Radiotherapy for Esophageal Squamous Cell Carcinoma Concomitant With Hypoproteinemia: a Case Report

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Case report

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Abstract

Background: Malignant tumors frequently combined with hyperfibrinogenemia, rarely with hypofibrinogenemia.

Case presentation: This study reports a 60-year-old male patient of mid-thoracic esophageal squamous cell carcinoma (ESCC) with hypofibrinogenemia who presented at our hospital because of a swallowing disorder and dull pain in the upper abdomen. An initial test indicated his plasma fibrinogen (FIB) level was 0.88 g/L (reference range: 2.38–4.98 g/L). After multiple infusions of fresh plasma and supplements of FIB and cryoprecipitate, he maintained a FIB level above 1.0 g/L. We administered radical radiotherapy (RT) for the ESCC, and his FIB level gradually normalized during the RT period. The symptoms from ESCC gradually resolved, and we classified the patient as having stable disease at the end of the RT period. After 10 months follow-up, the patient have achieved partial response (PR). At that time, the patient had no increased tendency for bleeding and his FIB level was 0.97 g/L. At the last follow-up, the patient has survival about 18 months.

Conclusions: it was considered the hypofibrinogenemia in this ESCC patient to be a consequence of paraneoplastic syndrome.

Background

Esophageal cancer is one of the most common malignant neoplasms and these patients typically have poor outcomes. Esophageal squamous cell carcinoma (ESCC) accounts for 80% of all esophageal cancers in Eastern countries [1]. Fibrinogen (FIB) is a glycoprotein synthesized in hepatocytes that functions in the final steps of the blood coagulation cascade, and as a precursor monomer of the fibrin hemostatic plug. FIB also functions in tumorigenesis, formation of stroma, angiogenesis, and tumor metastasis [2]. In general, tumor patients have increased risk for hypercoagulability and thrombosis. Studies of ESCC patients indicated that hyperfibrinogenemia was associated lymph node metastasis, distant organ metastasis, worse survival, and a higher rate of relapse [3, 4]. However, ESCC concomitant with hypofibrinogenemia has only been rarely reported. This paper reports an unprovoked case of ESCC concomitant with hypofibrinogenemia.

Case Presentation

In April, 2019, we admitted a 60-year-old male patient to the Department of Thoracic Surgery in our hospital. The patient reported having a swallowing disorder and dull pain in the upper abdomen for more than 1 month. The results of gastroscopy indicated esophageal mucosal erythema that was 30–35 cm from the incisors and light-stained spots after iodine staining of those sites. Examination of the biopsy specimens indicated a diagnosis of well-differentiated ESCC.

Barium esophageal radiography showed there was about 5 cm of disordered mucosa in the middle thoracic esophagus. CT imaging was then performed for the chest and abdomen, and we confirmed the

clinical stage as T2N1M0 according to the AJCC 9th staging criteria for ESCC. The results of routine blood, liver function, and kidney function tests were all normal. However, measurement of blood coagulation on April 16 indicated an abnormally long thrombin time (TT = 26.4 s, reference range: 10.3–16.6 s) and an abnormally low level of FIB (0.88 g/L, reference range: 2.38–4.98 g/L). A bone marrow biopsy on the same day indicated no reason for the hypofibrinogenemia. The patient also had no tendency for increased bleeding.

To correct the hypofibrinogenemia, we infused 600 mL of fresh plasma, but the FIB remained low (0.94 g/L) on April 17. Considering the high-risk of surgery, the patient was transferred to the Department of Hematology in our hospital. After FIB infusion, his plasma FIB level was 1.79 g/L on April 24. However, thoracic surgery was still considered a high-risk and the patient refused the operation. Thus, the patient was transferred to Tianjin Institute of Hematology for further diagnosis, although the cause of the hypofibrinogenemia was still unknown. The patient subsequently reported a gradually increasing difficulty in swallowing and dull pain in the upper abdomen. He was admitted to the Department of Radiotherapy in our hospital on May 8. At this time the patient received a semi-liquid diet. Reexamination indicated the plasma FIB level was 0.90 g/L, the TT was 15.7 s, and the international normalized ratio (INR) was 1.77 (reference range: 0.80–1.40). The preliminary diagnosis was ESCC combined with hypofibrinogenemia.

We infused the patient with 10 units of cryoprecipitate on May 10, and with 200 mL of leukocyte-free frozen plasma infusion on May 13. However, on May 14 his FIB level was 0.65 g/L, so we transferred him to the Department of Hematology once more. Following continuous infusion with FIB and treatment for anti-fibrinolysis, his FIB level reached about 1 g/L. After the patient's family signed an informed consent agreement, the patient was positioned under a computed tomography (CT) simulator. The gross tumor volume (GTV) indicated the primary tumor was in the middle thoracic segment of the esophagus and mediastinal metastatic lymph nodes. According to therapeutic principles, we enlarged the GTV to include the clinical target volume (CTV) and planning target volume (PTV). The dose at 95% coverage of the PTV was defined as 60 Gy in 30 fractions, 2 Gy per fraction, administered 5 days per week for 6 weeks. After approval, we implemented the treatment plan using intensity-modulated radiotherapy (IMRT) on May 20.

During the radiotherapy (RT) period, the patient experienced no skin congestion or ecchymosis and no subcutaneous hemorrhage, and his swallowing symptoms and dull pain in the upper abdomen gradually subsided. At the same time, his FIB level (Fig. 1) and TT (Fig. 2) both normalized. Upon completion of the RT (June 28, 2019), the patient could easily eat a soft diet without swallowing disorders or abdominal pain. At that time, we considered him to have stable disease (SD), based on a CT of the chest and abdomen and barium esophagography, and we discharged him from the hospital.

One month after the IMRT, our reexamination indicated the patient attained partial response (PR). We also performed a barium esophagogram at that time. The patient reported continued intake of soft food and, in agreement with the CT of the chest and abdomen, the esophagogram indicated PR. Our reexamination of the patient in April 2020 indicated he continued easy intake of soft food, and we confirmed his status

as PR. Importantly, his plasma FIB level at that time was 0.97 g/L. Because of the COVID-2019 pandemic, the patient has not recently visited the hospital. On Jaunary 26, 2021 (18 months after RT), we contacted the patient by telephone and he reported continued easy intake of soft food.

Discussion

Most patients with malignant tumors have abnormalities in one or more coagulation indicators, such as a shortened prothrombin time (PT), an increased plasma FIB level, or an increased D-dimer level [5]. FIB and D-dimer are specific indicators of hypercoagulability. Hypercoagulability in patients with malignant tumors can promote the formation of tumor thrombi and cause secondary hyperfibrinolysis [6]. FIB is the main coagulation factor in plasma, and its normal concentration is about 2 to 4 g/L [7]. A high level of plasma FIB in patients with lung cancer, ESCC, gastric cancer, colorectal cancer, ovarian cancer, and other cancers is independently associated with poor prognosis [8–11]. A reduced FIB level occurs in disseminated intravascular coagulation (DIC), severe hepatitis, cirrhosis, thrombolytic therapy, primary fibrinolysis, and several other diseases. Primary hypofibrinogenemia is an autosomal genetic disease and identification of the mutant gene is the gold standard for diagnosis, but this is difficult in clinical practice [12]. Secondary hyperfibrinolysis is a thrombo-hemorrhage syndrome that is the consequence of a primary disease and manifests as local or diffuse intravascular coagulation [13].

Plasma fibrin precipitates in blood vessels, thereby promoting the release of plasminogen activator in the circulating blood, leading to hyperfibrinolysis and an increased level of D-dimer. Several factors, such as severe trauma, postpartum hemorrhage, and liver transplantation, can lead to hyperfibrinolysis, and administration of tranexamic acid to these patients can reduce the risk of bleeding and death [14]. A multi-center study by Hagemo et al. [15] showed that various factors, such as hyperfibrinolysis, severe blood loss, blood dilution after rehydration, acidosis, and hypothermia, could lead to a decreased FIB level, and that the most direct and effective treatment was intravenous infusion of plasma, cryoprecipitate, and FIB. In addition, Hess et al. [16] reported that hypofibrinogenemia caused by trauma was related to a more favorable patient prognosis.

Hypofibrinogenemia secondary to a malignant tumor is rare, and there are only a few case reports with this finding. Rapaport et al. [17] reported a patient who had prostate cancer with concurrent hypercoagulability and hypofibrinogenemia. Libek et al. [18] reported a patient who had prostate cancer and a subcutaneous hematoma due to hyperfibrinolysis, and they considered this to be paraneoplastic syndrome (PNS). Aulmann et al. [19] reported a patient who had metastatic breast cancer combined with thrombocytopenia and hyperfibrinolysis, and they also considered this to be PNS [19]. Recently, Ma et al. [20] reported hypofibrinogenemia in patient who had relapsed gastric cancer after surgery. Hunault-Berger et al. [21] examined 214 patients with acute T lymphoblastic leukemia and T lymphoblastic lymphoma, and reported that administration of L-asparaginase chemotherapy inhibited the biosynthesis of liver L-asparagine-dependent protein, leading to acquired hypofibrinogenemia. Acute promyelocytic leukemia (APL) can also cause secondary hypofibrinogenemia [22]. These patients have increased levels of urokinase-type plasminogen activator, tissue-type PA, and annexin-α2 in APL cells, leading to synthesis

and activation of plasminogen, metabolism of FIB, and hypofibrinogenemia. Liu et al. [23] studied patients with APL and reported that administration of all-trans retinoic acid (ATRA) induced APL cell differentiation, down-regulated annexin-α2, and corrected the hyperfibrinolysis [23]. The main supportive treatments for these patients are infusion of fresh frozen plasma (FFP), cryoprecipitate, and/or concentrated FIB to maintain an FIB level above about 1.0 to 1.5 g/L [24].

Our patient had ESCC combined with hypofibrinogenemia. After fresh plasma infusion, FIB supplementation, and cryoprecipitate, his FIB level increased slightly to about 1 g/L. The patient accepted radical RT as treatment for the ESCC. His FIB level gradually rose during the RT period, and reached a maximum of 2.20 g/L. After the RT period, the patient's symptoms gradually resolved, and we evaluated the patient's status as SD. One month after RT, the patient had a status of PR, and he maintained this status for more than 10 months. The FIB level was 0.97g/L at the last follow-up. The patient had no increased tendency for bleeding during the entire course of disease, treatment, and recovery. We therefore considered the hypofibrinogenemia in this patient to be a consequence of PNS, although the exact mechanistic relationship of PNS with ESCC remains unknown.

Abbreviations

APL: Acute promyelocytic leukemia; CT: computed tomography; CTV: clinical target volume; ESCC: Esophageal squamous cell carcinoma; FIB: Fibrinogen; GTV: gross tumor volume; IMRT: intensity-modulated radiotherapy; INR: international normalized ratio; PR: partial response; PNS: paraneoplastic syndrome; PT: prothrombin time; PTV: planning target volume; RT: radiotherapy; SD: stable disease; TT: thrombin time

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the permitted assigns for publication of this case report and any accompanying images.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

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