with Krukenberg tumors are shown in table 2. The median age at presentation was 39.5 years (range 35–80). Five patients had ovarian metastases removed at first laparotomy. Four had adjuvant chemotherapy, and 1 had radiation therapy. One patient with ovarian metastases had extensive metastatic pelvic disease with malignant signet cells on both gastric and cervical biopsies and peritoneal cytology and was treated with chemotherapy alone. Excluding 1 patient who expired 4 days after surgery from sepsis due to intestinal perforation, the average survival times were from 6 to 26 months, average 14.3 months. While this series is too small to analyze a benefit from specific treatment modalities, aggressive multimodal therapy appears to offer benefit. The one patient who had a secondary debulking survived the longest (26 months).

Of the 788 colon cancers, 19 (2.4%) had oophorectomy performed at the time of primary colon cancer surgery. Of these, 8 had obvious pathology: 2 had clinically apparent metastatic tumors and 6 had benign ovarian tumors (2 thecomas, 4 simple cysts). Only 11 had prophylactic bilateral oophorectomies and all of these revealed histopathologically normal or atrophic ovaries on pathology. No patient who had resection of gastric cancer had prophylactic or indicated oophorectomy.

Discussion

Worldwide, GI cancers are responsible for more cancer deaths than any other organ system [18]. When gastrointestinal cancers metastasize to the ovary, known today as

Table 2. Clinical data on MMC/NCB patients with Krukenberg tumors

Patient	Age	Diagnosis	Management/treatment	Survival, months
1	44	gastric cancer (linitis plastica) metastatic to cervic and ovaries	5-FU, Adriamycin, mitomycin	6
2	36	tuboovarian abscess, Krukenberg tumor. 3 weeks later: colon cancer (sigmoid) metastatic to ovary and uterus	L partial salpingectomy, RSO. 3 weeks later: low anterior resection; transverse colostomy; TAH/LSO; radiation	12
3	35	11 days PP (NSVD), colon cancer (cecal) 5 months PP: Metastases to ovaries and omentum 15 months PP: liver metastases on CT	11 days PP: R hemicolectomy, lymph node dissection; 5-FU, leukovorin, interferon 5 months PP: BSO, debulking; 5-FU, hydroxyurea, interferon 15 months PP: no further treatment	26
4	38	gastric cancer metastatic to ovaries	exploratory laparotomy, TAH/BSO; 5-FU combination chemotherapy	19
5	41	8 days PP (NSVD), colon cancer (cecal) metastatic to ovary; bowel perforation, sepsis	supracervical hysterectomy, BSO	4 days
6	71	colon cancer (splenic flexure) metastatic to ovary and liver	exploratory laparotomy, oophorectomy; 5-FU, platinum	7
7	80	colon cancer (sigmoid) metastatic to ovaries and liver	supracervical hysterectomy, BSO, sigmoid resection, liver biopsy	16

5-FU = 5-fluorouracil; L = left; R = right; SO = salpingo-oophorectomy; TAH = total abdominal hysterectomy; NSVD = normal spontaneous vaginal delivery; PP = postpartum; B = bilateral; CT = computed tomography.

Krukenberg tumors, survival is uniformly poor [1–4, 9, 11, 15, 16]. Metastatic ovarian tumors were initially described in 1896 by Krukenberg [13] who believed that these tumors had a connective tissue origin. Krukenberg's criteria required (a) presence of tumor in the ovary, (b) evidence of intracellular mucin secretion by the formation of signet cells, and (c) diffuse infiltration of the stroma giving a sarcoma-like picture. In 1902, Schlagenhaufer [14] correctly described Krukenberg tumors as being epithelial in origin and metastatic to the ovary, mostly from the GI tract.

Menopausal status was not routinely mentioned in the Krukenberg tumor literature; however, when reported, the tumors were noted to be more common in premenopausal patients [1, 3, 10, 11, 19]. In 1965, Israel et al. [10] reported on 33 patients with a variety of tumors metastatic to the ovary and 63 patients with primary ovarian cancer. They noted that patients who developed metastatic cancer in the ovary are 'more youthful' than those with primary ovarian cancer, and supported the belief that the functioning ovary was prone to metastatic disease. Hale [1] reported on 81 patients in Hawaii with Krukenberg tumors. The average age was 45; 60% were premenopausal. Similarly, Yakushiji et al. [19], in Japan, reported that 65% of his 112 patients, average age 45, were premenopausal. Our higher incidence of Krukenberg tumors in premenopausal women, 71% (table 1), is consistent with the literature. Whether the functioning ovary is a more attractive site for metastases to develop due to hormones or rich vascularity, and whether younger women develop more aggressive, higher stage disease requires further study.

Krukenberg tumor is rarely associated with pregnancy, however, 2 of 7 patients (28.6%) in our small series were postpartum. Taylor et al. [3], Hale [1], Yakushiji et al. [19], and Diddle [20] reported that 2.0, 2.5, 2.7, and 3.9%, respectively, of their patients with Krukenberg tumors were pregnant, postpartum or had a recent pregnancy loss (table 3). The highest rate of pregnancy-associated Krukenberg tumors previously reported in the literature was 6.3% from a 17-year study (1943–1960) by Woodruff and Novak [21]. By Fisher's exact test, our rate was significantly higher than that found in all but the last of these studies. This may be due to our small sample size, suggesting that studies are needed in larger cancer centers.

Table 3. Pregnancy-associated Krukenberg tumors in present study compared to five large studies

Study	Site	Duration years	Pregnancy-associated		
			n[1]	%	p[2]
Present study, 1998	Bronx	11 (1985–1996)	2/7	28.6	
Taylor et al. [3], 1995	England	3.6 (9/89–5/93)	1/51	2.0	<0.05
Yakushiji et al. [19], 1987	Japan	20 (1965–1985)	3/112	2.7	<0.05
Hale [1], 1968	Honolulu	20 (1945–1965)	2/81	2.5	<0.05
Woodruff and Novak [21], 1960	Baltimore	17 (1943–1960)	3/48	6.3	NS
Diddle [20][3], 1955	Tennessee	28 (1927–1955)	26/664	3.9	<0.05

NS = Not significant.
1 Pregnancy-associated Krukenberg patients/all Krukenberg patients.
2 Fisher exact test.
3 9 patients of own plus literature review of previous 28 years.

Survival ranges of 6 weeks to 9 years have been reported [8, 10, 15] with average survivals of 7–17 months [1, 4]. In 1938, Novak and Gray [15] reviewed 21 cases over a 25-year period and concluded that the prognosis is 'practically hopeless'. However, in reviewing long-term survival, Webb et al. [11], in 1975, reported on a large series of tumors metastatic to the ovary; 9 (5.4%) of 169 GI cancer patients achieved a 5-year survival, 6 of whom survived at least 10 years. They stated that 'the situation is therefore not hopeless and demands aggressive therapy'. The mean survival of 8 Krukenberg tumor patients reported by Gilliland and Gill [4] in 1992 was 20.3 months (range 1–60+ months), 2 of whom lived at least 5 years after diagnosis. Miller et al. [8] reviewed the charts of 23 colon cancer patients with metastasis to the ovary at initial diagnosis and reported a median survival time of 17.8 months (range 1–86 months); one patient survived for longer than 5 years without evidence of recurrent disease.

In the past, secondary debulking generally had not been performed because the prognosis of bulky, recurrent or advanced disease has been so poor. With advances in chemotherapy and surgical modalities, survival times have lengthened, and secondary debulking is now considered for some patients with good performance status. Morrow and Enker [2] reported on 63 colorectal cancer patients who had late ovarian metastases occurring an average of 17.5 months after primary colon surgery, and who underwent aggressive surgery including pelvic exenteration and hepatic lobectomy. The mean survival was 16.6 months. The single most important discriminant of survival was whether or not the patient could be rendered free of disease surgically. The patients in whom this was possible survived a mean of 48 months compared to 8 months for the patients who had residual disease. They concluded that, although many patients do not show a survival benefit in the presence of gross ovarian metastases, significant palliation is achieved by removal of large tumor masses, and long-term survivors occasionally are found. Despite the fact that only 1 patient survived 5 years in a recent report by Miller et al. [8], they stated that 'in selected patients who can be rendered disease-free by surgery, prolonged survival is possible and an aggressive approach is recommended'. Although our patient who had a secondary debulking had the longest survival (26 months), our series was too small to show statistical significance.

Taylor et al. [3] reported on a large series which specifically addressed the value of chemotherapy for treating patients with Krukenberg tumors. They treated 51 patients with a 5-fluorouracil (5-FU) regimen for colorectal patients or cisplatin and 5-FU for esophagogastric, pancreatic or unknown primaries. The median survival was 9 months in nonresponders and 20 months in responders. They suggested that ovarian metastases from primary colorectal cancer are relatively resistant to chemotherapy. However, secondary debulking and chemotherapy (5-FU and Leucovorin followed by interferon and hydroxyurea) appeared to impact on survival in our postpartum patient (No. 3) with cecal carcinoma who survived 26 months from diagnosis, 21 months from secondary debulking. The benefits of secondary debulking and chemotherapy need to be addressed in a large prospective study.

Eleven of our postmenopausal patients had prophylactic oophorectomy at the time of their primary surgery for colon cancer. In 1951, Burt [22] stated that 'there has been

no uniformity in the operative procedures used in dealing with the problem of cancer of the ovaries secondary to cancer of the large bowel'. Although he suggested prophylactic oophorectomy in women over age 40, there is still controversy. Woodruff and Novak [20] concluded that although many years may elapse between the removal of the primary tumor and the appearance of the ovarian lesion, it would seem worthwhile to consider removal of the pelvic organs in women over 40 years with a malignancy.

Morrow and Enker [2] recommended bilateral oophorectomy in curative cases as well as palliative resections as 27% of patients in their series required a second operation to remove huge ovarian metastases. Taylor et al. [3], however, did not find a survival benefit in prophylactic oophorectomy. Abu-Rustum et al. [23] found that women with a history of colorectal cancer who underwent adnexectomy for a new pelvic mass had metastatic colon cancer to the ovary in 57%, benign ovarian neoplasm in 26%, and primary ovarian cancer in 17% of cases; theoretically, for the latter group, prophylactic oophorectomy might prevent the development of a new ovarian cancer. In our series, 9.6% of premenopausal women versus 0.2% of postmenopausal women had Krukenberg tumors ($p < 0.001$). Since premenopausal women with GI cancer are at increased risk of developing Krukenberg tumors and, according to Webb et al. [11], the premenopausal women have a significantly lower 5-year survival rate, it appears that prophylactic oophorectomy should be prospectively studied in premenopausal women undergoing primary surgery for GI cancer.

Our review brings up several points for further study on whether management can be improved. Since the clinical and pathologic details in the literature on patients with Krukenberg tumors vary widely, it is extremely difficult to compare studies. Uniformity in data collection is vital if we are to improve treatment modalities. Prospective multisite studies are needed to assess the risks, benefits, and impact on survival or an aggressive initial surgical approach, secondary debulking, and chemotherapy in patients with Krukenberg tumor, and the role of prophylactic oophorectomy in both pre- and postmenopausal women with primary GI cancer. In addition, because Krukenberg tumor is rare, it is important to establish a national registry to collect uniform information which can be analyzed to evaluate treatment and survival.

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