Editorial

Potential metastatic mechanisms and clinical aspects in patients with non-gastrointestinal tumor metastasis to the upper gastrointestinal tract

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Introduction

This editorial focuses on the rare phenomenon of non-gastrointestinal tumor metastasis in the upper gastrointestinal tract and explores potential mechanisms. It also discusses clinical aspects such as common symptomatology, diagnostic workup and the importance of multidisciplinary treatment.

Cancer development involves uncontrolled cell growth and alterations in the surrounding environment. While pathways such as activation of oncogenes or deactivation of tumor suppression genes have been described, the precise mechanisms of carcinogenesis remain largely unknown. Metastasis is a complex process (1,2) involving four primary pathways: local tissue invasion, lymphatic dissemination, vascular intravasation leading to distant spread, and passive dissemination, such as peritoneal exfoliation. Distant metastasis is the leading cause of cancer-related mortality (3) and therefore very important to evaluate both from a clinical and scientific aspect. Different cancer types exhibit distinct organotropisms, where metastases tend to follow predictable patterns. For instance, prostate cancer metastases are expected in the skeleton, while breast cancer spreads to many sites, including bone, lung, liver, and brain. Interestingly, triple-negative breast cancers preferentially metastasize to visceral organs (4). As described in the featured article metastasis to the upper gastrointestinal tract from non-gastrointestinal tumors is rare (5). This raises several interesting questions: Which histological types of non-gastrointestinal tumors are more likely to metastasize to the upper gastrointestinal tract? What are the potential metastatic pathways? Are some organs in the upper gastrointestinal tract more affected than others?

Non-gastrointestinal metastasis in the upper gastrointestinal tract

There are no large studies on non-gastrointestinal metastasis to the upper gastrointestinal tract. In the present paper, renal cell carcinoma was the most frequent origin (four out of seven cases), while others have reported a high proportion of breast cancer and melanoma (6). Autopsy reports suggest that gastrointestinal metastases from prostate and breast cancer occur in approximately 2% (7,8) and 1.5% (9), respectively. This high incidence implies that many patients were asymptomatic. When comparing the incidence of 49 endoscopically diagnosed metastasis from non-gastrointestinal tumors to the overall incidence

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for each tumor type, breast cancer was overrepresented in women, while melanoma and kidney cancer were more common in men (6). This suggests that these three specific histological tumor types—breast, kidney cancer, and melanoma—seem to be more successful in metastasizing to the upper gastrointestinal tract.

Tumor types and clinical presentation

Although a rare phenomenon, a comprehensive review of breast cancer metastasis to the upper gastrointestinal tract was recently published in this journal (9). The authors conclude that the differences in occurrence seen between autopsy and clinical studies suggest underdiagnosis. The study emphasizes a high degree of awareness as clinical presentations can be vague or mimic primary gastrointestinal conditions. In additional studies, lobular breast cancer in particular, appeared more prone to metastasize to the gastrointestinal tract (10,11). According to a retrospective multicenter study of 74 patients with renal cell carcinoma metastases to the gastrointestinal tract, male gender dominated, and most patients had disseminated disease at the time of gastrointestinal involvement. Only a third of the patients were asymptomatic, while the majority presented with anemia and/or gastrointestinal bleeding (12). In melanoma, the incidence of symptomatic gastrointestinal involvement has been estimated to 1–5%, while gastrointestinal metastasis has been demonstrated postmortem in up to 60% of these patients (13). In a smaller series, melanoma of the extremities and trunk were more likely to spread to the gastrointestinal tract than from other primary locations such as head and neck. Common symptoms in gastrointestinal metastatic melanoma include abdominal pain, obstruction, gastrointestinal bleeding and chronic iron-deficiency (14).

Notably, in all three tumor types, gastrointestinal metastasis can develop late after the initial cancer diagnosis. The median time from primary tumor diagnosis to gastrointestinal metastasis is 4 years for breast cancer (9) and 5.4 years for renal cell carcinoma (12), while it ranges from 2 and 180 months for melanoma (15).

Affected upper gastrointestinal organs

The stomach seems to be the most affected upper gastrointestinal organ, comprising 30–50% of all non-gastrointestinal metastases in the abovementioned series. In an autopsy study, 5.4% of 347 patients with solid malignancies had gastric metastases, with melanoma being the most frequent tumor type (16). In another series of 389 patients with gastric metastasis, detected by endoscopy, metastatic lesions were most often located in the middle or upper third of the stomach and multiple in more than a third of the cases. Of note, more than half of the gastric metastases were submucosal, superficial endoscopic biopsies may therefore be negative and necessitate repeat examinations until a correct diagnosis can be made. Interestingly, melanomas also appear to have a high affinity for the small bowel (17).

Organotropism and metastatic pathways

In the classic seed-and-soil theory, Paget described that metastases only develop in specific environments (soils) where the tumor cells (seeds) can thrive (18). While research has significantly advanced our understanding of the molecular mechanisms governing tumor spread, no clear incompatibility exists between non-gastrointestinal tumor cells and the upper gastrointestinal tract. However, the architecture of blood barriers in different organs may predispose for metastatic seeds with capacity for breaking down endothelial junctions. Recent theories include development of organotropism in the seed (tumor cell) before dissemination, and specific interactions between tumor cells and the soil. In specific organs, seed retention is facilitated by chemotactic and adhesive factors, and even overtaking of resident cells to remodel the microenvironment occurs.

Requirements for hematogenic spread

Metastatic success depends on the ability of tumor cells to undergo all steps of the invasion-metastasis cascade (19). This includes local invasion, intravasation, survival in circulation, arrest at the distant organ site, extravasation, and ability to colonization. Passing into the surrounding parenchyma and intravasation, requires an epithelial-mesenchymal transition program (20). Thereafter, tumor cells must overcome immunosurveillance, for example by enlisting platelets and leukocytes in the blood stream (21). The destination of tumor cells dissemination is believed to be mechanically controlled by reduced vessel diameter, such as in the liver sinusoids. After extravasation, tumor cells can begin to form distant metastasis, if they tolerate the new environment. In experimental models, it has been estimated that less than 3% of intravenously implanted

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cells survive to form microscopic metastases and less than 0.02% of implanted cells generate macroscopic metastases (22). Recent findings implicate specific molecules in the regulation of discrete cell-biological aspects of the invasion-metastasis cascade but fail to explain the rare occurrence of non-gastrointestinal metastases, and differing properties of histological tumor types. As demonstrated in the featured article, disseminated cancer cells can survive and retain the ability to form distant metastasis even after the removal of the primary tumor. These peripheral tumor cells, or even micrometastasis, were likely present at the time of surgery but have remained dormant and thus evaded elimination by the immune system.

As stated above, the liver sinusoids with narrow passages and low-pressure gradients (19) facilitate metastatic extravasation. The portal vein provides direct access to the liver for gastrointestinal cancers, explaining the high incidence of hepatic metastases in colorectal cancer. In a study, the concentration of disseminated colorectal cancer cells was proven higher in the liver than in peripheral blood (20). For non-gastrointestinal tumors, lacking direct access to the hepatic portal vein, passage through the venous system and into the arterial circulation is needed. This gives full access to all organs, like the random spread of septic emboli from endocarditis.

Alternative metastatic pathways

Direct spread of lung cancer by swallowing sputum containing malignant cells has been discussed (23). Interestingly, distal implantation of proximal gastrointestinal tumors seems extremely rare, despite the continuous exposure of exfoliated tumor cells to the intestinal lining. Possibly an intact mucosa prevents adhesion of passing tumor cells. However, traumatizing the gastric and abdominal wall with a percutaneous endoscopically introduced gastrostomy tube, contaminated with tumor cells from a head and neck tumor, can lead to direct implantation metastasis (24). Non-hematogenous spread to the abdominal organs is otherwise much more common in ovarian- and gastrointestinal cancers, where ascites fluid carries detached tumor cells within the abdominal cavity to the visceral peritoneum or omentum. This process requires local tumor penetration of the serosa, but not the active steps of intravasation and extravasation.

Clinical aspects on malignant processes in the gastrointestinal tract

Clinical diagnosis and management

Despite its rarity, gastrointestinal metastasis should be considered in patients with unexplained chronic anemia as well as specific gastrointestinal symptoms such as obstruction. Patient reports on hematemesis are doubtless, while the distinction between melena (black, tarry stools) and hematochezia (fresh blood in stool) often needs to be clarified further. The latter should initially be evaluated by proctoscopy, followed by colonoscopy if needed, as it originates from a distal source, while upper endoscopy is widely used to clarify all other gastrointestinal bleeding sites. Local endoscopic procedures such as adrenalin injections, clips and various types of thermal therapy can often manage the bleeding. If this fails, selective angiographic embolization can be considered before surgery as a last resort. Larger sites of diffuse bleeding can be controlled by endoscopic argon plasma coagulation or low-dose external beam radiation.

Dysphagia indicates esophageal involvement, while massive postprandial vomiting is associated with obstructions in the distal stomach, duodenum or proximal jejunum. Colicky pain usually originates from small bowel obstructions, while patients with colonic strictures initially presents with a distended, but rather painless, abdomen. The latter clinical finding may be confused with massive ascites but has a typical tympanic sound on examination. Abdominal symptoms exemplified above should be investigated with a computed tomography (CT) scan, followed by targeted exanimations such as upper endoscopy and a small bowel follow-through or barium enema, depending on the suspected level of the obstruction. Endoscopic stenting can manage strictures in the esophagus, gastroduodenal junction and colon, while surgery is often mandated to relieve remaining gastrointestinal obstructions. Jaundice should be evaluated by CT scan, and relieved by endoscopic placement of stents, if not due to massive liver metastasis. Ultrasound-guided percutaneous biopsies are valuable in determining the origin of liver metastasis, especially in patients without a known primary tumor.

Given the potential for underdiagnosis, maintaining a high index of suspicion is essential when encountering unexplained gastrointestinal symptoms in patients with

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a history of malignancy. In these patients, any suspicious finding should result in further investigations, with endoscopic or needle core biopsies and histopathological analysis on all specimens.

Multidisciplinary care and future perspectives

In addition to the symptomatic treatments above, patients should be managed by multidisciplinary teams. In many of the above-mentioned case series, the patients already had disseminated disease when gastrointestinal metastases were diagnosed. While systemic chemotherapy remains a cornerstone for many metastatic cancers, advancements in immunotherapy have improved survival rates, especially in melanoma. For patients with metastatic disease, new therapeutical options are under continuous development (25).

Conclusions

Metastasis of non-gastrointestinal tumors to the upper gastrointestinal tract is a rare but clinically significant phenomenon. Awareness of this condition, coupled with a high index of suspicion in non-gastrointestinal cancer patients with onset of unexplained gastrointestinal symptoms, is crucial for early diagnosis and successful intervention. Furthermore, all affected patients should be managed by multidisciplinary teams. In my opinion, future research should focus on improved diagnostic approaches and targeted therapies.

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References

1. Fares J, Fares MY, Khachfe HH, et al. Molecular principles of metastasis: a hallmark of cancer revisited. Signal Transduct Target Ther 2020;5:28.
2. Valastyan S, Weinberg RA. Tumor metastasis: molecular insights and evolving paradigms. Cell 2011;147:275-92.
3. Chaffer CL, Weinberg RA. A perspective on cancer cell metastasis. Science 2011;331:1559-64.
4. Chen X, Fan Y, Xu B. Distinct Characteristics and Metastatic Behaviors of Late Recurrence in Patients With Hormone Receptor-positive/Human Epidermal Growth Factor Receptor 2-negative Breast Cancer: A Single Institute Experience of More Than 10 Years. Clin Breast Cancer 2018;18:e1353-60.
5. Bakry M, Ahmadzai H, Fadia M, et al. Cancer metastasis to the upper gastrointestinal tract-a case series. J Gastrointest Oncol 2024;15:2728-34.
6. Kaila V, Jain R, Lager DJ, et al. Frequency of metastasis to the gastrointestinal tract determined by endoscopy in a community-based gastroenterology practice. Proc (Bayl Univ Med Cent) 2021;34:658-63.
7. Gandaglia G, Abdollah F, Schiffmann J, et al. Distribution of metastatic sites in patients with prostate cancer: A population-based analysis. Prostate 2014;74:210-6.
8. Moshref L, Abidullah M, Czaykowski P, et al. Prostate Cancer Metastasis to Stomach: A Case Report and Review of Literature. Curr Oncol 2023;30:3901-14.
9. Da Cunha T, Restrepo D, Abi-Saleh S, et al. Breast cancer metastasizing to the upper gastrointestinal tract (the esophagus and the stomach): A comprehensive review of the literature. World J Gastrointest Oncol 2023;15:1332-41.
10. Korhonen T, Kuukasjärvi T, Huhtala H, et al. The impact

of lobular and ductal breast cancer histology on the metastatic behavior and long term survival of breast cancer patients. Breast 2013;22:1119-24.
11. Montagna E, Pirola S, Maisonneuve P, et al. Lobular Metastatic Breast Cancer Patients With Gastrointestinal Involvement: Features and Outcomes. Clin Breast Cancer 2018;18:e401-5.
12. Carneiro F, Vinceneux A, Larroquette M, et al. Gastrointestinal metastases in renal cell carcinoma: A retrospective multicenter GETUG (Groupe d'Étude des Tumeurs Uro-Génitales) study. Eur J Cancer 2024;199:113534.
13. Asad-Ur-Rahman F, Abbass A, Majeed U, et al. Melanoma Metastasizing to the Small Intestine: A Case Report Illustrating Symptomatic and Asymptomatic Involvement. Cureus 2016;8:e608.
14. Gilg MM, Gröchenig HP, Schlemmer A, et al. Secondary tumors of the GI tract: origin, histology, and endoscopic findings. Gastrointest Endosc 2018;88:151-158.e1.
15. Silva S, Tenreiro N, Melo A, et al. Metastatic melanoma: An unusual cause of gastrointestinal bleeding and intussusception-A case report. Int J Surg Case Rep 2018;53:144-6.
16. Oda, Kondo H, Yamao T, et al. Metastatic tumors to the stomach: analysis of 54 patients diagnosed at endoscopy and 347 autopsy cases. Endoscopy 2001;33:507-10.
17. Kohoutova D, Worku D, Aziz H, et al. Malignant Melanoma of the Gastrointestinal Tract: Symptoms, Diagnosis, and Current Treatment Options. Cells 2021;10:327.
18. Fidler IJ. The pathogenesis of cancer metastasis: the 'seed and soil' hypothesis revisited. Nat Rev Cancer 2003;3:453-8.
19. Obenauf AC, Massagué J. Surviving at a Distance: Organ-Specific Metastasis. Trends Cancer 2015;1:76-91.
20. Yeung KT, Yang J. Epithelial-mesenchymal transition in tumor metastasis. Mol Oncol 2017;11:28-39.
21. Riggi N, Aguet M, Stamenkovic I. Cancer Metastasis: A Reappraisal of Its Underlying Mechanisms and Their Relevance to Treatment. Annu Rev Pathol 2018;13:117-40.
22. Luzzi KJ, MacDonald IC, Schmidt EE, et al. Multistep nature of metastatic inefficiency: dormancy of solitary cells after successful extravasation and limited survival of early micrometastases. Am J Pathol 1998;153:865-73.
23. Latif J, Ang ZH, Holmes M, et al. Metastatic lung adenocarcinoma presenting with small bowel obstruction. BMJ Case Rep 2024;17:e261080.
24. Adelson RT, Ducic Y. Metastatic head and neck carcinoma to a percutaneous endoscopic gastrostomy site. Head Neck 2005;27:339-43.
25. Ganesh K, Massagué J. Targeting metastatic cancer. Nat Med 2021;27:34-44.

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