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LETTER TO THE EDITOR

Small cell lung carcinoma metastatic to the stomach: Commonly overlooked, limited treatment options

Terence N Moyana

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Abstract

Small cell lung carcinoma metastatic to the stomach, whether synchronous or metachronous, is a rare phenomenon accounting for < 0.5% of lung cancers. Hence it can be overlooked by clinicians resulting in delayed diagnosis. This manuscript comments on Yang *et al*'s article which reported 3 such cases. The main diagnostic features are based on routine morphology comprised of small cells with hyperchromatic nuclei, scant cytoplasm, brisk mitoses and necrosis. This can be supplemented by immunohistochemistry demonstrating positivity for cytokeratin, thyroid transcription factor-1 and neuroendocrine markers as well as a high Ki-67 labelling index. Imaging modalities such as positron emission tomography/contrast computed tomography help to confirm lung origin and rule out the possibility of extra-pulmonary small cell carcinoma. The predominant mechanism of spread is most likely hematogeneous. Prognosis is generally poor since this represents stage 4 disease but survival can be improved by chemo/radiotherapy and palliative surgery in select cases. Though outcomes have not changed much in the last several decades, the recent Food and Drug Administration approval of immune checkpoint inhibitors was a significant milestone as was the delineation of small cell lung carcinoma molecular subtypes. Liquid biopsies are increasingly being used for biomarker studies in clinical trials to assess treatment response and prognosis.

Key Words: Gastric metastasis; Small cell lung carcinoma; Histopathology; Immunohistochemistry; Positron emission tomography/contrast computed tomography; Chemoradiotherapy; Immunotherapy; Surgery; Biomarkers; Clinical trials

Core Tip: Small cell lung carcinoma metastatic to the stomach is rare and can thus be overlooked. Diagnosis requires conventional morphology supplemented by immunohistochemistry as well as appropriate imaging modalities. While outcomes are generally poor, palliative chemo/radiotherapy with surgery in select cases can improve survival and quality of life. The recent Food and Drug Administration approval of immune checkpoint inhibitors was a significant milestone as was the delineation of small cell lung carcinoma molecular subtypes. Liquid biopsies and biomarkers are increasingly being used in clinical trials for therapeutic stratification and prognostication.

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TO THE EDITOR

Gastric metastases from small cell lung carcinoma (SCLC) are rare with only sporadic cases having been published over the past several decades[1,2]. The incidence of such cases is estimated to be less than 0.5% of lung cancers and as such, they can be easily overlooked by clinicians[1-3]. This manuscript comments on the article by Yang *et al*[4] which documents 3 such cases to highlight the context in which they can occur. Persistent unexplained upper gastrointestinal (GI) symptoms may end up being investigated by upper endoscopy and biopsy, and this was the case in their 3 patients. The biopsy findings culminated in a diagnosis of small cell carcinoma (SCC) which led to further investigations that showed the lung as the primary source. SCLC is a malignant epithelial neoplasm that is primarily diagnosed based on morphologic criteria[5-8]. It is composed of small cells with finely granular nuclear chromatin, absent or indistinct nucleoli and scant cytoplasm. The tumor has high mitotic activity (> 10 mitoses/2 mm^2), apoptotic bodies and frequent necrosis[5-9]. While it can be diagnosed on routine histologic and cytologic stains, immunohistochemistry may be required in cases with equivocal morphology to increase confidence in the diagnosis[5-8].

Immunohistochemistry

It may be judicious to further substantiate the diagnosis of SCLC with immunohistochemistry, *e.g.*, to rule out other histologic mimics such as basaloid squamous cell carcinoma, small round blue cell tumors, metastatic breast carcinoma and lymphomas. In this regard, an initial step may be to confirm its epithelial nature and this can be achieved using keratin stains[6,7,10]. Typically, it is the broad spectrum antibodies that are most helpful, *e.g.*, pancytokeratin AE1/AE3 which recognizes both the acidic and basic subfamilies of cytokeratin[6]. Yang *et al*[4] include a cytokine stain in their immunohistochemistry work-up. Given the context, the cytokine is meant to refer to cytokeratin, most likely AE1/AE3, which is in line with other studies[5-7]. In any case, since there are over 20 cytokeratin stains[11], the clone(s) should be specified. In addition to verification of cytokeratin positivity, it is important to demonstrate the immunophenotype of the tumor based on neuroendocrine markers, *e.g.*, synaptophysin, chromogranin A, CD56 and insulinoma-associated protein 1 along similar lines to what was done by Yang *et al*[4]. It can be difficult to distinguish SCLC from other neuroendocrine neoplasms (NENs), *e.g.*, typical carcinoids, atypical carcinoids, carcinoids with high mitotic index and large cell neuroendocrine carcinomas, especially in small biopsies[5-8,12]. Such cases require attention to detail particularly with regard to mitoses and/or Ki67 proliferation index (herein referred to as Ki67).

Mitoses and Ki67 in the classification of pulmonary NENs

In the gastroenteropancreatic (GEP) system, well differentiated neuroendocrine tumors are graded as G1, G2 or G3 based on mitotic rate and Ki67 (whichever is greater) as follows: G1 (< 2 mitoses/2 mm^2 or Ki-67 < 3%), G2 (2-20 mitoses/2 mm^2 or Ki-67 of 3%-20%), or G3 (> 20 mitoses/2 mm^2 or Ki-67 > 20%)[12-14]. Neuroendocrine carcinomas (SCC and large cell neuroendocrine carcinomas) are different in that, instead of having an organoid morphology, they are composed of highly atypical small cells or large cells with high proliferative activity (> 20 mitoses/2 mm^2 or Ki-67 > 20%). Furthermore, the molecular genetics of neuroendocrine carcinomas [*e.g.*, tumor protein p53 (TP53), retinoblastoma 1 (RB1), and cyclin dependent kinase inhibitor 2A mutations] more closely resemble that of adenocarcinomas than neuroendocrine tumors (multiple endocrine neoplasia type 1, death domain-associated protein 6, alpha-thalassemia mental retardation X-linked mutations)[12-14].

In the pulmonary system, traditionally, the classification of lung NENs was somewhat different from the GEP system in that it was largely based on light microscopic features particularly mitotic activity and necrosis[5-8]. Parenthetically, there is no mention of mitoses or necrosis in Yang *et al*'s article[4]. At any rate, the mitotic count is: < 2 mitoses/2 mm^2 for typical carcinoids, 2-10 for atypical carcinoids, and > 10 for carcinoids with high mitotic activity respectively[12]. For SCLC, though by definition mitoses are > 10, in practice they tend to far exceed this, with the average being 60 and the median being 80 mitoses/2 mm^2[5,12]. While Ki67 has had proven prognostic relevance in GEP NENs for > 30 years, the debate continues as to whether it should be included in the formal classification of pulmonary NENs[13,14]. The 2021 World Health Organization classification regards it as a non-essential but desirable criterion[14], but a growing body of evidence supports the idea of incorporating it into the grading system. Just as with mitoses, Ki67 for SCLC is often very high, typically in the 70%-100% range[7-9,12,13].

Extra-pulmonary SCC

The most common site for SCC is the lung where it accounts for approximately 15% of all primary malignant tumors[15]. While the majority of SCCs are of pulmonary origin (approximately 95%)[16], it should be recognized that a small proportion arise outside the lung, *e.g.*, genitourinary (prostate, urinary bladder, and kidney), digestive (esophagus, stomach, small and large intestine, pancreas, and gallbladder), gynecologic (cervix and ovary), head and neck (larynx, salivary glands, and sinonasal) and breast[16-21]. Based on conventional histopathology and immunohistochemistry, extra-pulmonary SCCs (EPSCCs) are indistinguishable from their pulmonary counterparts[22]. However, certain types of EPSCCs have features that make them easier to recognize, *e.g.*, SCC of the ovary, hypercalcemic type, mainly affects children and young adults (mean age 25 years)[23]. Furthermore, while TP53 and RB1 mutations are seen in the majority of SCCs regardless of site, other genetic alterations tend to be more commonly associated with certain sites, *e.g.*, switching/sucrose non-fermentable related matrix associated actin dependent regulator of chromatin subfamily A member 2 and member 4 mutations with ovary[23,24] and telomerase reverse transcriptase with urinary bladder[25]. For uterine cervical SCCs, a useful distinguishing feature is their tendency to be positive for human papillomavirus[26,27]. Yang *et al*[4] demonstrated thyroid transcription factor-1 positivity in all their 3 cases. It should be noted that while thyroid transcription factor-1 is a very good marker for pulmonary adenocarcinomas, in the setting of SCC, it is not specific for lung origin but can also be positive in EPSCCs[28,29]. Therefore, to strengthen the idea of lung origin, the histopathology, immunohistochemistry and genetic studies have to be supplemented by imaging findings[16,30] as indeed was done by Yang *et al*[4].

Imaging findings for SCLC

Patients with SCLC can present with the full range of radiologic findings of lung cancer. However, because of their rapid doubling time, they usually show a large central perihilar mass with bulky mediastinal adenopathy, and in advanced cases great vessel wall involvement[16,30]. Computed tomography (CT) with contrast is very useful for evaluating the primary tumor and the extent of intrathoracic disease. Since these tumors are highly metabolic, fluorodeoxyglucose-positron emission tomography imaging (PET)/CT has proved to be more accurate than conventional imaging in staging SCLC and can be used to guide therapy and assess treatment response[16,30].

Metastatic patterns of lung carcinoma

On the whole, the 3 most prevalent types of lung cancer are adenocarcinoma, squamous cell carcinoma and SCLC. The preferential metastatic sites of the tumors are mediastinal lymph nodes, liver, brain, bone and adrenal glands[15,16,31]. Uncommon/rare sites include the breast, thyroid, skin and GI tract[2,32,33]. From a GI perspective, most metastases arise from melanoma, breast particularly lobular type and the lung[2]. The majority of GI metastases emanating from the lung involve the esophagus, small bowel and colorectum with the stomach lower down in terms of incidence[1,2,34]. Thus, if one is only considering SCLC, the number of cases involving the stomach is quite small, a point that was well articulated by Yang *et al*[4] and others[35,36]. This is why these gastric metastases, whether synchronous or metachronous, tend to be overlooked. The reasons for the uncommon metastatic sites are not entirely clear. Some studies suggest that genetic alterations and/or related factors (*e.g.*, nuclear factor I B or yes-associated protein 1) in SCLC may influence homing patterns, organ tropism and the location of the metastases[37-39]. From a topographical perspective, most of the metastases tend to involve the proximal stomach, particularly the fundus and the body rather than the antrum or pylorus [4,32,35,36]. Histologically, there is a tendency to involve the more superficial layers, *i.e.*, mucosa and submucosa, at least initially[4,31,36,40]. The deposits can be single or multiple[4,35,36] and tend to have a central umbilication, presumably the result of rapid growth rate and necrosis[36].

What is the mechanism of metastatic spread

In most cases of SCLC metastatic to the stomach, this is usually in the context of disseminated disease as was the case for all 3 of Yang *et al*'s patients[4]. This may be why most authors attribute the gastric metastases to hematogenous spread[16, 32,35,41]. In fact, there are reports of gastric metastases combined with those to the skin, each site being a rare manifestation of SCLC[32,33]. On the other hand, lymphatic spread has also been postulated as a possible mechanism[35, 40]. Just as esophageal and gastroesophageal carcinoma can spread to mediastinal and cervical lymph nodes *via* the rich anastomosing peri-gastroesophageal/mediastinal lymphatic plexus, the rapidly proliferating SCLC can likewise gain access to this lymphatic pathway with retrograde spread in the altered cancer microenvironment. Yet another mechanism that has been put forward is that patients can expectorate/swallow the tumor cells thus giving them passage to the GI lining, so-called implantation metastases[1,35].

Prognosis

Patients with involvement of the stomach by SCLC have, by definition, stage 4 cancer. This is often extensive-stage disease which augurs for poor outcomes. The median overall survival for SCLC is approximately 12 months with conventional therapy and this has not significantly changed over the last 3 decades[42,43]. It is even shorter in patients with GI metastasis, on average < 100 days following diagnosis[1,33,35]. However, in select patients, *e.g.*, those with oligometastatic disease in the context of limited-stage thoracic disease (that can be encompassed within a tolerable radiotherapy field), outcomes can be improved by chemotherapy plus concurrent radiotherapy[16,44,45]. There may also be a role for palliative surgical resection of the metastatic site in cases where the gastric metastases are localized or complicated by hemorrhage or perforation[2,32-34,46,47].

After many years with little or no improvement in outcomes for extensive-stage SCLC, recent phase 3 clinical trials using immune checkpoint inhibitors (ICIs) (*e.g.*, atezolizumab and durvalumab) in combination with first-line platinum doublet chemotherapy resulted in improved median progression-free survival and overall survival (*e.g.*, the IMpower133 trial[48]). This paved the way for the Food and Drug Administration to approve this treatment approach in 2019 and others subsequently[48-51]. Lastly, on a somewhat optimistic note, since SCLC is strongly associated with smoking, its incidence is trending downward due to the anti-smoking campaigns[15,16,30].

Future directions

SCLC subtypes: Sequencing studies have shown a high degree of somatic mutations (mostly TP53 and RB1) in SCLC with considerable inter-and intratumoral heterogeneity, *e.g.*, TP53 missense mutations[52]. Thus, conventional treatments may be efficacious at the beginning but most patients quickly develop resistance[42]. This highlights the importance of expanding current therapeutic approaches[50,53,54]. Recent profiling studies have embarked on a new model of SCLC based on 4 major molecular subtypes (achaete-scute family bHLH transcription factor 1, neuronal differentiation 1, POU class 2 homeobox 3, and yes-associated protein 1)[50,53,55]. The subtypes are defined not necessarily by their mutational landscape but by the differential expression of transcription regulators. The hope is that this will lead to subtype-specific treatment strategies and improve outcomes[50,53].

Liquid biopsies and biomarkers: The rationale for effective treatments is based on reliable biomarker studies to target the correct pathways. Surgical resections are seldom performed in SCLC. Furthermore, procurement of tissue biopsies can be challenging especially after relapse, and they often fail to represent the full expression profile of the tumor. This has limited research into the biology of SCLC and hampered biomarker development[50,56]. In this regard, liquid biopsies could provide alternative opportunities for prospective biomarker-driven trials. This encompasses the analysis of blood/body fluid-based tumor components such as circulating tumor cells, cell-free and extrachromosomal tumor DNA, cell-free RNA, extracellular vesicles and tumor-associated proteomics to assess molecular phenotypes, treatment response and prognosis[50,56,57].

Tumor mutational burden: Studies have shown that tumor mutational burden (TMB) can be used as a biomarker of response to immunotherapy in SCLC[51,57,58]. TMB typically translates into a higher neo-antigen load, and therefore a higher chance that an antigen capable of stimulating an immune response is expressed on the tumor cell surface recognizable by cytotoxic T-cells. Considering that SCLC has a very high TMB, there should be a robust response for immune checkpoint blockage for this tumor[51,57,58]. However, the efficacy has been relatively modest when compared to breakthroughs that were achieved with non-SCLC[49].

Clinical trials: (1) Immunotherapy in limited-stage SCLC: Immunotherapy has had encouraging results in subjects with extensive-stage SCLC but however its efficacy with limited-stage SCLC remains unconfirmed. This has been and continues to be under investigation (*e.g.*, the STIMULI trial)[59]; (2) Anti-angiogenesis treatment: There are indeed several completed or ongoing clinical trials evaluating the efficacy of ICI in SCLC[50]. Other trials (*e.g.*, the ETER701) involve the addition of anti-angiogenesis treatment to immune-chemotherapy[60]; (3) Antibody-drug conjugates: More recently, antibody-drug conjugates are being tried for advanced lung cancer with the idea of selectively delivering cytotoxic payloads to an antibody-mediated process of targeting cancer cells[61,62]; and (4) Poly adenosine diphosphate-ribose polymerase (PARP) inhibitors: The high incidence of genomic aberrations in SCLC leads to an accumulation of DNA damage. The tumor cells rely on DNA damage repair pathways in order to survive. PARP proteins play a pivotal role in DNA repair and genomic integrity. There are currently studies evaluating the efficacy of PARP inhibitors (*e.g.*, olaparib, veliparib, and talazoparib) in SCLC[50,57,63].

Germline-mutated SCLC subtype: Since tobacco smoke is such a potent carcinogen, secondary causes of lung cancer may be underappreciated. However, recent work has shown that there is a germline-mutated SCLC subtype with a favourable response to DNA repair-targeted therapies[64].

Medical imaging: Most cases of gastric metastases from SCLC are asymptomatic and may therefore be overlooked[1]. However, since these tumors are markedly proliferative, they have a high fluorodeoxyglucose uptake, leading to a PET sensitivity of almost 100% and a specificity of 78% to 96%[65,66]. This makes it superior to standard imaging techniques for the detection of gastric metastases, leading to earlier diagnosis.

CONCLUSION

SCLC metastatic to the stomach is a rare occurrence and hence can be overlooked. The main diagnostic features are based on routine light microscopy supplemented by immunohistochemistry. Imaging modalities such as PET/contrast CT help to confirm lung origin and rule out the possibility of EPSCC. Prognosis is generally poor but survival can be improved by chemo/radiotherapy and palliative surgery in select cases. The recent Food and Drug Administration approval of ICIs in the treatment algorithms of SCLC was a significant milestone as was the delineation of SCLC molecular subtypes based on transcriptomic analyses. However, long-term survival of SCLC patients remains poor and the development of novel strategies should be prioritized. Hence a number of clinical trials are currently underway exploring various combinatorial regimens. Throughout this, liquid biopsies and biomarkers stand to play an increasingly important role in guiding patient management and therapeutic stratification. Although SCLC metastatic to the stomach is commonly overlooked, the hope is that Yang *et al*'s article will further increase awareness of this entity and thus avoid delayed diagnosis[4]. Furthermore,

with improvements in PET-CT, more asymptomatic cases can be detected.

FOOTNOTES

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