Case Report

Primary gastric squamous cell carcinoma in a young adult with immunotherapy complications: a case report

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Background: Primary gastric squamous cell carcinoma (GSCC) is a rare and aggressive malignancy, accounting for less than 0.1% of all gastric cancers. Its clinical presentation and management remain a challenge due to the lack of standardized treatment protocols and limited understanding of its molecular profile.

Case Description: We report the case of a 33-year-old male presented with significant weight loss, severe acid reflux, and progressive subcutaneous masses. Diagnostic imaging and biopsies confirmed stage IV GSCC, with no evidence of other potential metastatic origins. Genetic analysis revealed pathogenic variants in the phosphatase and tensin homolog gene (PTEN), ataxia telangiectasia mutated gene (ATM), and Fanconi anemia, complementation group M (FANCM), along with intermediate tumor mutational burden (TMB). The patient was treated with a combination of leucovorin calcium, fluorouracil, and oxaliplatin (FOLFOX) chemotherapy and nivolumab. Despite aggressive treatment, the patient experienced rapid disease progression and severe thrombocytopenia likely resulting from multifactorial causes, including severe sepsis, liver dysfunction, chemotherapy effects, tumor progression, and possible immune checkpoint inhibitor-related thrombocytopenia (irTCP). The severe complications led to death following palliative extubation.

Conclusions: This case highlights the complexity of diagnosing and managing GSCC, especially in younger patients. Identifying genetic alterations provides valuable insights into the disease's molecular profile. Further research is needed to develop effective and standardized treatment strategies for this rare malignancy.

Keywords: Gastric squamous cell carcinoma (GSCC); genetic alterations; immune checkpoint inhibitor-related immune thrombocytopenia (irTCP); nivolumab; case report

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Introduction

Primary squamous cell carcinoma (SCC) of the gastrointestinal tract is rare. Globally, primary gastric SCC (GSCC) occurs in just 0.04% to 0.09% of cases and represents only 0.2% of all primary gastric cancers (1,2). Due to its rarity, diagnosing primary GSCC often requires ruling out other potential sources of SCC metastasis, such as from the lung, breast, or liver, which adds a significant challenge to the diagnostic process (2). Previous case reports have provided valuable insights that guided clinical management of its complicated clinical course (3,4). Other retrospective studies have summarized the characteristics of GSCC but have not been able to solidify a strategy for managing complications and the rapid progression of the disease (2,5).

The molecular identification and genetic characterization of gastric cancers are currently well established, including gene mutations, differential gene expression, and somatic copy number alterations (SCNAs) in different subtypes (6,7). However, due to the rare incidence of GSCC and its unknown origin, its molecular identification and genetic characterization have not been well documented. The origin of GSCC remains unknown, and several possible theories have been proposed. These include potential origins from a "totipotent stem cell" capable of differentiating into any cell type, squamous metaplasia in pre-existing non-neoplastic glandular epithelium, ectopic squamous cell nests, squamous differentiation of adenocarcinoma, vascular endothelium, or infection with Epstein-Barr virus (EBV) or human papillomavirus (HPV) (3,8).

The prognosis of GSCC is generally poor, with a median overall survival ranging from 7 to 8.9 months (8). Compared to other gastric cancers at similar stages, the overall survival for GSCC is typically lower (5). It is often diagnosed at a later stage and typically found in individuals older than 60 (2,5). Currently, there are no established biomarkers or prognostic markers for GSCC, and prognosis is mainly based on the diagnosed stage (2). Furthermore, there are no guidelines established to direct its treatment, which poses challenges when managing patients, highlighting the need for further characterization of its clinicopathology, pathogenesis, disease progression, and treatment.

We present a 33-year-old male diagnosed with primary GSCC who experienced a rapid clinical decline due to disease progression and complications from chemotherapy of leucovorin calcium, fluorouracil, and oxaliplatin (FOLFOX) and nivolumab. These complications included obstructive hepatopathy and severe thrombocytopenia. We present this case in accordance with the CARE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-2024-884/rc).

Highlight box

Key findings

- We report a rare case of primary gastric squamous cell carcinoma (GSCC) in a young adult. The patient faced rapid disease progression and severe thrombocytopenia likely resulting from multifactorial causes, including sepsis, liver dysfunction, chemotherapy effects, and possible immune checkpoint inhibitor-related thrombocytopenia (irTCP), a rare and severe complication of immunotherapy.

What is known and what is new?

- GSCC is a rare and aggressive gastric malignancy typically diagnosed at advanced stages. There's a gap of genetic profiling and standardized treatment for GSCC.
- This case reported genetic profile, including *PTEN* pathogenic variant, *ATM* and *FANCM* gene alterations, intermediate tumor mutational burden (TMB) with a score of 8 and microsatellite stable (MSS), in a young patient. It also details severe immune-related complications following leucovorin calcium, fluorouracil, and oxaliplatin (FOLFOX) chemotherapy and nivolumab, contributing new insights into the disease's clinical and genetic aspects.

What is the implication, and what should change now?

- Our case emphasizes the importance of building genetic profiles in GSCC. Further studies should focus on developing tailored treatment guidelines to improve outcomes for GSCC patients.

Case presentation

An otherwise healthy 33-year-old male presented to the oncology office because he noticed firm masses for weeks with decreased appetite, difficulty tolerating oral intake, unintentional weight loss of approximately 20 to 30 pounds, severe acid reflux, and abdominal pain. He palpated a firm mass on the upper extremity and spread across to the arms, torso, and back over a few weeks. Initial physical examination revealed firm, raised subcutaneous nodules throughout the entire torso, arm, and back. No superficial skin lesion was identified. Initial labs revealed mild pancytopenia [white blood cell count (WBC) 4.97×10^9/L, hemoglobin (Hb) 9.9 g/dL, and platelets counts (PLT) 142×10^9/L]. Liver function tests (LFTs) were within normal limits with alanine transaminase (ALT) 7 U/L, aspartate

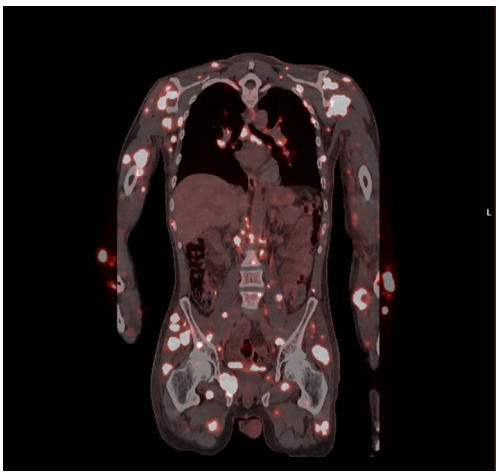

Figure 1 Positron emission tomography (PET)/computed tomography (CT) image.

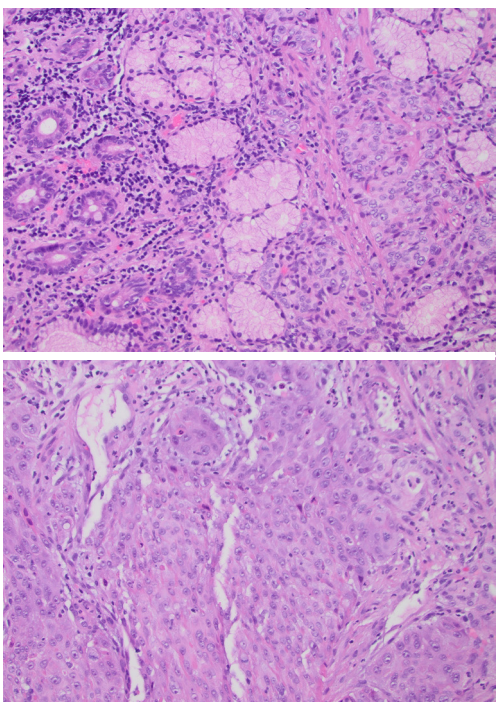

Figure 2 Biopsy pathology images [hematoxylin and eosin (H&E) stain, 20×].

aminotransferase (AST) 21 U/L, alkaline phosphatase (ALP) 42 U/L, and total bilirubin (T.bil) 0.5 mg/dL. The tumor marker CA19-9 was positive at 75.37 U/mL. The human immunodeficiency virus (HIV) test was negative.

A computed tomography (CT) scan of the chest, abdomen, and pelvis revealed asymmetric circumferential gastric antral wall thickening, raising concerns about an infectious or inflammatory process. Nonspecific peri-gastric and retroperitoneal lymphadenopathy and mediastinal, bilateral hilar, and supraclavicular lymphadenopathy were noted. Positron emission tomography (PET)/CT further revealed innumerable foci of intense hypermetabolic activity localized to the axial and appendicular osseous skeleton, the musculature of the trunk, bilateral upper and bilateral proximal lower extremities, and lymph nodes of the neck, chest, abdomen, and pelvis, as well as bilateral lungs, consistent with extensive metastatic disease (*Figure 1*). An esophagogastroduodenoscopy (EGD) was performed at another institute, and the written report revealed a circumferential, friable, obstructing, malignant-appearing mass in the pyloric channel, preventing the scope from passing through. No possible malignant esophageal lesion was noted. An endoscopic ultrasound (EUS)-guided gastrojejunostomy and lumen-apposing metal stent (LAMS) placement was subsequently done for gastric outlet obstruction.

The biopsy revealed moderately differentiated invasive SCC (*Figure 2*). A right axillary subcutaneous mass excision biopsy subsequently revealed metastatic moderately differentiated SCC, forming a 2.7 cm mass involving soft tissue and skeletal muscle. The immunohistochemical stain demonstrated diffuse positive staining for p63, CK5/6, and CK7, while CDX2 and p16 were negative. He was diagnosed with stage IV GSCC. Caris Life Sciences (CARIS) blood test results before the treatment revealed a *PTEN* pathogenic variant, as well as *ATM* and *FANCM* gene alterations. The test also revealed an intermediate tumor mutational burden (TMB) with a score of 8 and is microsatellite stable (MSS). While further molecular testing was initially planned, HER2 status and PD-L1 combined positive score could not be reported due to insufficient tissue (QNS) or issues with sample processing. The patient was also referred to genetic counseling, but this was never done due to the following clinical course.

He was started on chemotherapy with FOLFOX and nivolumab. At around the treatment of cycle two, he started to notice the rapid growth of subcutaneous masses, which resulted in massive right arm swelling and deep vein thrombosis. When coming back for follow-up for cycle three, acute worsening of his liver function with ALT 489 U/L, AST 477 U/L, ALP 1,575 U/L, T.bil 3.8 mg/dL, and PLT 50×10^9/L was noted. He was therefore admitted due to concern of immunotherapy-induced hepatotoxicity and started on systemic steroids at 1 mg/kg/day dose. His

hepatitis panel was unremarkable. A magnetic resonance cholangiopancreatography (MRCP) revealed a large mass involving the distal stomach and proximal duodenum, obstructing the common bile duct, which was severely dilated with moderate intrahepatic biliary ductal dilatation. Endoscopic retrograde cholangiopancreatography (ERCP) was not recommended by gastroenterologist due to the location of the primary tumor, and a percutaneous transhepatic cholangiography (PTC) drain was placed. His LFTs initially improved once the drain was placed, so systemic steroids were discontinued as the cause of LFT elevation was more likely due to anatomic biliary obstruction.

His hospital course was further complicated by persistent pancytopenia with prominent thrombocytopenia with platelets in the $(20–30)\times10^9$/L range. He developed septic shock secondary to E. coli bacteremia and further cardiovascular collapse, requiring emergent intubation and maximal pressor support. Peripheral blood smear revealed moderate macrocytic anemia with rare schistocytes (<1%) and severe thrombocytopenia. The disseminated intravascular coagulation (DIC) panel not remarkable. There was no evidence of hemolysis. The direct antiglobulin test was negative. The pancytopenia was thought to be multifactorial and related to possible immunotherapy-induced aplastic anemia, malignant involvement of his bone marrow, given the rapid progression of the disease, and severe septic shock. Similarly, severe thrombocytopenia was likely caused by a combination of factors, including sepsis, liver dysfunction, chemotherapy effects, tumor progression, and possible immune checkpoint inhibitor-related thrombocytopenia (irTCP). Initial plans to coordinate a bone marrow biopsy by hematologist were not feasible due to his clinical hemodynamic instability. Given the possibility of irTCP, he was placed on high-dose steroids as well as Eltrombopag, but did not result in recovery of his platelet counts. Platelets remained profoundly low in the setting of septic shock and liver failure, suggesting a very poor prognosis. The family subsequently decided not to pursue aggressive treatment after one week of intubation, and the patient passed away after palliative extubation.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent for publication of this case report and accompanying images was not obtained from the patient or the relatives after all possible attempts were made.

Discussion

Diagnosis of primary GSCC

There is limited literature to guide the diagnosis of GSCC due to its rare case presentation. Neither the European Society of Medical Oncology (ESMO) nor the National Comprehensive Cancer Network (NCCN) have established diagnostic guidelines. Few literature were published in the 1960s that defined the histological diagnostic criteria of GSCC to meet The Japanese Gastric Cancer Association (JGCA) has suggested that the diagnostic criterion for primary GSCC requires the histology must only consist of SCC without a feature of adenocarcinoma and the tumor location cannot be close to gastroesophageal junction (GEJ), or other SCC evidence in the other part of the body (2,3,9). In our case, the tumor located in the pylorus with histology revealed SCC. There was no other lesion at other places, such as the esophagus, anus, head, neck, lung, or skin, that could be the metastasis cited in the physical examinations and imaging findings. Although the patient's lesion was palpable, it was subcutaneous and not a superficial skin lesion.

Immunohistochemistry (IHC) findings can assist in differentiating metastatic cancers from primary GSCC. A recent study by Kanthan *et al.* used IHC protein markers such as CK5, p63, and p16 to confirm the diagnosis of cervical SCC metastasized to the duodenum (10). Our patient has diffuse positive staining for p63 and CK5, which suggests the SCC nature of the cancer. However, the utility of IHC studies in distinguishing primary from metastatic GSCC lesions remains limited. Additionally, while p16 is commonly expressed in HPV-related SCC, it was negative in our patient (11-13). The diagnosis of primary GSCC still relies on the oncologist's clinical judgment based on the patient's presentation.

Clinicopathology of primary GSCC

A previous cohort study with 163 cases reported a mean patient age of 69.6 years old, with a predominance of men over women (113:50). Additionally, patients were typically diagnosed at an advanced stage (2). What distinguishes our case from previously known features of primary GSCC is that the patient was diagnosed at the relatively young age of 33 years.

In addition to traditional patient general characteristics, our patient also has CARIS blood test results that revealed a *PTEN* pathogenic variant as well as *ATM* and *FANCM* gene

alterations. The tumor was found to have an intermediate TMB with a score of 8 and MSS. The study by Cho *et al.* revealed that high TMB accounted for significant tumors with higher host immune response, earlier cancer stage, and favorable prognosis. PD-L1 expression was significantly associated with microsatellite instability high (MSI-H), higher host immune response, and high TMB in gastric carcinoma (14). Other studies revealed that certain subtypes of gastric cancer in Chinese patients have poor prognoses with high TMB due to the disruptions in carbohydrate and lipid metabolism pathways, which may promote tumor progression (15). The impact of TMB is context-dependent, and thus, further studies are needed to establish the interpretation and usage of TMB in the management of GSCC. Studies have demonstrated that the loss or reduced expression of *PTEN* commonly occurs in the tumorigenesis and progression of gastric carcinoma and may correlate with advanced stages of the disease (16,17). A recent study by Lee *et al.* also revealed that patients with *PTEN* loss and epidermal growth factor receptor (EGFR) overexpression have been associated with poorer survival outcomes compared to those without these molecular alterations (18). Although limited data is available for predicting GSCC, our patient had a *PTEN* pathogenic variant, which might explain the rapid cancer progression. In addition, alterations of the *ATM* gene are among the most common somatic mutations in cancer and have generally been associated with a poorer prognosis (19). These alterations have also been linked to diagnosis at a significantly younger age, which might explain our patient's early age at diagnosis (20). Notably, *FANCM* alterations occur in 2.8% of gastric carcinoma cases, making it a relatively uncommon finding, yet it was present in our patient (21). Our case contributes meaningfully to the current body of literature. Further reporting of genetic profiles in GSCC is essential to deepen our understanding of the disease.

Treatment regimen

There is currently no standard treatment regimen for primary GSCC. Previous National Cancer Database research revealed that patients had various treatment strategies, including surgery, chemotherapy, and radiation (5). A review has indicated that the 3- and 5-year overall survival rates of the resectable GSCC were 62.2% and 51.9%, respectively (22). Another review of 9 cases of metastatic GSCC revealed that the clinicians decided to use platinum-fluoropyrimidine or platinum-taxane doublet chemotherapy, and the overall survival ranged from a few months to three years (8,23-31). The latest case report reported that the patient was using adjuvant chemotherapy with 5-fluorouracil plus cisplatin, capecitabine plus irinotecan, and paclitaxel, as well as immunotherapy of pembrolizumab (32). In our case, we decided to treat the patient as esophageal SCC and started treatment with FOLFOX and Nivolumab based on NCCN guidelines (33). Our patient has an MSS tumor, so other regimens, such as Nivolumab plus Ipilimumab, were not chosen. Unfortunately, the cancer progressed rapidly, and the treatment also led to complications. Our case demonstrated the difficulty of managing GSCC as it's a rare cancer. Further studies were needed to assess the treatment efficacy and safety of GSCC.

Thrombocytopenia

In the later stages of our patient's clinical course, he developed severe thrombocytopenia. In addition to possible causes such as sepsis, liver dysfunction, chemotherapy effects, and tumor progression, irTCP was also suspected. Unlike other immune-related adverse events, irTCP is associated with worse overall survival and has been observed to have the lowest incidence among patients treated with PD-1/PD-L1 monotherapy (34). Our patient, who received chemotherapy combined with nivolumab, subsequently developed pancytopenia with significantly reduced platelet counts. The complexity of the causes of thrombocytopenia, such as liver failure, severe sepsis, and irTCP, indicated a poor prognosis and high mortality. We decided to manage sepsis and other potential contributing factors aggressively, so the treatment for irTCP was started. Our case highlighted the challenges in managing the rapid progression of GSCC and its severe treatment complications.

Conclusions

This case report demonstrated the rarity and clinical challenges of GSCC, especially in a young patient experiencing rapid disease progression and severe complications. The patient's distinct genetic profile, featuring *PTEN*, *ATM*, *FANCM* gene alterations, and intermediate TMB, offered valuable insights into the nature of GSCC and its molecular profile. Given the rarity of GSCC, its management remains complex and

lacks standardization, highlighting the need for more comprehensive research and treatment guidelines.

The occurrence of liver dysfunction, thrombocytopenia, and other complications implies the complexities of managing GSCC and emphasizes the necessity of early and accurate diagnosis to optimize treatment strategies. As understanding of GSCC evolves, continued investigation into genetic profiles and clinical outcomes will be critical for refining therapeutic approaches and enhancing patient prognosis. Future research should focus on developing targeted therapies and establishing standardized treatment protocols to address the distinct challenges posed by this rare malignancy.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-2024-884/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent for publication of this case report and accompanying images was not obtained from the patient or the relatives after all possible attempts were made.

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