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Original Article

Histology-Proven Gastrointestinal Metastasis from Nongastrointestinal Malignancies: Experience of This Rare Occurrence in a Single Center

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Abstract

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Introduction Lymph nodes, lung, liver, bone, and brain are the commonest metastatic sites for malignancies arising in various body sites. Gastrointestinal (GI) tract is a very uncommon metastatic site and the present study describes the single-center experience of GI metastases from non-GI malignancies.

Aims and Objectives To study the spectrum of metastatic tumors to GI tract and elucidate their clinicopathological characteristics.

Materials and Methods This was a retrospective study done on cases diagnosed from 2015 to 2023 at our institute. All cases of non-GI malignancies metastatic to hollow GI tract were included. Cases with GI primary, hematological malignancies, cases with exclusive serosal deposits, and direct invasion of a GI organ from an adjacent primary tumor were excluded. Apart from hematoxylin & eosin (H&E)-stained slides, immunohistochemistry findings of these were reviewed.

Results Thirty-six patients were histologically proven GI metastases from non-GI malignancies diagnosed during the study period. Most cases were seen in 5th to 7th decade with a significant female preponderance (M:F of 1:8). The commonest metastatic GI sites were small bowel ($n = 11$), sigmoid colon ($n = 9$), and rectum ($n = 7$), followed by stomach ($n = 3$), appendix ($n = 3$), gall bladder ($n = 2$), and ampulla ($n = 1$). Stricture, perforation, and nodular mucosa were the most common endoscopic findings. The most common primary malignancies in females were ovarian serous carcinoma ($n = 21$) followed by squamous cell carcinoma (SCC) of cervix ($n = 8$). In males, there was no site preference, and the primary sites included prostate, lung, kidney, and oral mucosa.

Conclusion The study highlights the rare occurrence of GI metastases from non-GI malignancies. Females are at greater risk of such metastases primarily from ovarian serous carcinoma and cervical SCCs.

Keywords

- GI tract
- metastasis
- non-GI primary
- histology-proven
- immunohistochemistry

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Introduction

Lymph nodes, lung, liver, bone, and brain are the commonest metastatic sites. Metastases to the hollow organs of gastrointestinal (GI) tract are extremely rare[1,2] and are mostly asymptomatic and detected incidentally on autopsy or by imaging studies.[2] They usually present at advanced tumor stages with dismal prognosis.[2] This study aims to describes the spectrum of non-GI malignancies metastatic to hollow GI tract.

Materials and Methods

This was a retrospective study of 9 years duration from 2015 to 2023 at our institute, which is a tertiary care center. All cases of histologically proven non-GI metastases to hollow GI tract were included. Cases with GI primary, hematological malignancies, exclusive serosal deposits, and direct invasion from an adjacent primary were excluded.

The following data were reviewed and analyzed in each case:

Clinical data: age, gender, site of primary tumor, duration of onset of metastasis (time interval between diagnosis of primary and secondary tumors), tumor markers if any, clinical findings and indications for endoscopy, type of biopsy (endoscopic biopsy/resection), and endoscopic/imaging findings. The endoscopic/macroscopic appearance of the tumor was assessed using the descriptive terms such as polypoidal mass, nodule, intramural lesion, or ulcerated lesion.

Morphological data: histological diagnosis and location of lesion within the wall of GI tract, i.e., mucosa, submucosa, muscularis propria, or transmural involvement. Special stains such as Periodic acid Schiff and Alcian blue and ancillary tests such as immunohistochemistry (IHC) were done as a part of the routine pathological work-up based on primary site (if known)/morphology (in cases of carcinoma of unknown primary [CUP]) to confirm the secondary nature of these lesions.

All the data were analyzed using the Microsoft Excel sheet (Microsoft 365 MSO [Version 2204 Build 16.0.15128.20240] 64-bit).

Ethics

The study was approved by the Nizams Institute of Medical Sciences (NIMS) Institutional Ethics Committee with approval number EC/NIMS/3446/2024 dated 11.05.2024. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional) and with the Helinski Declaration of 1964, as reviewed in 2013. Consent waiver form was obtained from the Ethics Committee due to the retrospective nature of the study.

Results

Thirty-six patients were diagnosed with metastases to GI tract from non-GI malignancies in a span of 9 years). Samples received for histopathology included both endoscopic biopsies ($n = 12$) and resections ($n = 24$).

Age at the time of diagnosis of GI metastasis ranged from 39 to 70 years with an average of 56 years. Peak incidence was reported in 6th to 7th decade. There was a significant female ($n = 32$) preponderance with a male-to-female ratio of 1:8.

In majority (31/36), the diagnosis was made or known prior to presentation/diagnosis of GI metastasis. In these cases, the time interval between diagnoses of primary and secondary in GI tract ranged from 3 months to 20 years (240 months) with an average of 39 months (3.3 years). The remaining five cases presented with GI metastases with subsequent detection of primary tumor.

The most common endoscopic/gross finding was mass/infiltrative growth ($n = 20$; 55.5%), followed by ulcerated/nodular mucosa ($n = 6$, 16.6%), stricture ($n = 5$; 13.8%), and perforation ($n = 3$, 8.3%). In two cases, resection was done as a part of debulking surgery post-chemotherapy.

The commonest metastatic sites were small bowel ($n = 11$), sigmoid colon ($n = 9$), and rectum ($n = 7$), followed by stomach ($n = 3$), appendix ($n = 3$), gall bladder ($n = 2$), and ampulla ($n = 1$). One of these cases had simultaneous involvement of colon and jejunum. The most common primary in females was ovarian high-grade serous carcinoma followed by squamous cell carcinoma of cervix. No such preference in the primary site was noted in male patients with GI metastases. Data on follow-up were not available in most of the cases to assess the survival rate.

The details of primary malignancies in patients diagnosed with GI metastases are proved in ►**Table 1** below.

Discussion

GI metastases from non-GI malignancies are extremely rare and represent an advanced stage of disease.[1,2] Incidence of GI metastasis is largely unknown due to the rarity of the disease with a reported incidence of 3%.[2–4] Reported literature on GI metastases is sparse, mainly in the form of few case studies and not many large studies. Unlike similar studies in the literature, the present study was a single-center study which included both endoscopic biopsies and resection specimens and excluded the cases with direct extension to GI tract and metastatic lesions with a GI primary. To the best of our knowledge, this is the first Indian study reporting such a large number of cases over a long span of time.

The incidence of this GI metastasis from non-GI primaries was low (1–2 cases/year) in the earlier years of the study period with an increase in cases (4–5 cases/year) diagnosed in recent years, which is slightly higher when compared with other studies.[1,2] This could be due to increased awareness and increased use of IHC to confirm or assign a primary.

In the present study, the mean age at diagnosis of the GI metastases was 56 years, a decade earlier than that reported in other studies. The average time interval between diagnoses of primary and metastasis was 3.3 years in the present study. This time interval was longer when compared with other studies,[2] as the cases with direct extension from

Table 1 Gender-wise distribution of various GI metastasis and the IHC panel used for confirmation

Females ($n = 32$)	**IHC results (positive)**	**Primary site**	**No. of cases (%)**
High-grade serous carcinoma	CK7, PAX8, CA125, WT1, P53 mutant	Ovary	21 (%)
		Fallopian tube	1 (%)
Squamous cell carcinoma	P40, P16	Cervix	8 (%)
		Vaginal vault	1 (%)
Low-grade endometrial stromal sarcoma	ER, PR, CD10	Uterus	1 (%)
Males ($n = 4$)	**IHC results (positive)**	**Primary site**	**No. of cases (%)**
Adenocarcinoma	AMACR, PSA	Prostatic	1 (%)
	CK7, TTF1, Napsin A	Lung	1 (%)
Clear cell RCC	CD10, PAX8, CA IX	Kidney	1 (%)
Squamous cell carcinoma	P 40	Buccal mucosa	1 (%)

Abbreviations: GI, gastrointestinal; IHC, immunohistochemistry; RCC, renal cell carcinoma.

adjacent primary were excluded. In the present study, the longest interval was 20 years in a case of high-grade ovarian serous carcinoma followed by 13 years in a case of renal cell carcinoma and 10 years in case of low-grade endometrial stromal sarcoma.

The present study showed significant female preponderance with high-grade serous carcinoma of ovary and squamous cell carcinoma of cervix being the most frequent malignancies. This could be due to an increase in the incidence of gynecological malignancies as per recent statistics in India.[5]

Most of the lesions were diagnosed in the lower GI tract like other studies. The reason for this could be due to vicinity of the abdominal solid viscera to the lower GI tract with common lymphatic drainage. In this study, the small bowel (ileum) was the most affected site, followed by sigmoid colon and rectum; whereas stomach and colon were the most common sites reported in studies done on endoscopic biopsies alone.[1,6,7] The possible reason could be that stomach and colon were the organs most frequently examined via endoscopy unlike ileum which is not so easily accessible unless a flexible endoscopy is available. All the specimens from ileum in our study were resections and this was the reason for high incidence of metastasis in ileum. This suggests that many of the ileal metastases can be missed if endoscopy alone is used as a diagnostic modality. The small bowel is often the most involved GI site for metastasis, likely due to its greater mass and blood supply.[8–10] Metastasis from primary GI cancers commonly involves the small bowel followed by stomach[11]; however, these were excluded from our study.

Infiltrative growth ($n = 20$; 55.5%) followed by ulcerated/nodular mucosa ($n = 6$, 16.6%) and stricture ($n = 5$; 13.8%) were the most common endoscopic/gross appearances of the lesions. This suggests that biopsy of all the visible lesions on endoscopy could increase the incidence rate of metastasis especially in cases with a prior history of cancer elsewhere in the body.

Lung cancer is known to frequently metastasize to the GI tract,[2] with the small intestine being the most commonly involved site. The clinical incidence of lung cancer metastasis to GI tract typically ranges between 0.2 and 1.7%, with adenocarcinoma and squamous cell carcinoma being the most prevalent histological types.[12] However, in endoscopic biopsies, metastases from lung cancer are observed less frequently, ranking fifth in terms of occurrence.[13] We reported only one case of metastatic pulmonary adenocarcinoma to jejunum in a 49-year-old male who presented with perforation. A relatively low incidence of metastasis from lung cancer was observed in recent studies and is likely due to short survival associated with metastatic lung cancers.[1,4,14]

We reported a higher incidence of carcinoma ovary ($n = 21$) followed by cervix ($n = 8$) in females. Ovarian cancer was the most common cause of metastasis in both upper and lower GI tract. Among cases with metastasis from ovarian primary, the longest duration of onset of metastasis was 20 years in a 70-year-old female and the shortest duration was 3 months. Among the endoscopic biopsies ($n = 12$), seven cases of metastasis were from ovary and three cases were from cervix. In 4/5 cases of CUP, ovarian primary was confirmed by ancillary testing. There were no cases of metastases from carcinoma breast and melanoma in our study, which is a contradictory finding when compared to other studies.[1,6,7,14–16] Prostate and kidney were the common primaries reported in males similar to other studies.[1,2] In our study, prostatic adenocarcinoma metastasized to rectum and renal cell carcinoma metastasized to gall bladder.

Of the 36 cases, 11 cases showed mucosal involvement, 10 cases had deposits in submucosa, 6 cases involved muscularis propria, and 9 cases showed full-thickness involvement. Rarity of this lesion and lack of information about primary malignancies lead to misdiagnosis in these cases. Autopsy studies usually pick up the mucosal as well as mural metastasis; however, endoscopic studies miss the mural lesions of GI.[1,6,7] In our study, mucosal as well as mural metastases were detected and IHC confirmation was done for all the cases to confirm the metastasis and rule out a second primary.

The limitation of this study is that it only includes histopathology-verified cases, hence may not reflect true

incidence of GI metastasis. Many small, asymptomatic lesions may remain undetected. This brings forth the need for a careful endoscopic surveillance and biopsy of all visible lesions detected on endoscopy in a patient with prior history of non-GI malignancy presenting with GI manifestations. These cases when diagnosed represent an advanced disease with grave outcome.[14,17] The other limitation was follow-up data were not available to assess the survival rate in these cases.

Conclusion

GI metastases from non-GI malignancies are extremely uncommon. Females are at high risk of GI metastasis with ovary being the most common primary site followed by cervix. IHC helps in confirmation of metastases and to rule out second GI primary in patients with known malignancy. In addition, IHC helps in suggesting primary sources in cases presenting with unknown primary.

Author's Contribution

N.V. and S.G.U. were involved in the conceptualization and design of the study, defining its intellectual content, conducting literature searches, and acquiring and analyzing data. They also performed statistical analyses, prepared and edited the manuscript, and contributed to its review, serving as guarantors for the work. S.G. assisted with data acquisition, analysis, and manuscript preparation. M.S.U. and T.R.P. also focused on the conceptual and design aspects, as well as data acquisition and analysis. Collectively, the authors ensured a comprehensive approach to the research and manuscript development.

Ethical Approval

The study was approved by the NIMS Institutional Ethics Committee with approval number EC/NIMS/3446/2024 dated 11.05.2024. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional) and with the Helinski Declaration of 1964, as reviewed in 2013. Consent waiver form was obtained from the Ethics Committee due to the retrospective nature of the study.

Conflict of Interest

None declared.

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