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Understanding gastric metastasis of small cell lung carcinoma: Insights from case reports and clinical implications

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Abstract

Small cell lung cancer (SCLC) is a common type of primary lung cancer that contributes to approximately 15% of cases. It is closely associated with tobacco risk factors. It is also known as a type of lung cancer that has a high mortality rate within a short time due to its rapid growth rate (with tumor doubling time of 30 days) and its tendency to metastasize early in the disease process. The primary sites of metastasis in SCLC are similar to those in other primary lung cancers and often include the brain, bones, adrenal glands, liver, and lymph nodes. However, there are a few clinical reports of uncommon metastases, such as gastric metastasis from SCLC. Although the incidence of this clinical presentation is very low, reported cases have generally resulted in early mortality due to inadequate treatment. The purpose of this letter is to discuss the knowledge related to gastric metastasis from SCLC and remind clinical doctors not to miss atypical symptoms, thereby providing the right attitude to improve the prognosis for these patients.

Key Words: Gastric metastasis; Small cell lung cancer; Primary lung cancer; Immunohistochemistry; Clinical cases

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Core Tip: Small cell lung cancer rapidly metastasizes to distant sites from early stages, but the stomach is not a common metastasis site. The rarity of this situation means that it is rarely reported, so the clinical doctor's awareness of it is incomplete, resulting in inappropriate responses and poor clinical outcomes.

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TO THE EDITOR

Primary lung cancer, including small cell lung cancer (SCLC), is increasingly prevalent worldwide in terms of both incidence and mortality rates. Up to two-thirds of SCLC patients have distant metastasis at the time of diagnosis[1]. Gastrointestinal metastasis from SCLC has been reported primarily in the liver and colon[2]. Gastric metastasis is extremely rare and has been sporadically reported in a few clinical cases[3-5]. Peng *et al*[6] report that the current number of patients with gastric metastasis from SCLC is around 20. With such a small number of cases, a systematic description of this condition has not been conducted, and associated clinical features may be easily overlooked or misdiagnosed. The need for a deep understanding of the characteristics of this gastric metastasis of SCLC, with the purpose of early detection and timely, appropriate treatment, prompted us to write this article.

Diagnosis

The clinical symptoms observed in patients with SCLC metastasis to the stomach are entirely nonspecific and can easily be mistaken for other gastrointestinal conditions. The primary gastrointestinal symptoms include abdominal pain, bloating, and gastrointestinal bleeding. Additionally, respiratory symptoms may be present. Gastrointestinal symptoms may appear first and only, even without any obvious respiratory signs or symptoms[7]. In reported clinical cases, gastric metastasis from SCLC was identified through gastroscopy with biopsy. The diagnostic process for SCLC can be reversed when there are no suggestive respiratory symptoms. Currently, clinicians may return to search for primary pulmonary lesions through chest computed tomography (CT) scans and bronchoscopy. Several studies have demonstrated that positron emission tomography (PET) scans can improve staging accuracy in patients with SCLC due to its high metabolic activity. Some researchers have also explored gastrointestinal metastases and the application of fluorodeoxyglucose (FDG)-PET to detect them. In recent years, the role and potential benefits of FDG-PET scanning in identifying gastric metastasis have been investigated. Hayasaka *et al*[8] analyzed 308 patients who underwent whole-body FDG-PET scans for tumor detection and identified 4 cases of lung carcinoma metastasis to the gastrointestinal tract, including 1 to the duodenum, 1 to the jejunum, and 2 to the stomach. These observations indicate that this imaging technique is useful for detecting metastatic tumors in the gastrointestinal tract, potentially helping to prevent complications such as intestinal obstruction and severe bleeding caused by such tumors. While PET/CT seems to enhance staging accuracy in SCLC, histological confirmation is still necessary for PET/CT-detected lesions that result in upstaging[8].

In terms of the endoscopic characteristics of SCLC, previous reports have indicated that the most common locations of gastric cancer metastasis are usually in the body or pyloric antrum, with histopathological manifestations typically including raised lesions on the mucosa or submucosa, with central ulceration, ranging in size from 2 cm to 5 cm[9]. Gastric metastasis from SCLC is typically described as a single lesion, but there is also a case report of multiple lesions[7]. Thus, the number of lesions does not help distinguish gastric metastasis from SCLC or differentiate it from other types of tumors. Endoscopic features of SCLC metastases to the stomach are similar to those of patients with primary gastric neuroendocrine type III tumors, with individual lesions in the form of tumors, polyps, or pits with a diameter > 2 cm[10]. Although gastric metastasis from lung cancer, especially SCLC, is very rare, with only a few sporadic cases published over the past few decades, the diagnosis can only be confirmed through gastric endoscopy with biopsy. Gastrointestinal endoscopy should be performed in patients with SCLC who present with digestive symptoms, both for diagnostic purposes and to rule out other conditions. However, there are currently no specific guidelines nor recommendations regarding this matter.

Ultrasound endoscopy reveals hypoechoic lesions, but this characteristic does not distinguish SCLC gastric metastasis from other tumors. Histopathology and immunohistochemistry are the gold standards for distinguishing gastric metastasis from SCLC[11-13]. SCLC is defined as “a malignant epithelial tumor consisting of small cells with scant cytoplasm, ill-defined cell borders, finely granular nuclear chromatin, and absent or inconspicuous nucleoli”[14]. The cellular morphology of SCLC metastasized to the stomach is like that of a lung tumor. Histopathological specimens typically present little cytoplasm, indistinct cell borders, fine nuclear chromatin, and either absent or indistinct nucleoli. Tumor cells are round, elliptical, or spindle shaped[15]. Currently, immunohistochemistry is very important for determining the tumor’s origin. Gastric metastasis can be distinguished from pulmonary small cell neuroendocrine carcinoma through immunohistochemistry, as gastric metastasis will stain positive for neuro-oncological ventral antigen-1, thyroid transcription factor-1, p16, CD56, synaptophysin, neuron-specific enolase, and pancytokeratin[11-13].

Treatment

Gastric metastasis generally occurs in the advanced stages of SCLC. The treatment for SCLC typically focuses on chemotherapy rather than surgery[16-20]. In addition to targeted therapy, symptomatic and supportive treatments are necessary. Depending on the clinical manifestations in the stomach, the treating physician may consider the addition of proton pump inhibitors, hemostatic agents, functional dyspepsia modulators, or even interventional endoscopy (primarily for hemostatic intervention, spray coagulation) and surgical hemostasis if medical treatment fails. Treatment should be combined with the patient’s general condition, which is comprehensive but must be individualized. The first-

line treatment for extensive-stage SCLC involves four to six cycles of etoposide in combination with platinum-based chemotherapy, typically using either cisplatin or carboplatin.

In general, the presence of distant metastasis is considered a contraindication for surgery, as high perioperative mortality and poor outcomes have been noted in patients with gastric and/or duodenal metastasis. However, some studies have suggested that surgery might be a favorable prognostic factor for patients with gastric metastasis. As a result, patients with isolated gastric metastasis could potentially benefit from surgical intervention. Additionally, surgery may be required to prevent or manage life-threatening complications like severe hemorrhage or perforation. Therefore, we view surgery as an option for appropriately selected patients, such as those with solitary metastatic lesions in the stomach who are in generally good health or have uncontrolled severe complications. Regarding radical surgery for isolated gastric metastasis, the optimal surgical approach remains undetermined. The scope of gastric resection may vary based on tumor location and size. Recently, function-preserving procedures like proximal gastrectomy and pylorus-preserving gastrectomy have shown advantages in maintaining partial gastric function and improving postoperative quality of life while ensuring radical treatment. However, the effects of various surgical techniques, including total gastrectomy, subtotal gastrectomy, and function-preserving gastrectomy, on isolated metastatic gastric lesions remain uncertain and require further study[21].

SCLC is a chemo-sensitive tumor, and rapid responses are often observed. Chemotherapy is often initiated first to counter symptoms and to rapidly halt tumor growth. Early concurrent radiochemotherapy may not be suitable for all patients. In patients with large tumor volumes or poor performance status, early radiotherapy may increase acute and late toxicities. In these cases, a deferred start to radiotherapy or sequential treatment is preferred. Bulky tumors may require large treatment volumes. These can be reduced if initial chemotherapy shrinks the tumor, potentially reducing toxicity to the lungs. Radiotherapy plays a vital role in treating every stage of SCLC. Detailed information about the indications for radiotherapy is presented in Table 1[12]. Intrathoracic symptoms like obstruction caused by a tumor, pain, or coughing up blood (hemoptysis) can frequently be managed with radiation therapy in palliative care. Even symptoms stemming from tumors outside the chest (extrathoracic metastases) can benefit from radiation treatment. Effective care requires a collaborative approach involving multiple medical professionals to address all aspects of the patient's needs [12].

The prognosis of SCLC is poor because of its high degree of malignancy, and gastric metastasis is even worse. It contributes to a shorter survival time, especially when there is gastrointestinal bleeding. The prognosis is complicated and worse if the patient's general condition has adverse factors affecting survival time. Treatment of advanced stage SCLC is also difficult and involves multisystemic symptoms. Multidisciplinary diagnostic and treatment approaches should be considered to improve these patients' prognosis and quality of life.

Discussion

In the global cancer landscape, lung cancer ranks first in both prevalence and cancer mortality[22]. SCLC is a highly malignant neuroendocrine tumor with extremely rapid metastatic potential, accounting for up to 15% of all primary lung cancers[23]. This type of lung cancer is closely associated with tobacco use, with a significantly higher incidence in people who smoke for longer durations and in more significant quantities[24]. SCLC patients often present with multiple organ symptoms, including pulmonary symptoms (such as cough, dyspnea, chest pain, and hemoptysis) as well as extrapulmonary symptoms due to distant metastasis and paraneoplastic syndromes[25]. However, no clinical symptom is specific for SCLC, as the symptoms are shared by various syndromes that may not be related to malignant pathology. Approximately half of SCLC patients are diagnosed at stage 2 (extensive stage) at the time of initial diagnosis, with metastatic lesions in the brain, bones, and adrenal glands[26]. Gastrointestinal metastasis from SCLC is rare and has been primarily reported in isolated case studies, with most publications focusing on the liver and colon and a few more cases in the stomach recently described[7,27]. Worryingly, most reported cases of gastric metastasis are asymptomatic and are discovered only at autopsy. Those few patients with gastrointestinal symptoms are often overlooked because the symptoms are confused with manifestations of other common gastrointestinal diseases. Consequently, SCLC diagnosis is delayed, not performed, or reversed (after endoscopy combined with gastric mucosal biopsy confirms SCLC, a chest CT scan or bronchoscopy is performed).

Although gastric metastasis from SCLC occurs at a late stage with widespread malignant cells (possibly outside the digestive tract), gastrointestinal symptoms may be the patients' first and only abnormalities, prompting them to seek medical care[7]. If a gastric biopsy is not performed due to acute conditions, such as severe gastrointestinal bleeding or the risk of gastric perforation from deep ulcerative lesions requiring a biopsy of the lesion margin, the pathological results may be affected. The gold standard for diagnosing SCLC liver metastasis is immunohistochemistry, with positive markers including CD56, synaptophysin, neuron-specific enolase, pancytokeratin, neuro-oncological ventral antigen-1, thyroid transcription factor-1 and p16[11-13]. However, biopsies of gastric lesions located in the body or pyloric antrum, whether single or multiple, raised in the mucosa or submucosa, and possibly central ulcers, are not different in endoscopic appearance from those of other non-SCLC gastric tumors. Thus, immunohistochemistry may not be immediately performed, and the patient must undergo a second endoscopic biopsy procedure. The treatment for gastric SCLC metastasis follows the general principles applied to SCLC management, with chemotherapy remaining the mainstay of treatment. Gastric metastasis occurs at a widespread stage of SCLC, and the prognosis is poor. Survival time is limited. This situation will be worse if the patient's digestive manifestations include severe gastrointestinal bleeding. Therefore, supportive treatment and symptomatic relief are included in the necessary palliative treatment.

Table 1 Indications for radiotherapy in small cell lung cancer

Stage	Type of radiotherapy
Very early	Primary curative radiochemotherapy; post-operative mediastinal radiotherapy; prophylactic cranial irradiation
Locally advanced	Primary curative radiochemotherapy; prophylactic cranial irradiation
Extensive disease (metastatic)	Prophylactic cranial irradiation; consolidative mediastinal radiotherapy; palliative radiotherapy

CONCLUSION

Gastric metastasis from SCLC is quite rare and can be easily overlooked or misdiagnosed. The clinical symptoms of gastric metastasis from SCLC are nonspecific and may even appear in isolation without any suggestive respiratory symptoms. Therefore, clinicians need to be vigilant. Gastroscopy with biopsy to confirm histopathology, especially immunohistochemistry, is considered the gold standard for definitive diagnosis. Chemotherapy is generally the first primary treatment for SCLC, especially for patients with gastric metastasis. However, the clinical condition of patients with advanced-stage SCLC is often complicated by multiorgan damage, and a comprehensive treatment plan that considers many individualized factors is necessary. Interventional endoscopy or surgery may sometimes be necessary to address severe complications such as gastrointestinal bleeding when medical treatment fails. Early diagnosis and personalized treatment can potentially prolong survival and improve the quality of life for patients with gastric metastasis from SCLC.

FOOTNOTES

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