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Krukenberg Tumors from Gastrointestinal Cancer: Molecular Feature, Treatment, and Outcomes: A Case Series

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Abstract

Introduction: Ovarian metastases from gastrointestinal cancers (Krukenberg tumors) are rare, accounting for 1–2% of all ovarian malignancies. Despite their low incidence, they pose substantial diagnostic and therapeutic challenges. This study evaluates the clinicopathologic features, molecular profile, treatment strategies, and outcomes of patients with Krukenberg tumors. ***Methods:*** Between January 2023 and December 2024, we analyzed 12 ladies diagnosed with Krukenberg tumors of gastrointestinal origin. demographics, tumor characteristics, molecular markers, treatment modalities, and survival outcomes reviewed. Progression-free survival (PFS) and overall survival (OS) were calculated across treatment lines. Our ethical committee approved this study. ***Results:*** Primary tumors were colorectal (n=7) and gastric (n=5). Median age was 43 years; five patients were premenopausal. Six had synchronous and six had metachronous ovarian metastases. All tumors were pMMR with low TMB; KRAS mutations were present in 50% of cases, HER2 positivity was observed in one case, and BRAF was wild type in all. Four patients underwent ovarian metastasectomy. Median PFS1, PFS2, and PFS3 were 4.56, 2.13, and 3.3 months, respectively. At two years, 45.5% were alive, 75% of those who had metastasectomy. ***Conclusion:*** Krukenberg tumors often affect younger women and exhibit poor response to treatment. Ovarian metastasectomy may improve survival when metastases are isolated. Further research into their immune microenvironment is warranted.

Keywords: ***ovary, metastasis, Krukenberg tumor, molecular profile, survival.***

Introduction

Gastrointestinal (GI) cancers, among the most common cancers worldwide, rarely metastasize to the ovaries. Ovarian metastases from GI cancers, known as Krukenberg tumors (KT), account for 1-2% of all ovarian cancers [1]. KT have a poor prognosis, with median survival times for colorectal Krukenberg tumors ranging from 19 to 29 months [2-4]. To our knowledge, this is the first study addressing the molecular features of KT. There are a few studies about KT, most of them case reports. This study analyzes the clinicopathologic characteristics, molecular profile, treatment modalities, and outcomes of patients with KT tumors. This study seeks to enhance KT's understanding, diagnosis, and molecular profiling to improve patient prognosis, treatment, and quality of life.

Method

We retrospectively analyzed the demographic characteristics, molecular profile, treatment modalities, and outcome of 12 patients diagnosed with KT of GI cancer origin. These patients underwent treatment and follow-up between January 2023 and December 2024 at SQCCCRC-UMC in Oman. This study was approved by our Institutional Review Board and Ethics Committee

Results

Twelve patients with histopathologically confirmed KT tumors were included in the study. The primary cancer was colorectal in seven patients and gastric in five patients. The cohort included five premenopausal and seven postmenopausal patients, with a median age of 43 years (range: 34-79 years). At diagnosis, three patients were at stage III and nine at stage IV. All patients had good performance status at diagnosis. Six patients had synchronous tumors, while six had metachronous tumors. Symptoms at diagnosis included pain, GI symptoms, intestinal obstruction, and weight loss. The majority of cases were poorly differentiated adenocarcinomas. Molecular profiling revealed that all patients were pMMR, HER2 was positive in one patient, KRAS was mutant in six patients and wild type in six patients, BRAF was wild type in all patients, and TMB was low in all patients. Other metastatic sites included the liver and peritoneum. Ovarian metastasectomy was performed in four patients, and eight patients underwent surgery for the primary cancer. Eight patients received three lines of treatment. Six patients passed away, with a median time from ovarian metastasis to death of six months. Median PFS1, PFS2, and PFS3 were 4.56 months, 2.13 months, and 3.3 months, respectively. At the two-year follow-up, 45.5% of patients were still alive. Notably, 75% of patients who

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underwent metastasectomy were alive, compared to 28.6% of those who did not undergo the procedure.

Discussion

In this study, we retrospectively analyzed the demographic characteristics, molecular profile, treatment modalities, and outcome of 12 patients diagnosed with KT tumors of gastrointestinal (GI) cancers origin. The most common primary sites of KT are the stomach (70%) followed by colorectal, breast, and appendix cancers [5].

In our study, seven patients had colorectal cancer as the primary cancer, while five had gastric cancer. KT often remains asymptomatic until advanced stages and is more common in younger females [6]. This aligns with our findings, where the median age was 43 years, five patients were premenopausal, and most were diagnosed at advanced stages. Nonspecific symptoms characterize the onset, including abdominal pain, weight loss, and abdominal distention [7]. The presentation can be synchronous or metachronous. Synchronous tumors are Approximately 45.8% of cases, more common in gastric cancer compared to colorectal cases [8].

Metachronous Presentation can develop months or years after the primary tumor diagnosis and can sometimes be the first sign of malignancy with an unknown primary site.8 In our cases, 50% of cases were synchronous. KT Must be distinguished from primary ovarian tumors with signet-ring cell morphology. Primary mucinous ovarian tumors typically are usually unilateral and show complex papillary patterns. Immunohistochemistry helps differentiate between primary ovarian cancer and KT. Primary Ovarian Cancer Pattern Shows CK7+/CK20^{-} immunophenotype [9]. KT Tumor demonstrates either CK7^{-}/CK20+ or CK7+/CK20+ immunophenotype CK20 positivity particularly suggests gastrointestinal origin [7,10].

Radiologically, KT appears as complex masses with solid and cystic components. Tumors from the stomach tend to be predominantly solid, while those from the colon, rectum, appendix, or biliary tract often show mixed solid and cystic [11].

Regarding the molecular profile, the literature on this topic is minimal, suggesting the need for more extensive studies to validate these molecular patterns. Our study is the first study addressing the molecular feature of KT: KRAS mutations were found in approximately 50% of cases, with a balanced distribution between mutant and wild-type status. BRAF testing consistently indicated wild-type status across all examined patients. HER2 expression was low, with positivity observed in only one patient from the studied cohort. Furthermore, additional molecular testing revealed that all patients were proficient in mismatch repair (pMMR) and displayed a low tumor mutational burden (TMB).

Treatment of KT typically involves a multimodal approach. Surgical resection of ovarian metastases combined with systemic therapy shows survival benefits for colorectal origin, and surgical resection demonstrates significantly higher median survival (48.1 vs 30.6 months) and progression-free survival (22.2 vs 6.7 months) compared to medical management alone. Chemotherapy includes platinum-based agents (cisplatin/oxaliplatin) with 5-fluorouracil. Platinum-based therapy is preferred for disease recurring ≥6 months after prior treatment [12-14].

Cytoreductive surgery with HIPEC shows promise, particularly for cases with peritoneal involvement. However, HIPEC's benefit is less clear for isolated ovarian metastases without peritoneal disease [15,16]. In our study, four patients underwent ovarian metastasectomy, and eight patients underwent surgery for primary cancer. Eight patients received three lines of treatment.

Poor prognostic indicators include Peritoneal involvement, Synchronous presentation, Ascites, and elevated CEA [17]. Median survival of KT ranges from 7 to 14 months after diagnosis [17].

For colorectal origin, the median survival is 19-29 months. The 5-year survival rates are 9% for synchronous KT and 20% for metachronous KT. Surgical intervention for colorectal KTs significantly improves outcomes. Median survival with surgery is 48.1 months, compared to 30.6 months without surgery [18]. In our study, Median PFS1, PFS2, and PFS3 were 4.56 months, 2.13 months, and 3.3 months, respectively. At the two-year follow-up, 45.5% of patients were still alive. Notably, 75% of patients who underwent metastasectomy were alive, compared to 28.6% of those who did not undergo the procedure.

Conclusion

Krukenberg tumors present challenges in differentiation from primary ovarian cancers; early and accurate radiologic diagnosis, combined with molecular profiling, can guide surgical resection and chemotherapy decisions with varied survival outcomes depending on factors like primary tumor origin and peritoneal involvement, though data is limited, our findings inform treatment strategies and highlight the need for validation studies.

Abbreviations

GI: Gastrointestinal

PFS: Progression-Free Survival

OS: Overall Survival

pMMR: Proficient Mismatch Repair

HER2: Human Epidermal Growth Factor Receptor 2

KRAS: Kirsten Rat Sarcoma Viral Oncogene Homolog

BRAF: B-Raf Proto-Oncogene, Serine/Threonine Kinase

TMB: Tumor Mutational Burden

HIPEC: Hyperthermic Intraperitoneal Chemotherapy

Declarations

Ethical Approval and Consent to participate

This study was approved by ethical committee

Consent for publication

NA

Availability of supporting data

YES

Competing interests

The authors have no conflicts of interest to declare

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Authors' contributions

Aref and Ahmad wrote the article
Asim reviews it

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