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A 50-Year-Old Man with Fulminant Alpha-Fetoprotein-Producing Gastric Carcinoma and Disseminated Intravascular Coagulation

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Patient: Male, 50-year-old
Final Diagnosis: Disseminated intravascular coagulatio • gastric cancer
Symptoms: Paralysis
Medication: —
Clinical Procedure: —
Specialty: Oncology

Objective: Rare disease

Background: Alpha-fetoprotein-producing gastric carcinoma (AFPGC) is a rare but aggressive cancer with a poor prognosis. Disseminated intravascular coagulation (DIC) is usually associated with several tumors, including gastric cancer, but only a few cases have been reported in patients with AFPGC. This report describes a case of advanced-stage AFPGC associated with DIC in a 50-year-old White man.

Case Report: A 50-year-old, White, non-smoker man was hospitalized for a recent left hemiparesis associated with anorexia and loss of weigh. Clinically, we had multiple, hard, irregular, subcutaneous nodules, left supraclavicular lymph nodes, and a left, complete hemiparesis. Laboratory tests showed a DIC. A whole-body CT scan documented multiple lymph node, liver, subcutaneous, bone, and muscular metastases, a right femoral venous thrombosis, a left popliteal arterial thrombosis, and splenic and renal infarcts. The patient underwent an excisional biopsy of a subcutaneous lesion. Histology and immunohistochemistry confirmed the diagnosis of a metastasis from a high-grade AFPGC. Before starting any systemic treatment, the patient presented a massive intraventricular brain hemorrhage, quickly leading to his death.

Conclusions: We report a case of metastatic AFPGC associated with a DIC and multiple venous and arterial thromboses resulting in a fatal intracerebral hemorrhage. AFPGC is a distinctive and very difficult to diagnose tumor showing aggressive behavior and poor prognosis.

MeSH Keywords: alpha-Fetoproteins • Antineoplastic Agents • Stomach Neoplasms

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Background

Alpha-fetoprotein-producing gastric cancer (AFPGC) is a rare tumor needing an accurate histological diagnosis [1,2]. It is a very aggressive cancer usually associated with lymph node and liver metastases at diagnosis and a poor prognosis [2,3].

The diagnosis of AFPGC commonly refers to a gastric cancer (GC) positive for AFP on immunohistochemistry, often associated with increased AFP plasma levels, but a few cases with a negative serological AFP have also been described [4].

Presently, there is no a standard treatment, and systemic chemotherapy remains the only validated opportunity for metastatic patients [1–26].

The overall incidence of tumor-associated disseminated intravascular coagulation (DIC) is 6.8%, the most common cancers being lung, breast, and prostate tumors [27]. The reported incidence rate for GC is ~1.6% [27,28]. Only a few cases have been reported in patients with AFPGC [29]. In the absence of treatment, the prognosis of these patients is poor [27].

We report a case of a patient with a metastatic AFPGC presenting an acute DIC leading to a severe brain hemorrhage that quickly caused his death.

Case Report

A 50-year-old, White, non-smoker man was hospitalized in the Neurology Division for a recent left hemiparesis. He described a generalized osteo-articular pain and anorexia with a loss of weigh of 10 kg, starting several weeks before. He had no relevant comorbidities. At the clinical examination, we found multiple, hard, irregular, subcutaneous nodules, left supraclavicular lymph nodes, and a left hemiparesis. Biological tests revealed a moderate normocytic-normochromic anemia (8.5 g/dL) and thrombocytopenia (70 G/L), low fibrinogen levels (0.6 g/L; 2 g/L<NV>4 g/L), a prolonged prothrombin time at 28.8 seconds (NV<13.4 seconds), elevated D-dimer (>20.000 ng/ml; NV<500 ng/ml) and fibrin degradation products levels (>150 µg/ml), a perturbation of the liver function with transaminases (sGOT: 74 UI/L; NV <45 UI/L; sGPT: 47 UI/L; NV <45 UI/L), γ-GT (153 UI/L; NV <55 UI/L) and alkaline phosphatases (166 UI/L; NV <120 UI/L) augmentation, increased levels of LDH (3240 UI/L; NV <250 UI/L), troponin I (451.6 pg/mL; NV <19.8 pg/mL), and myoglobin (239 µg/L; 17 µg/L <NV <106 µg/L). Hemostatic factors II and VII were normal but factors V and X were abnormally low at 34% (70% <NV <150%) and 35% (70% <NV <150%), respectively. According to the International Society of Thrombosis and Hemostasis DIC [27], a laboratory diagnosis of acute DIC was made with a score >5. Autoanticorps (anti-cardiolipin, anti-β2glicoprotein, anti-DNA, anti-nuclear, anti-cytoplasmic and ANCA) were in the normal range. The serology for Lyme disease, syphilis, hepatitis, and HIV was negative. Tumor marker analysis documented high levels of the CA 19.9, CEA, and AFP, at 4751 UI/ml (NV <46 UI/ml), 209 ng/ml (NV <5 ng/ml), and 304 ng/ml (NV <9 ng/ml), respectively. Brain magnetic resonance imaging (MRI) showed multiple ischemic lesions (**Figure 1A**, red arrows). The whole-body computed tomography (CT) scan revealed multiple lymph node, liver, subcutaneous (**Figure 1B**, red arrows), bone, and muscular metastases, a right femoral venous thrombosis, a left popliteal arterial thrombosis (**Figure 1C**, red circle), and splenic (**Figure 1D**, red circle) and renal infarcts (**Figure 1E**, red circle).

The patient underwent an excisional biopsy of a subcutaneous lesion. Subcutaneous nodules are easier to analyze than left supraclavicular lymph nodes and have a lower risk of complications. Histology showed a massive tumor infiltration with mixed, pleomorphic, and "*signet ring*" cells (**Figure 1F**). Immunohistochemistry showed tumor cells positive for CK7 and CK20 and focally positive for AFP (**Figure 1G**), and negative for TTF-1 and CDX2 according to the diagnosis of a metastasis from a high-grade AFPGC.

Before starting any systemic treatment, the patient presented a focal, partial, epileptic crisis with confusion. The brain CT scan confirmed the presence of a massive intraventricular brain hemorrhage (**Figure 1H**) quickly leading to the patient's death.

The patient did not receive any symptomatic treatment such as fresh frozen plasma or cryoprecipitate because his clinical condition quickly worsened. Based on the brain MRI showing multiple ischemic lesions and considering the high risk of bleeding, no anticoagulant treatment was administered during his stay in the Neurology Department.

Discussion

AFP is an oncofetal glycoprotein that is often increased in hepatocellular carcinoma, yolk sac tumor, and teratoma, and in liver diseases, including hepatitis and cirrhosis [1].

AFPGC is a very uncommon tumor accounting for 1.5–7.1% of all GCs [2]. The first case was reported in the literature by Bourreille et al. in 1970 [3].

The diagnosis of AFPGC is a challenge and it is based on the immunohistochemical positivity of GC cells for AFP [1–3]. High AFP plasma levels are often documented but a few cases with a negative serological AFP have also been described [4].

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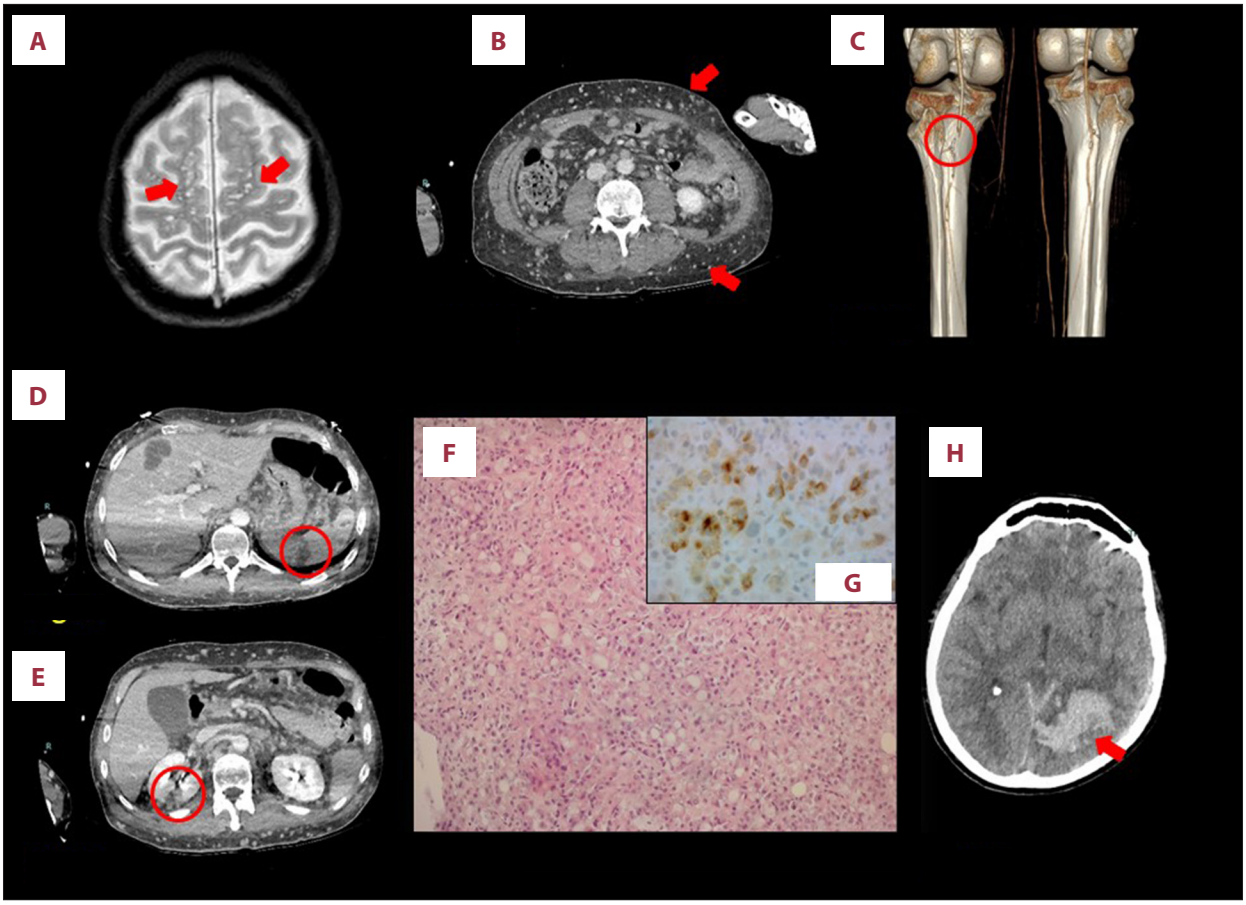

Figure 1. Magnetic resonance imaging (MRI), computed tomography (CT), histopathology, and immunohistochemistry in the diagnosis of a fulminant AFPGC in a 50-year-old man. (**A**) Brain MRI shows multiple ischemic lesions (red arrows). (**B**) CT imaging documents multiple and disseminated subcutaneous metastases (red arrows). (**C**) Computed tomography angiography (CTA) confirms a left popliteal artery thrombosis (red circle). (**D**) Abdominal CT imaging shows an infarction of the spleen (red circle). (**E**) Abdominal CT imaging shows a renal infarct (red circle). (**F**) Photomicrograph of the tumor histology reports pleomorphic malignant cells with 'hepatoid' appearance. Hematoxylin and eosin (H&E). Magnification ×10. (**G**) Photomicrograph of the immunohistochemistry for alpha-fetoprotein (AFP) shows focally positive staining of malignant cells. Magnification ×40. (**H**) Brain CT documents a massive intraventricular brain hemorrhage (red arrows).

Two hypotheses have been postulated to explain this entity [5–9]. The first is based on the de-differentiation of gastric tumor cells in fetal gut and yolk sac cells with the overexpression of some oncofetal genes, such as SALL4, that is closely associated with AFP expression in AFPGC [7]. Other authors suggest a potential role of the regeneration or proliferation of liver cells around liver metastases producing AFP, but this process is not exclusive of AFPGC [5–9].

Histologically, Motoyama et al. proposed 3 different sub-types: the hepatoid (the most common type), the fetal gastrointestinal, and the yolk sac-like tumor [10]. However, in addition to these 3 sub-types, another classification highlights a fourth mixed type [11].

The hepatoid and the yolk sac tumor-like type are supposed to derive from a metaplastic transformation of a common poorly differentiated medullary adenocarcinoma, whereas the fetal gastrointestinal type probably represents a common tubular adenocarcinoma imitating a fetal gastrointestinal epithelium [10].

In a recent Chinese study, 9 patients showed serum levels of AFP <100 µg/L and 29 (64.4%) had a tumor positive for AFP at immunohistochemistry [12]. Histologically, there were 25 (55.6%) cases of hepatoid type, 12 (26.7%) of fetal gastrointestinal type, 2 (4.4%) of yolk sac tumor type, and 6 (13.3%) of mixed type. Serum AFP levels were not significantly correlated with the histologic type. AFPGC patients often showed an advanced tumor stage and a poorer prognosis as compared to negative GC ones [12].

AFPGC presents a biological and clinical aggressiveness and it is usually associated with liver and lymph node metastases [2–12]. The poorly differentiated sub-type is commonly diagnosed in

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the antrum and in younger patients [13]. Histologically, AFPGC shows an increased proliferation index, neovascularization, and less cell apoptosis compared with AFP-negative GC [13].

The prognosis remains extremely poor [2–12]. The median overall survival (OS) is significantly shorter as compared to other GCs [10–12]. Liver metastases are usually diffuse and associated with an OS of less than 1 year [2–12]. The prognosis of AFPGC is strictly related to the tumor size and infiltration, the presence of lymphatic/vascular tumor invasion [14] and liver metastases, the pathological stage, and the expression of p21 [15].

In a recent study evaluating 82 AFPGC patients, a synchronous metastatic cancer was found in 29.27% of patients at diagnosis and the serum AFP level was significantly associated with tumor differentiation [1]. Histologically, 34.55% of these patients presented a hepatoid type, 58.18% had a fetal gastrointestinal type, 9.09% had a yolk sac tumor-like type, and 14.55% had a mixed type. The OS was 42.02 months and the 3-year cumulative survival rate was 53.13%. The prognosis was associated with age, TNM staging classification, serum AFP level, and surgical treatment [1].

Even if several molecular factors such as Ki-67, c-Mesenchymal-to-Epithelial transition (c-MET), Vascular Endothelial Growth Factor-C (VEGF-C), Signal Transducer and Activator of transcription 3 (STAT3), and Hepatocyte Growth Factor (HGF) seem to play an important role in the biological aggressiveness of this tumor [16–18], the exact mechanism is still unclear.

He et al. found a strong correlation between tumor overexpression of X-linked Inhibitor of Apoptosis (XIAP) and Insulin-like Growth Factor (IGF)-Irβ and poor prognosis in AFPGC patients [19]. Based on a risk model including XIAP and IGF-Irβ tumor expression and TNM stage, AFPGC was classified into 2 subgroups with a different prognosis [19].

In case of serological AFP overexpression, this marker could be useful for evaluating response to treatment and tumor recurrence [2].

Presently, in the absence of a validated standard treatment, the systemic chemotherapy used for the average GC patient is usually administered [2]. Radical surgery is the standard treatment for resectable patients [20]. Several studies confirmed a potential efficacy of the adjuvant chemotherapy regardless of the stage [2]. In addition to the usual protocols including 5-fluorouracil, cisplatin and irinotecan, S-1 showed promising results in Asian patients [21]. The efficacy of chemotherapy is probably related to the different sub-type [2]. Diffuse AFPGC seems to benefit more from paclitaxel, S-1, and irinotecan [2]. Several case reports showed moderate activity of sorafenib, afatinib, and trastuzumab [22–25]. Considering the different tumor expression of the Solute Carrier Transporters (SLC) of AFTGC compared to conventional GC, Shimakata et al. hypothesized a potential activity of a gemcitabine/fluoropyrimidine combination chemotherapy [26].

Conclusions

In our case, the patient presented with a metastatic AFPGC associated with a DIC causing multiple venous/arterial thromboses and massive brain bleeding, quickly leading to his death. AFPGC is a distinctive and very difficult to diagnose tumor showing an aggressive behavior and a poor prognosis.

Conflict of interest

None.

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