CASE REPORT

Advanced gastric cancer linitis plastica presented with disseminated intravascular coagulation

Sehem Ghazala, Jawad Bilal, Irbaz Bin Riaz

Department of Internal Medicine, University of Arizona, Tucson, Arizona, USA

Correspondence to

Dr Sehem Ghazala, sghazala@deptofmed.arizona.edu

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SUMMARY

An old man was found unconscious; on admission found to have disseminated intravascular coagulation with concern of upper gastrointestinal bleed after he was found to have melena. Esophagogastroduodenoscopy on admission showed diffuse thickened gastric folds, and biopsy showed mucosal oedema. Bone marrow biopsy concerning for lymphoma was obtained showed adenocarcinoma. MRI of the abdomen was significant for diffuse gastric wall thickening. A repeat endoscopic ultrasound showed a diffuse gastric wall thickening of 15 mm and submucosal tunneling technique biopsy suggested high-grade, invasive, signet ring adenocarcinoma of the stomach. Oncology was consulted to initiate palliative chemotherapy. In retrospect, the patient was questioned regarding gastrointestinal symptoms; he reported gradual early satiety, dysphagia and unintentional weight loss over the course of 4 months.

BACKGROUND

Disseminated intravascular coagulation (DIC) is a haemostatic complication that can potentially cause bleeding, thrombosis or both. It is well known to be associated with solid tumours with overall incidence of 6.8%.¹ The incidence rate of stomach cancer associated with DIC is rare and is reported to be ~1.6%.² In this present case, infusional fluorouracil (5-FU) and leucovorin were started as initial palliative chemotherapy to control DIC and associated complications. He had a significant improvement in clinical status and DIC within a week. Subsequently, oxaliplatin was introduced along with 5-FU. This case affirms the usefulness of a submucosal tunneling technique for submucosal biopsies in diagnosing diffuse-type gastric cancer. Furthermore, it also suggests early treatment with chemotherapy can control symptoms of DIC, improve quality of life and possible overall survival and eliminate the need for supportive therapy. There is no concrete evidence to support this approach, but there are several case studies reported in the literature in support of this.^{3–5} This area needs further research and more systematic approach considering fatal prognosis.

CASE PRESENTATION

A 71-year-old man with no known medical history presented after a witnessed syncopal episode. On physical examination, temperature was 38.5°C, pulse 87/min, blood pressure 150/50 mm Hg, respiratory rate 16/min and oxygen saturation 93% on room air. He was alert but not oriented to time,

place and person. Eye examination showed pale conjunctiva. Rectal examination revealed melena, and the fecal occult blood test (FOBT) was positive. The complete blood count showed severe microcytic anaemia (haemoglobin 4.2 g/dL, haematocrit 13.9%, MCV 78.6 fL) and thrombocytopenia (platelets $44 \times 103/\mu\text{L}$). White cell count was normal ($4.9/\text{mm}^3$). Comprehensive metabolic profile was normal except for hypoalbuminemia (albumin 2.6 g/dL). Coagulation profile revealed a prolonged prothrombin time (PT) of 22.7 s, an activated partial thromboplastin time (aPTT) of 40.2 s and an international normalised ratio of 2.0. Rest of laboratory workup revealed haptoglobin 172 mg/dL, fibrinogen 70 mg/dL, lactate dehydrogenase (LDH) 372 IU/L and D-dimer $>20 \mu\text{g/mL}$. Peripheral smear showed absolute lymphopenia, severe microcytic hypochromic anaemia, thrombocytopenia and rare schistocytes. Serology testing of *Helicobacter pylori* was negative. Gastroenterology service was consulted for evaluation of melena, and esophagogastroduodenoscopy (EGD) was performed which showed esophagitis and diffuse thickened edematous gastric folds with areas of erythema in stomach (figure 1). Gastric folds did not flatten with insufflation suggesting diffuse infiltration. Gastric mucosal biopsy demonstrated edematous gastric mucosa with mild reactive changes. There was no evidence of malignancy. The hematology and oncology service was consulted given concern for DIC and possible underlying malignancy. Bone marrow biopsy was performed which

Figure 1 EGD: Gastric body: abnormal mucosa—thickened folds and mucosal change (arrow). EGD, esophagogastroduodenoscopy.

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Figure 2 MRI: Diffuse gastric wall thickening (arrows).

Figure 3 EUS: Gastric body wall thickening to the level of serosa (arrows). EUS, endoscopic ultrasound.

was significant for widely infiltrated atypical large cells forming glands with a mucinous content, consistent with metastatic adenocarcinoma. In retrospect, the patient was questioned regarding gastrointestinal symptoms; he reported gradual early satiety, dysphagia and unintentional weight loss over the course of 4 months. He had a 50-pack-year smoking history while family history was non-contributory. MRI of chest and abdomen showed diffuse thickening of the stomach wall and gastro-oesophageal junction ([figure 2](#)). Endoscopic ultrasound (EUS) demonstrated diffuse thickened gastric walls up to 15 mm, primarily within the submucosa ([figure 3](#)). Several abnormal lymph nodes were visualised in the gastrohepatic ligament and perigastric regions ([figure 4](#)). Repeat EGD was performed with tunnelled biopsies. Pathology report of gastric submucosal biopsies suggested high-grade, invasive, signet ring adenocarcinoma of the stomach ([figure 5](#)). Cytology report was also consistent with malignant neoplasm favouring adenocarcinoma. MRI spine revealed multiple scattered lesions throughout the cervical and thoracic spine concerning for metastatic disease. MRI hip demonstrated 3 cm osseous lesion with cortical destruction of the right anterior ileum that was concerning for osseous malignancy.

DIFFERENTIAL DIAGNOSIS

In this case, differential diagnosis included DIC and thrombotic microangiopathy (TMA). The clinical setting (presence of cancer as inciting factor) and laboratory workup with elevated

Figure 4 EUS: Abnormal lymph node (arrow). EUS, endoscopic ultrasound.

Figure 5 Stomach biopsy: signet ring (arrows) adenocarcinoma.

D-dimer, LDH, PT and partial thromboplastin time (PTT) levels with significantly low fibrinogen supported the diagnosis of DIC. Specific criteria are outlined by International Society of Thrombosis and Hemostasis (ISTH), which includes an underlying disorder, platelet count, d-dimer, PT and fibrinogen level.⁶ Score of five or more is compatible with overt DIC. The sensitivity of the DIC score is 91–93%, and the specificity is 97–98%.⁷ On admission, our patient scored 8 as per scoring algorithm.

TREATMENT

The patient was diagnosed with stage IV invasive, high grade, gastric adenocarcinoma with signet ring features complicated by DIC. During hospital stay, supportive therapy was given which included packed red blood cell units for anaemia and cryoprecipitate for hypofibrinogenemia. After long discussion with the patient, early palliative chemotherapy was initiated for treatment of gastric cancer, which was the underlying cause of DIC. He was started on 5-FU and leucovorin, which significantly reduced the need for blood products. Coagulation profile improved and haemoglobin stabilised. The patient was discharged under stable conditions for continued chemotherapy and follow-up in an oncology clinic.

OUTCOME AND FOLLOW-UP

On day 13 after initiating chemotherapy, the decision was made to discharge the patient home and to follow-up with oncology as outpatient.

DISCUSSION

DIC is a haemostatic complication that can potentially cause bleeding, thrombosis or both. It is well known to be associated

with solid tumours with an overall incidence of 6.8%.¹ Certain types of solid tumours such as lung, breast and prostate are reported more commonly with DIC relative incidence of 14.4%, 10.5% and 10.5%, respectively. Likewise, DIC has been described in all types of histological tumours, but adenocarcinoma and squamous cell carcinoma are the predominant ones with incidence of 52.6% and 9.2%, respectively.¹

Stomach cancer is the fifth most common type of neoplasm in the world.⁸ It is rarely associated with DIC. The incidence rate is reported to be ~1.6%.² It presents as a myriad of non-specific symptoms, which often lead to diagnostic and therapeutic delay. Therefore, about 85% of patients are diagnosed with metastatic disease on initial presentation. Diffuse histological type is more frequently associated with DIC although occurrence of this particular histological variant is uncommon.^{9–10} Diagnosis of diffuse infiltrative gastric adenocarcinoma can be challenging because superficial mucosa is often normal which can give false-negative results.¹¹ In this case, first gastric mucosal biopsy was negative for malignancy. However, subsequent submucosal biopsy with a tunneling technique was positive for gastric adenocarcinoma.

The exact mechanism of developing DIC in solid cancer is not well elucidated, but there are several proposed mechanisms which include increased expression of tissue factor leading to activation of coagulation cascade, production of cancer pro-coagulant, a cysteine protease with factor-X-activating properties or increased expression of fibrinolytic proteins. It is also suggested that vascular endothelium may also contribute in this process by platelet activation secondary to increased plasma levels of von Willebrand factor.^{3–12–15}

The prognosis of advanced gastric cancer with DIC is poor. Few studies have compared the prognosis between patients undergoing palliative chemotherapy and best supportive care. Patients who received only supportive care had an overall survival of 9–16 days^{10–16} compared to 61–196 days in patients who were treated with palliative chemotherapy.^{2–10–16–17} Several palliative chemotherapy combinations have been proposed to control DIC symptoms and improve overall survival, but no actual guidelines exist.

Chemotherapy combining 5-FU and cisplatin is widely used in advanced gastric cancer that has demonstrated high tumour response rates and improved survival.¹⁸ Few other regimens include paclitaxel plus platinum regimen,¹⁶ docetaxel with cisplatin.¹⁹ Regardless of type of regimen, palliative chemotherapy has shown to improve overall survival compared to best supportive care. Unfortunately, the use of these chemotherapeutic agents is limited by the increased treatment-related toxicity. To circumvent this issue, weekly 24-hour infusion of high-dose 5-FU and leucovorin is often used as an initial therapeutic option, which has minimal bone marrow toxicity despite its higher dose intensity.⁹ It has shown to achieve a significant tumour response rate without worsening the manifestations of DIC.⁹ Subsequently, conventional chemotherapy can also be used to achieve remission. In this present case, infusional 5-FU and leucovorin were started as initial palliative chemotherapy to control DIC and associated complications. He had a significant improvement in clinical status and DIC within a week. Subsequently, oxaliplatin was introduced along with 5-FU.

This case affirms the usefulness of the submucosal tunneling technique for submucosal biopsies in diagnosing diffuse-type gastric cancer. Furthermore, it also suggests early treatment with chemotherapy can control symptoms of DIC, improve quality of life and possible overall survival and eliminate the need for supportive therapy. There is no concrete evidence to support this

approach, but there are several case studies reported in the literature in support of this.^{3–5} This area needs further research and more systematic approach considering fatal prognosis.

Learning points

- ▶ Disseminated intravascular coagulation (DIC) is well known to be associated with solid tumours with overall incidence of 6.8%.
- ▶ The importance of the submucosal tunneling technique for submucosal biopsies in diagnosing diffuse-type gastric cancer.
- ▶ Palliative chemotherapy improves quality of life and possible overall survival.
- ▶ Several palliative chemotherapy combinations have been proposed to control DIC symptoms, but no actual guidelines exist.

Contributors SG wrote the introduction, summary, case presentation and contributed to the discussion. JB focused mainly on the discussion. IBR involved inpatient patient care and drafted the final version.

Competing interests None declared.

Patient consent Obtained.

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